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Abstracts

1 | What Does Replicable and Robust Non-Randomized Database Evidence Look Like?

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Background: 'Real world' data analyses (non-randomized administrative and clinical healthcare databases) have become a vital tool, providing key insights for regulators, payers, and other healthcare decision makers. However, the credibility of database analyses suffers when 1) the results are not reproducible, 2) conflict with results from other database studies addressing the same question or 3) diverge from randomized clinical trial (RCT) results. Conducting causal inference in database studies can be complex. Implementation of a database study can involve a great deal of data manipulation to create appropriately temporally anchored analytic cohorts from data that were not collected for research purposes. The many subtle design and analysis decisions made during study implementation, have left some stakeholders concerned about selective reporting of study specifications that arrive at a favorable result. Healthcare decision-makers have emphasized the need greater transparency in research that make secondary use of databases. The REPEAT Initiative has embarked on several projects aimed at improving transparency, reproducibility and validity of database research. These projects include large scale replication of 150 published database studies, evaluation of the robustness of results for 50 studies to alternative design and implementation parameters, and development of a structured reporting template with design visualization to increase transparency of reporting and minimize misinterpretation.

Objectives: This symposium will ask the following questions: What does replicable and robust database evidence look like and how can we achieve it? Will structured reporting with design visualization help? How can we clearly communicate design and analytic choices, as well as results, when there are numerous sensitivity analyses? How do we interpret results from different database studies or sensitivity analyses that address the same PICOTS (Patients, Intervention, Comparator, Outcome, Time Horizon, Setting) but have discordant findings?

Description: The symposium panel agenda will include: 1. Presentation of empirical results from replication of 150 published database studies (Wang 25 min) 2. Structured reporting of design details with visualization (Rassen 15 min) 3. FDA perspective (Pinheiro 10 min) 4. Industry perspective (Berlin 10 min) 5. Moderator and audience questions (Schneeweiss) (20 min).

2 | How Do We Assess When Electronic Health Records or Claims Databases Are Fit for a Specific Research or Regulatory Purpose?

Cynthia J. Girman[1]; Mary E. Ritchey[2]; David Martin[3]; Wei J. Zhou[4]; Nancy J. Dreyer[5]

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Background: There is escalating interest in the use of real-world data (RWD) not only for safety but also for effectiveness evaluation. FDA released a framework for public comment at the end of 2018 which focused on randomized trials in clinical practice, potential observational designs, and data quality aspects for the use of real world evidence (RWE) in regulatory and clinical contexts. There is no 'one size fits all' approach to qualifying a data source for broad research or regulatory purposes as the feasibility of using RWD depends on how the results will be used, the anticipated effect size and the quality of the data for the study components critical to addressing the specific research question.

Objectives: To review the FDA framework on RWD and provide a new structured study-specific context by which to assess the feasibility of using RWD for a specific research question or regulatory purpose (new indication or expanded labeling). This should be of interest to all pharmacoepidemiologists and researchers involved in the design and conduct of real world studies for potential regulatory or other purposes.

Description: Accuracy and reliability of data (including extent of missing data) to define specific components of the research question, such as the population, intervention, comparator, and outcome), fundamentally drive whether RWD in electronic health record or claims databases can be useful for a specific envisioned study. The adequacy of ascertainment of these components along with sample size and anticipated treatment effect size leads to a practical structured approach for assessing utility of RWD in the context of the specific research question. Discussion will consider the perspective of the use of

RWD for regulatory labeling or new indications, as well as for other research purposes.

Dr. Zhou will introduce the concepts of data quality, relevance and validation based on the FDA Framework followed by Dr. Ritchey presenting a new practical approach to assess RWD feasibility in the context of the specific research question. Dr. Martin and Dr. Girman will review the utility of this study-specific contextual approach for assessing feasibility of RWD for fit-for-regulatory purposes and for general research studies, respectively. A 20-minute discussion led by Dr. Dreyer, involving audience participation with the speaker panel, will conclude the session.

3 | When Artificial Intelligence Meets Pharmacoepidemiology

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Background: The rapidly growing use of Artificial Intelligence (AI), in particular machine learning (ML) across both research and clinical settings is challenging epidemiologists' traditional choice of methods and indeed their very role with many epidemiologists unsure of the implications of AI for their profession. AI is increasingly being used to contribute to both, traditional and emerging epidemiological areas: traditional areas include, for instance, identification of risk factors and quantification of treatment effects. New areas stem from the increasing adoption of analytics-enabled technologies in clinical practice. While AI has already brought genuine innovation, most notably in the ability to accurately predict clinical events in data which is complex and often high dimensional, it could be argued that its greatest potential for novel insights lies in the ability to meaningfully link data in a world that is becoming increasingly digitized. However, all is not rosy. There are instances where AI algorithms have shown clear biases and inaccuracies, e.g. ML based real world analytics have been biased because of the lack of using inception cohorts and a clear time zero or conditioning on outcomes (Avati et al. 2018).

Objectives: The symposium will cover industry, research, regulatory and educational perspectives for various stakeholders around what is required to maximize the potential utility and impact of applying AI in pharmacoepidemiological research.

Description: The symposium will describe current AI approaches, including ML and neural networks, and provide examples where AI has brought clear added value. It will highlight uncertainties inherent in the approach and propose solutions as to how these might be managed. From a regulatory perspective if AI outputs are to find acceptability, a clear framework defining best practice is required. The session will discuss what such a framework could incorporate and in particular how pharmacoepidemiology can bring critical rigor to analytics supported by AI, e.g. advice on suitable study designs, the definition of metrics for assessing the quality and appropriateness of data sources, providing principles for transparency of reporting especially over time in the context of learning algorithms, and creating clear pathways for validation. From a research and education perspective, the session will discuss on the implications of the potential integration of AI in the pharmacoepi toolbox in terms of teaching/learning for trainees and professionals.

4 | Pregnancy Registries and Pregnancy Outcome Studies in Healthcare Databases: Trends and Complementary Research Approaches.

Steve Gao[1]; Krista Huybrechts[2]; Leyla Sahin[3]; John Seeger[2]; Daina Esposito[4]; Christina D. Chambers[5]

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Background: National drug regulatory authorities, such as the FDA, may require manufacturers to evaluate the risk of adverse pregnancy and infant outcomes associated with a new drug in the real-world setting as part of the post marketing requirements (PMRs) of a drug approval. Recently, some pregnancy outcome studies have required prolonged follow up for infant outcomes (e.g., through the first five years of life) and some PMRs have included both a prospective pregnancy registry and retrospective database-based study.

Objectives: The symposium objectives are (1) to discuss trends in safety requirements for the real-world and long-term data of safety in pregnancy and infant outcomes from industry, academia, regulators, and researchers poised to carry out these types of studies and (2) to provide an overview of methodologies in pregnancy registry studies, multi-database studies, and using the common data model to carry out these PMRs.

Description: The proposed symposium will offer a variety of perspectives on the pregnancy registries and database studies to obtain adequate post-marketing safety information in drugs used during pregnancy. The regulatory, industry, and academic perspectives will be presented. Case examples of pregnancy studies and related PMRs will be shared to illustrate regulatory trends, challenges that the pharmaceutical industry may face, and knowledge and experience that can help in the planning and design of future post-marketing requirements. The perspectives shared from the case examples from different research organizations will provide the audience an overview of the PMRs with in-depth discussion of methodology, the pros and cons, and how the different approaches complement each other for a more thoughtful consideration of the scientific designs to better understand safety in pregnancy. Audience participation in the discussion is encouraged. Krista Huybrechts and Steve Gao will serve as the moderators of the symposium. The agenda will include: 1) introduction of the topic (Krista Huybrechts, Harvard Medical School); 2) regulatory perspective on post-approval safety studies in pregnant women (Leyla Sahin, FDA); 3) a database perspective on post-approval safety studies

in pregnant women (John Seeger, Optum/Harvard or Daina Esposito, Boston University/Ciconia); (4) navigating a multi-database environment in pregnancy studies (Daina Esposito or John Seeger); 5) registry vs database: when is one plus one more than two (Christina Chambers, University of California, San Diego); 6) audience participation and Q&A; 7) closing comments (Steve Gao, Regeneron).

5 | Drugs and Germs: Dirty Details about Pharmacoepidemiology and the Microbiome

Daniel B. Horton[1]; Peter J. Turnbaugh[2]; Scott E. Plevy[3]; Soko Setoguchi[1]; Tobias Gerhard[1]; James D. Lewis[4]

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Background: The human microbiome is inhabited by trillions of microorganisms (microbiota such as bacteria, fungi, and viruses) that perform a variety of critical homeostatic functions, including production of energy, vitamins, and neurotransmitters, and immune regulation. Notably, gut microbiota possess enzymes that influence drug effects by, for example, regulating pharmacokinetics (e.g., digoxin) and producing toxic metabolites (e.g., NSAIDs). Furthermore, drugs such as antibiotics can alter microbiota in ways that may affect downstream process, including pharmacodynamic profiles (e.g., PD-1 inhibitors) or predisposition to certain diseases (e.g., childhood obesity). Microbiota may explain heterogeneity of treatment effects not explained by pharmacogenomic or other factors. Additionally, microbiota may be used to treat certain diseases (e.g., fecal microbiota transplantation for recurrent *Clostridium difficile* colitis). Better understanding about the roles and functions of microbiota in diseases and their effects on drugs may ultimately lead to novel, safer, more effective, personalized strategies for disease treatment and prevention.

Objectives: To educate attendees about (1) the basic ecology, function, and regulators of the microbiome, (2) the role of the microbiome in drug pharmacokinetics and pharmacodynamics, (3) approaches for studying drugs that affect or are affected by the microbiome, and (4) the development and monitoring of microbiome-based therapies such as fecal microbiota transplantation. This symposium is geared towards trainees, researchers, and members of industry and regulatory bodies interested in better understanding or performing microbiome-related pharmacoepidemiologic research.

Description: This symposium will feature speakers from academia and industry with experience in basic science, translational, and pharmacoepidemiologic research involving the microbiome, drugs, and short- and long-term outcomes. Following the talks will be a 25-minute panel discussion addressing questions from the audience and future directions.

Speakers:Horton - Introduction on the microbiome (5 minutes). Turnbaugh - A primer on pharmacomicrobiomics and how the microbiome mediates therapeutic variability (20 minutes). Horton - Methodologic considerations for pharmacoepidemiologic studies of microbiome-related drugs (10 minutes). Plevy - Strategies and challenges to developing live biotherapeutic products (15 minutes). Lewis - Monitoring the safety of live biotherapeutic products (15 minutes).

6 | Scientific Evidence Supporting Benefits of Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015–2017

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Background: The US Food and Drug Administration (FDA) exercises flexibility in the requirement that new drugs provide substantial evidence of benefit under the Food, Drug and Cosmetic Act. Provisions in law and policy provide numerous exceptions to the historical scientific standard of 2 or more controlled clinical trials demonstrating statistically significant evidence of benefit.

Objectives: To examine implementation of the FDA requirement for "substantial evidence" of benefit among a large group of recently approved new molecular entities (NMEs).

Methods: We used FDA annual drug approval reports to derive a list of approved NMEs between 2015 and 2017 and their approval pathways (e.g. breakthrough, accelerated approval). Trial data were obtained from FDA documents at drugs@fda, the clinicaltrials.gov web site, and the peer reviewed literature. The scientific standards of interest were: (1) reproducible results—defined as 2 or more clinical trials providing evidence of benefit; (2) randomized design-a trial with patients randomized to treatment, active drug or placebo comparison groups; (3) clinical scale or benefit-a measurable effect on the patient's health rather than a biomarker or surrogate endpoint; and (4) 100 or more patients treated with active drug-to assess biological variability and identify adverse effects.

Results: We identified 225 pivotal trials cited as evidence of benefit for the FDA approval of 101 new therapeutic agents from 2015 to 2017. Expedited pathways and incentives were common. Overall, 36 of 101 products (36%) met all 4 standards, and 3 drugs meet none of them. We identified 14 drugs (14%) approved on the basis of a single, uncontrolled trial, including 5 drugs with fewer than 100 patients treated. Extent of scientific evidence also varied by therapeutic area: all 4 standards were met by all the dermatological products (n = 9), respiratory products (n = 3) and 2 of 3 ophthalmological drugs. Oncology drugs (n = 29) varied the most, with 2 agents meeting all 4 standards but 8 meeting only 1 standard. Drugs approved under the orphan drug incentive (n = 43) included all 3 drugs meeting none of the standards and 16 of 20 drugs (80%) without a controlled trial.

Conclusions: FDA approval of new molecular entities now reflects a body of scientific evidence of benefit that varies from an uncontrolled trial in a few patients to randomized comparative trials enrolling

thousands. Without randomized controls, the scientific evidence of benefit is without protection against conscious or unconscious bias, atypical patient selection, and unmeasured confounding.

7 | Cost-Effectiveness of First Line Tyrosine Kinase Inhibitor Initiation Strategies for Chronic Myeloid Leukemia

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Background: First-line tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML) have demonstrated similar overall survival in clinical trials but differ in treatment costs and adverse event profiles. Understanding the relative cost-effectiveness of first-line TKIs may help identify the optimal treatment strategy for newly diagnosed adult patients with CML.

Objectives: To evaluate the one year cost-effectiveness of TKI initiation strategies for newly diagnosed adult patients with CML from a US Payer's perspective.

Methods: We constructed a decision analytic model to compare TKI initiation with imatinib, dasatinib, or nilotinib among a hypothetical cohort of newly diagnosed patients with CML. We assumed optimal TKI adherence among patients. Outcomes included quality-adjusted life years (QALYs), healthcare costs, net-monetary benefit, and incremental cost-effectiveness ratios. We used medical expenditures, TKI treatment patterns, and safety outcomes observed among patients with CML identified in the Truven Health MarketScan Commercial Claims and Medicare Supplemental database to inform model parameters. To calculate TKI costs, we used the Federal Supply Schedule estimates and median observed time on first-line TKIs. We evaluated cost-effectiveness under a willingness to pay threshold of 100,000 USD/QALY. We conducted deterministic and probabilistic sensitivity analyses using 10,000 Monte Carlo simulations to assess the model's sensitivity to uncertainty around probability, cost, and utility input values.

Results: In the base case analysis, imatinib was the favored initiation strategy and was associated with lower per patient costs compared to both dasatinib and nilotinib. Imatinib remained the favored strategy after deterministic variations in branded imatinib uptake, TKI costs (including assumed rebates for second generation TKIs), TKI switching, QALYs, adverse event risk, and CML progression to accelerated phase. Under a 100,000 USD/QALY threshold, imatinib dominated dasatinib and nilotinib in 63% and 10% of probabilistic simulations, respectively. With respect to net monetary benefit, imatinib was cost-effective at a lower threshold at 90,000 USD/QALY. Dasatinib and nilotinib were cost-effective in 50% of simulations at thresholds of approximately 205,000–215,000 USD/QALY.

Conclusions: Imatinib initiation was the favored strategy in this cost-effectiveness simulation of newly diagnosed patients with CML. Generic entry of imatinib may provide additional economically attractive treatment opportunities for patients with CML.

8 | Healthcare Resource Use and Expenditures in Patients Newly Diagnosed with Paroxysmal Supraventricular Tachycardia in the United States

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Background: Paroxysmal Supraventricular Tachycardia (PSVT) can be challenging to diagnose, however once diagnosed, PSVT can be treated medically or with ablation procedures. Little is known about healthcare resource use (HRU) or costs before and after PSVT diagnosis.

Objectives: To characterize HRU and costs in the three years before and after index PSVT diagnosis in patients < age 65.

Methods: Retrospective longitudinal study that used data from the Truven Health MarketScan® database. Study patients were newly diagnosed with PSVT (ICD-9: 427.0; ICD-10: I47.1) from January 1, 2011 to December 31, 2014 and observable three years before and after index diagnosis. Propensity matched controls were identified through the same database. Outcome measures included change in mean annual per patient HRU and costs paid by insurers pre- versus post-diagnosis.

Results: Of 13,092 newly diagnosed patients, 62.7% were female sex; mean age was 47.6 years (SD: 13.67). Mean annual costs per patient were $7,634 in the third year before index diagnosis (i.e., 36 to 25 months pre-diagnosis) and rose significantly to $11,212 in the year immediately preceding index diagnosis (i.e., 12 to 0 months pre-diagnosis; $P < 0.0001$). In the year following index diagnosis, costs increased to $22,958 per patient ($P < 0.0001$). Costs were significantly lower in each of the next 2 years (13–24 months post index: $11,377; 25–36 months post-index: $11,607; $P < 0.0001$) but did not return to earlier spending levels. Emergency Department (ED) visit rates increased in the pre-diagnosis years, from 0.26 per patient, on average, in the third year before diagnosis, to 0.45 in the year before and 0.51 in the year after diagnosis. Hospitalization rates also rose, from 0.09 in the third year pre-diagnosis to 0.11 in the year before diagnosis and 0.28 in the year ($P < 0.0001$). ED visit and hospitalization rates were significantly lower in the second and third years after diagnosis (both years: ED: 0.35; IP: 0.1). PSVT diagnoses accounted for 71% of cost increase in the year after diagnosis ($8,362/$11,746; 71%); cardiac ablations were 41% of this increase ($4,846/$11,746).

Spending and HRU over the 6-year observation window were stable for control patients.

Conclusions: Healthcare costs rise in the year immediately preceding PSVT diagnosis, consistent with the challenges in PSVT diagnosis. ED visit and hospitalization rates also increase, suggesting patients are seeking care for an undiagnosed condition. The increase in HRU and costs post diagnosis may reflect the high costs of monitoring and treatment.

9 | The Economic Impact of the Introduction of Infliximab-Biosimilar: Preliminary Results from a Study on Rheumatologic Patients in Tuscany, Italy

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Background: The introduction of biosimilars can be a chance to significantly impact on the sustainability of National Healthcare Systems; however the real economic impact still needs to be clarified.

Objectives: To assess the economic impact of the use of biosimilar infliximab (BI) considering rheumatoid arthritis (RA) patients and Tuscany (Italy) as case study, benefiting from the "counterfactual" set in 2015 when the Tuscan Health Authority encouraged physicians to switch patients from originator infliximab (OI) to BI.

Methods: We estimated the economic impact of the introduction of BI in Tuscan rheumatoid arthritis (RA) patients from the perspective of the Regional Health System and valuing direct costs related to biologics (infliximab and other treatment), emergency room visits, hospitalizations and specialist visits using data from Tuscan healthcare administrative databases. We performed two analyses on: 1) patients naïve to infliximab from January 1st, 2012 to December 31st, 2016, treated with OI before 2015 and with OI or BI after 2015; 2) prevalent infliximab users from January 1st, 2013 to December 31st, 2013 (before the BI recommendation) and from January 1st, 2015 to December 31st, 2015 (post the BI recommendation). We evaluated costs up to 1 year in the first analysis and up to 2 years in the second one.

Results: The mean annual direct costs related to infliximab (OI or BI) among naïve patients (n = 214) decreased from 9,823 ± 5,308 Euro in 2012 to 7,406 ± 4,406 Euro in 2016 (p = 0.025), similarly for the mean overall direct costs related to the disease management that decreased of about 4,000 Euro from the first (13,793 ± 6,222 Euro per patient/year) to the last observation year (9,989 ± 5,729 Euro per patient/year, p = 0.004). We also observed a decrease of both direct costs related to infliximab and overall direct costs by comparing prevalent infliximab RA patients in the pre-recommendation group (n = 354) to patients in the post-recommendation group (n = 334). In particular, mean costs related to infliximab over 2 years were 15,315 ± 9,843 Euro per patient among those treated with OI and 12,383 ± 9,141 Euro per patient among those treated with either OI or BI (p < 0.001); similarly, 2 years mean overall direct costs were 20,622 ± 9,712 Euro per patient and 18,414 ± 9,441 Euro per patient, respectively (p = 0.003).

Conclusions: The introduction of BI produced a reduction of direct costs for the management of RA patients. This template analysis can be repeated whenever a new biosimilar drug enters the market. Causal mechanisms underlying the economic impact warrant further analysis.

10 | Antithrombotic Stewardship

Albert Dreijer[1]; Marieke J.H.A. Kruip[1]; Jeroen Diepstraten[2]; Suzanne Polinder[1]; Rolf Brouwer[2]; Nanne Croles[1]; Esther Kragten[2]; Frank W.G. Leebeek[1]; Patricia van den Bemt[1]

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Background: Although the benefits of antithrombotic drugs are indisputable, they carry a high risk for patient safety. Studies on the implementation and (cost-) effectiveness of a hospital-based multidisciplinary antithrombotic team on bleeding and thrombotic outcomes are scarce.

Objectives: Main aim is to investigate the effect of implementing a hospital-based multidisciplinary antithrombotic team on the efficacy and safety of antithrombotic therapy during and after hospitalization. Secondary aims are to determine the effect of the multidisciplinary team on severity of bleeding, all-cause mortality and length of hospitalization.

Methods: Design: Prospective, observational multicenter cohort study. Setting: Patients admitted to Erasmus University Medical Center and Reinier de Graaf Hospital between October 2015 and December 2017, using one or more therapeutically dosed anticoagulants. Intervention: Implementation of a hospital-based multidisciplinary antithrombotic team. Primary outcome: proportion of patients with a composite end point consisting of ≥1 bleeding or ≥ 1 thrombotic event from hospitalization until 3 months after hospitalization. Secondary outcomes: proportion of patients with a major and non-major bleeding event, all-cause mortality and length of hospitalization before and after implementation of the multidisciplinary antithrombotic team. Statistical analysis: For analysis of the primary outcome we used segmented regression analysis for the interrupted time series data. For the secondary outcomes logistic regression analysis was used. T-Test analysis was performed for the length of hospitalization.

Results: 941 patients were included in the usual care period and 945 patients in the intervention period. Introduction of the multidisciplinary antithrombotic team led to a significant reduction in the proportion of patients with the primary outcome (−1.83% (95% CI: −2.58%; −1.08%). Lower all-cause mortality (odds ratio [OR] 0.71, 95%

confidence interval [95% CI] 0.53–0.95) was observed after introduction of the multidisciplinary antithrombotic team. No significant effect of the intervention was found for the severity of bleeding and mean length of hospital stay.

Conclusions: Introducing a multidisciplinary antithrombotic team contributes to patient safety.

11 | Privacy versus Public Good: The Methodological Approach of the Belgian Healthdata.be Platform to Protect Individual Privacy in Health Research

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Background: Healthdata.be was developed by Sciensano, (a federal public health research institute), to facilitate data exchange between healthcare professionals, patients and researchers according to the 'only once' principle and the re-use of data to advance public health science and support health care policy.

Objectives: To develop guidelines and statistical methodology compliant with the European General Data Protection Regulation (GDPR) that allow accessing data on the Healthdata.be platform for research purposes while protecting the privacy of patients and healthcare professionals (HCPs).

Methods: A review of existing guidelines and methods on sharing confidential data was carried out. We then developed a methodology to a) assess the risk of identity disclosure, b) assess the impact of a potential disclosure and c) reduce this risk through the implementation of disclosure control measures, trading-off disclosure risk/impact with the importance of the research. The statistical measures K-anonymity and M-sensitivity were used to assess the disclosure risk and impact, respectively. The 'data access request (DAR) and privacy impact assessment (PIA)' templates were developed, with the 'DAR' to be completed by the researcher requesting data access and the 'PIA' to be completed by an independent impact assessment assessor. The methodology was piloted with the Belgian Cystic Fibrosis Register (BCRF) and feedback was solicited from external experts.

Results: The initial risk of identity disclosure of BCRF patients was high: 90.7% of the samples violated 2-anonymity. Using a 'leave-one-out procedure' suggested that the highest reductions would be achieved by reducing details on year of birth, patient's residence, and anonymizing the treating physician. After applying data transformation steps, the 2-anonymity reduced to 3.7% and the M-sensitivity was above the critical value of 95% for 5.8% of the patients but restricted to 5 variables. The external expert committee agreed with the proposed methodology.

Conclusions: The developed template standardizes the 'PIA' and facilitates the disclosure risk/impact versus research importance trade-off discussion between the researcher and independent assessor. The methodology is currently routinely implemented.

12 | Infant Infections after Maternal Anti-TNF Treatment in Pregnancy

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Background: Agents that inhibit tumor necrosis factor (anti-TNF) increase the susceptibility to infections and most of them are transferred across the placenta in late pregnancy. There are limited data on the rate of infections in infants after maternal exposure.

Objectives: To assess the risk of infant infections in the first three years of life after maternal anti-TNF treatment during pregnancy.

Methods: A nation-wide population-based study including all births in Denmark, Finland and Sweden 2006–2013 based on the patient registers and medical birth registers. We identified women with diseases for which anti-TNF treatment is indicated; rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. The frequency of hospital admissions for infection and antibiotic prescriptions in the first three years of life in infants born to women treated with anti-TNF was compared to women of the general population and to women treated with non-biologic systemic treatment. Adjustments were made for maternal age, parity, smoking, BMI, country and calendar year.

Results: Among 1,633,909 births, 1,027 infants were born to women treated with anti-TNF and 9,399 to women with non-biologic systemic treatment. Compared with the general population, women with anti-TNF treatment and women with non-biologic systemic treatment had a higher rate of first year hospitalization for infection, odds ratio 1.5 (1.3–1.8) and 1.2 (1.1–1.2), respectively. For individual anti-TNF agents, the ratio was 1.4 (1.0–2.0) for adalimumab, 1.4 (1.0–1.8) for etanercept and 1.6 (1.2–2.2) for infliximab. The overall odds ratio decreased over time and was 0.9 (0.5–1.5) for anti-TNF treatment in the third year and 1.0 (0.8–1.1) for non-biologic systemic treatment. The result was similar whether treatment was in early pregnancy only, or also in late pregnancy. For antibiotic use, the odds ratios were 1.1 (1.0–1.3) and 1.1 (1.1–1.2) for year 1, respectively, and similar for year 2 and 3.

Conclusions: Anti-TNF treatment during pregnancy may increase the rate of hospital admissions for infection in the first year of life, and slightly for antibiotic use. However, treatment with anti-TNF and non-biologic systemic treatment were both associated with infant infections, regardless of treatment timing in pregnancy, implying that the association does not solely depend on the third trimester transfer of anti-TNF agents across the placenta and may be influenced by biases such as surveillance and confounding by indication.

13 | The Association between Atopic Eczema and Cancer in England and Denmark: Two Cohort Studies

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Background: The association between eczema and cancer risk is controversial, with two competing theories: immune surveillance (reduced risk) and immune stimulation (increased risk).

Objectives: To determine if eczema is associated with all-site cancer and with specific cancers, and if any increased/reduced risk is dependent on eczema severity.

Methods: We undertook two cohort studies in England (1998–2016) and Denmark (1982–2016) using data from English primary care practices contributing to the Clinical Practice Research Datalink and nationwide Danish registry data. We used stratified Cox regression to estimate hazard ratios (HR) for the association between eczema and cancer, to compare risk of new-onset cancer in those with eczema (England: ≥18 years; Denmark: no age restriction) to matched (age, sex, general practice [England only], and calendar period) cohorts of individuals without eczema. We also explored whether the association differed by eczema severity.

Results: In England we identified a cohort of 472,065 with eczema and 2,240,524 without (mean follow up 6 years, SD 5). In Denmark we identified 44,945 with eczema matched to 445,673 without (mean follow up 14 years, SD 9).

Lymphoma (excluding cutaneous lymphoma) risk was raised in those with eczema compared to those without (England: adjusted for calendar period, deprivation, implicitly adjusted for age, sex, cohort-entry date, and practice HR 1.22, 99% CI 1.11–1.33; Denmark: implicitly adjusted for age, sex and cohort-entry date HR 1.33, 99% CI 0.86–2.05), with evidence in England (Denmark underpowered) of a dose–response relationship (HR [99% CI]) compared to those with no eczema: mild 1.11 [0.95 to 1.16]; moderate 1.28 [1.08 to 1.51]; severe 2.08 [1.46 to 2.98]).

In England we found a small increased all-site cancer risk in those with eczema compared to those without (adjusted HR 1.04, 99% CI 1.02–1.06), which attenuated (HR 1.02, 99% CI 0.99–1.04) upon further adjustment for potential mediators (harmful alcohol use, smoking, body mass index). Findings were similar in Denmark.

We found no strong evidence for associations between eczema and the following site-specific cancers: prostate, leukemia, multiple myeloma, breast, pancreas, central nervous system or melanoma.

Conclusions: Our findings do not support an association between eczema and risk of most site-specific cancers. However, there appears to be an association between eczema and lymphoma that increases with eczema severity. Further work should explore underlying mechanisms and seek to understand the implications for treating severe eczema with existing and novel immunosuppressive treatment.

14 | The Association between Partner Bereavement and Incident Psoriasis or Atopic Dermatitis: A Matched Cohort Study

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Background: Psychological stress is commonly reported as an important risk factor for psoriasis and atopic dermatitis. However, epidemiological evidence for the relationship is limited by small sample sizes and difficulty measuring stress.

Objectives: To investigate the association between partner bereavement (an extreme life stressor) and psoriasis or atopic dermatitis.

Methods: We conducted a matched cohort study using routinely collected clinical data from the United Kingdom Clinical Practice Research Datalink between 01/01/1997 and 31/07/2017. We identified heterosexual couples using an existing algorithm. Among eligible couples, we matched up to 10 non-bereaved people to each bereaved person on age, sex and general practice. Outcomes were the first diagnosis of psoriasis or atopic eczema. We excluded people with a history of the relevant outcome. We used Cox regression stratified by matched set to estimate hazard ratios (HR) (complete case analysis), adjusted for Charlson Comorbidity Index, smoking status, body mass index, alcohol consumption and socioeconomic status. We further examined such associations by time since bereavement (0–30 days, 0–90 days, 0–365 days, 0–1095 days).

Results: For psoriasis, we identified 144,873 bereaved people and 1,211,218 without bereavement after excluding people with a history of psoriasis. For atopic dermatitis, there were 127,477 bereaved and 946,178 non-bereaved after excluding people with a history of atopic dermatitis. We found no evidence that bereavement was associated with psoriasis (HR: 0.97; 95% CI: 0.92–1.03) or atopic dermatitis (HR: 1.01; 95% CI: 0.98–1.04) during the entire follow-up. However, in analyses by time since bereavement, we saw a possible increase in risk in the first 90 days following bereavement for both psoriasis (HR: 1.14; 95% CI: 0.91–1.45) and atopic dermatitis (HR: 1.16; 95% CI: 1.00–1.33). For atopic dermatitis, the increased risk persisted in the first year (HR in 0–365 days: 1.13; 95% CI: 1.05–1.21) but attenuated in the 3 years following bereavement (HR in 0–1095 days: 1.06; 95% CI: 1.01–1.11). We found no evidence of an increased risk of psoriasis or atopic dermatitis in other periods following bereavement.

Conclusions: We found evidence that partner bereavement might be associated with a short-term increased risk of atopic dermatitis and psoriasis. Understanding psychological stress associated with recent

psoriasis and atopic dermatitis episodes could inform prevention and improve clinical care.

15 | Risk of Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis Treated with Methotrexate

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Background: Methotrexate (MTX) is a first-line treatment for psoriasis (PsO), psoriatic arthritis (PsA), and rheumatoid arthritis (RA). Serious liver complications are a concern with chronic MTX use. It has been suggested that patients with PsO are more susceptible to MTX toxicity than those with RA despite limited direct comparative data.

Objectives: To determine the risk of liver disease in patients with PsO, PsA, versus RA who received MTX.

Methods: Using national registry data, we performed a longitudinal cohort study of Danish patients with PsO, PsA, or RA diagnosis during 1/1/1997–12/31/2015 who received a prescription for MTX. Main outcome measures were mild liver disease, moderate-to-severe liver disease, cirrhosis, and hospitalization due to cirrhosis, as derived from ICD-10 codes. The start date was the latter of earliest diagnosis or earliest treatment by MTX, and the end date was the earliest of date of liver outcome, death, migration, or end of study. Cox regression analysis was performed to compare the risk of each liver outcome among PsO, PsA, versus RA, adjusted for age, sex, smoking, alcohol abuse, diabetes, hyperlipidemia and statin use, year of study inclusion, Charlson Comorbidity Index (without liver disease and RA), and average weekly MTX dose.

Results: A total of 5,687, 6,520, and 28,030 patients with PsO, PsA, and RA, respectively, received MTX. The average weekly MTX dose was similar across the groups but the duration and cumulative dose of MTX was greatest in RA, followed by PsA, then PsO. Drug survival was longest for patients with RA (50% discontinuation after 80 months), then PsA (50% discontinuation after 54 months), and shortest for PsO (50% discontinuation after 26 months). In adjusted analyses, patients with PsO had significantly increased risks for mild liver disease (HR 2.22, 95% CI [1.81–2.72]), moderate-to-severe liver disease (1.56 [1.05–2.31]), cirrhosis (3.38 [2.44–4.68]), and cirrhosis-related hospitalization (2.25 [1.37–3.69]) compared to patients with RA. Patients with PsA also had significantly greater risk of mild liver disease (HR 1.27 [1.01–1.60]) and cirrhosis (1.63 [1.10–2.42]) compared to RA.

Conclusions: Among MTX users, patients with psoriatic disease were more likely to develop liver disease than those with RA and relative risk differences were greatest for those with PsO, suggesting effect modification by disease indication. Further work is needed to dissect the drivers of these differences among PsO, PsA, and RA. These data demonstrate the need for careful monitoring of liver complications in patients receiving MTX for psoriatic disease.

16 | Prediction of Cardiovascular Events in Rheumatoid Arthritis Patients Using Protein Biomarkers and Clinical Factors

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Background: The ACC/AHA recommends preventive strategies for patients with a high-predicted risk of atherosclerotic cardiovascular disease (CVD). RA patients are at higher risk for CVD events, yet the role of systemic inflammation and the influence of traditional CVD risk factors are unclear with respect to risk prediction in RA.

Objectives: A simple and accurate algorithm for predicting CVD event risk that considers systemic inflammation might help risk assessment for RA patients and optimize preventive care.

Methods: We derived a cohort of RA patients by linking multi-biomarker disease activity (MBDA) test data to Medicare claims requiring ≥1 yr Medicare coverage prior to 1st MBDA test (baseline). Exclusions were past MI, stroke, or cancer. Follow-up ended at the earliest of 1) CVD event; 2) death; 3) loss of coverage; or 4) 12/31/16. CVD events defined as: incident MI, stroke or fatal CVD event, and were identified using validated algorithms (PPV ≥80%). The leptin-adjusted MBDA score (Curtis et al., *Rheumatol* 2018) and its 12 protein biomarkers were evaluated as predictors of CVD events, as were demographics, healthcare utilization, CVD-related comorbidities/medications, and RA-related features (e.g. DMARD/biologic use, steroid use). The cohort was randomly split 2:1 to use 2/3 patients for training and 1/3 for validation. Cox proportional hazard regression with LASSO was used for variable selection based on minimization of 10-fold cross-validated error + 1 SE. Model calibration (observed vs. expected) and discrimination were assessed for predicted CVD events at 3 yrs. Analyses are ongoing; model performance results are reported for the cross-validated training data.

Results: Eligible RA patients (26,261) were analyzed; mean (SD) age 68.6 (10.2) yrs, 80% female, 73% white, 23% diabetes, 43% statin use, 56% methotrexate, 44% on biologics/tofacitinib, 55% steroids, and median (IQR) adjusted MBDA score 40 (32–49). A total of 477 CVD events occurred over mean (SD) follow-up time of 1.7 (1.2) yrs yielding a CVD incidence rate of 16.5 (95% CI 15.0–18.0)/1000py. The most important predictors in the LASSO-selected models were age, beta-blocker use, sex, diabetes, adjusted MBDA score and a subset of MBDA biomarkers. The best performing model had a cross-validated area under the receiver operator curve of 0.70 and good observed: expected prediction at 3 yrs.

Conclusions: Preliminary results from this approach suggest a simple algorithm consisting of a limited number of protein biomarkers and clinical measures can provide an accurate method to predict short-term CVD risk in RA.

17 | Induction Immunosuppression Practices in Liver Transplantation Are Variable and Predict Post-Transplant Outcomes

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Background: Induction therapy is potent immunosuppression (IS) given prior to transplantation. Its benefits remain uncertain in liver transplant (LT) recipients, though its use has significantly increased over time.
Objectives: 1) To evaluate transplant center practice variability in the use of induction IS; 2) to assess the effectiveness of lymphocyte depleting (thymoglobulin, alemtuzumab, rituximab) and non-depleting (daclizumab, basiliximab) induction in a large sample of LT recipients.
Methods: This was a retrospective cohort study using the United Network for Organ Sharing national transplant database. All adult liver alone recipients between 1/1/05–1/31/18 were included. Center practice variability in induction use/type was described. The proportion of variance in the receipt of either induction type attributed to center was obtained through mixed-effects logistic regression. Induction IS as a categorical exposure (no induction, non-depleting induction [NDI], depleting induction [DI]) was evaluated as a predictor of graft failure or death using multivariable Cox proportional hazards models. Its association with estimated glomerular filtration rate (eGFR) at 6 months post-LT was assessed using multivariable mixed-effects linear regression.
Results: 69,349 recipients were transplanted at 114 centers during the study period: 27% received induction (60.8% NDI, 39.2% DI). 85 centers used no induction in ≥50% of LT recipients, while 19 and 6 centers favored NDI and DI, respectively. 65.7% of the variance in the receipt of induction was attributed to transplant center, independent of recipient and donor factors. Receipt of NDI and DI were associated with a significantly lower adjusted hazard of death/graft failure: HR 0.90 (95% CI: 0.86–0.95) and 0.91 (95% CI: 0.85–0.97), respectively ($p < 0.001$). Baseline eGFR at LT was an effect modifier of the association of induction and eGFR 6 months post-LT: patients with lower eGFR at LT had greater predicted gains in post-LT eGFR with NDI and DI. At mean baseline eGFR, NDI was associated with an adjusted gain in eGFR of 2.62 mL/min/1.73m^2 (95% CI: 1.72–3.53), and DI of 2.48 mL/min/1.73m^2 (95% CI: 1.25–3.71; $p < 0.001$ overall).
Conclusions: Marked variability in induction practices exists with center being a major determinant. Both NDI and DI are associated with significant improvements in death/graft failure and post-LT renal function. Given its marked increase in use, consensus guidance on induction IS for LT is needed.

18 | Comparative Safety of Antiepileptic Drugs and Risk of Major Congenital Malformations

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Background: The teratogenic potential of antiepileptic drugs (AEDs) has been recognized for decades but many patients require continued treatment during pregnancy. Direct comparison between AEDs will aid treatment decisions.
Objectives: To determine which AEDs are associated with an increased risk of any major congenital malformation (MCM), compared to lamotrigine monotherapy which has the most evidence for safety in pregnancy and is used for a range of epilepsy types and other AED indications.
Methods: We carried out a cohort study using linked data from Nordic birth and prescription registries from Denmark 1997–2017, Finland 1996–2014, Iceland 2003–2012, and Norway 2004–2017. We included singleton live births with prescription data covering 3 months before the last menstrual period (LMP) until birth. First trimester AED use was defined as ≥1 prescription fill from LMP to LMP + 97 days. We compared monotherapy of carbamazepine, valproate, pregabalin, oxcarbazepine, levetiracetam, gabapentin, and topiramate to lamotrigine. MCMs were identified by ICD-9/10 codes mainly recorded within one year of birth. We estimated RRs and 95% confidence intervals, adjusted for maternal age, year of birth, opioids, benzodiazepines/z-drugs, and antidepressants. We combined estimates from each country with fixed-effects meta-analyses. Iceland was only included in crude analyses due to small numbers.
Results: The baseline prevalence of MCM in over 3 million births with no first trimester AED exposure ranged from 2.7% in Finland to 4.5% in Denmark. In total, n = 4385 births were exposed to lamotrigine monotherapy and n = 6323 exposed to monotherapy of the other AEDs of interest. Lamotrigine exposed births had an elevated risk of MCM compared with the baseline (pooled RR: crude 1.3, 95% CI 1.2–1.5). Compared to lamotrigine, there was an increased risk of MCM associated with valproate (n = 1494, pooled RRs: crude 1.8, 1.5–2.3; adjusted 1.6, 1.1–2.1) and topiramate (n = 306, pooled RRs: crude 1.5, 1.0–2.3, adjusted 1.5, 0.7–2.2) with stronger estimates when we required at least 2 filled prescriptions. We found no differences for carbamazepine (n = 1739, crude RR 1.0, 0.7–1.3), pregabalin (n = 717, RR 1.2, 0.9–1.7), oxcarbazepine (n = 1053, RR 0.9, 0.6–1.3), or gabapentin (n = 474, RR 1.1, 0.7–1.6). Levetiracetam was associated

with a lower risk (n = 540, pooled RRs: crude 0.7, 0.5–1.2, adjusted 0.7, 0.3–1.1).

Conclusions: Among the most commonly used AEDs, use of valproate and topiramate in pregnancy are associated with the highest risk of malformations, whereas levetiracetam is associated with the lowest risk compared to lamotrigine.

19 | Use of Oral Fluconazole during Pregnancy and Risks of Spontaneous Abortion, Stillbirth and Major Congenital Malformation: An International, Multi-Centre Cohort Study

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Background: Vaginal candidiasis is common during pregnancy. Although intravaginal formulations of topical azole antifungals are first-line treatment, oral fluconazole is frequently prescribed, despite safety concerns. Currently, Health Canada recommends that oral non-prescription fluconazole products not be used when women are pregnant or trying to become pregnant, and that they talk with their doctor before using prescription fluconazole.

Objectives: To study the association between oral fluconazole exposure during pregnancy and risks of spontaneous abortion (SA), stillbirth (SB), and major congenital malformation (CM).

Methods: We undertook an international, multi-centre cohort study of women aged 12–55 y who had a pregnancy event (SA, induced abortion, SB, or live birth) between April 2002 and March 2016 recorded in administrative data from 5 Canadian provinces, the US MarketScan database, and the UK Clinical Practice Research Datalink. Our primary outcome measure was fetal death defined as a composite of SA or SB. Secondary outcomes were the components of the composite and CM. To minimize confounding by indication, exposure to oral fluconazole was compared with exposure to topical azoles. We estimated hazard ratios (HR) and odds ratios (OR) using high dimensional propensity score-adjusted proportional hazards regression and logistic regression, as appropriate, with time-dependent drug exposures. Sensitivity analyses excluded pregnancy losses during the first 6 w, 20 w gestation; considered exposures during 4–10 w gestation; and studied the first pregnancy per woman. Site-level results were pooled using random-effects models.

Results: Among the 63,346 pregnancies exposed to oral fluconazole, 14.2% resulted in fetal death vs 4.8% of 107,212 exposed to topical azoles. Just 20% of fluconazole-exposed women received a cumulative dosage greater than 300 mg during pregnancy. After adjustment, fluconazole exposure during pregnancy was associated with significantly increased risks of fetal death (HR 1.30, 95% CI 1.24–1.35), SA (HR 1.31, 1.22–1.41), and SB (HR 1.48, 1.29–1.69). It was not associated with an increased risk of major birth defects (OR 0.90, 0.75–1.09). Results of sensitivity analyses were consistent with those of the primary analyses.

Conclusions: In this large, multi-centre cohort study, use of oral fluconazole during pregnancy was associated with significantly increased risks of fetal death, SA, and SB relative to use of topical azoles. Oral fluconazole should be prescribed cautiously during pregnancy.

20 | Oral Fluconazole Use in Pregnancy and the Risk of Birth Defects

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Background: Prior studies suggest a possible increased risk of oral clefts and tetralogy of Fallot associated with oral fluconazole use during the first trimester. An FDA safety review further suggests maternal chronic high-dose use may be associated with musculoskeletal defects, but limited evidence is available regarding the potential risk at common therapeutic doses.

Objectives: To evaluate the effect of oral fluconazole use during the first trimester on the risk of congenital malformations.

Methods: We performed a cohort study using the nationwide Medicaid Analytic eXtract for 2000–2013, including pregnant women enrolled in Medicaid from ≥3 months before the last menstrual period (LMP) to ≥1 month after delivery and infants enrolled for ≥3 months after birth unless they died sooner. We ascertained oral fluconazole exposure as having ≥1 prescription filled between LMP and LMP + 90 and no filled prescription for other oral antifungal agents between LMP-90 and LMP + 90. We further classified the exposed into 3 cumulative dose groups: 150 mg, 150-300 mg and > 300 mg. The reference group included patients with topical azoles filled between LMP and LMP + 90 and no fills of any oral antifungal agents between LMP-90 and LMP + 90. Primary outcomes were musculoskeletal defects, tetralogy of Fallot and oral clefts diagnosed within 90 days after birth. Propensity score fine stratification was used to control for confounding and relative risks (RRs) were estimated using log-binomial models.

Results: Among 1,811,062 pregnancies, 34,025 (1.9%) were exposed to oral fluconazole, and 76,229 (4.2%) to topical/vaginal azoles. Overall, 220 (0.6%) oral fluconazole exposed and 363 (0.5%) topical azoles

exposed infants were diagnosed with musculoskeletal defects. The absolute risks of tetralogy of Fallot and oral clefts among the fluconazole exposed vs. controls were 0.04% vs. 0.05%, and 0.09% vs. 0.11% respectively. The adjusted RR for musculoskeletal defects was 1.29 (95% CI, 1.09–1.52). Compared to topical azoles, the magnitude of the increased risk for musculoskeletal defects was similar across the fluconazole dose groups [adjusted RR, 150 mg: 1.32 (1.09–1.59), 150 mg - 300 mg: 1.30 (0.97–1.75), >300 mg: 1.24 (0.82–1.89)]. For tetralogy of Fallot, the adjusted RR was 0.62 (0.34–1.15) while the adjusted RR for oral clefts was 0.88 (0.58–1.32).

Conclusions: Oral fluconazole use during the first trimester was not associated with tetralogy of Fallot and oral clefts, but was associated with a 30% increased risk for musculoskeletal defects independent of cumulative dose. Given the observed risk, oral fluconazole should be prescribed with caution during the first trimester.

21 | The Impact of In-Utero Prescription Opioid Exposure on Congenital Malformations

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Background: Prescription opioid use during pregnancy is widespread in the US. Prior studies suggest an association between opioid exposure and certain congenital malformations, but data are few and conflicting.

Objectives: To evaluate the risk of 1st trimester (T1) in-utero opioid exposure with respect to malformations previously suggested to be associated with such exposure: major malformations overall, cardiac malformations overall, ventricular septal defects (VSD), secundum atrial septal defects (ASD), central nervous system (CNS) malformations, neural tube defects (NTD), gastroschisis, club foot, and oral clefts.

Methods: We conducted a cohort study of pregnant women and their liveborn infants nested in the nationwide Medicaid Analytic eXtract database for 2000–2013. Exposure was defined based on ≥2 dispensings for any opioid during T1, on the assumption that if a woman is refilling the medication, she is likely to be taking it. Claims-based algorithms were used to define the malformations of interest. Relative risks (RR) were estimated using generalized linear models with propensity-score stratification to adjust for potential confounders including demographics, pain conditions, concomitant drug exposure, comorbidities, and measures of healthcare utilization.

Results: Of the 1,686,121 included pregnancies, 53,029 (3.1%) were exposed to any opioid (≥ 2 dispensings) during T1. Overall, there were 2,443 (4.6%) cases of malformations in the opioid exposed and 60,337 (3.7%) in the unexposed. The unadjusted RR was 1.25 (95% confidence interval [CI], 1.20–1.30) for malformations overall, 1.27 (1.17–1.38) for cardiac malformations, 1.18 (1.04–1.34) for VSD, 1.29 (1.08–1.55) for ASD, 1.12 (0.93–1.36) for CNS malformations, 0.94 (0.59–1.50) for NTD, 1.31 (0.99–1.73) for gastroschisis, 1.32 (1.09–1.59) for club foot, and 1.56 (1.27–1.92) for oral clefts. The adjusted RR was 0.99 (0.96–1.03) for malformations overall, 1.00 (0.92–1.09) for cardiac malformations, 0.96 (0.84–1.08) for VSD, 0.92 (0.77–1.11) for ASD, 1.01 (0.84–1.22) for CNS malformations, 0.64 (0.40–1.02) for NTD, 1.19 (0.90–1.57) for gastroschisis, 1.05 (0.87–1.26) for club foot, and 1.20 (0.97–1.47) for oral clefts.

Conclusions: After adjusting for relevant confounders, we observed no increase in the risk for malformations overall, cardiac malformations overall, VSD, ASD, CNS malformations, NTD, or club foot. Risk estimates were slightly increased for gastroschisis and oral clefts, but with relatively wide CI that intersect the null. Further evaluation of the impact of opioid type, dose, and duration of treatment on these outcomes is needed.

22 | Risk of Neonatal Abstinence Syndrome Following Prenatal Exposure to Methadone vs Buprenorphine

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Background: Rising rates of opioid addiction mean that pregnant women are more often on opioid maintenance therapy (OMT), necessitating a clinical choice between methadone and buprenorphine. In observational studies maternal methadone use has been associated with a 20% higher risk of neonatal abstinence syndrome (NAS), compared to buprenorphine. However, residual confounding may explain this, as women on methadone often have a more severe addiction.

Objectives: To estimate the risk of NAS in methadone vs. buprenorphine exposed pregnancies, with additional adjustment for addiction severity.

Methods: We used Norwegian National Registries data collected from 2009–2015 to identify a cohort of pregnant women on OMT at conception and identify newborns with NAS diagnoses. We used two definitions of exposure. Exposure in early pregnancy reflects the time at which a clinical decision is made to use methadone or buprenorphine during the pregnancy. Late pregnancy exposure is the more biologically-relevant exposure window for NAS. We used log-binomial regression to assess the risk ratio of NAS in methadone vs. buprenorphine exposed pregnancies and adjusted for confounders with inverse probability of treatment weights. In a sample linked to specialized addiction services data we further adjusted for additional addiction severity.

Results: 180 women were on OMT during pregnancy. The risk of NAS in the newborn was 77% in the 53 exposed to methadone in early pregnancy and 68% in the 106 exposed to buprenorphine in early pregnancy, with similar risks in the 83 women linked to the specialized addiction services data. Women on methadone vs those on buprenorphine more often reported heroin use, depression or anxiety, and switching OMT within the last 5 years. However, the risk ratio

only changed from 1.13 to 1.14 (95% CI 0.91 to 1.43) after adjustment. The crude and adjusted risk ratios for exposure in the 30 days before delivery were 0.96 and 1.04 (95% CI 0.86 to 1.24), respectively.

Conclusions: We found a slightly higher NAS risk for methadone than for buprenorphine treatment in early pregnancy but not near delivery, although confidence intervals were wide and overlapping thus chance, selection bias or residual confounding could explain these findings. However, we did not find evidence to support that the higher risk of NAS among methadone users early in pregnancy was explained by severity of addiction.

23 | Paternal Exposure to Finasteride - Before and during Pregnancy

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Background: Finasteride is used for the treatment of hair loss in men of reproductive age. The consumption is increasing. Administration of high oral doses of finasteride in female animals, has resulted in congenital malformations in male fetuses, but there is a general lack on human data concerning possible teratogenic effects of paternal exposure. This has caused concern among doctors and users of finasteride.

Objectives: The objective of this study was to examine the fetal risk of paternal exposure to finasteride between 90 days before pregnancy and during the first trimester.

Methods: We conducted a nationwide register-based cohort study consisting of all registered pregnancies in Denmark between 1997–2016. Births were identified from the Medical Birth Registry, and miscarriages and abortions from the National Hospital Register. Finasteride-exposure were identified from the National Prescription Registry.

Results: We identified 1,478,912 registered pregnancies with known paternity of whom 903 pregnancies were of finasteride-exposed fathers. Among these, 69 (7.6%) ended as a miscarriage compared to 131,221 (8.9%) among unexposed. The hazard ratio for experiencing a miscarriage in pregnancies with paternal finasteride-exposure was 0.89 (CI95% 0.70–1.12). There was no increased risk of having an offspring diagnosed with a major congenital malformation in general (OR = 0.65 (CI95% 0.40–1.05)), malformation of the genital organs or any other specific malformation group, according to the EUROCAT classification system. Furthermore, there were no increased risk of congenital malformations in children to fathers specificly exposed to finasteride in the three months period before pregnancy or specificly in the first trimester.

Conclusions: We did not find an increased risk of miscarriage or malformations in pregnancies with paternal exposure to finasteride. Although, the study has low power of detecting very rare malformations, paternal finasteride should not be of major concern.

24 | Modeling Effect Heterogeneity in the Presence of Heterogeneous Confounding: A Plasmode Simulation

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Background: Standard methods for identifying treatment effect heterogeneity (e.g. single interaction term) may be biased when covariate effects differ by subgroup (e.g. sex).

Objectives: Evaluate bias and precision of alternative modeling approaches when treatment and covariate effects differ by sex.

Methods: We simulated 1,000 plasmode cohorts, each with n = 6,000 sampled with replacement from NHANES respondents, 1999–2014, age 40–79, with labs and no statin use (n = 6,063). We simulated statin initiation as a function of demographic and cardiovascular risk factors such that covariate-exposure relationships differed by sex. We simulated outcomes as a function of exposure and 10-year ASCVD risk score, which differs by sex, thereby inducing heterogeneous confounding. Simulated treatment effects differed by sex (RR_{women} = 0.35, RR_{men} = 0.69). We produced estimates using conventional outcome models, g-computation, inverse-probability-of-treatment weighting (IPTW), and doubly-robust estimators. We evaluated various model forms to control for covariates including: main effects only, treatment-sex interaction, covariate-sex interactions, or full stratification. We report median absolute bias (log-scale) and 95% confidence interval widths (CIW) based on the 2.5^{th} and 97.5^{th} percentiles.

Results: Confounding was stronger in women, RR = 0.93 (bias = 0.97, CIW = 0.71), than men, RR = 0.94 (bias = 0.31, CIW = 0.55), with no evidence of heterogeneity in the crude. Three models without sex-specific covariate parameters were biased: 1) outcome model with covariate main effects and treatment-sex interaction ($bias_{women}$ = 0.16, CIW = 0.81; $bias_{men}$ = −0.07, CIW = 0.58); 2) g-computation with main effects ($bias_{women}$ = 0.17, CIW = 0.85; $bias_{men}$ = −0.05, CIW = 0.638); and 3) IPTW with main effects for covariates fit in the pooled cohort ($bias_{women}$ = 0.29, CIW = 0.89; $bias_{men}$ = −0.19, CIW = 0.95). (The last also failed to detect statistically significant effect heterogeneity.) All other model forms produced adjusted estimates with minimal bias (<0.1). Among these, models with treatment-sex and covariate-sex interactions were more precise. Sex-stratified g-computation models failed to converge in 0.6% of simulations for women and < 0.1% of iterations for men.

Conclusions: Various methods can be used for modeling effect heterogeneity, so long as the model form flexibly allows for confounding relationships to also differ (i.e. stratifying by subgroup or using covariate-subgroup interactions). G-computation produced precise, unbiased estimates but occasional non-convergence may indicate infeasibility in small studies.

25 | A Little off the Sides: Propensity Score Trimming in the Presence of Heterogeneity

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Background: Past simulation studies assessed bias and precision of types of propensity score trimming in the presence of uniform treatment effects. How this trimming affects estimates in populations with heterogeneous treatment effects is unknown.

Objectives: Assess change in average treatment effect in the treated (ATT) and average treatment effect in the untreated (ATU) after 5% asymmetric trimming (AT), 10% Crump trimming (CT), and 30%/70% preference score trimming (PT) given heterogeneous treatment effects.

Methods: We simulated 500 studies of the safety of treatment X for an outcome Y for 50,000 people in the presence of four independent confounders, three binary and one continuous, all associated logistically with X and log-linearly with Y. In those with no modifiers X had no effect on Y. One binary confounder (C_1) was a contraindication (treatment odds ratio (OR): 0.25) while another (C_2) was a compelling indication (treatment OR: 4.00); both were present in 15% of participants. Marginal probability of treatment was 26%. We considered scenarios where 1) treatment X had a RR for Y of 2.0 when $C_1 = 1$, 2) treatment X had a RR for Y of 0.60 when $C_2 = 1$, and 3) both C_1 and C_2 modified treatment effect. Propensity score models were correctly specified and included all confounders. We trimmed each population, re-estimated propensity score, and estimated ATT and ATU after weight-based standardization. We calculated true RRs in ATT and ATU populations to compute bias and change from untrimmed estimates.

Results: Median C statistic for the propensity score model across all replicates was 0.70. Weighting estimated ATT and ATU RRs in the trimmed populations without bias. Trimmed estimates were within 90–110% of pre-trimming estimates except ATU estimates in scenario 1 (untrimmed RR: 1.31, AT: 1.10, CT: 1.11, PT: 1.11) and scenario 3 (untrimmed RR: 1.20, AT: 0.99, CT: 0.98, PT: 1.00) and some ATT estimates in scenario 2 (untrimmed RR: 0.81, AT: 0.88, CT: 0.81, PT: 0.91). With AT and PT, when treatment effect modifiers predicted exposure logically (factors increasing exposure were associated with improved effects and factors decreasing it were associated with worse effects), ATT estimates typically moved upward after trimming and ATU estimates moved downward.

Conclusions: In these simulations, changes in ATT and ATU RRs after trimming were modest and in predictable directions despite potent modifiers strongly associated with exposure; estimates generally moved towards the RR in those with no modifiers. These findings may help limit concerns about treatment effects in target populations when trimming is deemed necessary to improve confounding control.

26 | Propensity Score Trimming - Lessons from a Study of Antipsychotic Augmentation for Depression

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Background: Propensity Score (PS) trimming has been suggested as a promising approach to reduce bias from unmeasured confounding.

Objectives: To evaluate the effects of PS trimming choices in a study examining the mortality risk of second generation antipsychotic (SGA) augmentation for adult depression.

Methods: Using near-national US Medicaid data (2001–2010), we examined all-cause mortality in a cohort of non-elderly adults (25–64 years) with depression who, after ≥3 months of antidepressant (AD) monotherapy, initiated either a SGA or a second AD. Patients with alternative SGA indications, e.g., schizophrenia or bipolar disorder, were excluded. PSs were calculated from >100 claims-based demographic, clinical, and healthcare utilization variables. Inverse probability of treatment (IPT)-weighted Cox models were used to assess all-cause mortality risk of SGA vs. AD augmentation before and after asymmetric PS trimming with 2.5th(treated) and 97.5th(untreated) percentiles as cut points. PS trimming was prespecified in the study protocol due to concerns regarding strong unmeasured confounding in the PS tails. (1) High tail: SGAs being withheld from patients with confounding factors unmeasured in claims data, such as obesity, that predispose to known SGA-associated adverse events as well as mortality. (2) Low tail: SGAs prescribed preferentially to patients with particularly severe depressive symptoms, that increase mortality risk but are not captured in claims data. To evaluate the impact of the protocol-specified approach on our study results, we separately estimated treatment effects in the PS tails and within deciles of the trimmed cohort. Other cut points and stratification approaches were examined in sensitivity analysis (not shown).

Results: We estimated IPT-weighted HRs for mortality of 1.45 (1.02–2.06) in the trimmed cohort (N = 39,582) and 1.21 (0.87–1.69) in the untrimmed cohort (n = 44,301). PS-stratified analyses indicated reasonably homogenous mortality risk across PS deciles in the trimmed cohort with HRs ranging from 0.84 (0.26–2.75) to 2.52 (0.73–8.64). In contrast, stronger heterogeneity was apparent in the trimmed PS tails, with HRs of 0.30 (0.12–0.74) in the high tail and 6.96 (0.72–66.9) in the low tail.

Conclusions: PS trimming substantially affected study findings. The heterogeneous and counterintuitive SGA effects observed in the PS tails (greatly decreased mortality risk in the high tail; greatly increased mortality risk in the low tail) are compatible with strong uncontrolled confounding in the PS tails. These analyses provide empirical support for the utility of PS trimming.

27 | Residual Confounding and Treatment Effect Heterogeneity: An Applied Example

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Background: Typical methods to assess treatment effect heterogeneity rely on balancing the marginal distribution of covariates for confounding control. If covariate effects differ between subgroups of interest, previously reported theoretical findings suggest that residual confounding may obscure or induce apparent treatment effect heterogeneity. The real-world impact of this bias has not been reported.

Objectives: Evaluate the impact of residual confounding due to the use of a pooled propensity score model versus age- and sex- specific models in an analysis of statin effects on 2-year all-cause mortality.

Methods: We used Medicare claims to select patients with an outpatient visit, 2007–2013. We restricted the cohort to patients ≥66 years with continuous enrollment and no prior statin prescription fills in the past year. We limited the cohort to patients at elevated cardiovascular risk without major statin contraindications. We classified patients with a statin claim in the 14 days after the index visit as exposed (otherwise unexposed) and assessed all-cause mortality over 2-years of follow-up. Covariates included demographic, clinical, and selected lab values based on level II CPT codes (low-density lipoprotein, HbA1C, blood pressure). We estimated propensity scores using a single model including all eligible patients or stratified by age and sex. We produced estimates of the risk ratio and risk difference in the target population of patients initiating a statin using standardized mortality ratio weights (SMRW) with 1% asymmetric trimming.

Results: Among n = 646,394 patients, estimates based on a pooled propensity score model indicated strong treatment effect heterogeneity by age but not by sex ($RR_{men \leq 75}$ = 0.89, 95%CI: 0.81–0.97; $RR_{men > 75}$ = 0.79, 95%CI: 0.74–0.85); ($RR_{women \leq 75}$ = 0.89, 95%CI: 0.82–0.97; $RR_{women > 75}$ = 0.76, 95%CI: 0.72–0.80). Estimates based on the age- and sex- specific propensity score models moved towards the null for both men and women >75 and away from the null for those ≤75. The resulting estimates indicated that treatment effects were similar among men regardless of age ($RR_{men \leq 75}$ = 0.85, 95%CI: 0.78–0.93; $RR_{men > 75}$ = 0.87, 95%CI: 0.81–0.93), and differences between women were greatly attenuated ($RR_{women-75}$ = 0.82, 95%CI: 0.76–0.89; $RR_{women > 75}$ = 0.79, 95%CI: 0.75–0.33).

Conclusions: Reliance on a pooled propensity score model created the appearance of strong treatment effect heterogeneity by age, largely due to residual confounding. These findings indicate that modeling confounding within categories of suspected effect modifiers may have important impacts on estimates and conclusions.

28 | Novel Approaches for Defining Binary Confounders in Claims Data: A Simulation Study.

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Background: When investigators have two claims-based definitions for the same binary confounder, it is unclear whether to prefer the more sensitive or specific definition. Utilizing both definitions may result in improved confounding control.

Objectives: To compare adjusting for the sensitive or specific definition alone versus two novel approaches: 1) a "two-algorithm indicator" approach, and 2) a "two-algorithm restriction" approach.

Methods: Each simulated patient had a binary exposure, outcome, and confounder. We randomly assigned the confounder to 25% of the cohort and used logistic regression models to generate the exposure and outcome conditional on the confounder. The true exposure effect was null. We created two misclassified versions of the confounder based on validated definitions of heart failure. The "sensitive" definition had a sensitivity of 0.98 and a specificity of 0.83, while the "specific" definition had a sensitivity of 0.77 and a specificity of 0.99. Patients were classified into 3 groups: those who did not meet the sensitive or specific definition (Group 1), those who met the sensitive but not specific definition (Group 2), and those who met both the sensitive and specific definition (Group 3). The two-algorithm indicator approach adjusted for indicators for Groups 2 and 3, while the two-algorithm restriction approach excluded patients in Group 2 and adjusted for an indicator for Group 3. Odds ratios (ORs) for exposure were estimated using logistic regression models after adjusting using each approach. Each 10,000 patient dataset was recreated and reanalyzed 2,000 times.

Results: The crude OR was 1.33 (95%CI: 1.07, 1.63). Using the sensitive or specific definitions alone resulted in partially adjusted ORs of 1.14 (95%CI: 0.91, 1.40) and 1.09 (95%CI: 0.87, 1.35), while the two-algorithm indicator method resulted in an OR of 1.07 (95%CI: 0.86, 1.33). The two-algorithm restriction approach resulted in the least biased OR of 1.02 (95%CI: 0.79, 1.29) but excluded 20% of the cohort. Across sensitivity analyses varying the validated definitions and confounder prevalence, the indicator approach always removed at least as much bias as the better of the two component definitions and was sometimes the least biased approach overall, particularly when covariate prevalence was high and overall measurement was poor.

Conclusions: Using two definitions can improve confounding adjustment in claims data. We recommend the two-stage indicator approach because it performed as well as the best component definition without any loss in sample size.

29 | An Empirical Evaluation of a Propensity Score Stratification Based Weighting Approach in Settings of More Than Two Treatment Groups

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Background: Propensity-score (PS) stratification based weighting has recently been shown to perform well with respect to bias and variance when comparing two treatment groups; however, the performance of this approach has not been tested when comparing >2 groups simultaneously.

Objectives: To compare covariate balance and treatment effect estimates after confounding adjustment with a novel weighting approach based on simultaneous stratification on a multinomial PS with matching weights and standardized mortality ratio weights (SMRW) in the setting of >2 treatment groups.

Methods: A cohort of early rheumatoid arthritis (RA) patients initiating tumor necrosis factor inhibitors (TNFi), hydroxychloroquine, methotrexate, or other non-biologic DMARDs, was followed for the outcome of incident hyperlipidemia. A multinomial logistic regression model provided 3 non-redundant PSs based on 18 covariates, one for each treatment except for TNFi, the reference group. For each PS, we trimmed regions of non-overlap and stratified (5 or 10 strata) based on the PS distribution in exposed patients followed by a simultaneous stratification procedure using all three strata indicators (resulting in 5^3 and 10^3 potential strata). All exposure groups were reweighted according to the number of TNFi exposed patients in their stratum. A weighted Cox proportional hazards model with robust variance estimation was used to calculate the hazard ratio (HR) and confidence intervals (CI).

Results: A total of 17,143 patients were included (6% TNFi, 36% hydroxychloroquine, 46% methotrexate, 12% other non-biologics). Standardized differences were slightly higher for all comparisons in the decile-based stratification compared to other approaches. HR (95% CI) for hydroxychloroquine, methotrexate, and other non-biologics vs. TNFi, respectively were comparable for quintile-based stratification (0.61 [0.41–0.91], 0.78 [0.55–1.12], 1.04 [0.64–1.68]), matching weights (0.65 [0.43–0.97], 0.75 [0.52–1.06], 1.06 [0.67–1.67]), and SMRW (0.64 [0.43–0.96], 0.76 [0.53–1.08], 1.07 [0.67–1.7]); but decile-based stratification resulted in numerically different estimates with higher variance (0.47 [0.29–0.74], 0.75 [0.5–1.12], 0.92 [0.53–1.61]).

Conclusions: PS-based simultaneous stratification approach may provide an alternative confounding adjustment approach in settings with >2 treatment groups. However, with many treatment groups, multidimensional stratification quickly results in a very large number of strata and highly variable estimates.

30 | Use of Stimulants in Adults and Risk of Cardiovascular Events: A Multi-Design Approach

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Background: Use of prescription stimulants (ex. methylphenidate) is known to elevate blood pressure and heart rate. The associated risks of cardiovascular (CV) events have been established in children, however, have not been rigorously studied in older adults. With the rising use of stimulants in older adults, the risks of CV events are considerable and require further study. Previous studies applying differing study designs have produced conflicting results, likely due to potential selection bias and the use of drug trials.

Objectives: To investigate whether stimulant use is associated with an increased risk of CV events among older adults.

Methods: We conducted a multi-design observational study among patients ≥66 years old dispensed a prescription stimulant between January 1, 2002- December 31, 2015. We used a multi-design approach applying a matched cohort, nested case–control, and case-crossover designs. We matched on age, sex, and comorbidities in the case–control design (matched 1:1) and matched using a high-dimensional propensity score in the cohort design (4 non-users:1 user). The primary outcome was a composite of hospitalization or emergency room visit for myocardial infarction, stroke, or arrhythmia. For both the nested case–control and case-crossover designs the look-back period was defined as 30 days from the event date. Conditional logistic regression was used for the case–control and case-crossover design. A Cox proportional hazard model was used for the cohort and assessed the risk of events at 30, 60, and 90 days after initiation.

Results: A total of 665 CV events occurred among 6,457 stimulants users. We found that stimulant use was not associated with an increased risk of CV events in both the case–control (Odds Ratio [OR] 0.9; 95% Confidence Interval [CI] 0.6–2.0) and case-crossover (OR 0.8; 95% CI 0.6–1.2) designs. The cohort design did find a significant association at 30-days after initiation (Hazard Ratio (HR) 1.4; 95% CI 1.1–1.8). This finding was not significant at the 60-(HR 1.2; 95% CI 0.9–1.5) and 90-day (HR 1.0; 95% CI 0.6–1.8) after index. Post-Hoc analysis found that the significant finding in the cohort design is largely due to a higher risk of arrhythmias (HR 3.0; 95% CI 1.1–8.7).

Conclusions: Overall, these results support previous studies that long-term stimulant use may not lead to more CV events among older adults. There may be an immediate risk at initiation, largely associated with tachycardia. Applying a multi-design approach allowed the ability to contrast results in a scenario where competing bias may greatly influence results.

31 | Mirabegron and the Risk of Arrhythmias: A Population-Based Cohort Study

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Background: Mirabegron, a ß-3 adrenoreceptor agonist, used to treat overactive bladder (OAB) has been shown in clinical trials to produce a minor increase in resting heart rate, blood pressure, and QTc interval. More patients are being prescribed mirabegron, owing to its limited adverse effects relative to antimuscarinic OAB drugs. However, there is a lack of cardiovascular safety data in older patients and those with existing cardiovascular disease.

Objectives: We aimed to evaluate the risk of cardiac arrhythmias and other adverse cardiovascular events in older patients using mirabegron relative to other OAB agents.

Methods: We conducted a population-based cohort study of patients ≥66 years old who were new users of OAB drugs between June 1, 2015 and March 31, 2017 in Ontario, Canada. We followed patients for one year after starting the medication or until they discontinued or switched treatment. The primary outcome was a composite of hospitilization or emergency room visit for arrhythmia and tachycardia events. The secondary outcome was myocardial infarction (MI) or stroke. Patients taking mirabegron were matched to subjects taking other OAB agents on age, sex, date of initiating medication, and a high-dimensional propensity score. The primary analysis used Cox proportional hazards regression.

Results: We matched 16,948 mirabegron users to 21,870 users of other OAB drugs. The median age of the cohort was 76 (Interquartile range 71–83), and most were female (*N* = 25,189, 64.9%). A large proportion of the cohort had hypertension (*N* = 30,393, 78.3%) and diabetes (*N* = 13,757, 35.4%). Overall, 624 (1.6%) patients experienced an arrhythmia or tachycardia event and 480 (1.2%) experienced an MI or stroke. The 1-year cumulative incidence of arrhythmia or tachycardia events was 3.3% in the mirabegron group and 3.5% in the other OAB drugs group (adjusted? Hazard Ratio [HR] 0.93; 95% Confidence Interval [CI] 0.80–1.09). Mirabegron was not associated with an increased risk of MI or stroke compared to other OAB drugs (HR 1.06; 95% CI 0.89–1.27).

Conclusions: In a population-based cohort of older patients, use of mirabegron was not associated with an increased risk of arrhythmia or other cardiovascular events compared to other OAB drugs. These results are supportive of current prescribing trends and give a balanced view of the real-world safety of this treatment option.

32 | Risk of Major Cardiovascular Events Associated with Varenicline and Nicotine Replacement Therapy: An Australian Population-Based Study

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Background: There are inconsistent reports that use of varenicline and nicotine replacement therapy (NRT) for smoking cessation may be associated with an increased risk of cardiovascular events. However, current evidence is insufficient to determine whether these concerns are valid.

Objectives: To determine whether varenicline and nicotine replacement therapy (NRT) are associated with an increased risk of major cardiovascular events relative to bupropion, another smoking cessation therapy.

Methods: A new user, active comparator cohort study in New South Wales, Australia, using linked pharmaceutical dispensing, hospital admission, and death data. We identified individuals dispensed varenicline, NRT patch, or bupropion for the first time during the study period (2008–2016 for varenicline, 2011–2016 for NRT). We defined exposure using an approach analogous to intention-to-treat, and followed patients for a maximum of 6 months. The primary outcomes were acute coronary syndrome (ACS), ischaemic stroke, cardiovascular death, and a composite of these (referred to as major cardiovascular events). We used inverse probability of treatment weighting with propensity scores to account for differences between treatment groups. We used Cox proportional hazard models to estimate adjusted hazard ratios (HR) and event rates, both with 95% confidence intervals (CI).

Results: Among the cohort of 346,473 varenicline users and 16,449 bupropion users, there was no difference in the rate of major cardiovascular events (7.12 versus 8.15, per 1000 person-years [PY]; HR = 0.85 [95% CI: 0.64, 1.12]). Varenicline was also not associated with increased risk of the individual outcomes (ACS HR = 0.81 [95% CI: 0.60, 1.10], ischaemic stroke HR = 2.17 [95% CI: 0.65, 7.24], cardiovascular death HR = 0.76 [95% CI: 0.38, 1.55]). Among the 110,294 NRT users and 8,065 bupropion users, there was no difference in the rate of major cardiovascular events (12.31 versus 19.12, per 1000 PY; HR = 0.67 [0.40, 1.13]). However, NRT was associated with a significant reduction in risk of ACS (8.19 versus 17.35, per 1000 PY; HR = 0.48 [0.27, 0.87]) in comparison to bupropion. There was no increased risk in cardiovascular death associated with NRT use (HR = 0.79 [95% CI: 0.23, 2.74]), while the risk of ischaemic stroke could not be estimated due to the low event rate.

Conclusions: Our results suggest there is no increased risk of any major cardiovascular events associated with varenicline relative to bupropion. Compared with bupropion, NRT is associated with a lower risk of ACS but not associated with other major cardiovascular events.

33 | Cardiovascular Safety of Prucalopride for Chronic Constipation: A Multinational Population-Based Cohort Study

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Background: The serotonin 5-HT_4 receptor agonist prucalopride is approved in the European Union (EU) for the treatment of chronic constipation, thus providing opportunity to include real-world observational data on cardiovascular safety to support approval of prucalopride in the United States.

Objectives: To estimate the pooled adjusted incidence rate ratio (IRR) for major adverse cardiovascular events (MACE, defined as hospitalization for non-fatal acute myocardial infarction or stroke, and in-hospital cardiovascular death) in adult initiators of prucalopride compared with initiators of polyethylene glycol 3350 (PEG) treated for chronic constipation, following a common protocol.

Methods: The pooled analyses from this observational, population-based cohort study (EUPAS9200) included data from the Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN), and the Information Services Division (ISD) of Scotland in the United Kingdom, and the Swedish National Registers (SNR) in Sweden. Up to 5 PEG initiators were selected for each prucalopride initiator, matched by age, sex, and year of first prucalopride or PEG prescription or dispensing. Standardized incidence rates (SIRs) and IRRs of MACE were derived using propensity score stratification. Sensitivity analyses explored the impact of exposure definition, outcome categories, cancer, and unmeasured confounding.

Results: The pooled analyses included 5,715 initiators of prucalopride and 29,372 initiators of PEG. Average duration of use was 175 days for prucalopride and 82 days for PEG. The pooled SIR per 1,000 person-years (95% confidence interval) of MACE was 6.57 (3.90–10.39) for patients initiating prucalopride and 10.24 (6.97–14.13) for PEG. The pooled adjusted IRR for MACE was 0.64 (0.36–1.14), and results were consistent for individual MACE components. Sensitivity analyses yielded results consistent to the main analysis, with IRRs for first episode of use only, extension to 30 days of risk, and past use of 0.69 (0.34–1.42), 0.65 (0.38–1.09), and 0.65 (0.45–0.92), respectively. Inclusion of out-of-hospital cardiovascular deaths in the MACE definition yielded an IRR of 0.43 (0.25–0.73) and inclusion of probable cases yielded an IRR of 0.75 (0.27–2.05). Adjustment for hypothetical additional confounding factors under various assumptions did not change the direction of the associations observed in the main analyses.

Conclusions: Results suggest no increased risk of MACE above the prespecified safety threshold of 3.00 in patients with chronic constipation using prucalopride as compared with PEG.

34 | Cardiotoxicity of Aromatase Inhibitors in Post-Menopausal Women with Breast Cancer: A Population-Based Cohort Study

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Background: Hormone-receptor positive breast cancer comprises 75% of all diagnoses of breast cancer. Recent changes in guidelines in North America and Europe recommend extended treatment of patients with hormone-receptor positive breast cancer with aromatase inhibitors (AIs) or tamoxifen for up to ten years. However, randomized controlled trials have suggested that AIs may be associated with adverse cardiovascular events.

Objectives: To examine this safety concern, we conducted a study in the real-world setting to determine whether AIs, in comparison with tamoxifen, are associated with increased risk of myocardial infarction, ischemic stroke, congestive heart failure, and cardiovascular-death.

Methods: We conducted a population-based cohort study using the United Kingdom Clinical Practice Research Datalink linked to Hospital Episode Statistics hospitalization data and Office for National Statistics vital statistics. The study population consisted of post-menopausal women newly-diagnosed with breast cancer and newly-treated with either AIs or tamoxifen between April 1, 1998 and February 29, 2016. Cox proportional hazards model with inverse probability of treatment and censoring weights were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing AIs with tamoxifen for each of the study outcomes. Secondary analysis was conducted by type of AIs.

Results: The study cohort included 8,139 and 9,783 patients newly-treated with AIs and tamoxifen, respectively. The patients were followed for a mean of 1.9 (SD: 1.7) years. Compared with tamoxifen, AIs were associated with a trend towards an increased risk of myocardial infarction (incidence rate: 51 vs 22 per 10,000 person-years, HR: 1.38; 95% CI: 0.93–2.07), ischemic stroke (incidence rate: 64 vs 35 per 10,000 person-years, HR: 1.23; 95% CI: 0.86–1.76), congestive heart failure (incidence rate: 167 vs 60 per 10,000 person-years, HR: 1.29; 95% CI: 0.79–2.12), and a significantly increased risk of cardiovascular-death (rate: 95 vs 47 per 10,000 person-years, HR: 1.44; 95% CI: 1.06–1.95). The results were consistent by type of AIs.

Conclusions: In this large real-world setting study, AIs were associated with increased cardiovascular mortality compared with tamoxifen. There were also trends towards increased, though non-significant, risks of myocardial infarction, ischemic stroke, and congestive heart failure with AIs compared with tamoxifen. Further research is needed to ascertain whether the observed increased risks are due to deleterious effects of AIs or cardioprotective effects of tamoxifen.

35 | Diagnosis of Immune Checkpoint Inhibitor Associated Myocarditis: A Systematic Review of Case Reports and Observational Studies

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Background: Immune checkpoint inhibitors cause a variety of immune mediated reactions, and myocarditis is a rare but severe adverse event associated with these drugs with a high case fatality rate. However little is known about the value of diagnostic tests to evaluate this condition.
Objectives: To characterize the diagnostic approaches to myocarditis associated with immune checkpoint inhibitors.
Methods: The systematic review was carried out according to the PRISMA protocol (PROSPERO CRD42018097247). We searched Medline and Embase on 10th June, 2018 for case reports, case series and observational studies published in journal articles or presented as conference abstracts that describe patients on any immune checkpoint inhibitor who developed myocarditis after therapy. Two reviewers independently and in duplicate screened citations and extracted data. We evaluated the completeness of information in the case reports and case series using the checklist provided by the International Society of Pharmacoepidemiology and the risk of bias in the observational studies using the New Castle Ottawa checklist. We pooled data from the case reports and case series to contrast these with findings from the controlled observational study.
Results: After a review of 2326 citations, we included 89 cases of myocarditis associated with immune checkpoint inhibitors (54 cases of in the case reports and case series and 35 cases in the observational study). Serum troponin was elevated in 95% of the case reports and 94% of participants in the observational study. ST changes including ST elevation were present in almost a third of case reports. Echocardiography revealed preserved left ventricular ejection fraction in 32% of case reports and 51% of cases in the observational study; however, preserved systolic function did not predict greater survival. On cardiac magnetic resonance imaging, late gadolinium enhancement was absent in 31% of case reports and 26% of participants in the observational study. Acute myocardial ischemia was ruled out in all cases (n = 31) when the diagnostic workup included coronary angiography. Limitations of the case report include incomplete reporting of clinical features, dose of the drug, and concomitant medications among.
Conclusions: Immune checkpoint inhibitor associated myocarditis is associated with elevation of cardiac troponin levels and non-specific electrocardiographic changes. Early coronary angiography may distinguish it from myocardial ischemia or myocardial infarction.

36 | Effects of Bisphosphonate Use on Knee Osteoarthritis Progression: An Analysis of the Osteoarthritis Initiative Study

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Background: Knee osteoarthritis (KOA) is a debilitating condition which is prevalent in older adults. Bisphosphonates (BP) have been explored for treating KOA; however, little data exist on effects of today's more potent BPs on radiographic disease progression.
Objectives: To determine if the use of BP is protective against 2-year radiographic progression of KOA in Osteoarthritis Initiative (OAI) cohort patients. Secondary objectives were to explore cumulative BP exposure effects and time to incident narcotic analgesic use.
Methods: The OAI is an 11-year longitudinal US cohort study which recruited men and women aged 45–75 from 2004–2006. Patients were enrolled into the progression (existing symptomatic KOA), incidence (high risk of developing symptomatic KOA), or healthy control sub-cohorts. We linked publicly available demographic, imaging, and clinical OAI datasets to identify incidence and progression patients at enrollment (baseline) with at least 1 follow-up visit. We excluded patients with other osteoporosis drug, corticosteroid, or narcotic analgesic use; missing or severe radiograph readings for both knees; and conditions which may impact bone. Patients were followed until first radiographic KOA progression in a non-prosthetic knee (1-unit change in Kellgren and Lawrence [KL] grade), or data were censored (first missed visit or end of 2-year follow-up). Discrete time logistic models were used to estimate hazard ratios between baseline BP users versus non-users by baseline KL grade. Models were adjusted for time-invariant (sex, age, enrollment date, race, symptomatic KOA diagnosis, Charlson score, smoking status, body mass index, vitamin D use, multivitamin use [healthy user proxy]) and time-varying (OA medication/analgesic use, fractures, falls) confounders.
Results: We identified 3,566 eligible patients (28% symptomatic KOA, 56% women, mean age 61 ± 9 years, 9% BP users [71% alendronate]). N = 564 patients experienced the primary outcome, and N = 308 were censored. BP users with KL grade < 2 were protected against progression (HR_{adj} 0.46 [95% CI 0.23, 0.95]), while BP use was not associated with radiographic progression in those with KL grade $\geq$ 2 (HR_{adj} 1.06 [95% CI 0.73, 1.53]). Years of BP use at baseline had no significant effect on progression, though sample size was limited. BP use did not affect time to narcotic analgesic use.
Conclusions: BP may be protective against radiographic KOA progression in early-stage patients, but less so for those with advanced disease. More study of the effects of BP type, cumulative dose, and potential confounding by indication is needed.

37 | The Effect of Beta Blocker Use on Bone Outcomes in the Framingham Osteoporosis Study

Christine W. Lary[1]; Kathleen Nevola[2]; Alexandra C. Hinton[1]; Theresa I. Shireman[3]; Katherine Motyl[4]; Karen L. Houseknecht[5]; Frances L. Lucas[1]; Sarah Hallen[6]; Andrew R. Zullo[3]; Sarah D. Berry[7]; Douglas P. Kiel[7]

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Background: Beta Blockers (BBs) have shown positive effects on bone mineral density (BMD) and fracture outcomes in several studies, with some but not all finding increased effect for Beta-1 selective BBs. It

is unresolved how Beta-1 selectivity influences this effect and how the effect varies by skeletal site.

Objectives: Test the hypotheses that 1) BB use and 2) Beta-1 selective BB use are associated with greater hip and spine BMD and lower incidence of osteoporotic fractures.

Methods: We used data from the Offspring (2nd generation) cohort of the Framingham Heart Study (*N* = 2,803), a prospective study of cardiovascular outcomes. BB use and Beta-1 selective BB use and covariates were assessed between 2005–2008, which was the index date. Femoral neck (FN), trochanter, total femur, and lumbar spine (L2-L4) BMD were measured using dual energy x-ray absorptiometry in cohort members willing to return for a call back visit (*N* = 1662). Occurrence of an osteoporotic fracture between the index date and the end of follow-up (August 2013) was noted. Covariates were age, height, weight, current smoking, cigarettes per day, prior cardiovascular disease, current treatment for diabetes, hypertension, hyperlipidemia, and menopause and hormone therapy for women. Analyses were done for the full cohort and stratified by sex, and models were adjusted for covariates using linear or logistic regression for BMD or fracture.

Results: Of the 1,662 who participated in the Osteoporosis study visit (53.1% female, average age 66), BB were used by 418 (25.2%) individuals, 358 (85.6%) of which were B1-selective users, with atenolol and metoprolol being the most common medications. FN BMD was significantly higher in BB users vs. non-users in crude and adjusted sex-combined models (0.019 g/cm^2 greater; 95% CI 0.003–0.035, p = 0.0171 in adjusted model). The effect of Beta-1 selective agents was similar (0.017 g/cm^2 greater; 95% CI 0.001–0.033, p = 0.0399). Sex-stratified models showed similar trends but were not significant. Other BMD sites showed significant results in crude but not adjusted models. Of the full cohort of 2,803, 204 (7.3%) had an osteoporotic fracture, 61 (8.4%) for BB users and 143 (6.9%) for non BB-users. There was no significant association between BB use and fracture in either crude or adjusted models (odds ratio of 1.09; p = 0.6758 in adjusted model).

Conclusions: BB use and B1-selective BB use were significantly associated with higher BMD of the hip, but there was no reduction in risk for incident fractures among users. This may due to insufficient influence of BMD to reduce fracture risk, or because BBs may affect other fracture risk factors such as falls.

38 | Sodium-Glucose Co-Transporter 2 Inhibitors and the Risk of Fractures among Patients with Type 2 Diabetes

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Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors are novel drugs used to manage type 2 diabetes. While they are favorably prescribed, there are concerns that their use may increase the risk of fractures. Indeed, large cardiovascular outcome trials have generated conflicting findings, and few real-world studies have been conducted to assess this association. As type 2 diabetes largely affects the elderly, and fracture incidence in this vulnerable population is associated with increased mortality, there is an urgent need to address this safety issue in the natural setting of clinical practice.

Objectives: To determine whether the use of SGLT2 inhibitors is associated with an increased fracture risk in patients with type 2 diabetes.

Methods: Using the UK Clinical Practice Research Datalink, we identified a cohort of 73,178 patients newly-treated with antihyperglycemic drugs between January 1, 2013 and December 31, 2017, followed until March 31, 2018. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident fractures associated with use of SGLT2 inhibitors overall, and according to specific types (dapagliflozin, empagliflozin and canagliflozin), when compared with use of dipeptidyl peptidase-4 inhibitors, a clinically relevant comparator. Models were adjusted for age, sex, smoking status, body mass index, alcohol-related disorders and markers of diabetes severity. We also assessed whether the risk was modified by history of fracture, osteoporosis, age or sex. We conducted several sensitivity analyses, including a marginal structural model and high-dimensional disease risk score, to assess the robustness of the findings.

Results: During 153,179 person-years of follow-up, there were 1,973 incident fracture events (incidence rate: 12.9/1,000 per year). Overall use of SGLT2 inhibitors was not associated with an increased risk of fracture (HR: 0.97, 95% CI: 0.79–1.19) when compared with dipeptidyl peptidase-4 inhibitors. Similar findings were observed when stratifying on specific SGLT2 inhibitors, with non-significant HRs ranging between 0.67 and 1.42. The risk was not modified by history of fracture, osteoporosis, age or sex. Sensitivity analyses yielded highly consistent findings.

Conclusions: The results of this large population-based study suggest that use of SGLT2 inhibitors is not associated with fracture incidence in patients with type 2 diabetes. This finding should provide reassurance on the safety of this new drug class.

39 | Immunosuppression, Fractures, and Post-Kidney Transplant Outcomes among Older Recipients

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Background: Older kidney transplant (KT) recipients are living longer with a functioning graft, and are at risk for age-related adverse events including fractures. However, fracture risk may be elevated in this population due to the life-long reliance on immunosuppression (IS), which often includes classes of medications, like steroids, that increase fracture risk in older adults. Understanding which IS agents elevate

fracture risk may help identify optimal IS regimens for older recipients to reduce adverse outcomes like graft loss and mortality.

Objectives: To estimate the risk of incident post-KT fractures associated with induction and maintenance IS and the risk of subsequent death-censored graft loss (DCGL) and mortality.

Methods: This was a cohort study of 47,815 patients aged 55 years and older who received KT (1/1/1999–12/31/2014). We linked data from the national registry of KT recipients to Medicare claims through the United States Renal Data System. Induction (none, ATG, IL2 receptor antagonist, alemtuzumab, other) and maintenance IS (steroid use, calcineurin inhibitors [tacrolimus, cyclosporin, none], and antimetabolites [MMF, mTOR, azathioprine, other, none]) at discharge was gleaned. We estimated the cumulative incidence of post-KT fractures and association between IS and post-KT fractures using adjusted competing risks models. We estimated risk of DCGL and mortality after fracture using adjusted Cox proportional hazards models treating fractures as time-varying.

Results: The 5-year incidence of post-KT hip, vertebral, and extremity fracture for those aged 65–69 was 3.8%, 1.6%, and 3.1%, respectively. No induction IS agents were associated with post-KT fractures. mTOR was associated with a 1.31-fold (95% CI: 1.07–1.59) increased risk of hip fracture compared to MMF. Lack of a calcineurin inhibitor was associated with 1.42-fold (95% CI: 1.05–1.91) increased risk of vertebral fracture compared to tacrolimus; and steroid use was associated with a 1.19-fold (95% CI: 1.04–1.35) increased risk of extremity fracture compared to no use. DCGL and mortality risk were higher after hip (DCGL aHR = 4.94, 95%CI:4.48–5.44; mortality aHR = 2.32, 95%CI:2.15–2.51), vertebral (DCGL aHR = 5.31, 95%CI:4.51–6.26; mortality aHR = 2.84, 95%CI:2.51–3.24), and extremity (DCGL aHR = 4.37, 95%CI:3.92–4.88; mortality aHR = 2.12, 95%CI:1.93–2.32) fracture.

Conclusions: Maintenance IS regiments that included mTOR and steroids but not calcineurin inhibitors, may increase the risk of post-KT fractures leading to mortality and graft loss and should be avoided among older recipients.

40 | Benzodiazepines and Risk of Fractures in Young People

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Background: Benzodiazepine (BZD) treatment has been associated with falls and fractures in older adults. BZD side effects such as slowed reaction time and dizziness could also lead to accidental falls in youth, including falls from heights or during athletic activities. Whether BZD treatment increases fracture risk in youth remains unknown.

Objectives: To determine if privately insured youth with anxiety disorders initiating a BZD have an increased risk of fractures compared to youth initiating an SSRI.

Methods: In a commercial claims database (2007–2016), we identified privately insured children (6–17 years) and young adults (18–24) with a recent anxiety disorder diagnosis, who newly initiated BZD or SSRI treatment (one-year washout). Following treatment initiation, youth were followed until fracture, treatment discontinuation or switching, insurance disenrollment, end of data, or 6-months. The endpoint was defined by ICD-9 and ICD-10 codes for long-bone fractures. We estimated separate propensity scores in children and young adults and applied one percent trimming. We then estimated crude and inverse-probability of treatment weighted fracture rates and adjusted hazard ratios (aHRs).

Results: The cohort included 12,840 child BZD initiators (107,875 SSRI initiators) and 57,684 young adult BZD initiators (122,084 SSRI initiators). Overall, BZD treatment was shorter than SSRI treatment: 5% of BZD initiators and 40% of SSRI initiators remained on treatment after 6 months. The crude fracture rate during treatment in children was 32.6 per 1000 person-years (PYs) in BZD initiators and 23.5/1000 PYs in SSRI initiators [HR = 1.29 (95%CI = 0.93–1.78); rate difference (RD) = 9.1/1000 PYs]. In the weighted cohort, the fracture rate was 38.7/1000 PYs and 23.5/1000 PYs in BZD vs. SSRI child initiators, respectively [aHR = 1.54 (0.91–2.58), RD = 15.2/1000 PYs]. In young adults, fracture rates were lower than in children with a weighted fracture rate during BZD treatment of 7.9/1000 PYs and of 8.5/1000 PYs during SSRI treatment [aHR = 0.94 (0.65–1.36), RD = -0.6/1000 PYs].

Conclusions: Initial findings suggest a potentially clinically relevant heightened rate of fractures in children with anxiety disorders initiating BZD treatment compared to SSRI treatment, but not in young adults. Increased caution in the weeks after BZD initiation in children with anxiety disorders may be warranted.

41 | Long-Term Budesonide Treatment and Risk of Osteoporotic Fractures in Patients with Microscopic Colitis

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Background: Due to a substantial first pass metabolism of oral budesonide the systemic bioavailability is low compared to other oral corticosteroids. This may lead to a low risk of adverse effects normally related to long-term use of corticosteroids.

Objectives: We aimed to determine whether use of oral budesonide is associated with osteoporotic fractures in patients with microscopic colitis.

Methods: Applying data from the Danish nationwide health registries, we conducted a case–control study nested within patients with a histologically verified diagnosis of microscopic colitis from 2004 to 2012. Cases were individuals with a first-occurrence of a fracture likely caused by osteoporosis i.e., fracture of hip (ICD-10: S72), wrist

(S525) or spine (S220 & 320). Cases were matched to controls by risk set sampling in a ratio of 1:3. We estimated odds ratios (ORs) for the association between ever use of budesonide and any osteoporotic related fractures, and for hip-, wrist and spinal fractures independently. Further, we investigated dose–response associations and associations for subgroups at suspected high or low risk of fractures. Potential confounding was adjusted for by risk set sampling and regression analyses.

Results: Results We identified 485 cases with a first occurrence of a fracture as defined above. The majority were women (86%) and the median age was 78 years. After adjustment for confounding, a modestly increased adjusted OR was observed for the overall association between use of budesonide and osteoporotic fractures (OR 1.39, CI: 1.09–1.76). Stratification by type of fracture revealed the highest risk of spinal fractures (2.15, CI: 1.09–4.25), followed hip-, and wrist fractures (OR 1.34 (CI: 0.94–1.93) and OR 1.26 (CI: 0.87–1.83), respectively). No dose–response association was evident (OR for doubling of cumulative dose 1.03 (CI: 0.91–1.16). When addressing differences across subgroups, we generally found moderately increased ORs (1.28–1.97).

Conclusions: Our results suggest a moderately increased risk increased risk of osteoporotic fractures related to use of budesonide among individuals with microscopic colitis. However, no dose–response association could be demonstrated.

42 | The Ascension of Real-World Evidence: Can (and Should) We Establish Thresholds for Validity?

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Background: While real-world data (RWD) have been used to evaluate medicine safety for decades, interest in appropriate use of real-world evidence (RWE) for regulatory decision making has grown rapidly due to the potential benefits associated with accelerated clinical development and the potential harm due to misleading evidence. The regulatory utility of RWE will likely depend on the extent to which researchers can demonstrate certainty about validity. To do so, researchers need methods and tools that are flexible, and easy to communicate.

Objectives: To understand current approaches to evaluating (a priori and post hoc) biases in real-world studies intended for regulatory decision making, identify key gaps in methods or tools that aid these evaluations, and to discuss the feasibility of setting thresholds for regulatory quality evidence. This symposium will be of interest to those involved in the design, implementation, or interpretation of comparative effectiveness/safety studies using RWD for regulatory decision-making.

Description: Internal validity (bucketed under "relevance") is a critical component of the recently released FDA RWE Framework. Much is known about the potential effects of biases in observational studies and there is comprehensive guidance to assess the validity of a completed study (e.g. GRACE Principles) or minimize bias through design (e.g. ENCePP). Sensitivity analyses (especially pre-specified) may help increase confidence in the robustness of results but are not applied systematically, and acceptable level of uncertainty around imperfect confounding control and misclassification (e.g. a sensitivity or specificity of <100% for a key inclusion diagnosis or primary outcome) is not well characterized. Acceptability may depend on the size of the treatment effect, seriousness of the outcome and other factors. In this symposium, researchers and decision makers will describe the current state of bias evaluation, and will discuss how ongoing validation studies, RCT replication projects and other supportive projects will look to derive principles within and across projects. The panel will discuss the current gaps in knowledge and tools, and the feasibility of establishing requirements for validity in regulatory guidance.

Structure (approx. times):

Introduction - 5 min (NG).
Current state: Evaluation of endpoint validity - 15 min (SL).
Current state: Evaluation of confounding control - 15 min (SS).
FDA led/sponsored validation projects - 15 min (DM).
EMA perspective - 10 min (JS).
Building validation into RWE generation platforms - 10 min (RR).
Summary - 5 min (CG).
Panel discussion −20 min.

43 | Heterogeneity and Validity in National and International Multi-Database Pharmacoepidemiologic Studies (MPES): Lessons Learned in North America, Europe, and Asia

Edward Chia-Cheng Lai[1]; Kenneth Man[2]; Darren Toh[3]; Robert Platt[4]; Jesper Hallas[5]; Soko Setoguchi[6]

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Background: Multi-Database pharmacoepidemiologic studies (MPES) can assess safety and effectiveness of medications with greater statistical power and identify treatment variations within a country and/or across countries. However, observed heterogeneity among databases can be due to genetic, cultural, and behavioral differences in the populations but also can arise from differences in clinical practice or technical issues in coding or mapping across databases.

Objectives: This symposium will share experiences in the US, Canada, Europe, and Asia to provide important lessons for those who want to

learn about and/or conduct national and international multi-database studies. The objectives are:

1. To describe how to recognize heterogeneity and how they affect the validity of national and international MPES. **2.** To start forming consensus on recommendations on the best practices to address/reveal measured and unmeasured heterogeneity across databases. **3.** To discuss when to aggregate the results from multiple databases and conclude the study appropriately.

Description: After a brief introduction of the topic (**Setoguchi S**), four presenters will present:

1.MPES of various databases within one country - the US FDA Sentinel System (**Toh D.**; 15 mins) **2.**MPES of Province-based databases within one country -Canadian Network for Observational Drug Effect Studies (CNODES) (**Platt R.**;15 mins) **3.**MPES of country-based databases within one union - experience from European network (**Man K.**; 15 mins) **4.**MPES of country-based databases within Asia -the Asian Pharmacoepidemiology Network (AsPEN) (**Lai E.**; 15 mins).

Panel discussion (**Setoguchi S. and Hallas J.**; 30 mins): The session will end with panel discussion addressing the questions below to bring the audiences and panelists towards consensus on the best practices for MPES regarding understanding and managing heterogeneity: **A.** How to recognize and prevent technical issues related to coding, mapping and common data models. **B.** How to recognize heterogeneity and other related validity issues. **C.** Suggestions on valid analytic approaches for dealing with the heterogeneity. **D.** When it is appropriate to aggregate the results from multiple databases. **E.** Consensus on practical guides to maintain transparency and increase producibility for a standard report in MPES.

44 | Thinking Globally While Acting Locally: Developing Time-on-Treatment Data in International Settings

Judith C. Maro[1]; Kristian B. Filion[2]; Achim Wolf[3]; Kevin Haynes[4]; Michael D. Nguyen[5]

[1] Harvard Medical School and Harvard Pilgrim Health Care Institute, Inc., Boston, MA; [2] McGill University, Montreal, QC, Canada; [3] Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [4] HealthCore, Wilmington, DE; [5] U.S. Food and Drug Administration, Silver Spring, MD

Background: Correct classification of exposed time is critical and challenging when integrating data streams. Differences in exposure measurement represent an important source of heterogeneity that needs to be considered in design and analysis of studies.

Objectives: Time-on-treatment information may be sourced from disparate data streams such as prescribing, dispensing and medication administration information. Prescribing data can identify clinical intent, but lacks assurance of use. Dispensing data is more widely used, but may not capture inpatient information or out-of-pocket payment. Finally, medication administration may lack needed granularity. However, as common data models and querying tools enable efficient use of multiple data sources, many are faced with decisions regarding how to define time-on-treatment within and across data sources. This symposium addresses approaches to these issues and identifies potential limitations when conducting multi-site research using disparate data streams to define exposure. We focus on illustrative examples including direct acting oral anticoagulants, Vitamin K antagonists, sodium glucose cotransporter (SGLT2) inhibitors, and selected antibiotics.

Description: 1. **Comparisons in dispensing data in the Canadian Network for Observational Drug Effect Studies (CNODES) and the US Sentinel System**. With common data models and querying tools, Canadian and US dispensing data are compared for a range of therapies. (15 min, Maro) 2. **Integrating prescribing data into CNODES:** CNODES has included UK Clinical Practice Research Datalink (CPRD) prescribing data in common-protocol studies to increase precision and leverage clinical data to examine residual confounding. (15 min, Filion) 3. **US dispensing vs. US prescribing data in the Patient-Centered Clinical Research Network (PCORnet)**. Data linkage within PCORnet allowed comparison of antibiotic prescribing and dispensing for the same patient, highlighting differences across multiple systems. (15 min, Haynes) 4. **UK CPRD experience with prescribing data formatted to the Sentinel Common Data Model (SCDM)**. Translation of the UK CPRD's Aurum database into the SCDM required creation and population of a prescribing data table for routine querying. Sample queries highlight differences between the UK CPRD and other data sources. (15 min, Wolf) 5. **Regulatory Impact:** The US Food and Drug Administration reflects on the use of heterogeneous treatment data from international collaborators in advancing the science of drug safety. (15 min, Nguyen) 6. **Discussion** (15 min, All).

45 | Machine Learning to Improve Causal Inference in Pharmacoepidemiology

Jason Roy[1]; Nandita Mitra[2]

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Background: Machine learning methods have largely been developed for prediction, but increasingly they are being used within a causal inference framework.

Objectives: To review some causal inference and machine learning methods. To describe ways in which causal inference methods can benefit from specific machine learning methods. To have a guided discussion on the use of machine learning methods in pharmacoepidemiology. To learn how to implement the methods in R. Researchers wanting additional information about modern causal inference methods should benefit by attending.

Description: This workshop will begin with a brief review of some popular causal inference methods, such as inverse probability of treatment weighting and g-computation. Opportunities will be identified for making these approaches more robust with the use of machine learning methods. As examples, two machine learning methods will

be introduced: super learner and Bayesian additive regression trees (BART). Illustrations of how these machine learning methods can be used in conjunction with standard causal inference methods will be presented. After each causal inference/machine learning combination is introduced and discussed in the context of specific pharmacoepidemiology studies, there will be a guided, interactive discussion. The workshop will include implementation of these methods in R, along with comparisons with more familiar regression versions of the methods. There will be a discussion of some of the benefits and limitations of these methods, especially in the context of EHR and claims database research.

46 | Measuring, Mapping, and Meshing of Genotype and Phenotype Data across Large Datasets: Challenges of Combining and Mining Genotype and Phenotype Data

Leah Sansbury[1]; Meg Ehm[1]; Marylyn Richie[2]; Amalia Issa[3]; Colin Palmer[4]; Edgar Simard[1]

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Background: Large datasets containing genetic information are utilized to understand mechanisms of disease and to identify therapeutic targets. Linking of numerous data sources facilitates broad phenotypic explorations and enhances our understanding of the target disease mechanisms. However, due to different data collection methods researchers face numerous challenges mapping concepts across datasets and merging disparate information.

Objectives: To discuss the various data resources available for conducting translational genotype and phenotype studies, including genetic and real-world data for translational research. The presenters will outline examples of the newest methods to define phenotypes and assess association with genetic data. Furthermore, the panelists will discuss opportunities that are emerging (e.g. the option to engage patients to get more phenotypic data). Finally, the presenters will discuss challenges associated with methods, data, and interpretation of large datasets that have combined genotype and phenotype data.

Description: With the convergence of greater access to large, deep, genetic datasets that also contain phenotypic insights (e.g. 23andMe, UK BioBank, FinnGen), and advances in analytic capabilities, our ability to merge and generate genotypic and phenotypic insights has greatly increased. Presenters will outline how we are using genetics for drug discovery and how to leverage the advantages of each dataset. In addition, presenters will provide examples of conducing PheWAS and the use of methods to derive phenotypes. Additionally, the presenters will provide examples of use of EHRs to understand pharmacogenic associations. Finally, there will be a focus on implementing complex methods, including polygenic risk score analysis.

47 | Using Negative Control Outcomes to Assess the Comparability of Osteoporosis Treatment Groups

Leah J. McGrath[1]; Leslie Spangler[2]; Jeffrey R. Curtis[3]; Vera Ehrenstein[4]; Henrik Toft Sørensen[4]; Bradley Saul[1]; Sara Levintow[1]; M. Alan Brookhart[1]; Brian D. Bradbury[2]

[1] *NoviSci, Durham, NC;* [2] *Amgen, Thousand Oaks, CA;* [3] *University of Alabama at Birmingham, Birmingham, AL;* [4] *Aarhus University Hospital, Aarhus, Denmark*

Background: Comparative safety and effectiveness estimates for osteoporosis (OP) treatments can be biased due to confounding by indication. The extent of bias can be assessed with negative control outcomes that are expected to have no plausible association with the biologic effects of OP medications.

Objectives: Using negative control outcomes selected by an expert panel, we evaluated whether women initiating different OP treatments were comparable after controlling for potential confounders.

Methods: We used the MarketScan Commercial and Medicare Supplemental claims data to identify OP treatment-naïve women aged 55 years or older initiating denosumab, intravenous (IV) zoledronic acid (ZA), or an oral bisphosphonate (BP) (risedronate, alendronate, or ibandronate) from October 1, 2010 through September 30, 2015. We required at least 12 months of continuous enrollment in a healthcare plan before initiation and excluded patients with history of Paget's disease or cancer. We compared individual oral BPs, as well as denosumab with ZA and with all oral BPs, with respect to 11 negative control outcomes grouped into three domains, defined by the expected source of bias: functional status, healthy user/adherer, and access to healthcare. We estimated the 12-month cumulative risk difference (RD) of each outcome, using inverse probability of censoring and treatment weights to control confounding by baseline demographics, healthcare utilization, comorbidities, and comedications. Individual RDs within each domain were pooled using inverse-variance weights.

Results: Among 148,587 eligible women, 53% were 55–64 years old, 10% had a history of fracture, and 30% had a history of corticosteroid use. Alendronate was the most common osteoporosis treatment (57%), followed by ibandronate (12%), ZA (11%), risedronate (10%), and denosumab (10%). Nearly all exposure comparisons indicated no meaningful association between treatment choice and negative control outcomes. Exceptions were comparisons of either denosumab or ZA with oral BPs on the healthy user/adherer domain. The pooled RD per 1,000 women was 9.1 (95% CI: 3.5, 14.7) comparing denosumab with oral BPs and 6.5 (95% CI: 1.8, 11.2) comparing ZA with oral BPs.

Conclusions: After adjustment, there was minimal evidence of residual bias for most negative control outcomes among women initiating OP treatments, supporting the potential for non-experimental comparative safety research. Caution is warranted when comparing injectable

versus oral medications and in extending these results to other populations, such as older adults with comorbidities.

48 | Can Adjustment Fail? Confounder Misclassification in Single-Arm Studies with Real World Comparators

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Background: Hybrid studies comparing outcomes in those on experimental therapy to untreated patients from real-world data (RWD) are becoming more common. These single-arm studies control for confounding with statistical methods, but it is unclear when these methods fail to reduce bias in the setting of confounder misclassification.

Objectives: Explore changes in bias after weighting by a confounder measured differently in two treatment arms using illustrative quantitative examples.

Methods: We considered treatment X with no effect on outcome Y, confounder C affecting X and Y, and C′ representing measured C. We held fixed effect of C on Y (RR = 5.0), sensitivity (0.60) and specificity (0.99) of C in the experimental arm (i.e. when X = 1), and prevalence of X (0.1) when C = 0. We varied prevalence of C, effect of C on X, and sensitivity and specificity for measurement of C in the RWD arm (i.e. when X = 0). We used prevalence and sensitivity parameters for smoking from the literature (10% prevalence, RWD sensitivity of 0.15, RWD specificity of 0.99) in situations where smoking tripled (scenario 1) or divided by 3 (scenario 2) probability of X. We also examined two generic scenarios with near-perfect sensitivity (0.99) of C when X = 1: scenario 3 where rare C (10% prevalence) tripled probability of X with low specificity (0.60) in the RWD; and scenario 4 where common C (80% prevalence) divided by 3 probability of X with low sensitivity (0.60) in the RWD arm. We then used inverse probability of treatment weighting (IPTW) to adjust for C′ and also performed separate analyses stratified by C′.

Results: In scenario 1, the unadjusted RR (RR_{unadj}) was 1.52 vs an IPTW RR of 1.17 (bias decrease versus the true null effect). In scenario 2 the RR_{unadj} was 0.762 vs an IPTW RR of 0.757 (minor bias increase). In scenarios 3 and 4, bias increased more substantially: in scenario 3 the RR_{unadj} was 1.65 vs an IPTW RR of 2.05; in scenario 4 the RR_{unadj} was 0.756 vs an IPTW RR of 0.723. Weaker effects of C on X or larger gaps in measurement error between the two arms increased bias. Even when the IPTW RR was less biased than the RR_{unadj}, estimates in at least one subgroup were often biased.

Conclusions: If there is differential misclassification of and confounding by C, collider bias from conditioning on C′ may increase bias compared to a crude estimate. The larger the gap in classification between treatment arms and the weaker the true confounder-exposure association, the more easily partial control for C is overwhelmed by this collider bias. Single-arm studies may need to consider methods (e.g. imputation) to remedy differential misclassification of confounders by treatment.

49 | Confounding by Indication in Drug-Cancer Association Studies: A Nested Case–Control Study of the Association between Calcium Channel Blockers and Renal Cell Carcinoma

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Background: Use of calcium channel blockers (CCBs) and other antihypertensive drugs has been associated with increased risk of renal cell carcinoma. Since hypertension is a risk factor for renal cell carcinoma, confounding by indication is a potential explanation for the association.

Objectives: To examine whether CCB use was associated with an increased risk of renal cell carcinoma and provide a framework for addressing confounding by indication in drug-cancer association studies.

Methods: We conducted a nested case–control study using Danish demographic and health registries. We identified all renal cell cancer cases in Denmark between 2005–2015 and selected ten controls for each case matched on age and sex. Using conditional logistic regression, we estimated odds ratios (ORs) with 95% confidence intervals (CI) for long-term (≥ 1000 defined daily doses) vs. never use of CCBs associated with renal cell carcinoma. We addressed confounding by indication in several analyses including (i) adjusting for severity of hypertension and concurrent antihypertensive drug use; (ii) evaluating dose–response patterns; (iii) estimating ORs for other antihypertensive drugs associated with renal cell carcinoma, and (vi) restricting to new users of antihypertensives and selecting long-term use of other first-line antihypertensive drugs as a referent.

Results: We included 5502 renal cell carcinoma cases of whom 16.4% were long-term users of CCBs. The corresponding proportion among controls was 9%, yielding a crude OR of 2.23 (95%CI 2.05 to 2.42). The association was attenuated upon adjusting for hypertension severity and use of other antihypertensives (OR 1.45, 95%CI 1.31 to 1.60). The OR increased with increasing cumulative dose in adjusted models (p_{trend} < 0.001). Long-term use of ACE-inhibitors, thiazides, and furosemide showed similar associations with renal cell carcinoma, including dose–response patterns. When restricting to new-users and using long-term use of other first-line antihypertensive drugs as referent, the adjusted OR was 1.68 (95%CI 1.47 to 1.91).

Conclusions: Long-term use of CCBs was associated with increased risk of renal cell cancer. We used a range of methods to address confounding by indication and demonstrated a smaller association when

adjusting for severity of hypertension and similar associations with other commonly used antihypertensive drugs. However, confounding by indication does not appear to fully explain the association between CCBs and renal cell carcinoma.

50 | Visualization Tool of Variable Selection for Inverse Probability Weighted Estimator in High-Dimensional Covariates

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Background: Inverse probability weighting (IPW) is a commonly used confounder adjustment method in pharmacoepidemiological studies and there is a need to adjust for a high-dimensional set of confounders in administrative datasets. Adjusting for all confounders may reduce bias, but at the expense of increased variance resulting in (near) positivity violations and unstable IPWs.
Objectives: We developed a SAS macro to generate plots displaying the impact of each confounder on the bias and variance of IPW estimates, propensity-matched estimates, and propensity score overlap.
Methods: Mean squared error (MSE) was used as a summary statistic for bias and variance of the IPW-weighted estimate. We presumed that the estimate from the fully adjusted model was the unbiased estimate. We calculated bias as the deviance between this unbiased estimate with the estimate from the model excluding certain confounders. We also showed the estimates from IPW truncation as a comparison to the approach of removing certain confounders. Among the two output plots, the first showed risk ratios (RRs) with 95% confidence interval from models that excluded the variable shown on the y-axis. The second plot showed the distribution of propensity scores of exposed and non-exposed groups from the corresponding models. These plots were sorted by MSE of the outcome model. We showed how our macro can visualize the impact of problematic confounders in two scenarios: (1) an empirical study examining the association between pre-pregnancy obesity and stillbirth in a cohort of linked birth and death records in Pennsylvania; (2) a plasmode simulation study to mimic a pharmacoepidemiologic study with high-dimensional covariates. We used data from the Clinical Practice Research Datalink and simulated the known effect of statin use post-myocardial infarction on one-year all-cause mortality keeping the original associations among covariates.
Results: In our empirical study examining pre-pregnancy obesity and stillbirth, we identified 35 confounders. Adjusting for all confounders led to RR = 1.37 (95% CI: 1.01, 1.90). After applying our macro, we identified one confounder (prior gestational weight gain) that increased MSE 3-fold compared to full model. Removing this confounder from the propensity score model resulted in RR = 1.68 (95% CI: 1.43, 1.99) and better propensity score overlap. The detailed results from the plasmode simulation will be demonstrated in a series of plots.
Conclusions: Our results suggest careful consideration of the analytic impact of all confounders should be made when fitting IPW and propensity-matched estimators.

51 | A General Propensity Score for Signal Detection Using Tree-Based Scan Statistics

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Background: Tree-based scan statistics (TBSS) appropriately adjust p-values for multiple testing of correlated hypotheses when screening thousands of potential adverse events for signal detection studies. Simulation has demonstrated the promise of TBSS with a propensity score (PS) matched cohort design. However, it is unclear which variables to include in the PS for applied signal detection studies of drug safety to adjust for confounding across thousands of potential outcomes.
Objectives: To develop a general PS applicable to different active-comparator cohorts and thousands of outcomes.
Methods: We selected 3 drug pairs with established safety profiles where few, if any signals were expected. For each pair, we evaluated 5 candidate PS that included different combinations of: predefined general covariates (demographics, comorbidity, frailty, utilization), empirically identified covariates (via high-dimensional PS algorithm) and covariates tailored to the drug pair. We identified 1:1 matched cohorts in MarketScan data using each PS, ran TBSS, ranked potential adverse events by log likelihood ratio (LLR) and set a threshold for alerting of $p \leq 0.01$.
Results: For each drug pair (N > 290,000 each), the top ranked outcomes were similar across PS matched cohorts. There were ≤ 2 unique alerts observed per example. Outcomes that met the threshold for alerting were expected or explainable. For example, when comparing macrolides versus fluoroquinolones, the top ranked outcome for each PS-matched cohort was hypertension complication in pregnancy. This was explainable by channeling of azithromycin (a macrolide) to pregnant women. Pregnancy was not a covariate in the predefined PS, the outcome hypertension in pregnancy had $p \leq 0.01$. When pregnancy was included as empirical and/or tailored covariates, the p-values were between 0.13–0.43. However, fewer pregnant patients were in the matched cohorts, achieving better balance but reduced power.
Conclusions: Including empirical covariates may provide better proxy coverage of confounders for numerous outcomes than predefined covariates alone, but could increase variance. Unlike covariates tailored to exposures, empirical and predefined general covariates can be applied "out of the box" for signal detection with different active-

comparator cohorts. Other than pregnancy, covariates tailored to exposure did not appreciably impact screening results in our examples. Potential signals should be followed up with pharmacoepidemiologic assessment where confounding control is tailored to the specific outcome(s) under investigation.

52 | Approaches to Overcome the Immeasurable Time Bias in Cohort Studies: Beta-Blockers and Risk of Mortality in Patients with Heart Failure

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Background: Immeasurable time bias, which occurs due to the lack of inpatient drug data in many databases, may exaggerate drug benefits in pharmacoepidemiologic studies. However, the optimal approach of minimizing this bias remains unclear.

Objectives: To compare different methodological approaches at reducing immeasurable time bias using the case study of β-blocker use and mortality among heart failure (HF) patients.

Methods: We conducted a propensity-score matched, new-user cohort of patients with incident HF between 2003 and 2013 using Korea's nationwide healthcare database. Exposure to β-blockers was treated as time-varying, and patients were followed until death or end of the study period. We estimated the gold standard hazard ratio (HR) and its 95% confidence interval (CI) using both in- and outpatient drug data. To assess methodological approaches to reduce immeasurable time bias, we used outpatient drug data only and conducted nine trimming and five weighting analyses: trimming those with cumulative hospitalization durations ≥90% of follow-up, decreasing in 10% intervals, weighting the number of observed days by 1) each exposed- and unexposed durations, and 2) unexposed duration. Proportional duration, defined as observed days divided by the total duration of follow-up, was also used for weighting by 3) each exposed- and unexposed durations, and 4) unexposed duration. An approach was considered successful when the 95% CI of the estimated HR overlapped with the 95% CI of the gold standard HR.

Results: From our matched cohort of 14,774 patients, the gold standard's HR for mortality associated with β-blocker use was 0.80 (95% CI 0.73–0.89). After assessing a total of 45 approaches, trimming with weighting by proportional durations was successful in minimizing the bias while trimming with weighting by observed days was not. The approach closest to the gold standard was trimming those hospitalization ≥10% of follow-up with weighting by each proportional durations (0.71, 0.59–0.86). Using trimming cutoffs of ≥20% (0.65, 0.55–0.78) and ≥ 30% (0.64, 0.53–0.76) were also successful approaches, while a cutoff of ≥50% (0.55, 0.48–0.63) was not. When weighting by proportional unexposed duration, only a trimming cutoff of ≥10% (0.69, 0.60–0.79) mitigated the bias whereas trimming cutoffs of ≥20% (0.65, 0.57–0.72) and ≥ 30% (0.59, 0.52–0.67) did not.

Conclusions: The magnitude of the immeasurable time bias was substantial in our real-world example. Trimming with weighting by proportional durations seem to be optimal for reducing the impact of immeasurable time bias.

53 | Risk of Pregnancy Loss in Patients Exposed to Mycophenolate Compared to Azathioprine: A Retrospective Cohort Study

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Background: Mycophenolate is one of the most commonly used immunosuppressant medications. Although it is not recommended for use during pregnancy due to its teratogenicity risk, the evidence is limited to case series and one transplant registry study.

Objectives: To evaluate the relative risk (RR) of pregnancy loss associated with the use of mycophenolate (MPA) versus azathioprine (AZA) during early pregnancy.

Methods: We conducted a retrospective cohort study using the IBM MarketScan commercial claims databases from January 1st, 2005 to June 31st, 2015. Pregnant patients had continuous enrollment ≥132 days before conception until the pregnancy end date. Conception was estimated using a claims-based algorithm created from pregnancy-related diagnoses and procedures codes. Patients with ≥1 MPA dispensing were compared with AZA users during the first trimester. The composite endpoint was pregnancy loss including stillbirth and spontaneous abortion. Potential confounders included age, drug indications, comorbidities, use of other teratogenic medications, and gestational age at first MPA or AZA prescription fill. The relative risk of pregnancy loss was estimated using a generalized estimating equation model with inverse probability of treatment weighting. In sensitivity analyses, we varied the exposure assessment window (6 weeks before conception to the end of first trimester and 6 weeks before conception to pregnancy end date), and the pregnancy loss definition (stillbirth, spontaneous, and induced abortions).

Results: A total of 108 and 445 pregnancies were exposed to MPA (mean [SD] age of 33.3 [9.41]) and AZA (mean [SD] age of 32.6 [5.61]), respectively. In the MPA group, 50 pregnancies resulted in pregnancy loss (46.3%) including 3 (2.8%) stillbirth and 47 (43.5%) spontaneous abortions. In the AZA group, 100 pregnancies had pregnancy loss (22.5%) including 5 (1.1%) stillbirth and 95 (21.4%) spontaneous abortions. The unadjusted RR of pregnancy loss for MPA was 2.06 (95% CI 1.56–2.67) and the adjusted RR was 2.08 (95% CI, 1.58–2.70) compared to AZA. In the sensitivity analyses, we observed similar adjusted RRs.

Conclusions: Exposure to MPA during pregnancy is associated with a significantly increased risk of pregnancy loss. Our results support the

recommendations for pregnancy prevention and use of alternative treatment options at least 6 weeks before planned pregnancy.

54 | Exposure to Antidepressants during Pregnancy and the Risk of Attention Deficit Hyperactivity Disorder in Offspring: Findings from a Nationwide Cohort Study with and without Sibling Design

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Background: Attention deficit hyperactivity disorder (ADHD) is a serious disease. Recent studies have suggested an association between maternal use of antidepressants during pregnancy and elevated risk of ADHD in offspring. However, the findings may be confounded by unmeasured socioeconomic or genetic factors.

Objectives: To examine the association between maternal use of antidepressants during pregnancy and the risk of ADHD in offspring by using a classical cohort design and a sibling design.

Methods: We included all singleton live-born infants in Denmark in 1997–2016. In a classical cohort design, we examined the association by applying three models with increasing number of confounders included for control: 1) a crude model (no adjustment), 2) a model controlling for birth- and disease-related factors, and 3) a model with additional control for socioeconomic factors. In a sibling design, we compared the outcome in exposure-discordant siblings, thus removing confounding by shared risk factors. In addition, we adjusted for covariates that could vary among siblings. As sensitivity analyses we performed former vs. current user comparison and unconditional sibling comparison. In addition, as a negative control analysis we performed paternal exposure analysis. In all analyses, we used Cox regression to calculate hazard ratios (HRs) for the risk of ADHD in offspring contrasting those with vs. those without exposure to antidepressants during gestation.

Results: The overall population consisted of 1,223,201 live-born singletons. The sibling population consisted of 30,578 siblings discordant for maternal use of antidepressants. The three models in the cohort design resulted in HRs of 2.09 (95% CI 1.92; 2.26), 1.46 (95% CI 1.32; 1.61) and 1.47 (95% CI 1.32; 1.65), respectively. The adjusted model in the sibling design resulted in a HR of 1.20 (95% CI 0.93; 1.54). The sensitivity analysis of former vs. current user comparison resulted in a HR of 1.19 (95% CI 1.06; 1.33) and the unconditional sibling comparison in 1.20 (95% CI 1.00; 1.45). The negative control paternal exposure analysis resulted in a HR of 1.17 (95% CI 1.05; 1.29).

Conclusions: There was an association between maternal use of antidepressants during pregnancy and the risk of ADHD in offspring in the classical cohort design. This association was attenuated when a sibling design was used, suggesting presence of uncontrolled confounding. The sensitivity and negative control analyses supported this conclusion.

55 | Does the Type of Antihypertensive Medication Used in Pregnancy Affect Risk of Pre-Eclampsia?

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Background: Hypertensive disorders are common in pregnancy and increase the risk of adverse maternal outcomes including pre-eclampsia. Several medications are used to treat hypertension in pregnancy, but it is unclear whether any are superior for preventing adverse outcomes.

Objectives: To compare the risk of pre-eclampsia with use of different antihypertensive medications in pregnancy.

Methods: We conducted a retrospective cohort study of women with a singleton live or stillbirth from 2005–2014 in 3 US healthcare systems: Kaiser Permanente Washington, Northern California and Southern California. Data came from electronic medical records and linked birth certificate data. We identified women with chronic or gestational hypertension using ICD-9 diagnosis codes, medication dispensings, and blood pressure values. We restricted the cohort to women who filled an antihypertensive medication during pregnancy after their first prenatal visit and before 35 weeks 6 days gestation, including new and prevalent users. The first medication fill in this time period was considered the index fill. We required women to have at least 150 days of enrollment and to be free of pre-eclampsia in this pregnancy before the index fill. Exposure category (specific medication used) was defined from the index fill. Pre-eclampsia was identified from inpatient ICD-9 diagnosis codes from 20 weeks gestation through 28 days after delivery, an algorithm with high positive predictive value in a validation study. We used logistic regression to compare the risk of pre-eclampsia with use of labetalol, methyldopa, nifedipine, or other beta blockers, adjusting for covariates including blood pressure before the index fill through propensity scores and inverse probability of treatment weighting.

Results: Among 6349 births to women treated for hypertension, there were 3019 (48%) with an index fill for labetalol, 1834 (29%) for methyldopa, 1106 (17%) for nifedipine and 390 (6%) for other beta blockers. Mean maternal age was 34 years and mean gestational age at the index fill was 18 weeks. 86% of women had chronic hypertension, and 66% were Hispanic or nonwhite. The incidence of pre-eclampsia was 33% for women using labetalol, 29% for methyldopa, 31% for nifedipine and 23% for other beta blockers. Compared to use of labetalol, the adjusted odds ratio for pre-eclampsia with use of methyldopa was 1.01 (95% CI 0.87–1.17), for nifedipine 1.01 (0.86–1.19), and for other beta blockers 1.02 (0.74–1.04).

Conclusions: In women with hypertension in pregnancy, the risk of pre-eclampsia did not differ by type of antihypertensive medication used.

56 | Prenatal Antidepressant Exposure and Perinatal Outcomes: An Analysis Utilizing Longitudinal Clustering Methods

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Background: Studies of antidepressant safety in pregnancy typically do not address complex patterns of use, precluding assessment of how changes in dose, timing of use, and coverage gaps affect the pregnancy.

Objectives: The objective of this study was to quantify patterns of antidepressant exposure in pregnancy, and test whether exposure patterns were associated with perinatal outcomes.

Methods: The study analyzed data from OptumLabs® Data Warehouse, which includes de-identified claims data from commercially insured individuals in the US. After enforcing continuous enrollment requirements, 226,932 singleton, live-births were identified between 2012–2016. All antidepressant dispensings between last menstrual period (LMP) and 35 weeks' gestation were converted into fluoxetine equivalents. We performed k-means longitudinal modeling to identify similar antidepressant utilization patterns. Multivariable log-linear regression with a Poisson distribution and robust standard errors was used to estimate risk ratios (RR) and 95% confidence intervals (CI) of preterm birth, low birth weight, neonatal respiratory distress, and postpartum hemorrhage. Models were adjusted for maternal demographics, diagnosis of depression, anxiety, pain or other mental health disorders, benzodiazepine or antipsychotics claims between LMP and 35 weeks' gestation.

Results: We identified 15,041 (6.6%) pregnant women with an antidepressant dispensing. Antidepressant exposure was best summarized into 5 trajectories: very low (average of 4 mg/day, *n* = 7,622), low sustained (18 mg/day *n* = 3,170), medium with first trimester discontinuation (12 mg/day, *n* = 1,907), medium sustained (38 mg/day, n = 1,918), and high sustained exposure (75 mg/day, *n* = 424). When compared with the lowest trajectory, medium sustained and high sustained trajectories were both associated with an increased risk of preterm birth [RR 1.31, 95% CI (1.16, 1.49); RR 1.78, 95% CI (1.48, 2.14)], low birth weight [RR 1.27 95% CI (1.10, 1.47); RR 1.65 95% CI (1.33, 2.04)], and postpartum hemorrhage [RR 1.35, 95% CI (1.03,1.78); RR 2.51, 95% CI (1.69, 3.71)]. All four trajectories increased the risk of neonatal respiratory distress: e.*G. medium* discontinued RR 1.23, 95% CI (1.05, 1.44); high sustained RR 2.23, 95% CI (1.83, 2.77) relative to the lowest trajectory.

Conclusions: Although these findings may reflect indication severity, they demonstrate the nuanced exposure assessment that longitudinal cluster analysis affords. Additional attention to women who require medium to high sustained antidepressant use across gestation is warranted.

57 | Incident Exposure to Benzodiazepine in Early Pregnancy and the Risk of Spontaneous Abortion

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Background: Studies show that benzodiazepine use in early pregnancy is associated with an increased risk of spontaneous abortion. However, no one has examined the association between specific benzodiazepine agent exposures and the risk of spontaneous abortion.

Objectives: To quantify the risk of spontaneous abortion associated with gestational benzodiazepine incident use as a class as well as by duration of action, and by specific benzodiazepine agents.

Methods: We conducted a nested case–control study within the Quebec Pregnancy Cohort, which includes all pregnancies covered by the Quebec Prescription Drug plan from 01/01/1998 to 31/12/2015. Conditional logistic regression models were used to calculate ajusted odds ratios (aOR), and 95% confidence intervals (CI). We defined spontaneous abortion as a pregnancy loss before the 19th completed week of gestation. Each case of spontaneous abortion was randomly matched on gestational age at the time of the event with up to five controls. We defined incident benzodiazepine exposure as ≥1 filled prescription between the first day of the last menstrual period (LMP) and the index date (date of spontaneous abortion) without prior LMP exposure. Benzodiazepine exposure was categorized as 1) any benzodiazepine use, 2) long-acting or short-acting, and 3) by specific benzodiazepine agents; non-use of benzodiazepine was the reference category.

Results: A total of 375 (1.4%) of the 27,149 pregnancies ending with a spontaneous abortion were exposed to benzodiazepine in early pregnancy, as compared to 788 (0.6%) of the 134,305 matched controls (crude OR, 2.39; 95%CI, 2.10–2.73). Adjusting for potential confounders including maternal mood and anxiety disorders before pregnancy, and compared to non-use, early pregnancy benzodiazepine exposure was associated with an increased risk of spontaneous abortion (aOR, 1.85; 95%CI, 1.61–2.12). The risk of spontaneous abortion was similar among pregnancies exposed to short-acting (aOR 1.81, 95%CI 1.55–2.12; 284 exposed cases) and long-acting benzodiazepines (aOR 1.73, 95%CI 1.31–2.28; 98 exposed cases). Specifically, early pregnancy exposure to diazepam, temazepam, bromazepam, alprazolam, clonazepam, lorazepam and oxazepam were all independently associated with an increased risk of spontaneous abortion (aOR from 3.43 to 1.48).

Conclusions: An increased risk of spontaneous abortion was observed among early pregnancies with incident exposure to short or long-acting benzodiazepines, as well as to any benzodiazepine types.

58 | Ondansetron Use in Early Pregnancy and Miscarriage

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Background: Ondansetron is commonly used to treat nausea and vomiting in pregnancy despite inconclusive evidence of its safety. Previous studies have reported no increase in risk of miscarriage but relied on non-user comparators or methods that failed to account for gestational weeks at risk.

Objectives: To evaluate the risk of miscarriage among women with orders for ondansetron versus alternative antiemetics during the first 20 weeks of pregnancy.

Methods: A pregnancy cohort was created using electronic health record (EHR) data from the UNC Health Care system in North Carolina, USA. Pregnancies were identified at the date of first record of the pregnancy in the EHR and followed until miscarriage, induced abortion, loss to follow-up (last record with evidence of pregnant status), or 140 days of gestation. Miscarriage was defined as spontaneous fetal loss before 140 days of gestation. Antiemetic exposure status was defined by first antiemetic ordered (ondansetron or comparators, metoclopramide and promethazine) in the first 140 days of gestation; pregnancies with orders for both antiemetic groups on the same day were excluded. Sensitivity analyses defined exposure using only administered (inpatient or intravenous) orders. Cumulative incidence of miscarriage was estimated on the gestational age timescale. Pregnancies were censored at gestational age of loss to follow-up or 140 days, whichever was first, and induced abortions were analyzed as competing events. We report adjusted risk differences (RD), risk ratios (RR), and 95% confidence intervals (CI). Confounding by antiemetic indication, maternal age, race, ethnicity, insurance status, smoking status, comorbidities, and medication use was controlled using stabilized inverse probability of treatment weights.

Results: We identified 2730 eligible pregnancies with antiemetic orders; 66% had first ondansetron order and 34% had first comparator antiemetic order. The median gestational age of first order was 64 and 67 days in the ondansetron and comparator groups, respectively. The crude risk of miscarriage was 13.1% (95% CI: 9.9, 17.4) in the ondansetron group and 12.1% (95% CI: 8.8, 16.7) in the comparator group. After covariate adjustment, there was no difference in risk of miscarriage for ondansetron users (RD 0.3%, 95% CI -5.8, 5.6; RR 1.02, 95% CI 0.63, 1.62). Sensitivity analyses with administered orders included 967 ondansetron users and 462 comparator users, and similar results were observed (RD 0.1%, 95% CI -9.5, 9.6; RR 1.01, 95% CI 0.56, 2.09).

Conclusions: We observed no increase in the risk of miscarriage for pregnancies exposed to ondansetron versus comparator antiemetics.

59 | Use of Psychotropic Drugs in Children and Adolescents with Tic Disorders in Denmark: A Nationwide Drug-Utilization Study

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Background: The pharmacological treatment of tic disorders, including Tourette syndrome and chronic tic disorders, is complex and mainly based on treating comorbid psychiatric disorders. Due to limited evidence, treatment mostly relies on clinical experience and preferences of the individual prescriber.

Objectives: To describe the use of psychotropics in children and adolescents with tic disorders in Denmark, including overall utilization patterns, regional variation, how psychiatric comorbidities affect use patterns, and the effect of the introduction of the European clinical guideline in 2011.

Methods: Based on the Danish National Patient Registry, we identified three cohorts of children and adolescents 6–17 years old with a recent (within 2 years) hospital diagnosis of a tic disorder in 2008 (n = 1662), 2012 (n = 2816), and 2016 (n = 2862; median age 11 years, interquartile range 8–13; 77% boys). Data on drug use was obtained from the Danish National Prescription Registry.

Results: The psychotropics most commonly used were ADHD medications (2008: 26%; 2012: 30%; and 2016: 25%), antipsychotics (2008: 21%; 2012: 16%; and 2016: 9%), melatonin (2012: 12%; 2016: 15%), and antidepressants (2008: 8%; 2012: 6%; and 2016: 5%). Medication use was more common in Tourette syndrome (47% used at least one psychotropic during 2016) and chronic tic disorders (45%) compared to transient tic disorder (34%) or other/unspecified tic disorders (23%). In Tourette syndrome, use of psychotropics followed recorded psychiatric comorbidity, e.g. use of ADHD medication in 62% of those with comorbid ADHD compared to 18% overall, and use of antidepressants among those with obsessive–compulsive disorder was 32% compared to 6% overall. Comparing the five Danish regions, differences in use were observed for ADHD medication (in 2016 highest vs. lowest one-year prevalence proportion 42% vs. 18%) and melatonin/hypnotics (23% vs. 12%) while no variation was seen for antipsychotics or antidepressants. In 2008 and 2012, risperidone accounted for the majority of antipsychotic use (46–57% of antipsychotic prescriptions) while in 2016, aripiprazol accounted for 40% and risperidone accounted for 34%.

Conclusions: The use of psychotropics among children and adolescents with tic disorders is considerable, in particular for Tourettes syndrome and chronic tic disorders, and is heavily influenced by psychiatric comorbidity. Regional variation is seen for use of ADHD medication and melatonin/hypnotics. Contrary to the 2011 European recommendations, antipsychotic use has shifted from risperidone to aripiprazol.

60 | Patterns of Drug Utilization over Age in Asthmatic Children

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Background: Children start using drugs for asthma treatment at different ages, and many stop using these after different periods of time.
Objectives: To study patterns of asthma drug utilization by age using group-based trajectory models in children, and investigate risk factors for different trajectories.
Methods: A retrospective cohort study (2007–2016) in asthmatic children, 5–17 years old in 2 primary care databases: IPCI (NL) and THIN (UK). Asthma was defined as ≥1 asthma disease code and ≥ 2 prescriptions of respiratory drugs in 1 year. Prescriptions were retrieved by ATC code from patient records. We used group-based trajectory analysis to model 4 trajectories of drug use of any asthma drug (ATC code R03) over age. Drug use was defined as ≥30 days covered by a prescription in a year. Patient characteristics at baseline were compared between trajectory groups using chi-square test.
Results: In total 24,276 children from the IPCI database and 138,734 children from the THIN databases were included. In both databases we found trajectories of 'late users' (22 and 20% of the patients in the THIN and IPCI database), 'late moderate users' (28 and 29%), 'early users' (26 and 20%) and 'early moderate users' (25 and 30%), with a median age of asthma onset 11, 13, 7 and 8 years, respectively. 'Early users' were significantly more often boys (65 and 63%, vs 41–49% in the two databases), had more often eczema (48 and 41% vs 25–44%) and gastro-oesophageal reflux disease (2 and 4% vs 1–3%) though less often rhinitis, depression or obesity compared to the other groups.
Conclusions: We found 4 different trajectories of asthma drug utilization in primary care databases. These groups had distinct patient characteristics, suggesting different asthma phenotypes by age of onset.

61 | Methylphenidate Treatment during Childhood Is Continued in Adulthood in Half of the Study Population

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Background: Until the beginning of 2018, methylphenidate was only approved in the Netherlands for children between 6 and 18 years old, because of the cardiovascular risk in adults. Despite the fact that it was not approved for use in adults, there was a considerable degree of off-label use in this group.
Objectives: To estimate the number of patients who started methylphenidate during childhood and continued treatment beyond the age of 18 and to study the determinants that may be associated with continuing treatment.
Methods: It is a nested case–control study in a cohort of methylphenidate users. The study population consisted of all patients with active follow-up during the study period between 1 January 1996 until 1 January 2017. Data were obtained from a longitudinal primary care database containing medical records from more than 450 general practitioners (GPs) throughout the Netherlands. Patients were included if they started methylphenidate before the age of 18 years and if they reached the age of 19 years (to guarantee at least 1 year of follow-up during adulthood) before the end date of the study. Potential determinants related to continued use of methylphenidate (sex, age, medication possession ratio (MPR), previous use of other psychostimulants and other psychotropic drugs and the presence of any potential contraindications). Cases were defined as users of methylphenidate who continued treatment beyond the age of 18 year, while controls were users who were treated with methylphenidate during childhood or adolescence but discontinued treatment before the age of 18 years. Logistic regression analyses were performed to assess the association between potential determinants and continuation with methylphenidate treatment after the age of 18 years.
Results: 53% of all methylphenidate users (n = 1,020) continued their treatment after the age of 18 years. Patients were more likely to continue treatment with methylphenidate if they started treatment at the age of 15 to 17 years than those starting at the age of 11 and younger (OR_{adj}: 5.84, 95%CI: 1.56–21.81), if they had a MPR between 0.80 and 1.00 compared to a lower MPR (OR_{adj}: 1.63, 95%CI: 1.04–2.54) or if they had a history of a psychiatric disorder (contraindication) (OR_{adj}:1.69, 95%CI: 1.24–2.30).
Conclusions: Methylphenidate treatment initiated during childhood was continued in half of the study population when reaching the age of 18. Adolescents were more likely to continue treatment than young children and patients with a history of a psychiatric disorder prior to methylphenidate initiation, were also more likely to continue treatment.

62 | Unintended Consequences of a National Policy Intervention to Curb Inappropriate Alprazolam Prescribing in Australia

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Background: Regulators and payers aim to promote evidence-based prescribing to reduce harm. Alprazolam, which is recommended for short-term use only, is subsidized on Australia's Pharmaceutical

Benefits Scheme (PBS) with prescribing requiring prior approval. In February 2017, the PBS de-listed 2 mg tablets, eliminated repeat prescriptions and listed a 10-tablet pack to curb long-term use.

Objectives: To quantify the impact of these changes on patterns of alprazolam prescribing and dispensing in naïve and previously-treated individuals.

Methods: Interrupted time series analysis and a retrospective cohort study of alprazolam-treated people using dispensings and prescribing approvals for a 10% sample of Australians (2014–2018). We used autoregressive regression to quantify changes in use over time, and logistic regression to compare patterns of use pre- and post-intervention.

Results: Overall, alprazolam prescribing approvals increased by 27.1% (95% CI 21.8 to 32.7%) yet dispensing rates fell by 25.2% (95% CI -30.3 to −19.8%). In the year post-intervention, 2976 people were dispensed alprazolam (63.6% female, median age 57 years), of which 20.9% were alprazolam-naïve in the 2 years prior to February 2017. Compared to people initiating pre-intervention, alprazolam-naïve people post-intervention were more likely to initiate according to subsidy restrictions with pack sizes ≤10 (20.8% vs 2.2%, adjusted Odds Ratio (aOR) = 11.85, 95% CI 7.65–18.36) and no second dispensing up to 180 days after initiation (28.4% vs 42.9%, aOR = 0.53, 95% CI 0.43–0.66). However, a subset of alprazolam-naïve people were also more likely to initiate on pack sizes >50 tablets post-intervention (23.3% vs 5.4%, aOR = 5.35, 95% CI 3.85–7.43). In people previously alprazolam-treated, post-intervention dispensings were more likely to be for >100 tablets (16.3% vs 4.2%, aOR = 4.63, 95% CI 3.85–5.57), less likely to be for ≤50 tablets (38.4% vs 72.3%, aOR = 0.24, 95% CI 0.22–0.26), and more likely to be for >100 mg (13.6% vs 10.8%, aOR = 1.37, 95% CI 1.17–1.60) compared to pre-intervention.

Conclusions: Alprazolam dispensing decreased post-intervention, but we observed two divergent effects on adherence to subsidy restrictions. Some patients were prescribed smaller pack sizes at initiation, but most were still receiving treatment outside restrictions, notably increased pack sizes to overcome the lack of repeats. While eliminating repeat prescriptions may facilitate increased monitoring of patients, it places a greater burden on prescribers and the health system, and for many may not reduce inappropriate long-term use.

63 | Prescribing Systemic Steroids for Acute Respiratory Tract Infections in US Outpatient Settings

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Background: Evidence and clinical guidelines do not support use of systemic steroids for acute respiratory tract infections (ARTIs), but such practice may be common in the US. Detailed utilization patterns and predictors of such practice have not been evaluated.

Objectives: To describe prescribing pattern of systemic steroids for ARTI and determine its predictors.

Methods: We used a large US national commercial claims database, the IBM MarketScan, to identify all patients aged 18–65 with an ARTI diagnosis (acute bronchitis, sinusitis, pharyngitis, otitis media, acute upper respiratory infections, allergic rhinitis, influenza, and pneumonia) recorded in an ambulatory visit from 2007 to 2016. We excluded those with systemic steroid use in the prior year and an extensive list of steroid-indicated conditions, including asthma, chronic obstructive pulmonary disease, and many autoimmune diseases. We estimated the proportion of the cohort receiving systemic steroids within 7 days of the ARTI diagnosis. We used multivariate logistic regression to assess the association between systemic steroid use and 55 factors, including patient demographics and an extensive list of co-morbidities.

Results: Among 11,192,974 patients with an eligible ARTI encounter, 11.6% were prescribed systemic steroids (45.8% parenteral, 47.6% oral, and 6.6% both). Among systemic steroid users with detailed medication information (53.7% of all users), 46.0% were prescribed prednisone equivalents <20 mg, 23.6% 20-39 mg, and 30.4% ≥40 mg. Most (84.4%) were prescribed a steroid prescription of 7 days or fewer, 15.1% 8–29 days, and 0.5% ≥30 days. All ARTI diagnoses but influenza were predictive of receiving systemic steroids. There was remarkable geographical variability: the adjusted odds ratio (aOR) of receiving parenteral steroids was 14.48 (95% confidence interval [CI]: 14.25–14.72) comparing southern vs northeastern US. The corresponding aOR was 1.67 (95% CI: 1.65–1.68) for oral steroids. After multivariate adjustment, other positive predictors for prescribing included emergency department (ED) or urgent care settings (vs. regular office), otolaryngologist/ED doctors (vs. primary care), fewer co-morbidities, and older patient age. There was an increasing trend from 2007 to 2016 (aOR 1.91 [95% CI: 1.90–1.93] comparing 2016 to 2007).

Conclusions: Systemic steroid use in ARTI is common with great geographical variability. These findings call for an effective national education program about this non-evidence based practice.

64 | Characteristics of Febuxostat and Allopurinol Initiators and Utilization Patterns in Real-World Settings

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Background: The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout (CARES) trial reported an increase in cardiovascular and all-cause mortality in febuxostat users compared to allopurinol users. The CARES trial included a population enriched for cardiovascular disease (CVD), raising concerns about the generalizability of the findings to users of urate-lowering therapies (ULT) in real-world settings.

Objectives: To determine if patients and utilization of ULTs in the CARES trial reflect the gout population and ULT utilization in real-world settings.

Methods: A retrospective cohort study was conducted among patients with a new diagnosis of gout in the Sentinel Distributed Database (SDD), from January 1, 2009 to September 30, 2016. New initiators of ULT (febuxostat, allopurinol, pegloticase and probenecid) were identified. Characteristics of new initiators and the cumulative duration and switching patterns for febuxostat and allopurinol use were examined. Findings from SDD were compared to the CARES population.

Results: Allopurinol was the most commonly initiated ULT (*n* = 1,049,462) in SDD and febuxostat use was comparatively rare (*n* = 80,083). ULT users in CARES were younger than in SDD, with only 48.9% febuxostat and 51.3% allopurinol users aged 65+, compared to 66.0% and 64.2% in SDD, respectively. There were more male ULT users in CARES, with 84.1% and 83.8% in the febuxostat and allopurinol arms, respectively, compared to 62.6% and 65.1% in SDD. As expected, patients in the CARES trial had more CVD and chronic kidney disease (CKD). Although the prevalence of CVD indicators was lower in SDD, distributions were similar between ULT initiators. For example; 38.6% and 39.8% of febuxostat and allopurinol users, respectively, in CARES had a history of myocardial infarction, compared to 1.5% of each in SDD. ULT users in CARES had more severe gout than those in SDD, indicated by tophi in 21.6% and 21.0% of febuxostat and allopurinol users, compared to 14.8% and 8.6% in SDD. Median duration of ULT use was longer among febuxostat and allopurinol users in CARES at 728 days and 719 days, respectively, compared to 210 days and 334 days in SDD. The proportion of ULT initiators in SDD that switched between ULTs during follow-up was low (generally <10%) and the largest proportion of switches occurred from allopurinol 100 mg to 300 mg.

Conclusions: Compared to users in real-world settings, ULT users in CARES were younger, more adherent to ULTs, more likely to be male, had more severe gout and had a higher prevalence of both CVD and CKD. These differences need to be considered in interpreting the results of the CARES study.

65 | Analysis of Sodium-Glucose-Cotransporter-2 Inhibitor Use in Patients with Type-1 Diabetes Mellitus and Rates of Diabetic Ketoacidosis

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Background: Sotagliflozin is the first sodium-glucose cotransporter-2 inhibitor (SGLT2i) seeking approval for type-1 diabetes mellitus (T1DM). Preapproval clinical trials detected increased rates of diabetic ketoacidosis (DKA), compared with placebo.

Objectives: To estimate real-world off-label utilization of approved SGLT2i (only indicated for T2DM) in patients with T1DM, estimate rates of DKA, and compare observed and expected counts of DKA during off-label use of approved SGLT2i in patients with T1DM, based on DKA rates observed in sotagliflozin clinical trials.

Methods: Using claims data from 17 Sentinel System Data Partners (3/2013–6/2018), we identified new users of canagliflozin, empagliflozin, and dapagliflozin with T1DM-broad (> 50% of DM diagnosis codes during days [−365, −5] relative to index dispensing were specific to T1DM) or T1DM-narrow (T1DM-broad with ≥1 prescription for short- or rapid-acting insulin and no oral antidiabetic drug dispensing other than metformin). DKA was identified using inpatient and emergency department claims. Standardized incidence ratios (SIRs) were calculated using age- and sex-specific follow-up time in Sentinel and pooled age- and sex-specific DKA rates from sotagliflozin trials 309, 310, and 312.

Results: Among 475,527 initiators of SGLT2i, 0.92% met criteria for T1DM-broad and 0.50% met criteria for T1DM-narrow across all age categories. Patients with T1DM-broad comprised 11.3%, 7.28%, 1.84%, 0.90%, and 0.68% of SGLT2i initiators ages 12–18, 19–24, 25–44, 45–64, and ≥ 65 years, respectively. Rates of DKA were 7.3 per 100 person-years among T1DM-narrow patients and 4.5 per 100-person-years among T1DM-broad patients using SGLT2i, across all age categories. Rates of DKA were highest among T1DM-narrow patients age 25–44, especially females age 25–44, who had a DKA rate 19.7 per 100 person-years. More DKA events were observed in T1DM-narrow patients during off-label use of approved SGLT2i in Sentinel than would be expected based on sotagliflozin clinical trials (SIR = 1.83; 95% CI, 1.45–2.28). The SIR was 2.57 among patients ages 25–44 and decreased with increasing age.

Conclusions: Real-world off-label use of SGLT2i in patients with T1DM was relatively rare in the overall study population but more frequent in younger patients. The risk for DKA during off-label use was notable, especially among patients under the age of 45. Although real-word rates of DKA exceeded the expectation based on clinical trials, results should be interpreted with caution due to differences in study methods, patient samples, and study drugs.

66 | Clinical Outcomes in Patients with Type 2 Diabetes Newly Initiating SGLT2 or DPP4 Inhibitors

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Background: Real world evidence on comparative effectiveness of sodium-glucose co-transporter 2 inhibitors (SGLT2i) is limited to cardiovascular outcomes. Other clinical outcomes indicating adequacy of glycemic control have not yet been assessed.

Objectives: To determine the time to diabetes-related hospitalization and to treatment intensification following initiation of SGLT2i relative to dipeptidyl peptidase-4 inhibitors (DPP4i).

Methods: We conducted a retrospective cohort study using the de-identified Optum® Clinformatics® Data Mart (2000–2017) database.

Patients with Type 2 Diabetes aged 18 years or older newly initiating SGLT2i or DPP4i between April 2013 and May 2017 were included in the cohort. Patients were required to have continuous enrollment during a 365-day baseline period and those with prior insulin use or renal impairment were excluded. Outcomes were hospitalization for diabetes-related complications and treatment intensification. Treatment intensification was defined as addition of insulin to index medication. Patients were matched 1:1 on propensity score and followed from the date of first dispensing of SGLT2i or DPP4i until the earliest occurrence of outcomes, treatment discontinuation, death, disenrollment, or end of data (December 2017). Cox Proportional Hazards models were used to estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI).

Results: There were 130,486 patients that met our selection criteria. After 1:1 propensity score matching, there were 32,646 comparable patients in each treatment group. The average age in the matched cohort was 56.8 (±12) years; 44% were female; 42.8% had at least 1 complication of diabetes. Patients were followed for a median 192 (64–399) days over which 1.3% were hospitalized for diabetes and 3.8% intensified treatment. The median time to a diabetes-related hospitalization was 181 (65–405) days overall and 169 (64–374) in those initiating SGLT2i vs. 187 (67–413) in those initiating DPP4i. The median time to treatment intensification was 124 (41–297) days overall and 116 (36–297) in those initiating SGLT2i vs. 127 (44–297) in those initiating DPP4i. Initiation of treatment with SGLT2i was associated with a 22% decrease in risk of diabetes-related hospitalization (HR: 0.78 [0.68–0.90]) and a 38% decreased risk of treatment intensification (HR: 0.61 [0.57–0.67]) relative to DPP4i.

Conclusions: Initiation of treatment with SGLT2i was associated with better clinical outcomes relative to DPP4i in this large cohort of commercially insured adults with Type 2 Diabetes in the United States.

67 | Incidence Rate of Fournier's Gangrene in Type-2 Diabetic Patients Using Second-Line Anti-Diabetic Drugs

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Background: On August 29, 2018, the FDA issued a warning that cases of a rare but serious infection called Fournier's gangrene (FG) have been reported with sodium-glucose cotransporter-2 inhibitors (SGLT-2i).

Objectives: To evaluate the safety signal in longitudinal claims data in a population of patients with type 2 diabetes mellitus (T2D).

Methods: We used administrative claims data from Horizon Blue Cross Blue Shield of New Jersey from 2014 through 2017 to estimate incidence rates of FG (ICD-9 code of 608.4 or ICD-10 of N49.3) or necrotizing fasciitis of the perineum (NF, ICD-9: 728.86 or ICD-10: M72.6) among patients treated with a second-line antidiabetic drug (SGLT-2i, DPP4i, GLP-1 and Sulfonylureas [SU]). We used the combined endpoint (FG or NF) due to our sample size and very low incident rate of FG. Patients were censored at time of switch therapy. For the comparative analysis, we restricted cohorts to new users (no exposure in the prior 180 days) and conducted four pairwise comparisons (SGLT-2i vs. DPP4i; SGLT-2i vs. GLP-1; SGLT-2i vs. SU; SGLT-2i vs all other). Potential confounders (baseline UTI, hospitalization for bacterial infections, prior immune-modulating or -suppressing drug use, HIV, obesity, and others) were balanced using 1:1 propensity score (PS) matching. Analyses were performed using the Aetion Evidence Platform, version 3.0.

Results: We identified 68,004 patients receiving second-line antidiabetic medication. The incidence rate per 1,000 person-years (95% CI) for FG or NF among SGLT-2is, DPP-4i, GLP-1, and SU users were 0.77 (0.25–1.79), 0.87 (0.44–1.29), 0.98 (0.12–3.56), and 1.21 (0.80–1.61), respectively. The unadjusted rate ratios of FG or NF in patients initiating SGLT-2i compared to DPP-4i, GLP-1, and SU were 0.88 (0.38–2.05), 0.78 (0.15–4.01), and 0.63 (0.25–1.62), respectively. In the PS-matched comparative analyses, the rate ratios (95% CI) for FG or NF in SGLT-2i users compared to DPP-4i and GLP-1 users were 0.89 (0.13–6.34) and 1.42 (0.13,15.7), respectively. There were no events among SU users after PS-matching.

Conclusions: In a population-based analysis of T2D patients using claims data, we found very low incidence rates of FG or NF. We found no indication of an increased risk among SGLT-2i users compared to similar patients treated with other second-line antidiabetic medications. However, the small number of events yielded wide confidence intervals that cannot rule out a six-fold increase.

68 | SGLT-2 Inhibitors and the Risk of Community-Acquired Pneumonia in Patients with Type-2 Diabetes

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Background: Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of antidiabetic drugs whose use has increased dramatically since their entry into the market. However, the US Food and Drug Administration announced labeling changes related to infections associated with their use, possibly due bacterial proliferation. It is possible that SGLT-2 inhibitors may act on receptors in the lung, possibly leading to respiratory infections such as community-acquired pneumonia (CAP). In contrast, the DECLARE-TIMI trial found a smaller number of bronchitis events with the SGLT-2 inhibitor dapagliflozin than with placebo, suggesting a possible protective effect on respiratory infections. To our knowledge, the risk of CAP with SGLT-2 inhibitors has not been investigated previously in a real-world setting.

Objectives: To compare the rate of CAP among patients with type 2 diabetes prescribed SGLT-2 inhibitors compared to that in patients prescribed dipeptidyl peptidase-4 (DPP-4) inhibitors.

Methods: We used data from the United Kingdom's Clinical Practice Research Datalink linked to Hospital Episodes Statistics hospitalization data and Office for National Statistics vital statistics data. Patients entered the study cohort upon a prescription for a new antidiabetic drug between 2013 (the year SGLT-2 inhibitors entered the market) and 2018. Patients were excluded if they were aged less than 18 years, had a diagnosis of CAP or were hospitalized in the 30 days prior to cohort entry or had cancer any time before cohort entry. Current exposure was modeled using a time-varying approach and defined by the prescription duration + a 30-day grace period. The primary endpoint was incident CAP, defined by an inpatient or outpatient diagnosis. We used time-dependent Cox proportional hazards models to compare the rate of CAP with current use of SGLT-2 inhibitors versus current use of DPP-4 inhibitors.

Results: A total of 30,237 patients entered the study cohort. In all, 728 CAP events were observed over an average follow-up duration of 1.8 years (SD: 1.2), representing an overall event rate of 13.7 (95% confidence interval [CI]:12.7–14.7) per 1,000 person-years. Incidence rates for SGLT-2 and DPP-4 inhibitor users were 5.8 (95% CI: 3.5–9.6) and 17.6 (95% CI: 15.2–20.5) per 1000 person-years, respectively. After adjustment, current use of SGLT-2 inhibitors was associated with a decreased rate of CAP compared to current use of DPP-4 inhibitors (hazard ratio: 0.54, 95% CI: 0.32, 0.93).

Conclusions: Use of SGLT-2 inhibitors is associated with a decreased risk of CAP compared to use of DPP-4 inhibitors in patients with type 2 diabetes.

69 | Risk of Inflammatory Bowel Disease with Sodium Glucose Co-Transporter-2 Inhibitors Compared to Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes

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Background: Recent reports to the Food and Drug Administration Adverse Event Reporting System suggested a higher risk of inflammatory bowel disease (IBD) with sodium glucose co-transporter-2 inhibitors (SGLT2-i) but the risk remains uncertain.

Objectives: We aimed to assess the risk of IBD with SGLT2-i compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) among patients with type 2 diabetes.

Methods: A retrospective cohort analysis using Truven Health Commercial and Medicare Supplemental database was conducted among patients with a diagnosis of type 2 diabetes (ICD-9: 250.x0 or 250.x2) between January 2014 and December 2017. New-users of SGLT2-i or DPP-4i who had no prior use for at least twelve months prior to treatment initiation (index-date) were included. Patients with a diagnosis of type 1 diabetes or end-stage renal during the pre-index period were excluded. The risk of IBD was compared between SGLT2-i and DPP-4i. Follow-up continued until the first occurrence of IBD, end of enrollment, switch to the comparator, or end of study period. Cox-proportional hazard model after propensity score matching (PSM) was used to obtain hazard ratios (HR) and 95% confidence intervals (CI). Heterogeneity of treatment effect was examined in selected subgroups including patients with baseline chronic kidney disease (CKD).

Results: A total of 103,917 new-users of SGLT2-i (mean age, 54 years, 54% male, 2% CKD) and 103,916 new-users of DPP-4i (mean age 54 years, 53% male, 2% CKD) were identified. Incidence rates of IBD were 6 and 5 per 1000 person-years in the SGLT2-i and the DPP-4i groups, respectively. After PSM, a 10% increased risk of IBD was observed with SGLT2-i compared to DPP-4i (HR, 1.10; 95% CI, 1.01, 1.21). Subgroup analysis found no statistically significant difference in the risk of IBD between SGLT2-i and DPP-4i in patients with CKD (HR, 1.28; 95% CI, 0.73, 2.23).

Conclusions: In this population-based analysis, SGLT2-I use was associated with a modestly higher risk of IBD compared to DPP-4i use. We found no evidence of heterogeneity among the small number of patients with prior CKD.

70 | Sodium-Glucose Co-Transporter 2 Inhibitors and the Risk of Venous Thromboembolism in Patients with Type 2 Diabetes: A Cohort Study

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Background: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) induce glycosuria and diuresis and are known to increase hematocrit values. Thus, there are concerns that their use could be associated with a higher risk of venous thromboembolism (VTE).

Objectives: To assess the risk of VTE associated with use of SGLT2i compared with use of dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with type 2 diabetes in Germany.

Methods: We used the InGef database to conduct a cohort study with nested case–control analysis in new users of non-insulin antidiabetic drugs with type 2 diabetes between 12 November 2012 (date of first SGLT2i launch) and 30 June 2018. VTE cases were selected based on ambulatory diagnoses in combination with prescriptions of oral anticoagulants or hospital discharge diagnoses. For each case, up to 40 controls were randomly selected using risk-set sampling. We applied conditional logistic regression to estimate confounder adjusted odds ratios (OR) with 95% confidence intervals (CI) of VTE comparing current use of SGLT2i (alone or in combination with other antidiabetic drugs, but not DPP4i) and current use of DPP4i (alone or in

combination with other antidiabetic drugs, but not SGLT2i). In secondary analyses, we stratified by individual SGLT2i, age, sex, VTE history and use of loop diuretics. In sensitivity analyses we excluded patients with cancer and used current use of glucagon-like peptide-1 receptor agonists (GLP1ra) instead of DPP4i as reference.

Results: The cohort comprised 219,538 new users of non-insulin antidiabetic drugs with a mean age of 62.9 years (40% females). The crude incidence rate of VTE was 3.7 cases per 1,000 person-years. For the nested case–control analysis, 2,152 VTE cases were matched to 85,104 controls. Overall, no increased risk of VTE was observed when comparing current use of SGLT2i to DPP4i in the crude analysis (OR: 0.70; 95% CI: 0.56–0.88) and confounder adjusted analysis (OR: 0.75; 95% CI: 0.59–0.94). Similar results were found for current use of individual SGLT2i, (dapagliflozin OR: 0.77; 95% CI: 0.57–1.03/empagliflozin OR: 0.71; 95% CI: 0.52–0.98), and no effect modification was observed in the other secondary analyses. In addition, no increased risk of VTE was found after excluding cancer patients (OR: 0.74; 95% CI: 0.58–0.95) or when comparing current use of SGLT2i to GLP1ra (OR: 0.83; 95% CI: 0.60–1.14).

Conclusions: Our study suggests that SGLT2i are not associated with an increased risk of VTE compared to DPP4i in patients with type 2 diabetes. The observed protective effects for SGLT2i require further evaluation.

71 | Association of Aripiprazole with the Risk of Psychiatric Hospitalization, Self-Harm, or Suicide

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Background: Aripiprazole is a frequently used antipsychotic because of its reduced metabolic side effects. However, concerns have emerged regarding a potential psychiatric worsening associated with first-time use of aripiprazole in patients already treated with other antipsychotic drugs.

Objectives: To assess whether switching to or adding aripiprazole is associated with serious psychiatric worsening compared with switching to or adding another antipsychotic drug in patients previously exposed to antipsychotic médications.

Methods: This population-based cohort study was conducted using the United Kingdom Clinical Practice Research Datalink. Within a base cohort of new users of antipsychotic drugs between 2000 and 2015, we identified a study cohort of all patients prescribed aripiprazole or another oral antipsychotic drug (switch or add-on to the previously used antipsychotic) on or after January 1, 2005 (the year aripiprazole was licensed in the UK). Each patient starting aripiprazole was matched 1:1 to a patient starting another antipsychotic on calendar year of cohort entry, time since first antipsychotic prescription, psychiatric disease history (schizophrenia, bipolar disorder, depression, other psychiatric diseases, unknown), age and time-conditional propensity score. Patients were considered exposed to the antipsychotic prescribed at study cohort entry until the end of follow-up (maximum one year). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of serious psychiatric worsening (a composite of psychiatric hospitalizations, self-harm, or suicide) associated with switching to or adding aripiprazole compared with other antipsychotic drugs.

Results: The cohort included 1,643 patients starting aripiprazole propensity-matched to 1,643 patients starting another antipsychotic. During 2,692 person-years of follow-up, 391 incident serious events of psychiatric worsening occurred, with a crude incidence rate of 14.52 (95% CI 13.16–16.04) per 100 person-years. First-time use of aripiprazole was not associated with an increased rate of psychiatric treatment failure (HR 0.87; 95% CI 0.71–1.06), psychiatric hospitalizations (HR 0.85; 95% CI 0.69–1.06), or self-harm/suicide (HR 0.96; 95% CI 0.68–1.36) compared with starting another antipsychotic drug. Results were consistent across several sensitivity analyses.

Conclusions: Compared with other antipsychotics, initiating aripiprazole use, after a previous antipsychotic exposure was not associated serious psychiatric worsening.

72 | Changes in the Population Characteristics of U.S. Youth Receiving Psychotropic Polypharmacy: 1996 to 2016

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Background: Novel therapies, such as selective serotonin reuptake inhibitors and second generation antipsychotics, had rapid uptake in youth. This contributed to the rise of psychotropic polypharmacy among US youth over the past 20 years. Few studies have investigated if the demographic and clinical characteristics of youth who receive psychotropic polypharmacy have changed over time.

Objectives: To determine the associations between the growth in psychotropic polypharmacy over the past 21 years among US youth and a) changes in psychiatric diagnoses, b) change in the severity of mental health impairment, and c) expansion in prescribing to very young children and females.

Methods: The 1996–2016 Medical Expenditure Panel Survey was used to identify youth ≤18 years old who received psychotropic polypharmacy, defined as ≥3 psychotropic classes reported in at least one interview in a year. The 21-years were divided into three periods: before (1996–2004), during (2005–2010), and after (2011–2016) the emergence of novel therapies. The dependent variables were binary measures of a) <5 years old; b) female; c) psychiatric diagnosis: mood disorder (bipolar disorder or depression), attention-deficit/hyperactivity disorder, schizophrenia/psychoses, anxiety; and d) severe mental health impairment, defined as a Columbia Impairment Scale total score ≥ 16. Survey weights generated nationally representative estimates and 95% confidence intervals. Logistic regression models estimated the trend in change across periods for each dependent variable.
Results: The total number of youth reporting psychotropic polypharmacy increased from 109,381 in 1996–2004 to 292,110 in 2011–2016. Psychotropic polypharmacy for youth <5 years old was not reported until 2011–2016 (1.1%). Females, as a proportion of youth with psychotropic polypharmacy, increased from 30% (95%CI = 19.4, 40.5) in 1996–2004 to 38% (95%CI = 25.8, 49.2) in 2011–2016, but this trend was not significant [OR: 1.03 (95%CI = 1.00, 1.08)]. The trend for mood disorders as a proportion of youth with psychotropic polypharmacy was significant [OR: 1.13 (95%CI = 1.04, 1.22)], increasing from 9% (95%CI = 2.9, 15.8) to 49% (95%CI = 40.5, 57.7) to 60% (95%CI = 50.0, 69.3), in each respective period. The proportion with severe mental health impairment increased from 73% (95%CI = 64.5, 82.1) in 1996–2004; 72% (95%CI = 63.1, 80.3) in 2005–2010; and 84% (95%CI = 76.5, 91.6) in 2011–2016. This trend was significant [OR: 1.04 (95%CI = 1.01, 1.08)].
Conclusions: Growth in psychotropic polypharmacy among US youth was associated with mood disorders and severe mental health impairment.

73 | Trends in Antipsychotic-Related Polypharmacy among U.S. Youth from 1996 to 2016

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Background: Antipsychotics are often prescribed to youth concomitantly with other psychotropics, despite the concerns over the metabolic side effects of second generation antipsychotics. While a few reports of single US state experiences show less antipsychotic use in recent years, it is unclear if antipsychotic-related polypharmacy has decreased nationally in light of the safety concerns.
Objectives: To evaluate 21-year trends in antipsychotic-related polypharmacy among US youth.
Methods: The 21-year trend in antipsychotic use was derived from the 1996–2016 Medical Expenditure Panel Survey. Psychotropic use was based on reported use in at least one interview in the year. We identified three mutually exclusive antipsychotic user groups, a) antipsychotic-related polypharmacy (≥3 concomitant psychotropic classes, of which one was an antipsychotic), b) dual-therapy (antipsychotic with one other psychotropic) and c) monotherapy (sole use of an antipsychotic). We collapsed years into three periods: 1996–2004 (emergence of SGAs); 2005–2010 (emergence of safety concerns); 2011–2016 (post-safety warnings). We estimated the population prevalence among all youth ≤18 years old and changes of prevalence across periods for each antipsychotic user group. We used survey weights to derive nationally representative estimates and 95% confidence intervals, and linear regression to estimate the annual prevalence change within each period.
Results: Antipsychotic-related polypharmacy prevalence overall increased from 0.05% (95%CI = 0.03, 0.07) to 0.20% (95%CI = 0.15, 0.25) to 0.29% (95%CI = 0.14, 0.42) in 1996–2004, 2005–2010, and 2011–2016, respectively. Antipsychotic dual-therapy increased from 0.07% (95%CI = 0.05, 0.09) to 0.27% (95%CI = 0.21, 0.33) to 0.32% (95%CI = 0.24, 0.41) in each respective period. The overall prevalence of antipsychotic monotherapy increased from 0.01% (95%CI = 0.00, 0.02) to 0.06% (95%CI = 0.02, 0.09) to 0.19% (95%CI = 0.16, 0.52) in each respective period. Within the 1996–2004 period, antipsychotic-related polypharmacy increased 0.02% (95%CI = 0.01, 0.03) per year, antipsychotic dual-therapy 0.03% (95%CI = 0.01, 0.05) per year, and antipsychotic monotherapy 0.005% (95%CI = 0.00, 0.01) per year. Prevalence change plateaued for all groups in 2005–2010. Antipsychotic monotherapy prevalence revealed a significant increase within the 2011–2016 period: 0.03% (95%CI = 0.01, 0.05) per year.
Conclusions: Antipsychotic monotherapy continued to increase over time at faster rate than antipsychotic-related polypharmacy.

74 | Off-Label Use of Antipsychotics among US Commercially-Insured Youth

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Background: In the US, antipsychotics are FDA approved in youth for bipolar disorder, schizophrenia, and autism. All other use is considered off-label. Recent evidence shows that off-label antipsychotic use has increased among youth with attention-deficit/hyperactivity disorder (ADHD). It is unclear if antipsychotics are used more often in youth with ADHD who have comorbid disruptive behavior disorders (DBD).
Objectives: The goal of this study was to assess the prevalence of concomitant antipsychotic + stimulant use among US youth with ADHD, with and without a comorbid DBD.
Methods: IQVIA™ PharMetrics Plus adjudicated claims were used to identify US commercially-insured youth ≤18 years-old who were diagnosed with ADHD anytime between 2007 and 2015 (n = 169,433). Youth with an FDA antipsychotic indicated condition were excluded. We created four comorbidity subgroups: a) ADHD only, b) ADHD+DBD only (i.e. conduct disorder, oppositional defiant disorder, and impulse disorder), c) ADHD+other disorders (i.e.

depression, anxiety, adjustment disorder, and PTSD), and d) ADHD +DBD + other disorders. The primary outcome was the use of a regimen including an antipsychotic + stimulant or all other use. Descriptive analysis estimated the cross-sectional, annual prevalence of antipsychotic + stimulant use from 2007 to 2015, overall and within each comorbidity subgroup. Generalized estimating equations (GEE), for repeated measures, estimated the odds of antipsychotic + stimulant use in 2015 versus 2007 and across each subgroup. We also tested the interaction between comorbidity subgroup and year.

Results: The overall prevalence of antipsychotic + stimulant decreased from 3.5% in 2007 to 2.3% in 2015 (OR = 0.89; 95%CI = 0.81–0.99). Relative to 2007, antipsychotic + stimulant use in 2015 significantly decreased in youth with ADHD only (OR = 0.63; 95%CI = 0.56–0.72) and ADHD+DBD + other disorders (OR = 0.73; 95%CI = 0.53–0.99). Antipsychotic + stimulant use among youth with ADHD+DBD only and ADHD+other disorders did not change significantly in 2015 versus 2007. When comparing comorbidity subgroup, the odds of antipsychotic + stimulant use was significantly lower in youth with ADHD only (OR = 0.26; 95%CI = 0.24–0.29), ADHD+DBD only (OR = 0.76; 95%CI = 0.68–0.85), and ADHD+other disorders (OR = 0.50; 95%CI = 0.45–0.55) compared to youth with ADHD +DBD + other disorders. The interaction between comorbidity subgroup and year was not statistically significant.

Conclusions: Among youth with ADHD, off-labeled antipsychotic use is more likely among youth with complex comorbidities. Antipsychotic + stimulant use has decreased among youth with ADHD only.

75 | Risk of Psychosis with Amphetamine versus Methylphenidate in Attention Deficit Hyperactivity Disorder

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Background: The use of prescription stimulants amphetamine and methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) is increasing. In 2007, the US Food and Drug Administration mandated changes to stimulant prescribing labels based on findings of new-onset psychosis in patients without pre-existing disease. Although these changes were mandated over 10 years ago, there has been no systematic study of the comparative risk of psychosis between amphetamine and methylphenidate.

Objectives: We sought to compare the risk of psychosis in adolescents and young adults with ADHD who are new users of amphetamine versus methylphenidate.

Methods: This is a cohort study of patients 13–25 years old with an outpatient diagnosis of ADHD from two commercial insurance claims databases (Optum Clinformatics and IBM Marketscan) who started taking amphetamine or methylphenidate between January 1, 2004 and September 30, 2015. The outcome was a diagnosis of psychosis requiring treatment with an antipsychotic medication within 60 days of initial psychosis diagnosis. We used 1:1 propensity score (PS) matching to match patients on a set of 50 covariates measuring ADHD severity, psychiatric comorbidity, psychotropic medication use, substance use and healthcare utilization. For the pre-specified primary analysis, we estimated hazard ratios (HR) in PS-matched patients and then pooled results across the two databases using fixed effects meta-analysis.

Results: A total of 221,846 participants in the propensity score matched subsets with 143,286 person-years of follow-up experienced 343 psychotic events (2.4 per 1,000 person-years). Use of amphetamine tripled over the study period with preferential prescribing of amphetamine to older patients. The majority of patients were prescribed stimulants by family/internal medicine physicians, who had the highest prescribing rates of amphetamine (72.5%) compared to pediatricians (51.6%) and psychiatrists (63.7%). Use of amphetamine was associated with an increased risk of psychosis based on 237 psychotic events in amphetamine users and 106 psychotic events in methylphenidate users (HR 1.65, 95% CI 1.31 to 2.09).

Conclusions: Amphetamine use is associated with an increased risk of treatment-emergent psychosis compared to methylphenidate among adolescents and young adults with ADHD.

76 | The Occurrence of Suicide-Related Outcomes among Patients Initiating Tegaserod in Routine Clinical Practice

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Background: Irritable bowel syndrome with constipation (IBS-c), while not life-threatening, is a painful condition that is associated with anxiety, depression and suicidal ideation. Tegaserod is a 5-HT_4 serotonin receptor agonist that relieves IBS-c by increasing gastrointestinal motility. Approved in 2002 for treatment of IBS-c, an indication that was later expanded to include chronic idiopathic constipation. Tegaserod was withdrawn from the US market in 2007, although a recent FDA advisory committee voted in favor of resuming marketing of tegaserod.

Objectives: The objective of this study was to assess the effect of tegaserod initiation on the occurrence of suicide-related outcomes.

Methods: This cohort study identified tegaserod initiators from 2002 through 2006 within the Optum Research Database (ORD), a commercial US health insurance claims database. These tegaserod initiators were matched to a contemporaneous cohort of patients who had similar patterns of healthcare services but who did not initiate tegaserod. Matching was on the basis of propensity scores that incorporated over 200 characteristics associated with tegaserod initiation. Suicide-related outcomes (self-injury and death) were identified by ICD-9 codes for self-injury along with all-cause and cause-specific mortality. Follow-up for outcomes included screening for claims codes along

with review of medical records to confirm outcomes. Members of each cohort were followed for up to 6 months from cohort entry for the occurrence of an outcome or censoring.

Results: There were 52,229 tegaserod initiators and 52,229 comparators, and the mean follow-up was 5.1 months. There were 25 claims-based self-injury events among the tegaserod initiators and 34 among the comparators (HR = 0.74, 95% CI 0.44–1.25). There were 83 deaths among the tegaserod initiators and 72 among the comparators (HR = 1.01, 95% CI 0.73–1.39). Additionally, there were 13 potential self-injury events during current use of tegaserod and 33 during non-use time (RR = 0.81, 95% CI 0.42–1.53). There were 38 potential deaths during current tegaserod use and 72 during non-use (RR = 1.14, 95% CI 0.77–1.68). Medical record confirmation (available for 85% of initiators and 84% of non-users) were largely consistent with the claims-based analysis and suggest that there is no increased risk of suicide-related outcomes among the tegaserod initiators.

Conclusions: Suicidal ideation may be a consequence of IBS-c and may be influenced by medications used for treatment. This study suggests that tegaserod does not increase the risk of suicide or self-injury.

77 | Cholesterol-Lowering Medication and Breast Cancer Recurrence in Postmenopausal Women Treated with Adjuvant Aromatase Inhibitors: A Danish Population-Based Cohort Study

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Background: Observational studies suggest that cholesterol-lowering medication (CLM) use is associated with longer recurrence-free survival in breast cancer patients. Since 2007, aromatase inhibitors (AIs) have been guideline treatment for estrogen receptor positive (ER+) postmenopausal breast cancer. AI therapy is associated with increased cholesterol levels.

Objectives: To investigate the association of CLM use and breast cancer recurrence rate in patients treated with AIs.

Methods: We included a cohort of all postmenopausal women diagnosed with stage I-III ER+ breast cancer from 2007–2016, treated with AI in the adjuvant setting, and registered in the Danish Breast Cancer Group database and Danish Cancer Registry. We ascertained incident CLM exposure (≥1 prescription post-diagnosis) from the Danish National Prescription Registry and modeled CLM as a time-varying exposure lagged by 6 months. Follow-up began 6 months after diagnosis and continued to the first event of recurrence, death, emigration, 5 years, (and 10 years in overall follow-up), or 25th September 2018. We estimated incidence rates (IR) of recurrence at 5 years and overall, and used Cox regression models to compute crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI), comparing CLM exposure with non-exposure.

Results: We enrolled 12,947 eligible patients. Median follow-up was 4.6 years. During the first 5 years, there were 35 recurrences in 3,290 person-years of follow-up for CLM exposed, and 525 recurrences in 46,590 in the unexposed group (IR per 1000 person-years: 10.64 [95% CI: 7.41–14.80] and 11.27 [95% CI:10.33–12.28], respectively). Overall, there were 646 recurrences in 56,171 total person-years in the unexposed group and 64 recurrences in 5,246 total person-years of follow-up in the CLM exposed group (IR per 1,000 person years: 11.50 [95% CI: 10.63–12.42] and 12.20 [95% CI: 9.40–15.58], respectively). There was some evidence of a reduced risk of recurrence associated with CLM exposure during the first 5 years of follow-up (adjusted HR: 0.76 [95% CI: 0.52–1.12], but this was not evident during overall follow-up (adjusted HR: 0.90 [95% CI: 0.68–1.20].

Conclusions: CLM use was not associated with a substantially reduced risk of breast cancer recurrence among AI users.

78 | Association between Hydrochlorothiazide Exposure and Skin, Lip and Oral Cancer: A Series of Population-Based Nested Case–Control Studies

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Background: Hydrochlorothiazide (HCTZ) exposure has been associated with non-melanoma skin cancer in recent studies from Denmark. The proposed mechanism is photosensitivity increasing the risk of skin cancer from UV exposure.

Objectives: The aim of the studies presented in this report was to attempt to replicate these associations in a different population and data source, and to assess the impact of adjusting for missing confounders of smoking and body mass index (BMI).

Methods: The UK THIN database was used to perform five nested case control studies assessing the association between HCTZ exposure and squamous cell carcinoma, basal cell carcinoma, melanoma, lip cancer and oral cancer matching up to 20 controls using risk set sampling. Oral cancer was included as a negative control outcome. The exposures analyzed included ever use and cumulative use of HCTZ stratified into dose categories as per the original studies. Further adjustment for smoking status and BMI was undertaking following multiple imputation of missing data values.

Results: The crude incidence of each outcome in the adult population per 100,000 person years was: 1.1 for lip cancer; 11.7 for squamous cell carcinoma; 137.5 for basal cell carcinoma; 17.9 for melanoma; and 5.7 for oral cancer. An increased relative incidence of lip cancer was observed for high-dose cumulative HCTZ exposure but this was not statistically-significant in standard analysis (IRR 2.23, 95%CI 0.54–9.16). When the lag-time for HCTZ exposure was increased

from 2 to 5 years, a statistically significant association with lip cancer was observed (IRR 2.85, 95%CI 1.32–6.15). Statistically significant associations were observed with high-dose cumulative HCTZ exposure for squamous cell carcinoma (IRR 2.93, 95%CI 1.85–4.62) and basal cell carcinoma (IRR 1.30, 95%CI 1.03–1.65) but not melanoma (IRR 0.90, 95%CI 0.33–2.45). No association was observed with HCTZ exposure and oral cancer (IRR 0.84, 95%CI 0.56–1.26). The associations following adjustment for smoking and BMI were similar to the main results.

Conclusions: Statistically significant associations with high-dose cumulative hydrochlorothiazide exposure and non-melanoma skin cancer and lip cancer were replicated in a UK population and data source. Adjustment for smoking and BMI did not material change the size of the observed associations.

79 | Voriconazole and Cutaneous Squamous Cell Carcinoma Risk among Lung Transplant Recipients

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Background: Solid organ transplant recipients have greatly elevated risk of cutaneous squamous cell carcinoma (SCC), an aggressive skin cancer. Voriconazole (vori) is used to prevent and treat invasive aspergillosis in lung transplant recipients. It can cause phototoxicity and has been associated with increased SCC risk in modestly sized studies.

Objectives: Investigate the association between voriconazole (vori) use and cutaneous SCC among lung recipients.

Methods: The Scientific Registry of Transplant Recipients (SRTR) was used to identify White lung recipients in the US (2008–2016). Pharmacy claims for immunosuppressants and antifungals (vori, itraconazole [itra], posaconazole [posa], other) were linked from a nationwide claims data warehouse. SCC was ascertained from the SRTR. Follow-up began at transplantation and ended at the earliest of SCC, transplant failure/retransplant, death, loss to follow-up or 12/31/2016. Person-time was divided into 30-day intervals, with medication exposure assessed at the start of each interval. We excluded all persons missing >25% of immunosuppressant interval coverage. Intervals lacking an immunosuppressant or antifungal claim were assigned unknown exposure status. Antifungal use was treated as a time varying exposure. Cox models adjusted for sex, age, transplant reason and number, induction therapy, smoking history, total ambient ultraviolet exposure, and other antifungal use were used to assess the association between vori and SCC.

Results: We evaluated 9,738 lung recipients (median age 59 years, interquartile range [IQR] 48–65), of whom 59% were male. Median follow-up was 3.0 years (IQR 1.4–5.0), and recipients had immunosuppressant medication data for 75% (IQR 51%–90%) of 30-day intervals. There were 1,031 SCCs observed over 32,064 person-years (PY) (incidence 322 per 10,000 PY). Overall, 41%, 26%, and 13% of recipients had a claim for vori, itra, and posa, respectively. Compared to individuals with no observed vori use, those with 1–3, 4–7, 8–15, and > 15 months of vori experienced increasingly elevated SCC risk: adjusted hazard ratio (aHR) 1.1 (95%CI 0.9–1.3), 1.4 (1.2–1.7), 2.0 (1.7–2.5), and 3.0 (2.4–3.9). For each 30-day vori use, SCC risk increased 5% (aHR 1.05, 95%CI 1.04–1.06). There was no association between other antifungals and SCC.

Conclusions: In a dose–response manner, vori was associated with increased cutaneous SCC risk in a large population-based sample of lung recipients. Vori may play a role in the etiology of skin cancer, and high-risk lung recipients (e.g., fair skin) should be counseled on the potential adverse effects of vori prior to initiation.

80 | Detection of Prevalent Cancer among New Users without Routine Care

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Background: Elevated incidence rates of algorithm-identified cancers shortly after treatment initiation are common in new-user studies, but are unlikely to be real.

Objectives: To characterize features that may be driving high incidence rates after initiation within a new-user study.

Methods: We performed a new-user, cohort study using a 20% random sample of Medicare beneficiaries (2007–2014), aged 66+ initiating an antihypertensive (AHT), exclusive of betablockers. The outcome was colorectal cancer (CRC), and was identified with ≥2 ICD-9 CRC diagnosis codes within 60 days. The diagnosis date was the date of the 1st observed CRC claim. Cohort members had ≥2 claims, ≥360 days of continuous Medicare (A/B) enrollment, no evidence of CRC prior to AHT initiation, and ≥ 180 days of part D enrollment with no AHT claim. Person-time/cases began accrual after the 2nd prescription. CRC rates were calculated and stratified by time. We calculated the number of office visits (OV) in the 60–360 days prior to initiation and stratified users into those with 0, 1, 2–3 or ≥ 4 OVs. We calculated CRC incidence stratified by time (0–90, 91–180, 181–365, 366–730, 731+ days) and strata of OV. Among cases, we identified claims post initiation that suggested prevalent CRC (history of colon or rectal cancer) or incident CRC (physical symptoms, pathology). We calculated the number and proportion of these events stratified by time since initiation and number of office visits.

Results: There were 417,458 AHT initiators and 2,127 cases identified over 683,097 person years (incidence 311 per 100,000). Incidence was highest in the 0–90 days post initiation and varied by the number of office visits (0:758, 1:475, 2–3:456, ≥4:414). Incidence for all OV

strata dropped in the 91–180 days post initiation, stabilizing after 180 days. The decrease was most pronounced in those with 0 OVs. The proportion of probable prevalent cases was higher in the 0–90 days (7.5%) after initiation than in all other time strata (91-180d 4.0%; 181-365d 2.4%; 366-730d 3.9%; ≥731d 2.9%). The proportion did not vary by strata of OVs. The proportion of probable incident cases did not vary substantially by time since initiation or by the number of OV.

Conclusions: Individuals with no office visits in the 60–360 days prior to medication initiation have markedly higher CRC incidence in the 0–90 days post initiation and drive much of the observed high incidence in the cohort overall. Compared with cases diagnoses after 90 days, a higher proportion of cases diagnosed within 90 days of initiation appear to be prevalent cases. Induction periods after drug initiation reduce misclassification of prevalent as incident cancers.

81 | Automatic Detection of Drug–Drug Interactions in Cancer Patients: A French Population-Based Cohort Study

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Background: Risk management and appropriateness of care are public health priorities. Promoting optimal oncological care pathways requires an analysis of risk situations and contexts of use of anticancer drugs, especially since oncological care are switching to the outpatient setting.

Objectives: This study aimed at estimating the prevalence of outpatient potential drug–drug interactions (DDI) in the French population with cancer to identify situations requiring actions to prevent or promote the appropriate use of drugs.

Methods: A retrospective cohort was conducted using reimbursement data from the national health insurance system (*Echantillon Généraliste de Bénéficiaires*). All patients aged 18 and over with a new cancer diagnosis between January 1st, 2009 and December 31st, 2014 were included. Potential DDI were identified during the year following cancer diagnosis according to the national thesaurus published by the French Medicines Agency (September 2016). Potential DDI were defined as the dispensing within a period of 15 days of drugs that could interact and were automatically detected using the Thériaque® database. Potential DDI were described according to i) nature of drugs involved, ii) mechanism and iii) severity.

Results: A total of 18,614 patients were included in the cohort (median age: 67 years; 50% female). During the one-year follow-up, 11,249 patients (60.4%) had at least one potential DDI; the prevalence was 6.1% for contraindicated potential DDI and 16.0% for potential DDI that should be avoided. The contraindicated potential DDI most frequently observed concerned biguanides and contrast media. Among the cohort, 4,335 patients (23.3%) had anticancer drug dispensings (median age: 67 years; 59.5% female). In this population, 2,802 patients (64.6%) had at least one potential DDI during the one-year follow-up. The most frequent severe potential DDI (contraindicated and that should be avoided) involving anticancer drugs concerned folic acid analogues (methotrexate). Among less severe potential DDI (that should be taken into account) involving anticancer drugs, those concerning protein kinase inhibitors and proton pump inhibitors were the most frequent.

Conclusions: This study provides a global description of outpatient DDI in the French population with cancer that enables to consider preventive actions. A further analysis of the clinical consequences of specific potential DDI would be of interest in this population.

82 | Treatment Pattern and Real World Effectiveness on Non Small Cell Lung Cancer Patients Harboring Major Single and Double EGFR Mutations

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Background: Although the clinical outcome of EGFR-positive advanced non-small cell lung cancer (aNSCLC) patients has been well studied, the analysis of real world treatment effectiveness on specific mutation combinations is lacking to direct drug development for enhancing personalized healthcare.

Objectives: To characterize treatment and effectiveness on aNSCLC patients with the most common EGFR mutations using electronic health records (EHR) real world data (RWD).

Methods: Patients with aNSCLC diagnosed between 2011 and Nov 2018, who were tested EGFR mutation-positive were identified from the Flatiron Health EHR-derived database. Those with the common single mutations, exon 19 deletion (del19) and L858R (LR); and T790 M (TM) acquired from EGFR-targeted tyrosine kinase inhibitors (TKI) were studied for treatment pattern and overall survival. Cohorts for survival comparison were balanced using standardized mortality ratio weighting. Median overall survival (mOS) was estimated using Kaplan–Meier curve and hazard ratios (HR) using Cox proportional hazards.

Results: The study included 4489 EGFR-positive aNSCLC patients (median age 69 years old: 1909 with del19, 1504 with L858R and 660 with T790 M). Among them, 23 had both del19 and LR, 231 had the double mutation TMLR, 338 had TMdel19 and 6 had triple mutation (TMLRdel19). De novo TM mutation was detected in 4.4% (182/4129) NSCLC patients with biopsy dates before first/second generation TKIs. Usage of these TKIs as first line for LR and del19 mutations

peaked in 2014 at ~80% of all treatment categories, and dropped to ~25% in 2018, in which ~50% were treated with first line osimertinib. Among patients who acquired the TM mutation after first line TKIs, the TMLR double mutation resulted in worse OS (HR 1.57, p = 0.007), with mOS of 30.4 months (95% CI: 26.9–32.9) from start of first line treatment, compared to TMdel19 (mOS 41.5 months, 95% CI: 35.0–53.4). In this study, mOS of LR patients (double-mutation patients excluded) was 19.8 months (95% CI: 18.0–21.5) and that of del19 was 22.5 months (20.7–23.9, HR 1.14 [p = 0.05]).

Conclusions: The large number of NSCLC patients in the Flatiron Health EHR-derived database allowed a more comprehensive retrospective study of patients with specific mutations. Patients with TMLR mutations had worse OS than TMdel19 after first line first/second generation TKIs. This difference is more prominent in patients harboring double mutations than those with single mutations. More data on recent osimertinib treatment is needed to see its real world effectiveness on the different double mutation patients.

83 | Impact of a Two-Tier Intervention on Statin Prescribing and Adherence Levels among Latino Patients with Diabetes

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Background: Type 2 Diabetes Mellitus (T2DM) is a risk factor for cardiovascular disease (CVD), the leading cause of death in the United States. To increase primary and secondary prevention of major cardiovascular events (CVE), current guidelines recommend starting diabetic patients ≥40 years of age on a statin. Unfortunately, there is lack of consensus among primary care physicians (PCPs) to prescribe, and poor patient adherence to comply with statin therapy for CVE prophylaxis. Repercussions of PCP noncompliance and poor patient adherence could adversely affect the benefits of the statin therapy among diabetic patients, especially among those with a high prevalence of T2DM and a high incidence of CVE, such as the Latino group.

Objectives: The objectives for this study are: 1) Estimate the prevalence of diabetes in a group of Latino patients; 2) Calculate the proportion of diabetic beneficiaries ≥40 years age receiving a prescription for a statin during the study period; 3) Determine diabetic beneficiaries adherence level to statin therapy.

Methods: This study follows a descriptive design using data from beneficiaries of a Latino based pharmacy benefit manger (PBM) with continuous enrollment from January 1, 2018 to October 31, 2018. Diabetes beneficiaries were defined as those with at least two generic product identifiers (GPIs) for a diabetic agent during the study period. GPIs for statin products were used to the estimate the prevalence of statin prescribing among diabetic beneficiaries. Proportion of days covered (PDC) was used to estimate diabetic beneficiaries' adherence to the statin therapy.

Results: The prevalence of diabetes among beneficiaries of the PBM aged 40–75 was 6% (6,243/111,572). The mean age for the diabetic beneficiaries was 55 (SD ± 7), and 53% were males. A total of 3,401 (54%) diabetic beneficiaries received at least one prescription for a statin during the study. Among those diabetic beneficiaries who received at least one prescription for a statin during the study period, 1,932 (57%) had PDC ≥ 80%.

Conclusions: Although treatment guidelines recommend placing diabetic patients ≥40 years of age on a statin, this study found suboptimal prescribing among Latino diabetic patients. In addition, among those Latino diabetic patients who received at least one prescription for a statin, the adherence levels to the statin pharmacotherapy was suboptimal. Therefore, prompting a bigger issue addressing poor adherence by means of intervention through educating physicians and patients.

84 | Secondary Adherence to Oral Anticoagulants. Preliminary Results of a Systematic Review and Meta-Analysis of Real-World Studies

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Background: Since the release of the first non-vitamin K antagonist oral anticoagulant (NOAC), several observational studies have been carried out to estimate adherence to oral anticoagulants (OAC), many of them, being funded by NOAC marketers. There are no studies summarizing systematically the available evidence on secondary adherence in the real world using pharmacy claim databases or atrial fibrillation registers and taking into account potential biases.

Objectives: To describe secondary adherence to OACs, to compare adherence between OACs and to analyze potential biases in OAC secondary adherence studies using databases.

Methods: We searched on PubMed, SCOPUS and Web of Science databases to identify longitudinal observational studies reporting days' supply adherence measures to OAC in patients with AF from claims databases or AF registers. The main study endpoint was the percentage of patients exceeding the 80% threshold in proportion of days covered (PDC80) with 12 months follow-up. We used random-effects meta-analysis to pool study estimates, stratified by the presence of conflict of interest (CoI; defined by funding or authorship).

Results: We found 22 studies reporting PDC80 (or MPR80) at 12 months (from 2013 to 2018) fulfilling inclusion criteria, reporting data from 30 cohorts, 19 without CoI and 11 with CoI (all related with Rivaroxaban marketers). Total PDC80 pooled estimates by drug were: 59% (Warfarin), 62% (Dabigatran), 67% (Rivaroxaban) and 71% (Apixaban). In studies without CoI, adherence estimates increased for Warfarin (63%), Apixaban (75%) and Dabigatran (64%) without changes for Rivaroxaban. In the opposite direction, in studies with CoI adherence estimates were clearly reduced for Warfarin (from 63% to 53%) and Apixaban (from 75% to 68%).

Conclusions: Conflict of interest bias is a relevant factor in studies assessing adherence to OAC in AF patients.

85 | Persistence and Adherence to Biologics in Patients with Psoriasis: A Nation-Wide New User Cohort Study

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Background: Adalimumab, etanercept and ustekinumab are biologics approved to treat moderate-to-severe psoriasis in patients who fail to respond to conventional topical and systemic agents or phototherapy in Taiwan. Persistence on the biologics can be a proxy of effectiveness in Taiwan, where reimbursement is only provided with clinical improvement evaluated every 6 months. No population-based studies have evaluated how biologics are used for the treatment of psoriasis in Asia.
Objectives: To describe characteristics of new users of biologics and to evaluate treatment persistence and adherence to biologics using the National Health Insurance Research Database in Taiwan.
Methods: New users of biologics aged at least 18 years with a confirmed diagnosis of psoriasis (ICD-9 code 696.1) from 1 November 2014 to 31 December 2015 were identified. Exclusion criteria were < 12 months duration in the database prior to the diagnosis, malignancy, active TB, active hepatitis B and/or C within 6 months before the index date. Patients were followed up until 31 December 2016. Persistence was defined as time (consecutive days) from treatment initiation until discontinuation. Discontinuation was defined as a treatment gap of at least 90 days for etanercept and adalimumab, and 180 days for ustekinumab. A sensitivity analysis assessed 30-, 60-, 90-, and 120-day treatment gaps. A Kaplan–Meier analysis estimated the proportion of patients who remained persistent on the index biologic following the index date throughout the follow-up period. We used a log-rank test to compare persistence between groups. Confounding factors; gender, age, co-medications were adjusted.
Results: There were 811 patients with psoriasis who were new users of biologics, of whom 558 (study population) had no other co-morbidities that required treatment with biologics. The mean age was 44.9 years (SD 13.5) and 76.2% were male. The persistence rate in psoriasis patients without co-morbidities at 1 year was 68.8%, 81.2% and 93.4% for patients taking etanercept, adalimumab, and ustekinumab, respectively ($p < 0.0001$). Results were consistent ($p < 0.0001$) in a sensitivity analysis conducted using different treatment gaps to define persistence. The adherence rate (i.e., the correct quantity of drug prescribed) at 12 months was 67.2% for etanercept, 62.8% for adalimumab and 94.7% for ustekinumab ($p < 0.0001$). Adherence at 18 months was 64.3%, 47.3%, and 91.4%, respectively ($p < 0.0001$).
Conclusions: Drug persistence and adherence was highest in patients with psoriasis treated with ustekinumab.

86 | Investigating the Impact of Statin Intensity on Patients' Discontinuation of Statin Therapy: A Nationwide Cohort Study

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Background: Statins are among the most widely prescribed drugs in many countries. Current treatment guidelines in the UK recommend high-intensity statin therapy (atorvastatin 80 mg) for secondary prevention of cardiovascular disease (CVD). However, information regarding the impact of recommending this high statin dose on treatment discontinuation is limited.
Objectives: To evaluate the impact of high-intensity therapy on statin discontinuation in patients in Scotland.
Methods: Retrospective cohort study using the Scottish prescribing dataset linked with hospitalization records, comprising patients (≥ 18 years) initiating statins between January 2010 and December 2015; statin intensity was defined as high, moderate or low based on current National Institutes for Health and Care Excellence classifications. Discontinuation was calculated using the refill-gap method; Kaplan–Meier and Cox proportional hazard models, adjusted for age, sex, comorbidity and whether statins were used for primary or secondary prevention, were used to determine differences in discontinuation.
Results: A total of 73,716 patients (mean age 61.4 years [SD 12.6]) were identified. Overall, 62.9% of patients discontinued treatment; the majority of these however re-initiated treatment. Discontinuation rates varied among intensity levels, being lowest among high intensity (50.9%) and highest among low intensity statins (75.5%). Furthermore, rates differed between patients with a diagnosis of ischaemic heart disease, angina, myocardial infarction or stroke (secondary prevention), and those without (primary prevention) - ranging from 36.3% (high intensity) to 58.8% (low intensity) among the former, and from 55.9% (high) to 76.3% (low) among the latter. Similarly, median time to discontinuation was shortest among low intensity (207 days, 95% confidence interval (CI) 168–244), and longest among high intensity statins (911 days, 95% CI 843–1007). Adjusted hazard ratios (HR) for high intensity treatment, as compared to moderate intensity, were 0.43 (95% confidence interval (CI) 0.34–0.55) and 0.80 (95% CI 0.74–0.86) among patient with and without prior CVD, respectively.
Conclusions: Compared to moderate and low intensity, high-intensity statin therapy was associated with lower discontinuation rates. However, the clinical impact of these differences in discontinuation needs further investigation.

87 | Does Single-Tablet Regimen Improve Adherence to Antiretroviral Therapy in Brazil? A Group-Based Trajectory Modeling Analysis of Patients Switching Regimens

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Background: Combination Antiretroviral Therapy (cART) in a single-tablet regimen (STR) was adopted in Brazil in 2015. The simplification of the therapeutic regimen is one of the factors that influence patients' adherence.

Objectives: We evaluated if this simplification strategy impacted on adherence and clinical outcomes.

Methods: We conducted a retrospective cohort study of 1206 patients using efavirenz 600 mg, tenofovir 300 mg and lamivudine 300 mg in multiple-tablet regimen who switched to a STR containing the same formulation between March and June 2015. We obtained data from the Brazilian Ministry of Health electronic databases. The index date was defined as the day of the switch (i.e. the date of the first prescription fill for the STR). Adherence was measured by the proportion of days covered (PDC) and patients were followed for 18 months prior (pre-switch period) and after (post-switch period) the switch. We calculated the cumulative and monthly PDC considering 95% of adherence as threshold. Adherence patterns to cART regimen over time for each period (pre- and post-switch) were identified using group-based trajectory modeling. We also identified predictors of each trajectory group.

Results: We observed an increase of 14% in the proportion of adherent patients after switching to STR ($p < 0.001$). There was also an increase in the number of patients with CD4 count >500cells/µl (6.2%, $p < 0.001$; $N = 490$). The proportion of patients with undetectable viral load after the switch remained similar (96.4 vs. 96.7%; $p = 0.871$; $N = 699$). The group-based trajectory analysis revealed four groups of adherence probability: 1) early non- adherence; 2) insufficient adherence; 3) slow increase in adherence; and 4) nearly-always adherence. After the switch, the trajectory patterns were more uniform as the adherence probabilities have remained more constant over time. Moreover, we observed a migration of patients towards a group representing a higher probability of adherence after the switch, where 55% of the patients shifted to a group with a higher level of adherence, 40% remained at the same level and only 5% shifted to a group with lower adherence level. Patients belonging to the group with the worst chance of adherence were more likely to be women, have lower education, or longer time on cART than the nearly-always adherent patients.

Conclusions: The strategy of introducing STR in Brazil for HIV treatment had a positive impact on adherence and clinical outcomes. Patients belonging to different adherence patterns over time may warrant different types of clinical interventions.

88 | Risk Factors for Non-Persistence with Antiplatelet Agents in Patients after a Transient Ischemic Attack

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Background: Antiplatelet medication represents an important tool of secondary prevention in patients after a transient ischemic attack (TIA).

Objectives: The study was aimed at evaluating non-persistence with antiplatelet medications in patients after a TIA and identifying patient-related characteristics influencing the probability of non-persistence.

Methods: Data for our study were collected from the database of the General Health Insurance Company, the largest health insurance provider of the Slovak Republic. Our study cohort included 1298 patients (62.1% of them women), in whom antiplatelet therapy was initiated between 1 January 2010 and 31 December 2010. Patients were followed for three years from the index date. Patients with a treatment gap were classified as non-persistent. A treatment gap was defined as a 6-month period without any antiplatelet medication prescription. The Cox proportional hazards model was used to identify patient-associated characteristics influencing the patient's risk for non-persistence.

Results: At the end of the follow-up period, 647 (49.8%) of 1298 patients were identified as non-persistent with antiplatelet agents. Older age ≥ 65 years (hazard ratio HR = 0.53) and certain comorbid conditions: arterial hypertension (HR = 0.72), diabetes mellitus (HR = 0.71), hypercholesterolemia (HR = 0.75) and dementia (HR = 0.73) represented protective factors associated with a decreased patient's risk for non-persistence.

Conclusions: The results of our study indicate that in TIA patients aged <65 years and those without certain comorbid conditions special attention should be paid to the improvement of their persistence with antiplatelet medications. Funding: This study was funded by grant of the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic VEGA 1/0112/17.

89 | Treatment Patterns and Adherence in a UK Primary Care Migraine Population

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Background: Migraine is estimated to affect 7.6% of men and 18.3% of women in England but use of preventive therapies is reported to be low. There is limited evidence on adherence to such treatments.

Objectives: To estimate cumulative migraine incidence and describe prophylactic treatment patterns and adherence in 2015.

Methods: Patients ≥18 years old in the Clinical Practice Research Datalink with incident migraine during 01/01/2007–31/12/2017. Cumulative incidence of migraine was estimated, and cohort factors

described. Treatments were categorized as none, acute only, prophylactic only, acute and prophylactic. 12-month treatment patterns were described in patients initiating prophylactic treatment with amitriptyline, propranolol or topiramate in 2015. These were classified as continuous use (<90 days between prescriptions), augmentation (new treatment ≥57 days after index treatment & before end of index treatment), switching (new treatment ≤56 days before end of index treatment & ≤90 days after end of index treatment) or discontinuation (≥91 days between prescriptions). Adherence was defined as the proportion of days covered (PDC) (days in possession/365) and medication possession ratio (MPR) (days in possession/days on treatment). Patients were 'adherent' if their PDC or MPR was ≥0.80.

Results: 89,442 patients had incident migraine. Mean age at diagnosis was 40 years [SD 15]; 76.6% were females. Mean follow-up after diagnosis was 1666 days [SD 927]. The cumulative incidence of migraine was 25.8/10,000 person-years [95%CI:25.6–26.0]. Common comorbidities included depression [19.2%], asthma [19.7%] and anxiety [16.5%]. 26% of patients received acute treatment only, 86.7% received prophylactic and/or acute treatment; 37.6% and 20.1% received ≥2 and ≥ 3 different prophylactic treatments during follow-up, respectively. 1,636 patients initiated prophylactic treatment in 2015. Propranolol (47.8%) and amitriptyline (47.4%) were most commonly prescribed. 79% of propranolol users and 83% of amitriptyline users discontinued treatment within 12 months; mean time to discontinuation was 92.2 and 82.7 days, respectively. The discontinuation rate for topiramate was 69.2% and mean time to first change was 99.5 days. Median MPR was 1.00 and median PDC was 0.31. Using MPR, 80–85% of patients were adherent while on treatment, though only 20–30% continued treatment up to 12 months.

Conclusions: Most migraine patients receive one or more treatments. Despite being adherent while on treatment, most discontinue prophylactic treatment within 12 months. Reasons for discontinuation and strategies to reduce this should be explored.

90 | The Impact of Reduced Copay for Hormonal Therapy on Primary and Secondary Non-Adherence for Breast Cancer Medicare Patients

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Background: Several large randomized controlled trials have clearly documented the survival benefit of hormonal therapy (HT); however, many women with breast cancer fail to initiate (primary non-adherence) and among those who are initiate, many fail to remain adherent to HTs (secondary non-adherence). Prior studies have found that costs impact secondary non-adherence to medications, but have failed to examine primary non-adherence.

Objectives: To estimate how primary and secondary adherence was impacted by reducing copays for medications by the introduction of generic HTs.

Methods: We examined monthly adherence to HT after active treatment ceased using the proportion of days covered (PDC) for women diagnosed with stage 1–3 breast cancer between 2008–2009 using SEER-Medicare data. We followed patients for up to five year or until they were censored due to insurance disenrollment or having evidence of cancer recurrence. We examined adherence for 1 year before and up to 4 years after generic HT was available. We compare women whose copays would change and those whose copays would not due to the receipt of cost-sharing subsidies. To examine primary and secondary non-adherence we use a multi-state model with 4 states (Never used, Low adherence (PDC < 0.80), Adherent (PDC ≥ 0.80), and Former User). Additionally, we used the model to simulate the expected time a person is adherence to the drug, effectively combining the results for the primary and secondary adherence components. We implemented the multi-state model using a clock forward approach and used a Cox proportional hazard model adjusting for demographic and clinical factors.

Results: We identified 38,626 women with breast cancer. We find that reduced copays results in faster initiation of treatment (hazard ratio (HR) = 1.11; 95%CI = 1.04–1.19; p-value <0.01). Among adherent individuals, reduced copays results in being less likely to move to having low adherence (HR = 0.68; 95%CI = 0.62–0.75; p-value <0.01) and less likely to stop taking medication adherent (HR = 0.49; 95%CI = 0.42–0.57; p-value <0.01). Among individuals with low adherence, they are less likely to stop taking the HT (HR = 0.65; 95%CI = 0.57–0.82; p-value <0.01). However, if a patient stops using the HT, those with low copays are less likely to reinitiate HT (HR = 0.48; 95%CI = 0.42–0.57; p-value <0.01). Simulations document that lower copays increase the amount of time a person is using and adherent to HT.

Conclusions: This study finds that both primary and secondary non-adherence were positively impacted by reduced copays.

91 | Uncertain Association between Benzodiazepine Use and the Risk of Dementia: Population-Based Matched Cohort Study

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Background: Controversy exists regarding the increased risk of dementia associated with benzodiazepine use. The Asian population may be at a higher risk of benzodiazepine-induced dementia due to the genetic variation in CYP2C19.

Objectives: To examine the association between benzodiazepine use and the risk of dementia.

Methods: We conducted a retrospective cohort study using a nationwide healthcare database from 2007 to 2016 in South Korea. Study

subjects included new-users aged 50 years or older without having a prior prescription record of benzodiazepines or a history of dementia within the 5-year eligibility period, 2002–2006. Outcome was defined as an incident dementia with pre-specified algorithms using diagnosis and prescription records with the application of 5-year lag time. We used multivariable cox proportional hazard models to estimate hazard ratio (HR) and their 95% confidence interval (CI). Comorbidities and co-medications were treated as time-varying variables on 90 day unit. Active comparator was used to control for bias from confounding by indication.
Results: Our final subjects included 612,256 patients, after propensity score estimation and matching in 1:1 ratio. We observed a 23% increased risk of dementia associated with the use of benzodiazepine, as compared with non-users, over a mean follow-up of 5.5 years (HR = 1.23, 95% CI = 1.14–1.32). Consistent finding was observed with varying the lag-time duration, but close to the null association with 7-year lag time (HR = 1.17, 95% CI = 1.04–1.30). Contrary to this, repeated analyses with active comparator produced no increased risk in benzodiazepine users.
Conclusions: While we found a significant association between the use of benzodiazepine and the risk of dementia, null or negative results produced by the longer duration of lag-time and use of active comparator meant the absence of causal association.

92 | Risk of Cardiovascular Adverse Events and Domperidone Use: A Case-Crossover Study

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Background: Recent epidemiological studies have suggested that domperidone may increase the risk of severe cardiac arrhythmias, and new safety concerns regarding other cardiovascular (CV) disease also exists.
Objectives: The aim of this study is to investigate whether the use of domperidone increases the risk of cardiovascular adverse events, including arrhythmias, hypertension, myocardial infarction, ischemic stroke and heart failure.
Methods: We conducted a case-crossover study using the Sample Cohort data from the National Health Insurance Service in South Korea from 2002 to 2015. From a total of 254,840 incident patients with CV events, our final case series included 60,783 patients with a prior prescription for domperidone or metoclopramide. Exposure to domperidone in a 7-day hazard period prior to each patient's CV event was compared with domperidone use in an earlier 7-day control period. We conducted conditional logistic regression analysis to estimate odds ratios (ORs) and 95% confidence interval. Also, the risk was estimated for each category of average daily domperidone dose (≤30 mg and > 30 mg) and whether co-medication of CYP3A4 inhibitors or QT prolonging drugs with domperidone. We produced repeated analysis with the use of metoclopramide as an active comparator.
Results: The odds ratio for overall CV events was 1.57 (95% CI 1.46–1.69) versus non-use, and 0.59 (95% CI 0.50–0.70) versus metoclopramide use. Myocardial infarction showed the highest odds ratio (OR 2.86, 95% CI 1.21–6.76) versus non-use, followed by ischemic stroke (OR 2.33, 95% CI 1.72–3.14), hypertension (OR 1.53, 95% CI 1.42–1.66), arrhythmias (OR 1.45, 95% CI 1.13–1.85) and heart failure (OR 1.44, 95% CI 0.94–2.21). A higher CV risk was observed in patients taking the higher daily dose of domperidone (>30 mg, OR 2.54, 95% CI 1.74–3.72), and those who were co-exposed with CYP3A4 inhibitors (OR 2.69, 95% CI 2.31–3.12) or QT prolonging drugs (OR 2.87, CI 2.53–3.24). However, no increased risk was observed for specific outcome with respect to metoclopramide.
Conclusions: Our results suggested that domperidone use was associated with overall CV events, with a suggestion of high risk for myocardial infarction, ischemic stroke and hypertension not only for arrhythmias. However, no increased risk in comparison of metoclopramide imply the absence of causal relationship between domperidone and CV risk.

93 | A Multi-Institutional Health Screening Records Database (HSRD) of Korea: Evaluation of Its Characteristics and Representativeness

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Background: The Health Screening Records Database (HSRD) is the largest multi-institutional health screening records derived from an organization of 16 hospitals in Korea. Although laboratory data from health screenings may be extensively used for medical studies, representativeness of such data have yet to be evaluated.
Objectives: To evaluate the characteristics and representativeness of the HSRD for its use as a reliable data source for medical studies.
Methods: This comparative study used data from HSRD and Korea's National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database, on 2015. The NHIS-HEALS is a 10% sample cohort randomly extracted from nationwide health screening programme participants of 5,150,000. Common variables from both databases were selected, which included gender, age group, laboratory results, personal and family disease history, risk factors (cigarette smoking, alcohol, obesity, physical activity), and cognitive and mood function. Gender-based analyses were conducted for each variables included in the study, in which the mean or proportion, where appropriate, were used for comparison. The NHIS-HEALS was considered to be the gold standard. The HSRD was considered to have

statistical resemblance if the mean or proportion of the NHIS-HEALS lied within the mean or proportion's 95% confidence interval of the HSRD.

Results: The HSRD contained additional clinical information compared to NHIS-HEALS such as, personal disease history, lower body function and laboratory results (bone mineral density). The HSRD included less elderly participants (18.5% vs 30.9%) but more females (53.2% vs 41.3%) than NHIS-HEALS. On the contrary, participants' insurance type distributions were similar between HSRD and NHIS-HEALS. All variables except diastolic blood pressure were determined to have clinical resemblance, with fasting blood glucose, serum creatinine, and hemoglobin having statistical resemblance as well.

Conclusions: The HSRD had more clinical information and a wider age population than NHIS-HEALS, while showing high level of clinical resemblance with NHIS-HEALS. The HSRD may serve as an alternative database by providing a comprehensive range of clinical data for medical studies.

94 | The Association between Use of Opioid Analgesics and Benzodiazepines and the Risk of Death: A Population-Based Case-Crossover Study

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Background: A number of previous studies examined the association between concomitant use of opioids and benzodiazepines and the risk of death; however, it is still unclear.

Objectives: The aim of study is to investigate whether co-prescription of benzodiazepines and opioids increased the risk of death in a population-based crossover setting.

Methods: We conducted a case-crossover study using a National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. In this design, cases served as their own controls. We introduced a 30-day hazard period preceding the onset of death and consecutive 3 previous 30-day control periods along with 30-day washout period. Exposures to opioid analgesics and benzodiazepine during the hazard period were compared with those of 3 control periods. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression analyses and adjusted for time varying comedication.

Results: A total of 11,097 individuals with the prior record of benzodiazepine or opioid analgesics and death were included in the study. We found the highest risk of all-cause mortality in the concurrent use of two medications (aOR: 1.79, 95% CI: 1.68–1.91), as compared with non-use of two medications. In the subgroup analyses, increased risks were observed in patients with respiratory disease (aOR: 1.48, 95% CI: 1.35–1.61) and in patients less than 20 years old (aOR: 3.74, 95% CI: 1.89–7.43).

Conclusions: Co-prescription of opioid analgesics and benzodiazepines was associated with an increased risk of mortality, especially in the young age group (< 20 years old). This results may strengthen the previous hypothesis of higher mortality in patients used two medications concomitantly, and will give evidence on cautious use of opioids and benzodiazepines which can be prescribed simultaneously in the clinic.

95 | Comparative Mortality Risk of Antipsychotic Medications in Elderly Patients with Stroke: Adjusting for Unmeasured Confounders with Stroke Registry Database Using Propensity Score Calibration

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Background: Elderly patients are at risk for developing psychosis after stroke. According to previous guidelines, antipsychotics are the first-line pharmacological intervention for psychosis. However, studies examining mortality risk associated with antipsychotic use in post stroke elderly patients remain inconclusive.

Objectives: To evaluate comparative mortality risk of antipsychotic use in elderly patients after a stroke by using an active comparator and new user design with an external adjustment method.

Methods: Design and setting: We conducted a retrospective cohort study using the Multi-Center Stroke Registry (MCSR) and retrieving patients aged above 65 years old admitted for stroke in the National Health Insurance Database (NHID) from 2002 to 2014. These patients were not prescribed antipsychotics before their discharge date and were followed until they started to receive antipsychotic treatment. The date of antipsychotic use was set as the index date. The covariates were retrieved from claims during the one-year period prior to the index date. We then linked the MCSR with the NHID to retrieve additional variables, including smoking history, BMI, National Institute of Health Stroke Scale, the Barthel index, and the modified Rankin Scale. Exposure: Antipsychotics. Main outcome: One-year all-cause mortality. Statistical analysis: To compare antipsychotics with respect to risk of all-cause mortality, we performed Cox proportional hazard models using the propensity score calibration (PSC) method to adjust for unmeasured confounders in order to estimate the relative risk among antipsychotics in elderly stroke patients.

Results: We selected the antipsychotics, including quetiapine, haloperidol and risperidone, which were prescribed for post-stroke psychosis treatment, and compared the mortality risk among these antipsychotics. In the PSC-adjusted intent to treat analyses, haloperidol [adjusted hazard ratio (aHR) = 1.22; 95% confidence interval (CI) 1.18–1.27] and risperidone (aHR = 1.31; 95% CI 1.24–1.38) users had a higher mortality risk as compared to quetiapine users. Haloperidol and risperidone exhibited a dose–response related to mortality risk after controlling for confounders. The sensitivity analyses assessing the influence of the study population showed similar patterns.

Conclusions: The significant variations in the differences in mortality risk among antipsychotic agents suggests that antipsychotic selection and dosing may affect survival in elderly stroke patients.

96 | Trend of Isoniazid Prophylaxis and TB Infection for Rheumatoid Arthritis Patients Receiving TNF Inhibitors: A Nationwide Population-Based Analysis

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Background: The Taiwan Food and Drug Administration issued a risk management plan (RMP) for tumor necrosis factor inhibitor (TNFi) in 2012, requiring isoniazid (INH) prophylaxis regimen in latent tuberculosis infection (LTBI) patients receiving TNFi.

Objectives: To evaluate the trend of INH prophylaxis regimen and the incidence of TB infection in patients with rheumatoid arthritis (RA) receiving TNFi before and after RMP implementation.

Methods: We used the Taiwan National Health Insurance Database (NHID) from 2000–2016 for the study. Study cohort included RA patients aged 20+ years who newly received TNFi. Cases of TB infection were identified by both ICD-9 diagnosis code and the use of at least three kinds of anti-TB drugs within one year after TNFi initiation. We compared the incidence of TB infection and the rate of INH prophylaxis among our study cohort before and after RMP implementation. We also explored the utilization pattern of INH prophylaxis including duration and adherence which evaluated by medication possession ratio (MPR).

Results: We identified a cohort of 10,430 patients with mean age of 55.2 (SD 12.8) and 81% of them were female. The incidence rate of TB infection before RMP implementation ranged from 7.65 to 14.52 cases per 1,000 person-years (PYs); then the rate decreased after RMP was implemented (ranged from 4.47–5.27 cases per 1,000 PYs). Only 5% of the study population received INH prophylaxis, which was lower than estimated LTBI rate (18%) in similar population in Taiwan. Annual rate of INH prophylaxis increased from 4% to 8% after RMP was implemented. The trends of duration (median: 274 days) and adherence (median MPR: 89%) of INH prophylaxis were stable over years.

Conclusions: The findings suggested that TB incidence rate among RA patients receiving TNFi has decreased and INH prophylaxis rate has increased after RMP implementation; however the prophylaxis rates remained lower than our expectation. The study provided strong grounds for the enforcement of RMP implementation to prevent TB infection among patients receiving TNFi.

97 | Risk of Neuroleptic Malignant Syndrome among Patients Exposed to Antipsychotics

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Background: Antipsychotics are associated with neuroleptic malignant syndrome (NMS), a rare but serious adverse reaction. However, the epidemiology and risk estimation of NMS among antipsychotic users is unknown.

Objectives: To determine the risk of NMS associated with exposure to any antipsychotic, and four antipsychotics commonly implicated in cases of NMS: haloperidol, olanzapine, quetiapine, and risperidone. To characterize the incidence and case fatality risk of NMS in patients taking antipsychotics.

Methods: This study was a population-based cohort and case-crossover study analyzing health records from the Hong Kong Hospital Authority. Among 297,647 antipsychotic users identified from January 1st, 2004 to December 31st, 2016, 328 patients had their incident diagnosis of NMS during the same period. We further extended the NMS identification period to November 30th, 2017 and analyzed data for a total of 336 eligible patients. In the primary analysis, the use of antipsychotics was compared during day 1 to 30 (case period) and day 91 to 120 (reference period) preceding the diagnosis of NMS to estimate the risk of NMS associated with any antipsychotic, haloperidol, olanzapine, quetiapine, and risperidone (case-crossover study). We also calculated the incidence and case fatality risk of NMS (cohort study).

Results: In the case-crossover study, 336 patients were diagnosed with NMS (210 males [62.5%]; mean age, 49.7 years; case fatality risk 6.0%). After adjustment for time trends in exposure, concurrent medications, and medical conditions, diagnosis of NMS was associated with exposure to any antipsychotic (OR, 4.77; 95% CI, 1.95–11.66), haloperidol (OR, 4.40; 95% CI 1.97–9.81), and quetiapine (OR, 4.32; 95% CI, 1.70–10.97), while there was no observed association for risperidone (OR, 2.00; 95% CI, 0.93–4.32) or olanzapine (OR, 1.23; 95% CI, 0.47–3.18). In the cohort of patients exposed to antipsychotics, NMS occurred with an incidence of 1.10 per 1000 persons.

Conclusions: Antipsychotics are associated with an acutely increased risk of NMS. Patients had statistically significant increased odds of exposure to, haloperidol and quetiapine but not risperidone or olanzapine, during the 30 days prior to the diagnosis of NMS, as compared with the earlier reference period. Clinicians who prescribe antipsychotics should weigh the acutely increased risk of NMS with the potential benefits of antipsychotic therapy, especially for haloperidol and quetiapine.

98 | The Use of Long-Acting Insulin Analogues and the Risk of Colorectal Cancer in Patients with Type 2 Diabetes Mellitus

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Background: The long-term safety of long-acting insulin analogues is controversial, with some studies reporting a possible association with colorectal cancer. However, these studies had important methodological limitations. Thus, additional studies with long-term follow-up are needed to investigate this possible association.
Objectives: To examine whether the use of long-acting insulin analogues is associated with an increased risk of colorectal cancer, when compared with use of intermediate-acting insulins in patients with type 2 diabetes.
Methods: We used the United Kingdom Clinical Practice Research Datalink to identify patients, at least 40 years of age, newly-treated with either insulin analogues (glargine, detemir, degludec) or intermediate-acting human insulins (neutral protamine Hagedorn, lente) between September 1, 2002 and March 31, 2017, with follow-up until March 31, 2018. All patients were required to have at least one year of follow-up, necessary to account for a minimum cancer latency. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of colorectal cancer, comparing overall use of long-acting insulin analogues with intermediate-acting insulin, adjusted for high-dimensional propensity score deciles. We also assessed for the presence of a duration-response relationship using restricted cubic splines and whether the association varied according to specific type of analogue.
Results: A total of 17,378 patients initiated their insulin treatment with long-acting analogues versus 9703 patients with intermediate-acting insulin, with the cohorts followed for up to 16 years. Overall, long-acting analogues were not associated with an increased risk of colorectal cancer, when compared with intermediate-acting insulin (2.2 (95% CI: 1.9–2.6) vs 1.9 (95% CI: 1.4–2.4) per 1000 person-years, respectively; HR: 1.27, 95% CI: 0.91–1.78). There was no clear duration-response relationship in restricted cubic splines. Furthermore, no single long-acting analogue was associated with colorectal cancer, although the HR was elevated for glargine (glargine: HR: 1.35, 95% CI 0.96–1.91; detemir: HR: 0.91, 95% CI: 0.53–1.56; degludec: no events).
Conclusions: The results of this population-based study indicate that long-term use of long-acting insulin analogues is not associated with an overall increased risk of colorectal cancer.

99 | Methodologic Considerations for Data Source Selection and Study Design of Non-Interventional Studies Comparing the Safety and Effectiveness of Biosimilars and Reference Biologics: Insulin Glargine Products as a Case Example

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Background: Careful consideration of the features of real world data (RWD) systems and study design options for non-interventional studies (NIS) of biosimilar and reference biologic safety and effectiveness is critical to ensuring generation of robust real world evidence (RWE) to support clinical and policy decision making related to biosimilars.
Objectives: To establish an organizing framework and set of best practice recommendations to support planning and critical evaluation of non-interventional comparative safety and/or effectiveness research (CSR/CER) studies of biosimilars and their reference biologics.
Methods: The Biologics and Biosimilars Collective Intelligence Consortium convened a multi-stakeholder Workgroup consisting of research scientists and practicing clinicians from payers, industry, and academia to establish a framework for the design and conduct of non-interventional biosimilar-to-reference biologic CSR/CER studies. The Workgroup members participated in 5 teleconferences between June 2018 and November 2018 to discuss specific topics and build consensus recommendations. Insulin glargine products was used as a case example to illustrate selected aspects of the framework.
Results: The Workgroup developed a data source and study design selection framework to help guide the planning and evaluation of biosimilar-reference biologic CSR/CER studies, highlighting specific considerations and recommendations regarding: (1) relative strengths and limitations of selected types of RWD systems (claims, electronic health records, registries, and linked data) vis a vis significant general features of reference biologics and biosimilars, and specific features relevant to insulin glargine products, that influence study design choice and (2) methodologic considerations for design and analytic options including cohort, case only, and 2 quasi-experimental approaches - cohort design with instrumental variable analysis and interrupted time series analysis.
Conclusions: This framework and set of recommendations may be helpful in supporting a systematic approach to assess methodologic considerations and approaches to mitigate potential sources of bias

in the design and conduct of post-marketing NIS of biosimilars and reference biologics.

100 | Adherence and Discontinuation for Infliximab Biosimilar and Originator Drugs Covered by Public Provincial Insurance in Canada

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Background: In 2014, Inflectra® (biosimilar infliximab, INF-B) was approved for inflammatory arthritis and inflammatory bowel disease in Canada. However, no population-based comparisons of patterns of use for Inflectra and its originator product Remicade® (INF-O) are available.

Objectives: To compare infusion-based adherence and discontinuation among initiators of INF-B and INF-O, in the context of public provincial insurance in Canada.

Methods: We analyzed National Prescription Drug Utilization Information System (NPDUIS) claims data from provincial drug plans across Canada (except Quebec). We studied infliximab-naïve patients (≥18 years) with at least 2 infliximab infusions from January–December 2016. Adherence was defined as having more than 4 infusions over a 6-month follow-up period. We used two discontinuation measures: a) time to first missing dose (according to scheduled infusions of 0, 2, and 6 weeks and every 8 weeks thereafter); b) complete discontinuation of therapy, defined as a ≥ 90-day gap between infusions without restarting therapy until the end of follow-up. Descriptive analysis included age, sex, province, and prior biologic/systemic steroid use. We used logistic regression to compare INF-B and INF-O sers in terms of adherence and Cox regression to compare time to discontinuation. All models adjusted for age, sex, prior use of biologic/systemic steroid, and province (Ontario versus other provinces).

Results: We studied 2118 infliximab-naïve patients, 188 (9%) INF-B and 1930 INF-O (91%) users; half were women and the mean age was 45 ± 17 years. Most patients were from Ontario (32%), and 87% were biologic-naïve. Adherence at 6 months was 56% among INF-B users and 40% among the INF-O group (95% confidence interval, 95%CI for the difference = 5% to 26%). During follow-up, 14% of all patients missed at least one infusion, 8% for INF-B and 14% for INF-O (95%CI for the difference = 2% to 10%). Only 3% of patients had a complete discontinuation of therapy. Comparing INF-B to INF-O, the adjusted odds ratio, OR was 1.27, (95%CI = 0.78–2.09) for adherence. Hazard ratios (INF-B versus INF-O) were 0.66 (95%CI 0.38–1.15) for time to first missing dose and 1.12 (95%CI 0.39–3.20) for complete discontinuation.

Conclusions: Canadian public drug plan beneficiaries initiating INF-B and INF-O had similar rates of adherence and discontinuation. The decision to prescribe INF-B vs. INF-O and the cause for nonadherence/treatment gaps are not available in claims data. These issues should be explored in future investigations.

101 | Abatacept in Rheumatoid Arthritis and the Risk of Cancer: A Disproportionality Analysis in Vigibase

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Background: Two recent cohort studies found an increased risk of cancer overall and particularly non-melanoma skin cancer (NMSC) when comparing abatacept as a first or second line of biologic disease-modifying antirheumatic drugs (bDMARDs) in the treatment of rheumatoid arthritis (RA) with other bDMARDs. These studies were performed in two different data sources, the Swedish Rheumatology Register and the Truven MarketScan US database. As these results need to be corroborated, we investigated the risk of cancer with abatacept using a different data source, the WHO's global database of individual case safety reports, Vigibase®.

Objectives: To assess whether abatacept used in patients for RA, when compared to other bDMARDs, is associated with an increased risk of reporting overall cancer and specific cancer, including breast, cervical, lung, lymphoma, melanoma and NMSC.

Methods: We performed a pharmacovigilance study within Vigibase®, from 2007 to 2017 to compare the cases of cancer (and specific cancers) reported in RA patients exposed to abatacept with those reported in RA patients exposed to other bDMARDs. We conducted disproportionality analyses allowing the estimation of reporting odds ratios (ROR) with their 95% confidence interval (CI) of the exposure odds among spontaneous reporting of cancer (and specific cancer) to the exposure odds among reported other adverse effects.

Results: We identified 15,846 adverse effects reported in RA patients who received abatacept and 290,568 adverse effects reported in RA patients treated with other bDMARDs. Compared with other bDMARDs, the use of abatacept was associated with an increased risk of reporting cancer overall (931 reports for abatacept and 14,915 for other bDMARDs (ROR 1.13; 95% CI 1.05, 1.21). The analysis by specific cancer sites showed a significantly increased ROR of NMSC (1.31

95% CI 1.12, 1.53) and melanoma (1.68 95% CI 1.27, 2.34), but no significant difference for other specific cancer sites.

Conclusions: Compared with other bDMARDs, exposure to abatacept in patients treated for RA was associated with a slight increased risk of reporting cancer overall and particularly skin cancers. With a different data source and a different method, this study corroborated previous results from two large cohort studies. The increased risk of NMSC and melanoma is consistent with the pharmacodynamic properties of abatacept (analog of the cytotoxic T-lymphocyte-associated protein 4, CTLA-4) since it has an opposite action than ipilimumab, an antibody that blocks CTLA-4 and approved for the treatment of malignant melanoma.

102 | Predictors of Infection in Rheumatoid Arthritis Patients Using Anti-Tumor Necrosis Factor Agents

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Background: Rheumatoid arthritis (RA) is an incurable autoimmune disease that can cause permanent joint damage and loss of function. Anti-tumor necrosis factor (anti-TNF) agents inhibit the function of tumor necrosis factor (TNF), which leads to a reduction in the progression of joint damage. However, an increased risk of serious infections in RA patients using anti-TNF agents has been observed in previous studies.

Objectives: To determine predictors of hospitalized infection among patients with RA who were prescribed anti-TNF agents (adalimumab, etanercept, or infliximab).

Methods: A nested case–control study was conducted using de-identified Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN) data from January 1, 2010 to December 31, 2013. Patients were included based on ≥1 RA diagnosis, age, enrollment eligibility, number of RA diagnoses, exposure to an anti-TNF agent, and excluded based on certain comorbidities. A follow-up period of 1-year was selected to identify serious infections requiring hospitalization. Cases and controls were matched 1:1 based on gender, region, and RA cohort entry date (quarter, year). Predictors were identified from multivariable conditional logistic regression from which odds ratios (ORs) and 95% confidence intervals (CI) were calculated.

Results: In a cohort of 15,181 RA patients, 255 eligible cases and matched controls were identified. Predictors of hospitalized infection within the 1-year after anti-TNF exposure included prednisone use in the 90 days prior to hospitalization (OR 1.87, 95% CI 1.02–3.46); diabetes in the 90 days prior to hospitalization (OR 2.96, 95% CI 1.44–6.08); chronic obstructive pulmonary disease (COPD) in the 90 days prior to hospitalization (OR 9.23, 95% CI 2.76–30.95); and previous history of infection within 12 months of the RA cohort entry date (OR 8.98, 95% CI 1.90–42.60). No associations were observed with specific anti-TNF agents (adalimumab, infliximab, or etanercept) or incident/prevalent anti-TNF use.

Conclusions: Recent prednisone use, diabetes, COPD, and previous history of infection increased the risk of hospitalization for an infection among those treated with anti-TNF agents. The use of specific anti-TNF agents was not independently associated with an increased risk of hospitalized infection in RA patients. Efforts to mitigate risk of infection among RA patients with these characteristics should be considered.

103 | Blood Utilization among U.S. Elderly Medicare Beneficiaries in the Institutional Outpatient Setting, during 2007–2018

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Background: As the elderly use most of transfused blood in the United States, population-based assessments of blood utilization are needed to assure adequate national blood supply and safety.

Objectives: To evaluate blood use among the U.S. elderly in the institutional outpatient setting during 2007–2018.

Methods: This retrospective study used large Medicare administrative databases from January 2007 through October 2018 to evaluate blood components and number of units transfused, including percentage of leukoreduced (LR) components, overall and annually, among institutional outpatient elderly Medicare beneficiaries ages 65 years and older. We used revenue center and procedure codes to identify transfused blood components. Blood utilization trends were assessed by total units transfused and mean units per visit using linear time series models.

Results: Among 51,611,023 elderly Medicare beneficiaries during 2007–2018, 1,869,251 (3.6%) had transfusion of blood in the institutional outpatient setting, with a total of about 5.6 million transfusion visits and 12 million units of blood transfused, for an average of 2.2 units per transfusion visit. Blood use significantly declined over time: from 1,008,777 units in 2007 to 876,575 units in 2017, a 13% decline (p = 0.015), and from 2.3 to 2.0 units per visit (p < 0.01), respectively. Of all transfusion visits: 4.1 million visits (74%) had LR Red Blood Cells (RBCs) only transfused, 513,501 (9.2%) had LR Platelets only, 377,180 (6.7%) had non-LR RBCs only, and 327,739 visits (5.8%) had LR Platelets and RBCs. Overall, 95.4% of all platelet components transfused were leukoreduced, ranging from 93.9% in 2007 to 97.3% in 2018; and similarly, 91.0% of all RBCs components were leukoreduced, ranging from 83.3% in 2007 to 96.2% in 2018. Immunocompromised recipients comprised 46.4% of all transfused elderly and had 67.8% of total units transfused and 65.8% of all transfusion visits, with an average of 4.25 transfusion visits per person.

Conclusions: Our investigation shows a significant decline in blood use among U.S. elderly in the institutional outpatient setting during study

period. LR RBCs was identified to be the most frequently transfused component, followed by LR Platelets. The study suggests a substantially increased proportion of LR blood components transfused, with virtually all platelets and RBCs leukoreduced in 2018. Although comprising less than a half of transfused elderly, immunocompromised used most of transfused blood and required most transfusion visits, thus suggesting the importance of monitoring blood use and safety in this population.

104 | Identification of Exposure to Reference Biologics and Biosimilars - Use of Medical Claim National Drug Code and Healthcare Common Procedure Coding System Code Modifier

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Background: Optimal post-approval surveillance of biologics (reference and biosimilar) requires accurate identification of the specific product used from administrative claims databases when billed using Not Otherwise Specified (NOS) HCPCS codes or HCPCS codes that are not specific to a single product (e.g., biosimilars of the same reference biologic administered by a healthcare provider between 1/1/2016 and 3/31/2018).

Objectives: To assess the capture of biologic dispensings in the claims databases of the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Distributed Research Network (DRN) partners, with a focus on the utilization of medical claim National Drug Code (NDC), a novel data field, and HCPCS modifiers.

Methods: A cross-sectional observational study was conducted among patients with medical and pharmacy benefits enrolled in participating insurance plans of the BBCIC DRN between 1/1/2013 and 9/30/2017. We calculated the proportion of medical claims with ≥1 NDC code. For select biologics (insulin glargine, anti-inflammatory biologics, erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, and biosimilars), dispensings were identified using 4 different approaches: 1) specific HCPCS alone, 2) specific HCPCS and NDC, 3) NOS HCPCS with NDC, and 4) HCPCS with modifiers (applicable to biosimilars). Numbers of dispensings were calculated for each biologic by the approach and by select patient and health plan characteristics.

Results: More than 1.5 million eligible participants contributed approximately 4 million person-years of data, including 1.2 billion medical claims. The proportion of medical claims with ≥1 NDC increased from 1.2% in 2013 to 3.0% in 2017. Medical claim NDC code and NOS HCPCS code identified 2,074 dispensings of vedolizumab in 2014 and 2015 (FDA approved vedolizumab in 2014), accounting for 39% and 28% of all vedolizumab dispensings identified from the claims during the two years. Out of 26,381 dispensings of filgrastim biosimilars (Zarxio) identified from medical claims, 51% had a HCPCS modifier and an additional 12% had a medical claim NDC code. We identified 1,244 dispensings of infliximab biosimilars from medical claims; the manufacturer was confirmed for 38% of the biosimilar dispensings using HCPCS modifier, and an additional 3% using NDC code.

Conclusions: Use of medical claim NDC codes and HCPCS modifiers improves identification of exposure to select biologics that do not have a product-specific HCPCS code.

105 | Batch-Level Pharmacovigilance Following Manufacturing Change of Biological Products

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Background: Protamine sulfate is produced from trout and salmon milt and used as a heparin antagonist and as an excipient in insulin formulations to prolong insulin action. As a result of the March 2011 Japan earthquake and subsequent tsunami, the fishing industry was unable to maintain operations in the former Honshu fishing grounds. To ensure an adequate protamine supply, the fishing grounds for wild chum salmon were moved to the Hokkaido Island region.

Objectives: To describe a batch-specific pharmacovigilance program for protamine-containing insulin products following the introduction of a manufacturing change in the source of protamine sulfate.

Methods: Side-by-side Proportional Reporting Ratio (PRR) disproportionality analyses were performed on the manufacturer-maintained database of adverse event reports for insulin suspensions. Batch-level analyses included Hokkaido-sourced protamine batches for reports submitted between May 2013–January 2018 (new); Honshu-sourced batches for reports between January 2007–December 2008 (historic); and Honshu-sourced batches for reports between January 2010–January 2018 (concurrent). MedDRA PT of interest included changes in insulin effect and hypersensitivity (including immunogenicity and injection site reactions). New batches were compared to concurrent and historic batches separately. Concurrent batches were also compared to historic batches to minimize signal drift due to ripple-effect. Drug-event combinations with PRR ≥ 2.0 are considered potential signals that warrant further review.

Results: A total of 14,103 reports for new batches were compared to 5,999 reports for historic batches; 14,093 reports for new batches were compared to 5,672 reports for concurrent batches; and 5,810 reports for concurrent batches were compared to 5,999 reports for

historic insulin batches. Signal detection results were: lack of drug effect (new vs. historic, PRR = 1.0; new vs. concurrent, PRR = 0.93; concurrent vs. historic, PRR = 1.06); increased drug effect (new vs. historic, PRR = 0.86; new vs. concurrent, PRR = 1.04; concurrent vs. historic, PRR = 0.83); and hypersensitivity reactions (new vs. historic, PRR = 0.82; new vs. concurrent, PRR = 0.66; concurrent vs. historic, PRR = 1.26).

Conclusions: No signal has been identified implicating a worsening of glycaemic control or hypersensitivity in users of Hokkaido-sourced protamine-containing insulin suspensions. Batch-level pharmacovigilance provides an objective assessment of biological product comparability before and after changes in the manufacturing process.

106 | Evidence of Residual Confounding in Healthcare Database Studies of Oseltamivir and Influenza Complications

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Background: Oseltamivir is recommended for treatment and prevention of influenza. It has been shown to reduce influenza symptoms but its effects on complications are less certain. Observational studies report conflicting findings and no study has explicitly examined the presence of residual confounding.

Objectives: To evaluate whether there is evidence of residual confounding in healthcare database studies of the relationship between oseltamivir and influenza complications (pneumonia and all-cause hospitalizations).

Methods: Using MarketScan® Databases during the 2014–15 influenza season (Oct - May), we identified enrollees aged ≥18 with new outpatient influenza diagnosis claims after a 90-day washout, during which there was no claim for influenza diagnosis in any care settings or outpatient influenza antivirals. We compared those initiating oseltamivir with those not initiating on the influenza diagnosis date (index date) with respect to incident pneumonia and all-cause hospitalizations. Follow up started from the day after the index through day 30, censoring for death and disenrollment (primary risk period). Assuming oseltamivir only has short term effects, the 2nd and 3rd months following index diagnosis served as negative control risk periods during which estimates away from the null suggest residual confounding. We estimated hazard ratios (HR) and 95% confidence intervals (CI) after 1:1 matching on propensity scores predicting oseltamivir initiation, conditional on baseline covariates.

Results: Oseltamivir initiators (*n* = 149,530) and non-initiators (*n* = 84,940) had similar baseline characteristics. During the 1st month after influenza diagnosis, oseltamivir was protective against pneumonia (HR: 0.84, 95% CI: 0.77, 0.91) and hospitalization (HR: 0.65, 95% CI: 0.59, 0.72). During negative control periods, estimates moved closer to the null, though still suggesting some residual confounding: HRs of 0.86 (95% CI: 0.68, 1.09) and 0.77 (95% CI: 0.57, 1.02) for 2nd and 3rd months respectively for pneumonia. For hospitalization, HRs were 0.93 (95% CI: 0.80, 1.08) and 0.90 (95% CI: 0.76, 1.05) for 2nd and 3rd months respectively, suggesting less residual confounding.

Conclusions: Our study suggests the evidence of some residual confounding in studies of the relationship of oseltamivir and influenza complications: pneumonia and to a lesser extent, hospitalizations. Residual confounding could be due to unmeasured influenza severity and frailty. Next step is to evaluate residual confounding in the Sentinel System after stratifying on age and influenza test status.

107 | Use of Statins and Risk of Acute Exacerbations in Patients with Chronic Obstructive Pulmonary Disease

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Background: Chronic obstructive pulmonary disease (COPD) poses a substantial disease burden worldwide. A number of observational studies have reported that statins may decrease risk of acute exacerbations in patients with COPD. However, most of these studies applied a "prevalent user, non-user comparison approach", which may have methodological concerns of "healthy user bias" and comparability between treatment groups leading to overestimation of clinical effectiveness of statins.

Objectives: We aimed to examine the effectiveness of statins in reducing acute exacerbations in patients with COPD using a new user, active-comparison cohort design.

Methods: We identified patients with COPD who initiated a statin or a fibrate in the Taiwan National Health Insurance Database. Patients were followed up to the earliest of hospitalization due to acute exacerbations (i.e., outcome of interest), treatment change or discontinuation, death, or the end of the data. Stratified Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of acute exacerbations comparing statins versus fibrates after variable-ratio propensity score (PS) and high-dimensional PS (hd-PS) matching, respectively.

Results: We identified a total of 134,909 eligible patients (110,726 initiating statins and 24,183 initiating fibrates); 8,326 experienced acute exacerbations during follow-up. The HRs were 1.09 (95% CI, 0.94–1.26) after PS matching and 1.03 (95% CI, 0.89–1.20) after hd-PS matching. The results did not differ materially by patient characteristics or statin types.

Conclusions: This large-scale, population-based study did not show use of statins was associated with reduced risk of acute exacerbations in patients with COPD using state-of-the-art pharmacoepidemiologic methods. The findings emphasize the importance of methodology issues in observational studies.

108 | Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation

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Background: Non-vitamin K antagonist oral anticoagulants (NOACs) are alternatives to warfarin in patients with nonvalvular atrial fibrillation. Randomized trials compared NOACs to warfarin, but none have compared individual NOACs against each other for safety and effectiveness.

Objectives: To compare each of the NOACs (dabigatran, rivaroxaban, and apixaban) with warfarin, and with each other, for the outcomes of thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding, and all-cause mortality.

Methods: We performed a retrospective new-user cohort study of patients with nonvalvular atrial fibrillation enrolled in US Medicare who initiated warfarin (n = 183,318), or a standard dose of dabigatran (150 mg twice-daily; n = 86,198), rivaroxaban (20 mg once-daily; n = 106,389) or apixaban (5 mg twice-daily; n = 73,039) between October 2010 and September 2015. Multinomial logistic regression was used to estimate stabilized inverse probability of treatment weights for the warfarin and individual NOAC cohorts. For each outcome, a single weighted Cox proportional hazards regression model with robust estimation was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI), comparing each NOAC with warfarin, and with each other NOAC.

Results: Compared with warfarin, each NOAC was associated with reduced risks of thromboembolic stroke (20%–29% reduction; P = 0.002 [dabigatran], P < 0.001 [rivaroxaban, apixaban]), intracranial hemorrhage (35%–62% reduction; P < 0.001 [each NOAC]), and mortality (19%–34% reduction; P < 0.001 [each NOAC]). The NOACs were similar for thromboembolic stroke but rivaroxaban was associated with increased risks of intracranial hemorrhage (vs. dabigatran: HR = 1.71; 95% CI 1.35–2.17), major extracranial bleeding (vs. dabigatran: HR = 1.32, 95% CI 1.21–1.45; vs. apixaban: HR = 2.70, 95% CI 2.38–3.05), and death (vs. dabigatran: HR = 1.12, 95% CI 1.01–1.24; vs. apixaban: HR = 1.23, 95% CI 1.09–1.38). Dabigatran was associated with reduced risk of intracranial hemorrhage (HR = 0.70; 95% CI 0.53–0.94) and increased risk of major extracranial bleeding (HR = 2.04; 95% CI 1.78–2.32) compared with apixaban.

Conclusions: Among patients treated with standard dose NOAC for nonvalvular atrial fibrillation and warfarin users with similar baseline characteristics, dabigatran, rivaroxaban, and apixaban were associated with a more favorable benefit-harm profile than warfarin. Among NOAC users, dabigatran and apixaban were associated with a more favorable benefit-harm profile than rivaroxaban.

109 | Replication of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation in a Cohort Study Using Electronic Primary Care Database

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Background: Imitating the design of a randomized controlled trial in an observational study is one of the recent methodological approaches that has been developed to improve the usefulness of observational studies in assessing drug effectiveness (efficacy of drugs in routine clinical care); however, the usefulness of this approach has not been investigated from non-inferiority perspective.

Objectives: To imitate the design of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) non-inferiority trial in an observational study.

Methods: A retrospective cohort study was conducted using the British Clinical Practice Research Datalink (CPRD). Applying the eligibility criteria of the trial, patients who were diagnosed with non-valvular AF and were prescribed either rivaroxaban or warfarin (incident users) from October 2008 were included and followed to the end of the study period (December 2017). Non-inferiority of rivaroxaban to warfarin in the prevention of the composite endpoint of stroke or systemic embolism was assessed using a non-inferiority margin of hazard ratio (HR) 1.46 (the margin that was used in the triak). Cox-proportional hazards regression was used to estimate the study outcomes adjusting for time-fixed and time-varying confounders.

Results: We included 25,473 incident users of rivaroxaban (n = 4,008) or warfarin (n = 21,465). Similar to the trial, non-inferiority in the primary outcome was demonstrated: HR 1.04 (95% confidence interval [CI] 0.84 to 1.30) in the intention-to-treat population and in another two analysis populations. The target population of the trial is mostly treated in the real-world settings (i.e. the proportion of patients who did not meet the exclusion criteria was small), thus affecting the precision of analysis in the latter. Finally, the event rate of the primary outcome in warfarin

group was lower compared with that in the trial and this may affect the applicability of the trial's non-inferiority margin in our study.

Conclusions: imitating the design of a non-inferiority trial in observational study led to consistent results with that of the trial in similar patient population, however, an adjustment for the trial's non-inferiority margin is needed to take into account the variation in the effect of the active comparator in observational settings.

110 | Carboplatin-Based Chemotherapy (C) versus Immunotherapy (IO) in Metastatic Urothelial Carcinoma (MUC)

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Background: There are limited data comparing first-line (1 L) C versus IO in cisplatin-ineligible mUC patients. The primary evidence guiding treatment decisions was a May 2018 Food and Drug Administration (FDA) safety alert based on early review of two ongoing phase III trials, reporting shorter survival in PD-L1 negative patients receiving IO relative to chemotherapy. Final results from these trials are unknown and may not be applicable to a real-world cohort.

Objectives: To compare the effectiveness of C versus IO in first-line cisplatin-ineligible mUC patients.

Methods: We conducted a retrospective cohort study of mUC patients receiving 1 L C or IO from January 1, 2011 to May 18, 2018 using the Flatiron Health electronic health record-derived database. The primary outcome was overall survival (OS) from start of 1 L treatment to date of death. We compared 12- and 36-month OS, and hazard ratios before and after 12 months. Propensity score-based inverse probability of treatment weighting (IPTW) was used to address confounding in Kaplan–Meier (KM) and Cox multivariable regression model estimates of comparative-effectiveness.

Results: Of 2,243 patients (median age 76, 73% male, 74% white, 73% smokers, 7% PD-L1 tested), 562 received IO and 1,681 received C. Baseline characteristics were balanced between IO and C initiators, with exception of IO initiators having a worse ECOG performance status (ECOG $\geq$2: 22% vs 12%) and mean Elixhauser comorbidity score (2.28 vs 1.07). IPTW-adjusted KM curves showed 12-month and 36-month OS rates were 40.7% and 29.1% in IO and 46.4% and 13.7% in C initiators. In the first 12 months, IO was associated with an increased hazard of death compared to C (HR 1.38, 95% CI 1.16–1.66). Among patients who survived one year, survival was improved with IO compared to C (HR 0.50, 95% CI 0.27–0.92).

Conclusions: In routine clinical practice, 1 L IO was associated with inferior 12-month OS relative to C, but superior OS beyond 12 months. Clinicians and patients should carefully consider how to balance the early benefit of C against the late benefit of IO. Currently pending trial results will contribute additional evidence to inform treatment decision making.

111 | Optimal Duration of Anticoagulant Thromboprophylaxis in Total Hip Arthroplasty - New Evidence in 55,540 Patients with Osteoarthritis from the Nordic Arthroplasty Register Association (NARA) Group

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Background: The recommended optimal duration of the thromboprophylaxis treatment among total hip arthroplasty (THA) patients has been a matter of debate for years.

Objectives: We examined the association between short (1–5 days), standard (6–14 days) and extended (> = 15 days) duration of thromboprophylaxis, with regards to the risk of VTE, major bleeding, and death in unselected THA patients.

Methods: We performed a cohort study using prospectively collected data from the population-based hip arthroplasty registries, prescription databases and patient administrative registries in Denmark and Norway. We included primary THA patients with osteoarthritis (OA) (n = 55,540).

Results: The 90-day cumulative incidence of VTE was 1.0% for patients with standard treatment (reference), 1.1% for those with short-term treatment (adjusted hazard ratio (aHR) of 1.1, 95% confidence interval (CI) 0.8–1.5) and 1.0% for those with extended treatment (aHR of 0.9, CI 0.8–1.2). The aHRs for major bleeding were 1.1 (CI 0.8–1.6) for short and 0.8 (CI 0.6–1.1) for extended vs. standard treatment. In addition, patients with short and extended treatment had aHRs for death of 1.2 (CI 0.8–1.8) and 0.8 (95% CI 0.5–1.1) vs. standard treatment, respectively. Patients who started short treatment postoperatively had aHR for death of 1.8 (CI 1.1–3.1) and absolute risk difference of 0.2%, whereas patients who started short treatment preoperatively had aHR for death of 0.5 (CI 0.2–1.2) and absolute risk difference of 0.3% compared to patients with standard treatment post and preoperatively start, respectively.

Conclusions: In routine clinical practice, we observed no overall clinically relevant difference in the risks of VTE and major bleeding within 90 days of THA with respect to thromboprophylaxis duration. However, our data indicates that short-term thromboprophylaxis started postoperatively is associated with increased 90-day mortality. The significance of these data should be explored further.

112 | Causal Inference Modeling in Comparative Effectiveness Research for Antiplatelet Agents

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Background: Because the randomized controlled trials (RCT) have shown significant benefits of ticagrelor in preventing ischemic endpoints when compared to clopidogrel, time-varying confounding and informative censoring pose a challenge in real-world data studies.

Objectives: To apply causal modeling to quantify the effect of antiplatelet agents on preventing ischemic events by addressing time-varying confounding and selection bias due to informative loss to follow-up.

Methods: This study included patients who underwent percutaneous coronary intervention (PCI) due to an acute coronary syndrome (ACS) from 2011 to 2015 captured by the Optum Clinformatics™ database. Patients were excluded with a contraindication to either agent, fibrinolytic therapy, oral anticoagulation, or concomitant use with P-450 inducers or inhibitors. Five methodologies were employed: PP, ITT, AT, time-varying exposure (TD), intention to treat (ITT-CW) and time-varying exposure (TD-CW) both with censoring weights. The primary outcome was composite incident myocardial infarction (MI), ischemic stroke, or death. Patients were followed until the event, one calendar year, or end of insurance eligibility. We used marginal structural Cox models fit with inverse probability treatment and censor weighting to adjust for time-varying confounding and censoring and with a robust sandwich variance estimator to account for the within-cluster correlation.

Results: There were 17,344 patients initiated on clopidogrel and 2,457 initiated on ticagrelor with no difference in unadjusted rates of MI, stroke, or death (T: 5% vs C: 6%). Patients initiated on ticagrelor were younger (64.8 years vs 65.6 years), more male (68% vs 62%), had higher rates of hypertension (77% vs 72%), hyperlipidemia (73% vs 66%), medication switching (25% vs C: 3%), and loss of eligibility (47% vs 39%) than those on clopidogrel. The PP (HR: 1.0, 95%CI: 0.69–1.5), ITT (HR: 0.93, 95%CI: 0.77–1.1), AT (HR: 1.1, 95% CI: 0.87–1.3) approaches showed no difference in MI, stroke, or death between clopidogrel and ticagrelor groups. The TD and CW methods showed a 9%–13% reduction in risk (TD HR: 0.89, 95%CI: 0.73–1.1; ITT-CW HR: 0.91, 95%CI: 0.75–1.1; TD-CW HR: 0.87, 95%CI: 0.71–1.1), which are more consistent with the RCT results although did not achieve statistical significance.

Conclusions: Informative censoring should be considered when artificial censoring and imbalances of loss to follow-up occur between comparison groups. Accounting for time-varying confounding due to unbalanced drug switches can lead to improvements in the accuracy of effect estimates.

113 | Comparing the Safety of Apixaban, Rivaroxaban and Dabigatran: Indirect Treatments Comparisons Using Real-World Studies

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Background: According to the direct comparisons from observational studies using real-world evidence, the risk of bleeding is lower with apixaban compared to rivaroxaban and dabigatran, when used to prevent stroke in patients with atrial fibrillation.

Objectives: This study is aimed at comparing the risk of bleeding of apixaban with rivaroxaban and dabigatran, through adjusted indirect treatment comparisons.

Methods: A literature search was conducted to identify real-world data studies assessing the safety of apixaban, rivaroxaban and dabigatran to prevent stroke in patients with atrial fibrillation, using warfarin as control. Outcome measures included major bleeding, gastrointestinal bleeding and intracranial bleeding. Relative risks and 95% confidence intervals were estimated. Adjusted indirect treatment comparisons were performed using STATA 13.0.. Chi-square test assessed between-studies heterogeneity, identified when $p < 0,05$.

Results: Twenty-one studies were included. Apixaban reduced the risk of major bleeding compared with rivaroxaban (RR 0,53; 95%CI 0,44 - 0,63; heterogeneity: p < 0,0001) and dabigatran (RR 0,58; 95%CI 0,44-0,76; heterogeneity: p < 0,0001). The risk of gastrointestinal bleeding is low with apixaban when compared with rivaroxaban (RR 0,46; 95%CI 0,33-0,65; heterogeneity: p < 0,0001) and dabigatran (RR 0,31; 95%CI 0,20-0,49; heterogeneity: p < 0,0001). For intracranial bleeding, no risk differences were identified between apixaban and the other two anticoagulants.

Conclusions: The results of this adjusted indirect treatment comparison are in line with the evidence from direct comparisons, where apixaban demonstrated to be safer than rivaroxaban and dabigatran in real-world clinical practice. However, between studies heterogeneity was identified in the risk estimates.

114 | Statin Use and Fall-Related Hospitalizations among Residents of Long Term Care Facilities: A Case–Control Study

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Background: Statins are associated with muscle-related adverse events but few studies have investigated the possible association with fall-related hospitalizations among residents of long-term care facilities (LTCFs).

Objectives: To investigate whether statin use is associated with fall-related hospitalizations among residents of LTCFs.

Methods: A case–control study was conducted among residents aged ≥65 years admitted to hospital from 2013–2015. Cases were residents admitted for falls and fall-related injuries. Controls were residents admitted for infections. Cases and controls were matched 1:1 by age (±2 years), index date of admission (±6 months) and sex. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression for statin use in residents admitted for falls compared to infections. Models were adjusted for history of falls, hypertension, dementia, functional comorbidity index, polypharmacy (nine or more regular pre-admission medications) and falls risk medications. Unmatched sub-analyses were performed for residents with and without dementia, and comparing high vs low/moderate intensity statin use.

Results: Overall, 32% of cases and 22% of controls used statins. Statin use was associated with fall-related hospitalizations (aOR = 2.34, 95%CI 1.27–4.33). After stratifying by dementia status, statin use was only associated with fall-related hospitalizations among residents with dementia (aOR = 3.27, 95%CI 1.26–8.47). There was no association between statin intensity and fall-related hospitalizations (aOR = 2.19, 95%CI 0.75–6.40).

Conclusions: Statin use is associated with fall-related hospitalizations from LTCFs, particularly among residents with dementia. However, there is minimal evidence for a dose-dependent relationship between statin intensity and fall-related hospitalizations.

115 | Risk of Culpable Traffic Accident by Frailty in Drivers with Advanced Age

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Background: Although older drivers has been increasing, medical screening of older drivers is not evidence based.

Objectives: This study was conducted to evaluate the influence of the frailty measured from claims data on the risk of culpable traffic accident.

Methods: Setting: We extracted the data of drivers who died of motor vehicle crashes (MVCs) during 2010–2014 from the Korean Traffic Accident Analysis System and linked it to the Korean National Health Insurance database. **Main outcome measures**: We calculated the responsibility score of an accident to quantify the driver's culpability using the responsibility analysis method, which will categorize drivers into culpable drivers (responsibility score < 12) or non-culpable driver (responsibility score ≧ 12). **Exposures:** Frailty score using ICD-10 codes was calculated to categorize driver's frailty into low risk (frailty score < 5), intermediate risk (frailty score 5 to 15), and high risk (frailty score ≧ 15). **Statistical analysis**: Logistic regression analysis was used to evaluate the influence of frailty on the culpability of drivers, adjusting for age, sex and medications which were known to be related to traffic accidents.

Results: We found 8,881 deaths during the study period, among whom 8,828 were successfully linked to the national insurance data. Among them, 2,081 drivers were categorized into the culpable group and 6,747 into non-culpable group. The mean age of the participants was 48.9 (±17.7), and 8,169 (92.5%) were males. Culpable drivers had more frequent prescription of hypnotics, narcotics, muscle relaxants, and antispasmodics 1 year prior to the traffic accidents. When adjusted for demographic factors and medications, high frailty (odds ratio 1.224: 95% confidence interval 1.030–1.454) was significantly related to the culpable crashes. Interestingly, age older than 65 was protective against culpable accidents (0.995: 0.992–0.998).

Conclusions: High frailty score measured using claims data was associated to the culpable traffic accident which could be attributed to the fault of driver. Methods to screen drivers with advanced age using frailty score will help preventing traffic accident related to aging of drivers.

116 | Multidose Drug Dispensing and Longitudinal Changes in Psychotropic Prescribing Patterns among Older Adults: National Matched Cohort Study

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Background: An increasing number of frail and multimorbid older adults are dispensed drugs in machine-packed disposable pouches that contain all the drugs that are intended for a given dose occasion ('multidose'). It has been suggested that multidose may promote psychotropic overuse.

Objectives: We aimed to compare the use of psychotropic drugs before and after the transition to multidose drug dispensing among older adults in Sweden.

Methods: Matched cohort study using individual-level drug dispensing data with national coverage in Sweden. Older adults (≥65 years) who initiated multidose drug dispensing between 1 January and 31 December 2013, matched 1:2 on sex, age and index date with older adults who remained on manually dispensed medications. Initiation of multidose dispensing was assessed using a 5-year washout period. Study participants were followed from 24 months before until 24 months after the index date, with censoring at time of death or

emigration. Main outcome was psychotropic polypharmacy (≥3 drugs acting on the CNS).

Results: A total of 31,612 cases and 63,224 controls were included. Mean age at index date was 83.9 (7.4) years. The prevalence of psychotropic polypharmacy increased substantially among multidose initiators, from 15.1% two years before the transition, to 37.5% the month after, up to 43.7% two years after. This psychotropic polypharmacy was fueled by a dramatic increase in the incident use of long-acting benzodiazepines (e.g. clonazepam), Z-drugs (e.g. zopiclone), strong opioids, antipsychotics, antidepressants, and - to a lesser extent - antidementia drugs. For instance, the incidence rate of benzodiazepine initiation increased from 0.70 per 1000 person-month 12 months before multidose initiation to 4.78 per 1000 during the first month after. No change was observed among controls.

Conclusions: Older adults who switch to multidose drug dispensing are at high risk of adverse drug-related events due to a sustained increase in exposure to substantial psychotropic polypharmacy.

117 | Danish Health Care Professionals' Attitudes towards Deprescribing in Older Patients with Limited Life Expectancy: A Qualitative Focus Group Study

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Background: Deprescribing may be particularly relevant in older patients with limited life expectancy as many preventive medications can no longer be expected to provide clinical benefit at this point in life. In order to effectively carry out deprescribing in this population, it is important to understand the perspectives of health care professionals involved in the management of these patients' medication.

Objectives: To explore different health care professionals' attitudes towards deprescribing in older patients with limited life expectancy.

Methods: Six focus group interviews were conducted, using a semi-structured approach, with a) health care assistants (*n* = 5), b) nurses (*n* = 6), c) clinical pharmacists (n = 6), d) geriatricians (n = 5), e) general practitioners (n = 5), and f) clinical pharmacologists (n = 5). Interviews were audio recorded and transcribed verbatim. Results were analyzed using systematic text condensation.

Results: The analysis elicited three themes related to health care professionals' attitudes towards deprescribing in older patients with limited life expectancy, namely 1) how different health care professionals approach deprescribing in this population, 2) how different health care professionals perceive their own as well as others responsibility/role in the deprescribing process, and 3) how collaboration and recognition between different health care professionals impact the deprescribing process.

The participants recognized the importance of deprescribing and considered it as being an essential aspect of providing good care for older patients with limited life expectancy; however, they also considered several characteristics related to the patient population to complicate the deprescribing process. Although the general practitioners generally were seen as those being primarily responsible for such deprescribing initiatives, a general perception was that all health care professionals have an important role to play in the deprescribing process. Despite this, the participants also considered some groups of health care professionals to be lacking in taking the necessary responsibility as well as not acknowledging other groups' skills/competencies.

Conclusions: Our results imply that Danish health care professionals recognize the importance of deprescribing among older people with limited life expectancy. However, uncertainty about how to approach deprescribing in this population as well as lack of responsibility and acknowledgement may complicate or hinder deprescribing initiatives.

118 | Frailty and Use of Psychotropic Medications in Long-Stay Nursing Home Residents

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Background: Frailty, characterized by decline of physical function and physiologic reserve, affects 30–89% of older adults in nursing homes (NH) and may also predict adverse health outcomes. Psychotropic medication is extensively used in older adults in NHs and is associated with higher risk of falls, hospitalization, and mortality.

Objectives: To examine use of psychotropic medication by frailty status in long-stay NH residents in the U.S.

Methods: The Minimum Data Set (MDS) 3.0 assessment is mandated for all Medicare/Medicaid-certified NHs. Using MDS 3.0 data from 2015, we identified 265,101 newly-admitted, long-stay NH residents. Frailty was defined by FRAIL-NH, a scale with MDS 3.0 items on fatigue, resistance, ambulation, incontinence, weight loss, nutrition approach, and help with dressing. At baseline and at the 90-day assessment, residents were categorized as non-frail (0–5), pre-frail (6–7) and frail (8–14) based on their FRAIL-NH score at baseline. Psychotropic medication use was measured by the receipt of antipsychotic, antianxiety, antidepressant and hypnotic medications in the past 7 days.

Results: At admission, 34% were aged 75–84 years, 44% were 85 or older, and 66% were women. Fifty-nine percent had moderate and 20% had severe impairments in activities of daily living. Most were cognitively impaired; 29% had moderate and 39% had severe cognitive impairment. Depression diagnosis was present in 39% of residents. At admission, 28% were pre-frail, of whom 31% were frail at the 90 assessment. Of the 56% of the residents with frailty at admission, 82% remained frail at the 90 assessment. Similar rates at admission and the 90-day assessment were observed for receipt of antipsychotic (20%), antianxiety (20%) and hypnotic (4%) medications, with no substantial variation across frailty levels. Receipt of antidepressants in all residents increased from 46% at admission to 53%

by 90 days, with the highest increase in those who were frail, from 47% to 54%. In residents with frailty, 61% were on at least one psychotropic medication at admission, which increased to 67% at the 90 assessment.

Conclusions: Psychotropic medication use is high at admission, regardless of frailty status, but appears to increase in residents with frailty in the first 90 days of a NH stay. Additional research is needed to assess if psychotropic medication use in NH is appropriate and the extent to which the presence of frailty places residents at higher risk for adverse health outcomes associated with psychotropic medications.

119 | Meaningful Measurement Matters: How to Best Define Potentially Inappropriate Medication Use to Target Cognitive Outcomes

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Background: Deprescribing in the geriatric population is often focused on improving clinical outcomes, such as preventing cognitive or functional decline (CFD). Clinicians may consider polypharmacy or consult explicit lists of potentially inappropriate medications (PIM) when deprescribing. However, the association between measures of PIM use and CFD has not been well established.

Objectives: In this study, we aim to 1) estimate the prevalence of PIM use for those with and without cognitive or functional impairment (CFI), and 2) identify the PIM measure that best predicts risk of CFD after one year.

Methods: We used 2005–2017 data from adults aged ≥65 years compiled by the National Alzheimer's Coordination Center. First, in a cross-sectional study, we assessed the prevalence of CFI (Clinical Dementia Rating [CDR] global score ≥ 0.5) and PIM use at enrollment. We considered eight PIM definitions based on polypharmacy (≥4 and ≥ 5 total medications) and the number of medications present in existing explicit criteria (≥1, ≥4, and ≥ 5 medications in Beers' 2015 and STOPP). Then, in a retrospective cohort study, we investigated which definition of PIM use at enrollment best predicted CFD (defined as an increase in the CDR sum of boxes score after one year). We used Poisson regression to calculate risk ratios (RR) and 95% confidence intervals (CI) adjusted for baseline clinical and demographic characteristics.

Results: We assessed PIMs and CFI prevalence at enrollment for 24,522 subjects (56.0% female; mean age 75.8 [SD 6.9] years). 62.7% of subjects had some degree of CFI. PIM prevalence ranged from 58.5% (STOPP) to 74.2% (polypharmacy, ≥4 medications). In the cohort study, 16,354 subjects experienced CFD after one year. There were no clinically significant correlations between the CFD risk and the PIM definitions of polypharmacy or ≥ 1 medication in either criteria. However, subjects who reported ≥4 or ≥ 5 medications in the Beers' criteria or ≥ 5 medications in STOPP at enrollment had a higher risk of CFD compared to patients who reported no such medications (RR [CI] 1.33 [1.08–1.64] and 1.46 [1.12–1.89] respectively for Beers'; 1.41 [1.14–1.74] for STOPP).

Conclusions: The results of this study indicate that neither polypharmacy nor ≥1 medication in Beers' and STOPP criteria predict CFD well. Clinicians may consider focusing their deprescribing efforts on the total burden of PIMs (using Beers' or STOPP) to decrease CFD risk in the geriatric population. Further research into the clinical relevance of existing tools used to identify PIM use is warranted.

120 | Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and the Risk of Suicide: A Nested Case Control Study

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Background: Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used to lower blood pressure. Both drug classes have central effects which include modulation of neurotransmitter release and may influence mood and mental health. Recent studies suggest ARBs, but not ACEIs, may increase the risk of suicide.

Objectives: The objective of this study was to examine the association between suicide and uste of ARBs relative to ACEIs among older adults.

Methods: We conducted a population-based nested case–control study among over 2.3 million residents of Ontario, Canada aged 66 years and older from January 1st, 1995 to December 31st, 2013. Cases were patients who died of suicide within 100 days of receiving a prescription for an ACEI or ARB. Cases were matched 4:1 using on age, sex, and previous diagnoses of hypertension and diabetes. We compared baseline characteristics of cases and controls and used multivariable conditional logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for potential confounders.

Results: Over the 18-year study period, we matched 820 cases to 3,280 controls exposed to either an ACEI or ARB within 100 days prior to the index date. In the primary analysis, relative to ACEIs, ARB exposure was associated with a higher risk of suicide (adjusted odds ratio = 1.73; 95% CI = 1.38–2.17).

Conclusions: We found that ARBs were associated with a higher risk of suicide relative to ACEIs. The mechanisms explaining how ARBs or ACEIs might have differential risks of suicide are unknown. Our findings should be considered preliminary and need to be replicated in future studies. Given the high prevalence of use of these medications, the outcome severity, and the interchangeability of these drug classes for the same indications clinicians may opt for preferential use of ACEIs over ARBs where possible.

121 | Impact of a new pharmaceutical care model on polymedication and potentially inappropriate medications in long term care facilities in Canada

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Background: Polypharmacy and potentially inappropriate medications (PIMs) are known to be predominant in long-term care (LTC) facilities and are associated with morbidity. A new pharmaceutical care model based on inter-professional collaboration and pharmacists' expanded scope of practice might improve pharmacotherapy in LTC facilities.

Objectives: The purpose of this study was to determine the impact of a new model on (1) the number of medications prescribed and the proportion of individuals exposed to excessive polypharmacy (at least 10 medications) and (2) the proportion of individuals receiving at least one PIM, in elderly living in LTC facilities.

Methods: We performed a quasi-experimental study. Eligible patients were aged 65 and over living in 2 LTC facilities exposed to the pharmaceutical care model (±359 beds) and 2 non-exposed LTC facilities (±241 beds). The new model was implemented during 12 months through educational sessions offered to all health care professionals. The new model proposed to take advantage of pharmacists' expanded scope of practice and thorough medication reviews to empower pharmacists and nurses in collaborating for a more efficient resolution of pharmacotherapy problems among residents. Data on medications and clinical information was obtained through electronic records. We computed all active prescriptions at a specific day at 0, 3, 6, 9 and 12 months following the beginning of implementation to assess (1) the average number of prescribed medications per resident and the proportions of seniors exposed to excessive polypharmacy and 2) the proportion of seniors receiving at least one PIM, according to the 2015 Beers criteria. We compared exposed and non-exposed groups before and after implementation.

Results: The total number of prescriptions per patient went from 11.53 ± 4.83 to 9.49 ± 4.25 (exposed group) and from 13.59 ± 5.24 to 13.15 ± 5.14 (non-exposed group). The average number of regular prescriptions per patient went from 9.17 ± 4.02 to 7.05 ± 3.42 drugs (exposed group) and from 9.56 ± 3.96 to 8.85 ± 3.88 (control group). The proportion of elderly receiving excessive polypharmacy went from 63.4% to 45.7% (exposed group) and from 76.9% to 76.0% (non-exposed group). The proportion of seniors receiving at least one PIM went from 60% to 56% (exposed group) and from 73% to 69% (non-exposed group).

Conclusions: Although PIM use decreased in both groups, the pharmaceutical care model led to the reduction of excessive polypharmacy and overall medication consumption. The impact of such medication burden reduction on health outcomes has to be evaluated.

122 | Abstract Withdrawn

123 | How to estimate long-term treatment effects in multiple sclerosis registry studies

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Background: Analysis of long-term treatment effects in patients with relapsing–remitting multiple sclerosis (MS) can be challenging, particularly as patients may discontinue treatment or switch disease-modifying treatments (DMTs) over time. The main issue is to define long-term effects regarding exposure, outcome, and models, and to determine which estimand is most relevant.

Objectives: To assess effects of treatment change over time, adjusting for other confounders, with different estimands and models, using data from the Swedish MS register.

Methods: Between 1997–2014, patients initiating subcutaneous (sc) interferon-beta (IFNβ)-1a (n = 1413) or intramuscular (im) IFNβ-1a (n = 2378) were followed from first prescription until death, conversion to secondary progressive MS, or loss to follow-up, whichever occurred first. Main outcome was time to disability progression. We considered two populations: 1) *discontinuous exposure* - patients remained exposed regardless of treatment changes over time, and 2) *continuous exposure* - patients censored at treatment discontinuation. Analyses with Cox cause-specific models and Fine & Gray models were compared considering discontinuous and continuous exposure definitions. Depending on populations considered, death and treatment discontinuation were competing risks. For discontinuous exposure, Cox Marginal Structural Models (MSM) adjusted for post-baseline treatments and relapseswereused. All models were adjusted for baseline confounders.

Results: For discontinuous exposure, the risk of disability progression was significantly higher, except with MSM, for im IFNβ-1a exposure vs. sc IFNβ-1a exposure, with an adjusted hazard ratio (aHR) of 1.23 (95% Confidence Interval [95%CI; 0.98–1.53]) in the MSM, 1.28 [95%CI 1.04–1.57] in the Cox model, and 1.28 [95%CI 1.04–1.56] in the Fine & Gray model. For continuous exposure, the risk of disability progression was not significant differently between DMTs with an aHR for im IFNβ-1a vs. sc IFNβ-1a of 1.06 [95%CI 0.78–1.43] in the Cox model and 1.24 [95%CI 0.92–1.68] in the Fine & Gray model.

Conclusions: Magnitudes of aHR were similar in all models, except for continuous exposure in the Cox model. Discontinuous exposure might better capture treatment effects in day-to-day practice with gaps and

switches. This study supports the use several exposure definitions to assess the impact of treatment changes on the relative benefit attributable to DMTs. Estimand frameworks proved useful in navigating through the nuances of interpretation from different exposure populations and models.

124 | Recommendations for disproportionality analysis in small databases

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Background: Disproportionality analysis (DA) is the most common quantitative approach to guide signal detection in collections of spontaneous reports. Yet, little is known about when DA can be expected to be robust. Such knowledge would be useful for countries and other organizations with newly set up pharmacovigilance systems, and for signal detection software users.

Objectives: To determine safe lower limits on the number of reports for performing DA in (i) general subsets of larger databases, and (ii) country-specific databases.

Methods: 500 subsets each of sizes between 500 and 100,000 reports were randomly sampled from VigiBase, the WHO Global Database of ICSRs, as of 31st December 2017. In addition, each subset of reporting country of origin was studied. For each subset, a permutation analysis was performed to determine the rate of spurious DA associations: first, the number of drug-event combinations with a positive lower endpoint of a 95% credibility interval for the Information Component measure ($IC_{025} > 0$) was computed. Then, the drugs of each report were paired with the events of a randomly selected report, and the IC analysis was repeated on this permuted version of the subset. The spurious rate was then computed as the ratio between the number of associations in the permuted data and the number of associations in the original data. If there were fewer than 5 associations in the original data, the subset was excluded from analysis.

Results: The spurious rate converged to a value of about 10% with growing subset size, both for the random and the country-specific subsets. 21 countries were excluded because of too few associations, all of which had fewer than 500 reports. Among the remaining 110 countries, the median spurious rate was 7.0% (range 0.0%–14%), with only 7 countries exceeding a spurious rate of 10%. For the random subsets of sizes between 500 and 2,000 reports, the median spurious rate was low (0.0%–7.2%), but variability was considerable: consistently, more than 1/5 of the data sets exhibited a spurious rate above 10%. For subset sizes between 3,000 and 5,000 reports, this proportion varied roughly between 1/8 and 1/20, and for subsets of 7,500 reports or more, it was close to zero.

Conclusions: For DA in generically constructed subsets of databases of spontaneous reports, we recommend a lower subset size of about 3,000–5,000 reports. For DA in country-specific databases, we recommend at least 500 reports. However, while DA may produce robust results in very small databases, its utility is likely to be minor as few associations will be generated. Signal detection based on case-by-case assessment is likely to be more effective in such cases.

125 | Missing data techniques in longitudinal epidemiologic research: A case study

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Background: Missing data are pervasive in observational research, particularly in longitudinal studies. Researchers often exclude patients with missing outcome data when calculating treatment response rates, but this results in loss of statistical power and may impact validity. There are several alternative approaches for addressing missing data and the choice of method can have a profound impact on interpretation of results.

Objectives: To present alternative imputation methods for the handling of missing outcome data and to compare their impact on calculation of treatment response rates.

Methods: These analyses used real world data from a prospective cohort study of patients receiving drug therapy for a non-fatal chronic disease. The primary outcome was proportion of patients in remission after 6, 12, 24, and 36 months of drug therapy. At each time point, a patient could be in remission, not in remission, or have missing outcome data. As alternatives to excluding patients with missing outcome data (Complete Case Analysis), the following imputation methods were applied to the data: (1) assuming all missing observations were remission [responder imputation], (2) assuming all missing observations were not remission [non-responder imputation], (3) last observation carried forward [LOCF], (4) multiple imputation [MI], and (5) inverse probability weighting [IPW].

Results: At 6 months follow-up, 30.5% of patients were missing outcome data. Remission rates were: Complete Case Analysis, 61.0%; responder imputation, 72.9%, and non-responder imputation 42.4%. At 36 months, 20.7% of patients were missing outcome data. Remission rates were: Complete Case Analysis, 36.9%; responder imputation, 50.0%, and non-responder imputation 29.3%. MI and IPW analyses yielded remission rates similar to Complete Case Analysis except at 36 months, where MI was lower (33.7%), while LOCF finding were consistently lower than Complete Case analysis.

Conclusions: Consideration needs to be given to the analysis of missing data and how this impacts interpretation of treatment response rates. For transparency, a range of imputation methods should be included in a standard analysis. Although inherently biased, responder

and non-responder imputations are simple to calculate and useful in providing upper and lower estimates of the unknown true remission rate. In this case study, Complete Case, MI and IPW analyses yielded similar results, suggesting that outcome data were missing completely at random.

126 | Prospective testing of hypothesis-free signal detection utilizing a disturbance algorithm: Nifedipine use case

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Background: Hypothesis-free signal detection within Longitudinal Observational Databases (LODs) is an emerging field of pharmacovigilance research with no consensus on best practice. Methodologic developments and evaluations are, however, of interest to regulators, academics and pharma. The chronograph has shown promise in pharmacovigilance work; however, manual review can be time consuming. The prospective application of a disturbance algorithm filter may be an effective tool for triaging clinical reviews. A methodological study was initiated to evaluate the feasibility for hypothesis-free signal detection in LODs.

Objectives: To develop and test a systematic approach for hypothesis-free signal detection equipped to highlight signals of disproportionate recording (SDRs) for integration into existing signal management systems and processes.

Methods: .A process model was developed via team consensus to ensure study reproducibility and integration with routine signal detection processes. Nifedipine data within the Truven MarketScan database (2010–2015) were evaluated and chronographs were generated for 1,461 pre-identified drug-event pairs. An ARIMA-based disturbance algorithm was applied to each chronograph to identify chronographs that contained clear indications of an increase in Information Component scores that might be indicative of SDRs. The subsequent data matrix was analyzed and outliers were compiled for clinical review and SDR determination.

Results: Following data logic checks, 87% (n = 1,275) of the drug-event pairs were excluded because signals either occurred prior to drug exposure or were in a negative direction. A total of 186 drug-event pairs were eligible for pattern review. Of those, approximately 54% (101 of 186) were excluded as non-SDRs leaving 85 drug-event pairs for clinical review. Following clinical review, 30 drug-event pairs were conditionally validated as SDRs, 33 were not considered SDRs and 22 were known or labeled events associated with nifedipine. Difficulties determining the timing of drug exposure relative to maternal and neonatal events were, however, noted. The review extended over a 3 hour period with the support of a clinician and 2 epidemiologists.

Conclusions: Hypothesis-free signal detection in LODs is tractable and aligns with routine signal detection processes. Although limited signal detection capability enhancement was seen with nifedipine, the data suggest that signal detection in LODs may have a complementary role to signal detection in spontaneous reports and other data sources from a process-driven perspective.

127 | Toxicity latent classes in chemotherapy-refractory, metastatic colorectal cancer patients treated with anti-epidermal growth factor receptor monoclonal antibody: Latent class analysis of clinical trial data

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Background: Cancer patients experience concurrent and inter-related toxicities. Little is known about the clinical factors that predict these toxicities.

Objectives: To identify, among metastatic colorectal cancer patients (mCRC) receiving anti-epidermal growth factor receptor (EGFR) monoclonal antibody, subgroups of patients with similar toxicities and to asses their association with clinical characteristics.

Methods: There were 660 participants randomized to treatment with anti-EGFR monoclonal antibody. We selected 14 toxicity indicators for the latent class analysis. Six patient-reported toxicities, graded according to NCI's Common Terminology Criteria at grade > 3 and prevalence of >5%: fatigue, pain, dyspnea, rash, infection, and anorexia and eight laboratory tests: granulocyte count ($<1.5x10^9$/L), platelet count ($<75x10^9$/L), hemoglobin (<80 g/L), total bilirubin (>1.5X upper limit of normal (ULN) or 2.0X ULN with liver metastasis), ALT and AST (>2.5X ULN or 5.0X ULN with liver metastasis), serum creatinine (>1.5X ULN) and magnesium (<0.5 mmol/L). Latent class analysis was implemented using a Bayesian stabilizing prior to handle sparseness and adjusting estimates for clustering by study center. Optimal number of latent classes was determined using Bayesian Information Criterion (BIC). The relation between age, sex, primary site of tumor, and liver metastasis and latent class membership was examined.

Results: We identified three classes: all low toxicity (75.1%), all high toxicity (18.7%) and high renal toxicity (6.2%). Age, sex and liver metastasis predicted class membership (p < 0.01). Odds ratios (OR) were estimated relative to the all low toxicity class. For every year increase in age the odds of all high toxicity class membership increased by 1.01 (95% confidence interval [CI]: 1.00, 1.02) and the odds of renal toxicity class membership by 1.01 (95%CI: 1.00, 1.02), male sex was associated with decreased odds of all high toxicity class membership (OR: 0.80 (95%CI: 0.72, 0.89) and renal toxic-

ity class membership (OR: 0.82, 95%CI: 0.68, 0.98). The presence of liver metastasis was predictive of all high toxicity class membership (OR: 5.95, 95%CI: 3.43, 10.30) but not renal toxicity class membership (OR: 0.27, 95%CI: 0.23, 0.32).

Conclusions: Three toxicity latent classes were identified that may help guide more individualized toxicity interventions in mCRC patients given anti-EGFR monoclonal antibodies.

128 | Identifying risk factors for 30-day hospital readmissions among heart failure patients using machine-learning techniques

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Background: Understanding patients most at risk for hospital readmission is of great interest to clinicians and policymakers. Heart failure (HF) patients are known to have a substantial risk for early hospital readmission, but prior studies show fairly low predictive accuracy. For example, a recent machine-learning (ML) analysis using data from a single US hospital had an AUC of 0.64 (Kutyifa, 2018, Cardiology Journal).

Objectives: The objective of this study was to identify risk factors for 30-day readmissions among HF patients using an ML approach.

Methods: This single cohort retrospective analysis used the HealthCore Integrated Research Database (HIRD), an administrative claims database with over 50 million members. The study cohort consisted of patients with a first-listed diagnosis of HF between 1/1/08 and 3/31/15, one year of eligibility prior to the HF hospitalization ("Index"), and at least 30 days of eligibility following discharge from the index stay. A priori defined features included patient characteristics, index stay characteristics, and baseline resource use. Additional features were generated empirically based on the frequency of medications, diagnoses, and procedures summarized to a CCS or Multum level for the year prior to index and during the index stay. An ML model using XGBoost with all features and a 15% holdout with a 75%/25% train/validation split was used. The most important features were described. The analysis was undertaken using the Instant Health Data (IHD) platform (BHE, Boston, MA, USA).

Results: A total of 112,653 HF patients were identified (median age: 70 years; 47% female), of whom 19.9% were readmitted within 30 days. The ML model's performance was: Accuracy: 71.7%, AUC: 67.3%, Recall: 60.0%, Precision: 36.5% and F1: 0.45. Important features identified included patient demographic characteristics (eg, age, region), discharge status, admission through the emergency department (ED), baseline resource use (eg, number of inpatient visits, number of ED visits), select clinical characteristics (eg, cardiovascular, ophthalmic, and infectious diagnoses), and cardiovascular and infection-related medication use (eg, beta-blockers, macrolides). The Quan-Charlson and Elixhauser Comorbidity Indexes and the LACE index were identified as important predictors as well.

Conclusions: In this cohort of HF patients, our ML approach identified risk factors for 30-day readmission that were similar to a previous study, with a slightly higher AUC. Further testing and evaluation would be useful in varied databases with additional information from clinical notes.

129 | Replication of risk characterization in a cohort with women with advanced ER+/HER2- breast cancer using a new analytic tool

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Background: Estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BCa) is the most common subtype of BCa. Identifying a cohort of women with advanced ER+/HER2- BCa using real world data (RWD) allows for risk characterization and contextualization of potential safety concerns in this population. There is an increasing interest to improve the speed of safety analyses.

Objectives: Use a rapid-cycle analytic tool to 1) identify a cohort of women with advanced ER+/HER2-BCa to estimate incidence rates (IRs) for selected safety outcomes of interests (SOIs), and 2) compare results obtained from traditional *de novo* SAS programming.

Methods: A retrospective cohort of women with advanced ER+/HER2- BCa during 1/1/2007 and 7/1/2017 was identified from Optum EHR data using Aetion Evidence Generation Platform (AEP), a rapid-cycle analytic tool. An a priori algorithm using clinical insight was applied, consisting of females aged 55+ at 1st diagnosis of BCa or > 18 on the treatment index date of hormonal or other ER+/HER2- therapy, with ≥6 months of enrollment. IRs and 95% confidence intervals (CIs) were estimated for 10 SOIs: neutropenia, febrile neutropenia, leukopenia, anemia, thrombocytopenia, pulmonary embolism (PE), other venous thrombosis and embolism (VTE), embolism and thrombosis of unspecified (ETN), diabetes mellitus, and hyperglycemia. ICD-9/10 codes, NDC codes, and unstructured data were used to identify the cohort and SOIs.

Results: A total of 14255 women with advanced ER+/HER2- BCa were identified using the AEP, providing a 100% match with SAS programming. IRs and 95% CIs per 100 person years for Anemia, neutropenia, leukopenia, thrombocytopenia, hyperglycemia, other VTE, diabetes mellitus, febrile neutropenia, PE, and ETN were 24.9 [24.2, 25.6], 15.2 [14.8, 15.7], 13.0 [12.6, 13.4], 5.3 [5.1, 5.6], 3.5 [3.3, 3.7], 3.0 [2.9, 3.2], 2.9 [2.7, 3.1], 1.7 [1.6, 1.8], 1.5 [1.4, 1.6], and 0.1 [0.1, 0.2] respectively. All IRs were near equal to results using SAS. Cohort generation and safety analysis using AEP took approximately 4 weeks, compared to up to 8 weeks using traditional SAS programming.

Conclusions: Rapid-cycle analytics with AEP enabled rapid replication of a cohort with advanced ER+/HER2- BCa and IR calculation for several safety endpoints. The results verified against traditional SAS programming were near identical. Rapid-cycle analytics can serve as an important method for rapidly responding to potential safety concerns and leveraging RWD for drug safety surveillance.

130 | Consistency between prescription symmetry sequence analysis and symmetry analysis cohort design: Study using claims data in Japan

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Background: Since Hallas advocated the prescription sequence symmetry analysis (sometimes called simply as "symmetry analysis" (SA)) in 1996, SA has been used mainly to raise signals of possible adverse drug reactions from the database. With slight modification of SA, a "symmetry analysis cohort design" (SACD) was proposed by Kubota (PDS, 2016) as a method suitable in the study involving the primary data collection without a comparator group.

Objectives: In the current study, we examined whether SACD can provide results compatible with those by SA.

Methods: We used claims data (Medi-Scope) between May 2013 and April 2018 covering 1.3 million persons provided by corporate insurance plans in Japan. We used positive and negative events in the study by Wahab (PDS 2013) which was conducted to test SA. The rate ratio (RR) was estimated by SA (RR (SA)) and SACD (RR (SACD)) by analyzing the data after 6-month run-in period using 12-month time-window. We estimated the sensitivity and specificity for SA and SACD. We conducted functional relationship analysis (Kendall, 1979) to know the relationship between SA and SACD. The study was approved by the ethics committee of Nihon University School of Pharmacy.

Results: We found a total of 52,722 (man: 43.0%, age: 46.0 ± 13.9 years old) and 10,743 (man: 43.8%, age: 53.2 ± 11.5 years old) patients who initiated a causative drug and had an outcome for 37 positive and 60 negative events, respectively. The sensitivity was 22% (8/37) with SA and 19% (7/37) with SACD. The specificity was 98% (59/60) with both SA and SACD. The functional relationship analysis revealed RR (SACD) = βRR (SA) where β = 0.960 (95% confidence interval: 0.950–0.969). Though the specificity was similar between our study using SA (98%) and that by Wahab (93%), the sensitivity in our study using SA (22%) was substantially smaller than that in the study by Wahab (61%).

Conclusions: The rate ratio by SACD was close to that by SA. The sensitivity in our study was substantially smaller than that by Wahab potentially due to the difference of age structure of study population and treatment pattern with drugs used as a surrogate of the outcome occurrence.

131 | To censor or not to censor: Impact of death censoring in estimating excess length of stay in relation to nosocomial infection

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Background: Nosocomial infection can prolong length of stay (LoS). Death is a competing risk for discharge and key component for estimating excess LoS due to nosocomial infection.

Objectives: To assess the impact of death censoring in estimating excess LoS attributable to a nosocomial infection.

Methods: Using a large Japanese hospital-based administrative database, all hospitalizations during April 2008 to March 2017 for patients ≥18 year-old were extracted. Clostridioides (Clostridium) difficile infection (CDI) during the hospitalization was identified by treatment plus diagnosis or immunoassay positive result. Hospitalization with CDI was matched to a hospitalization without CDI at the timing of the onset using the propensity score. Excess LoS was calculated in each matched pair by subtracting days after matching. In order to assess the impact of censoring, Kaplan Meier methods were applied to excess LoS with and without regarding transfer to other hospital and hospital death as censoring events.

Results: In total, 11,722 hospitalizations were associated with the nosocomial infection. In the matched cohort, 21.5% hospitalization with infection resulted in death while it was 14.6% in hospitalization without the infection. Median excess LoS attributable to CDI was 3 days (interquartile range: −14, 22), without censoring transfer to other hospital or death. It was 4 days (3, 14) when censoring only transfer and 16 days (4,77) when both transfer and death were censored.

Conclusions: In this study, the excess LoS was largely varied by censoring based on the type of event that terminated the hospitalization. Which estimand to choose should depend on the objective of the study. If the estimated excess LoS is to be used in a purely economic context, death might be reasonably used as an event that terminates the stay. However, if excess LoS is to be considered in a broader context with death being the burden of the infection, discharge with death may be better regarded as censoring.

132 | Codelist proximity analysis - an innovative, data driven, semi-automated system, underpinned by neural networks on the Thin database, to create candidate clinical Codelists for cohort extraction and data exploration

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Background: Constructing a specific clinical coding list to extract a patient cohort from an Electronic Medical Records (EMR) database is essential to high quality research. Compiling code lists is usually time consuming and requires input from experts in the specific database design, coding system, and medical speciality. We sought to make the process less resource intensive using innovative data driven methods.

Objectives: To create a semi-automated system to produce a set of candidate clinical codes for searching an EMR database for patients with specific medical conditions.

Methods: In order to explore and document the relationship between clinical codes in the Health Improvement Network (THIN) database of over 12 million UK primary care patient records, a neural network was fitted to patient medical histories to produce a vector for each READ clinical code encountered throughout patients' medical histories. Cosine similarity was used to measure "association" between codes based on how often they appeared together in each patient record. A web application was then built to allow any researcher, on inputting a specific READ code of interest, to view the top 200 clinical codes with the highest association to the original code. A comparison was made of traditionally prepared code lists and the semi-automatic method described here and named Codelist Proximity Analysis.

Results: There was a close comparison between code selections derived from Codelist Proximity Analysis and pre-existing compiled clinical code lists created using the traditional method of examination of the coding dictionary by both free text and hierarchy. The Codelist Proximity Analysis system was found to have a high user acceptance being intuitive, fast, & needing less expert input than traditional code list generation.

Conclusions: Neural Networks represent one of the many techniques in the machine learning field. This application of the method to EMR has been used to create a system to reduce the costs, time and expertise needed to extract cohorts. This new approach can also be used to explore clinical and therapeutic relationships providing further research insights in a data driven way.

133 | Variation in grace period used to define exposure to anticoagulants impacts incidence rates of major bleeding in patients with atrial fibrillation

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Background: While direct oral anticoagulants (DOACs) are prescribed at fixed doses, warfarin requires frequent dose adjustments by physicians. Pharmaceutical dispensing data are therefore less likely to reflect the true duration of warfarin supply compared with DOACs. The use of fixed grace periods to define episodes of drug exposure may lead to differential misclassification of exposure to DOACs and warfarin.

Objectives: To assess whether the length of the grace period used to define use of oral anticoagulants has a differential impact on the incidence rates of major bleeding associated with warfarin and DOACs.

Methods: Using the administrative healthcare databases of Québec, we formed the cohort of all patients with atrial fibrillation newly dispensed warfarin, dabigatran, or rivaroxaban between 2010 and 2016. First, in an as-treated approach, patients were followed from treatment initiation until drug discontinuation. Second, we used a time-varying exposure definition, in which each day of follow-up was classified as exposed or unexposed to anticoagulants. In both scenarios, current use of oral anticoagulant was defined by the duration of each prescription plus a grace period of 0, 3, 7, 30 and 60 days. We estimated the crude incidence rates (IRs) of major bleeding associated with each oral anticoagulant and each grace period based on a Poisson distribution.

Results: The cohort included 55,220 patients newly treated with anticoagulants. Using the as-treated approach, the mean follow-up varied from 0.27 year with 0-day grace period to 1.65 year with 60-day grace period. The highest IRs were observed with 0-day grace period (warfarin 18.2, dabigatran 10.7, rivaroxaban 16.5 per 100 person-years). IRs attenuated with longer grace periods (60-day grace period, warfarin 11.3, dabigatran 7.3, rivaroxaban 11.0). Using the time-varying approach, the mean follow-up was 2.71 years. Conversely to the pattern observed using the as treated definition, for all drugs, IRs were lowest with 0-day grace period (warfarin 10.6, dabigatran 6.7, rivaroxaban 10.1) and highest with 60-day grace period (warfarin 11.2, dabigatran 7.2, rivaroxaban 10.4).

Conclusions: Varying the length of the grace period to define exposure to oral anticoagulants did not have a differential impact on IRs of major bleeding for DOACs and warfarin. However, for all drugs, the length of the grace period had an opposite effect on the IRs estimated using as-treated and time-varying definition of exposure, probably related to depletion of susceptibles and protopathic bias.

134 | Big data and real world evidence: Rapid cycle analysis capability via emerging analytic tools - insights in atopic dermatitis and lessons for wider adoption

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Background: Several analytic tools have emerged to meet increasing demands for rapid real world evidence generation on real world data (RWD). It is well appreciated that RWD vary enormously and underlying population characteristics (across regions or even data sources) can differ greatly, often requiring access to multiple data sources to provide a range of background rates for risk characterization. There is an increasing need to improve the speed of such analyses.

Objectives: To explore how a range of tools and data sources can provide rapid insights into Atopic Dermatitis (AD) population risk

characterization, and further our understanding of disease population variation in general.

Methods: Four analytic tools licensed from different vendors (SÆfetyWorks, Aetion, IHD, and E360) were used to understand the demographic characteristics of patients with AD and the incidence rates (IRs) of 2 endpoints of interest: herpes zoster (HZ) and melanoma. A total of 684,928,490 patients with at least 2 AD diagnostic codes aged ≥12 from 13 distinct healthcare databases across 8 unique countries (United States (US), Canada, United Kingdom (UK), Italy, France, Germany, Belgium, Australia) comprised the study's base population. IRs and incidence proportions (IPs) of HZ and melanoma during 2012–2017 were calculated. A ≥ 6 month washout period prior to the 1st diagnosis of each endpoint was applied.

Results: 525,489 and 74,742 AD patients across 5 US and 8 non-US databases were identified. IRs of HZ and melanoma per 1000 person years (PYs) are 0–10.17 and 0–1.89 for all databases and tools: 7.51–10.17 and 1.21–1.89 for US claim data; 7.40–7.67 and 1.15–1.16 for US EHR data (same data source); 0 for US hospital based data; and 6.11 and 0.31 for UK EMR data. IPs of HZ and melanoma (%) are 0- < 2.57 and 0–0.46 for all databases and tools: 0–2.46 and 0–0.46 in US; 1.74 and 0 in Canada; 1.32 and 0 in Australia, and 0.45- < 2.57 and 0–0.92 in EU respectively. It took ~5 hours to execute all analyses. Variability per tool was observed, but was primarily driven by differences in data in each tool.

Conclusions: Analytic tools enabled rapid analyses for risk characterization for AD using a vast amount data. Variation in results underscores the importance of access and use of a wide range of RWD to further our understanding of disease outcomes in real world settings. Rapidity facilitates iterative learning and the opportunity to develop data-driven and more complex follow up analyses as needed. These tools provide great potential for leveraging real world data for proactive and rapid drug safety surveillance.

135 | Application of machine learning algorithms to a large primary care database analysis: Random Forest in evaluation of body weight and other characteristics as predictors of antidepressants prescribing

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Background: Antidepressants medications (AD) can cause weight gain, and patients with excess weight may have poor response or non-response to AD treatment. Therefore, patient's body weight needs to be considered when prescribing AD. As a first step to optimize pharmacological treatment of depression in obese and overweight patients, it is important to evaluate whether weight is a prominent predictor of AD prescribing. Electronic medical records (EMR) contain data on multiple factors, including patient's body weight and prescribed medications. Advanced machine learning algorithms have promising potential to be more efficient than conventional statistical models when analyzing complex data.

Objectives: Using a large primary care database, to apply a Random Forest (RF) machine learning algorithm to evaluate patient's body weight and other socio-demographic and health characteristics in prediction of AD prescribing, and to compare performance of RF model to an existing approach (multivariable binary logistic regression model).

Methods: Source: EMR from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) for 2011–2016; adult patients (18 years of age and older) with depression. **Measure:** Prescribing of at least one AD (outcome), body mass index to categorize patients into weight groups (primary exposure); age, sex, network identification number (ID), and comorbidities (secondary exposure variables). **Analysis:** RF classification model with the number of trees set to 300 and multivariable binary logistic regression (MLR) were used to evaluate weight and other patient characteristics as predictors of AD prescribing.

Results: Among 61699 patients with depression, 41389 were prescribed AD. Five most important predictors of AD prescribing with RF were ranked as follows: network ID (Mean Decrease Accuracy [MDA] = 77.8%), age (MDA = 32.3%), epilepsy (MDA = 31.5%), hypertension (MDA = 21%), and weight (MDA = 13.8%). In the RF model, out-of-bag prediction error = 34%; sensitivity = 93.4%, specificity = 11.6%. Areas Under the Curve were 57.2% and 58.5% for the RF and the MLR, respectively.

Conclusions: RF model showed high sensitivity but low specificity, and its performance was not superior as compared to the MLR model; however, applying RF to analyze large primary care database allowed to determine the importance of socio-demographic and health characteristics in prediction of AD prescribing. Weight was ranked among the most important predictors of AD prescribing.

136 | Reproducibility of a population-based cohort study characterizing newly diagnosed multiple myeloma patients in the UK using an EHR database

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Background: The recent abundance of real-world evidence from studies using large databases, including electronic health records (EHR), has resulted in increasing efforts to improve the reproducibility of research by promoting transparency of the analytical decisions and replicating studies using the same data.

Objectives: To evaluate the reproducibility of a study characterizing newly-diagnosed multiple myeloma (NDMM) patients within a UK-based EHR database.

Methods: A large population-based EHR, from general practices (GP) within the primary care settings in the UK, the Clinical Practice

Research Datalink (CPRD), was used. We identified NDMM patients between January 1, 2006 through December 31, 2016; follow-up period extended to December 31, 2017. The study cohort included patients ≥18 years with NDMM, no history of solid tumors, and a registration at the GP for at least two years prior to diagnosis. Baseline demographics and clinical characteristics were assessed prior to, and including the day of, MM diagnosis. A common study protocol and statistical analysis plan were deployed to evaluate reproducibility using the Aetion Evidence Platform (AEP), a rapid-cycle analytics tool. Traditional programming using SAS was carried out independently and in parallel as a gold standard method. The reproducibility of study results was evaluated by calculating the absolute difference in prevalence between SAS (original) and AEP (reproduced) data, with an absolute difference of 0.0 representing exact concordance.

Results: Both approaches yielded near-identical number of eligible patients diagnosed with NDMM during the study period (*N* = 2,646 in AEP versus N = 2,648 in SAS). We observed exact concordance on the distribution of gender and median age, and high agreement for clinical characteristics including osteopenia, osteoporosis, osteoarthritis, gout, CKD, CVD, and hypertension (absolute difference in prevalence range 0.0 to 0.3). Distribution by age categories was slightly discordant, due to varying methods for imputing incomplete dates (i.e. missing month or day). We observed exact agreement in prevalence for record of bone pain (combined and site-specific) as well as skeletal-related events.

Conclusions: In this direct replication study evaluating early signs and symptoms of NDMM within a UK-based EHR, a rapid-cycle analytics tool achieved near-exact reproduction of findings obtained using traditional SAS programming. Transparency of the study design and operational choices shared by independent investigators was critical to this reproducibility.

137 | Using SNOMED to automate clinical concept mapping

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Background: The International Classification of Disease (ICD) is a widely used diagnostic ontology for the classification of health disorders. However, it poses several challenges: (i) it is an evolving ontology and complete cross-walks do not exist between previous versions (e.g. ICD-9 to ICD-10) resulting in the need for custom mappings and (ii) performing analytics on a code level directly results in a highly sparse representation which is difficult to interpret.

Objectives: Clinical knowledge can be employed to map ICD codes to aggregated medical concepts, however, this process can be highly time-consuming and costly. We propose an automated solution to these challenges that does not sacrifice the accuracy of the results.

Methods: Our solution leverages the SNOMED ontology whereby medical concepts are organized in a directed acyclic graph. This performs two functions, (i) provides a mapping between ICD-9 and ICD-10 by associating codes to concepts closely related on the SNOMED graph and (ii) for any graph/tree-based ontology, our custom rollup algorithm groups together codes/concepts into higher level, more easily interpretable features. To assess impact, the performance of a Gradient Boosted tree (XGBoost [1]), developed to classify patients with Exocrine Pancreatic Insufficiency (EPI) disorder, was compared when using features constructed by our solution vs clinically-driven methods. Data were extracted from US prescription and open-source medical claims reserving a held-out set for testing.

Results: The data set comprised 23,204 EPI patients and 277,324 non-EPI patients. Preliminary results showed 62% and 25% precision at 25% and 50% recall, respectively, when using the clinically defined mapping. Our algorithmically defined SNOMED features performed comparably.

Conclusions: Our ontology agnostic rollup algorithm could be used to automatically incorporate clinical domain knowledge into an empirically-orientated approach without comprising the accuracy of the solution and obviating the need for time-consuming manual mapping.

138 | How to imply the needs of marginal structural model to clinicians: An application in Parkinson's disease - from a junior Statistician's aspect -

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Background: J-FIRST was a large-scale observational study for non-motor symptoms (NMs) and treatment in patients with PD in Japan. One of the antiparkinsonian medications, Istradefylline (adenosine A2A receptor antagonist), was first approved as in Japan 2013. In order to estimate the treatment effect for NMs, we planed different kinds of analysis including marginal structural models (MSMs). But the results did not have dramatical differences between MSMs, either to the conventional regression model. Although MSM is widely used to deal with time-varying problems, to nonfamiliar clinicians, it may be confused and questionable: What had MSM exactly done? Can we just use a simple method?

Objectives: The aim was to demonstrate how to explain the needs of MSM to clinicians in a smooth way.

Methods: We followed the next steps to construct MSMs.1.Decide the causal directed acyclic graph (DAG) and choose the possible time-fixed and time-varying confounders by clinical opinions. 2. Test the time-dependent nature of confounders. 3. Use the selected covariates to conduct MSMs and compare the weights and distribution of confounders. 4. Estimate the treatment effect by MSMs. After meetings with clinicians, we pick up 4 frequently asked question. And try to answer the questions by the interim results which already existed in our steps.

Results: The 4 questions and answers are described as below. Q1. What do the results of pseudo population mean? Q2. Is it ok to not to adjust all unbalanced covariates? Q3. After adjusting the confounders, why the results were not change dramatically? Q4. Can we just use the conventional regression model? A1. Use DAG to demonstrate the relationship between covariates, treatment, and outcome. A2. Show the testing result of time-dependent nature to point out which covariates are really predicted by prior exposures or influenced next outcome. A3. Emphasize the goal is to adjust confounders not the outcome. Also Illustrate the balance of confounders after adjusting. A4. Among A1–3, the time-dependent confounders were indeed existed in our study, and the treatment is also time-varying. It's exactly why we need MSM to estimate the total effect of time-varying treatment on outcome without bias in the presence of time-dependent confounders.

Conclusions: MSM method can be easily performed by statistical packages nowadays. Without further understanding and attention, the results may be mistaken and lead to the wrong conclusion. Following some necessary steps, MSM can be conducted efficiently. And each step is also the material to sharpen clinicians' understanding.

139 | The feasibility of federated analysis for multi-site real world evidence studies

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Background: In the generation of real-world evidence for rare diseases, there may be no single site with a sufficiently large patient population for generating statistically meaningful results. Consequently, there has been a great demand for studies that pool information from multiple sites. One approach to multi-site analysis is to pool individual patient data (IPD) from multiple sites. However, this has become increasingly challenging due to newly imposed restrictions on data privacy, such as, the EU General Data Protection Regulation (GDPR). Another approach involves a meta-analysis of site-level statistics which can be less informative as information contained in IPD is ignored. We propose the method of federated analysis (FA), an analytical technique to obtain results mathematically equivalent to pooling IPD that fully preserves data privacy as IPD is never shared outside the host site. In FA, a global statistical model is fit over a centralized network of contributing sites. Each site independently computes a model update based on local IPD and communicates this update to a central server where all updates are aggregated to a new global model.

Objectives: To explore the feasibility, advantages, and limitations of FA for multi-site real world evidence studies.

Methods: A literature review of FA methodologies and case studies was undertaken to summarize the advantages and limitations of FA as a means to conduct studies in a privacy preserving manner in pharmacoepidemiology. IQVIA's European Oncology Evidence Network (E-OEN) was used as a case study to explore the feasibility of executing federated studies on research databases.

Results:FA performed on a research database network could potentially accelerate research timelines as the analysis is performed consistently and simultaneously across the network. Several technical challenges remain with FA, such as developing and validating robust software solutions. Additionally, the epidemiological limitations of IPD pooled analyses and use of harmonized data are not avoided in FA. For instance, electronic medical records (EMR) are typically collected to facilitate treatment not research. As such, methods of data collection vary across sites which may result in the loss of nuanced information in harmonized data.

Conclusions: Increasing concerns on data privacy, new legislation, and potential gains in efficiency and statistical power has led to a demand for FA in real world EMR databases. In rare diseases where single sites have only a small number of patients, one needs to combine the analytical power of pooled analyses while fully preserving data privacy.

140 | A simulation-based comparison of confounding adjustment methods in observational studies of administrative data

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Background: Propensity score (PS) methods are common for controlling for confounding bias when estimating the effect of an exposure on an outcome using observational data. However, when analyzing administrative data, the application of PS methods raises questions regarding how to select confounders and the risk of unmeasured confounding.

Objectives: To compare different methods for confounding adjustment in the context of observational studies based on administrative data.

Methods: Four methods for selecting confounders were compared using simulation studies: high-dimensional PS (hdPS), Outcome-adaptive Lasso (OAL), Bayesian Causal Effect Estimation algorithm (BCEE) and scalable collaborative targeted maximum likelihood (SCTMLE). For hdPS and OAL, four PS adjustment approaches were considered: 1:1 greedy matching on the logit of the PS with a 0.2 SD caliper, covariate adjustment in the outcome model using cubic splines, matching weights and inverse probability of treatment weighting (IPTW). BCEE and SCTMLE are doubly robust approaches that combine PS with outcome modeling. Two simulations based on synthetically generated data with 1000 observations and 100 potential confounders have been realized. In Simulation 1, covariates are uncorrelated, whereas correlations between 0.1 and 0.2 were present in

Simulation 2. More simulations are underway, including simulations with unmeasured confounders. Approaches were compared according to relative bias, mean squared error (MSE) and proportion of 95% confidence intervals (CI) that included the true effect over 1000 replications of each scenario.

Results: BCEE performed best, with very low bias and MSE and CI that included the true effect close to 95% of the time. SCTMLE performed as well as BCEE in terms of bias and MSE, but its CI included the true effect 80–85% of the time. For OAL and hdPS approaches, IPTW produced the best results, followed in order by covariate adjustment in the outcome model, matching weights and matching. In Simulation 1, both hdPS and OAL eliminated almost all bias and CI included the true effect around 95% of the time. In Simulation 2, where confounders are correlated, only OAL yielded adequate results; substantial bias remained for hdPS after adjustment and CI included the true effect only 15–35% of the time.

Conclusions: BCEE and OAL are interesting approaches for selecting confounders in high dimension settings, such as administrative databases. While hdPS is a popular approach, our results indicate potential for substantial residual bias when confounders are correlated, which is likely in most real-life situations.

141 | A real-world evidence study of BRCA mutations and survival in HER2-negative breast cancer

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Background: Limited data exist on the natural history (treated with standard of care) of metastatic breast cancer (mBC) characterized by germline breast cancer susceptibility gene mutations (g*BRCA*m).

Objectives: To evaluate clinical characteristics and overall survival (OS) among g*BRCA*m, g*BRCA* wild type (wt) and g*BRCA* unknown mBC.

Methods: Patients (pts) with human epidermal growth factor receptor 2 negative (HER2-) mBC diagnosed from January 2013–August 2017 were retrospectively selected from the Flatiron Health Oncology electronic medical record database. Pts were classified as having g*BRCA1*m, g*BRCA2*m, or g*BRCA*wt disease. Those who did not receive genetic testing or who had equivocal results were classified as g*BRCA* unknown. OS was calculated from first diagnosis of mBC, and from the start of first- and second-line therapy for metastatic disease. Lines of therapy included both hormonal and systemic therapies. Kaplan–Meier analyses provided median OS with 95% confidence interval (CI). Unadjusted log-rank tests compared OS between g*BRCA1*m and g*BRCA2*m, and between overall g*BRCA*m and g*BRCA*wt.

Results: Of 8,080 pts selected, mean age at first mBC diagnosis was 64 years, 98.7% were female, and 82.0% had evidence of hormone receptor positive disease. g*BRCA* status was known for 1,852 (22.9%) of pts, of whom 89 (4.8%) had g*BRCA1*m, 152 (8.2%) had g*BRCA2*m, and 8 (0.4%) had both g*BRCA* mutations. Pts with known g*BRCA* status were younger, with mean ages of 52 years for g*BRCA*m, 55 years for g*BRCA*wt, and 67 years for g*BRCA* unknown. Hormone receptor positive disease was less common among pts with known g*BRCA* status (71.9% for g*BRCA*m and 77.2% g*BRCA*wt) as compared to unknown g*BRCA* status (83.6%). Median (95% CI) OS from mBC diagnosis was 22 (14–26) months for g*BRCA1*m and 30 (27–37) months for g*BRCA2*m (p = 0.01), though numbers were small by the median timepoint. Overall g*BRCA*m disease was associated with median OS of 28 (25–32) months, compared to 32 (30–35) months for g*BRCA*wt (p = 0.07); OS was similar between groups for the first 24 months but declined thereafter in the g*BRCA*m group. Similar patterns were observed for OS after the start of first- and second-line therapy, although no comparisons showed statistically significant differences. Further analyses will present adjusted results and comparisons with outcomes for the pts with g*BRCA* unknown.

Conclusions: This real-world study of pts receiving care in largely community oncology clinics suggests that OS after diagnosis of mBC is reduced in pts with g*BRCA1*m compared to g*BRCA2*m and may be reduced in g*BRCA*m mBC overall. Effective treatments targeted for g*BRCA*m subtypes of mBC appear to be warranted.

142 | Racial disparities in survival among women who have HER2+ metastatic breast cancer: A systematic review and meta-analysis

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Background: Non-Hispanic Black women have a lower incidence rate of breast cancer than non-Hispanic white women, yet have higher mortality rates. Several well studied disparities contribute to worse outcomes among Black women. These disparities include diagnosis at a later stage, specific molecular sub-type of breast cancer, and delayed initiation or under utilization of first line therapeutic treatments.

Objectives: To determine whether Black women with HER2+ metastatic breast cancer experience shorter survival times than non-Hispanic white women.

Methods: A systematic review and meta-analysis was conducted using individual studies identified from PubMed, WorldCat, EBSCOHOST, Embase, and Proquest published until April, 2018. Conference abstracts from the San Antonio Breast Cancer Symposium were also searched. Studies which included female patients with metastatic HER2+ breast cancer which was either HR+ or -, or HR unspecified and a sub group analysis of survival outcomes between non-Hispanic white, and non-Hispanic Black patients were included. A meta-analysis was completed in RevMan; hazard ratios (HR) were pooled and the 95% confidence interval (CI) for survival at 12 months was calculated. I^2 statistic was calculated to determine heterogeneity between included studies.

Results: Four retrospective cohort studies were identified and included in the meta-analysis. Overall survival and breast cancer specific survival significantly favors non-Hispanic white women with HER2+ metastatic breast cancer over non-Hispanic Black women with the same diagnosis. In the adjusted (HR: 1.53, CI: 1.23–1.90, p-value: 0.0002)model for overall survival Black women were 53% more likely to die during the follow up period than non-Hispanic white women. And in the the adjusted model for breast cancer specific survival (HR: 1.44, CI: 1.18–1.76, p-value: 0.0004) Black women were 44% more likely to die during the same period.

Conclusions: Black women with HER2+ breast cancer have poorer overall survival and breast cancer specific survival, despite lower incidence. Opportunities exist for identifying the factors affecting these disparities in survival and also developing and implementing targeted interventions aimed at improving survival in this disparate group.

143 | Metastatic breast cancer sub-type classification using biomarker and treatment information in electronic health records

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Background: Correctly classifying metastatic breast cancer (mBC) subtypes (estrogen receptor, ER; progesterone receptor, PR; and human epidermal growth factor receptor 2, HER2) is important when identifying disease cohorts in electronic databases. Classification difficulties can arise due to timing or missing-ness of biomarker and treatment information.

Objectives: To characterize biomarker testing and estimate the concordance in between classified sub-type and the type of treatment initiated for mBC in EHR.

Methods: Using Flatiron Health EHR-derived data (data records between 2011–2018) on ER, PR, and HER2 testing and corresponding treatment information were obtained for mBC patients over 18 years old. Various mBC sub-type classifications were explored at mBC and primary BC according to ER, PR and HER2 test timings, and their concordance with HER2 targeted therapies, endocrine therapies, or chemotherapies-only in the metastatic setting was investigated. Patients with positive tests +/−90 days around primary or metastatic diagnosis were considered positive for the respective biomarker at that timepoint; patients with concurrent negative tests for ER, PR, and HER2 were classified as TNBC. Applicable biomarker test results were evaluated by looking at the first, last, closest test to diagnosis date, and applying a hierarchical selection ('+' >'-'>'equivocal' >'unknown'). Kappa, sensitivity (SE), and specificity (SP) values were calculated to estimate concordance between test results and treatment types received.

Results: Of *N* = 13,899 mBC patients, 19% of patients received at least one HER2 targeted therapy (10% HER2+/HR+; 9% HER2+/HR-), 63% at least one endocrine therapy, and 18% chemotherapy only in the metastatic setting. Among patients with initial mBC diagnosis, the concordance estimates between tests at mBC diagnosis date (K, SE, SP) were 0.7, 0.6 and 0.99 for HER2+/HR-; 0.7, 0.9 and 0.92 for HER2+/HR+; 0.8, 0.96 and 0.8 for HER2-/HR+; and 0.7, 0.6 and 0.99 for TNBC. For patients with an initial eBC diagnosis, the concordance estimates (K, SE, SP) were 0.7, 0.6 and 0.99 for HER2+/HR-; 0.6, 0.7 and 0.96 for HER2+/HR+; 0.7, 0.94 and 0.8 for HER2-/HR+; and 0.6, 0.6 and 0.97 for TNBC.

Conclusions: Overall, mBC test results showed good concordance with targeted therapies in the metastatic setting. The poorer concordance for TNBC biomarker and treatment, highlights a limitation of the validity of classifications based on treatment only e.g. in claims data. In this dataset, oral (endocrine) therapies are abstracted manually, so there may be some under-recording.

144 | Derivation of anthropometric-based equations to predict lean body mass composition of cancer patients

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Background: The lean body mass (LBM) composition of cancer patients is a significant predictor of chemotherapy-related adverse events. However, there are currently no validated measures of LBM that can easily be implemented in routine oncologic settings. "Gold standard" LBM measures such as dual-energy x-ray absorptiometry (DXA) are expensive and not frequently used in routine oncologic settings.

Objectives: Therefore, we aimed to derive and validate anthropometric equations that can estimate the LBM of cancer patients in routine oncologic settings.

Methods: Eight cycles of the National Health and Nutrition Examination Survey (NHANES) 1999–2014 were analyzed to build predictive models given the presence of anthropometric and DXA measures in this national data sample. A population of participants with self-reported physician diagnosis of cancer was randomly divided into training (75%) and validation (25%) sets. First, we utilized the training data to predict DXA measures of LBM using a combination of 8 different common anthropometric measures - height, weight, circumference measures (arm, waist, thigh, and calf), and skinfold (subscapular and triceps). Next, the best fitting and most parsimonious models were utilized to estimate the predicted LBM of the validation group. Absolute differences and correlation coefficients between DXA measured LBM and predicted LBM were used to validate the equations. Last, we tested how well predicted LBM predicts mortality status of the sample population. Models were stratified by sex and adjusted for race and age to account for anatomical differences. The fit of models were measured as R^2.

Results: Predictive models were derived from a sample of 682 adult (≥18 years old) participants (representing 3,763,122 persons in the

US) with self-reported cancer diagnosis and who had complete DXA and anthropometric measures. Overall, a combination of anthropometric variables accurately predicted the LBM composition of cancer patients (R^2 = 0.95). The model predicted LBM better among male (R^2 = 0.94) than among female (R^2 = 0.86) cancer patients. The predicted LBM discriminated death to the same magnitude as direct LBM measures from DXA scans, C-statistics: 0.76.

Conclusions: Anthropometric measures can be used to accurately estimate the LBM of cancer patients and help optimize chemotherapy dosing. Our next step is to apply these derived equations to measure LBM thresholds associated with the risk of chemotherapy adverse events.

145 | Characterizing active multiple myeloma populations identified by published claims-based algorithms

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Background: The smoldering and active phases of multiple myeloma (MM) have different progression, treatment, and outcomes; however, distinguishing the phases is difficult in claims data since both are assigned the same diagnosis code. Published algorithms combine rules with treatment, diagnostic tests, and CRAB symptoms (hypercalcemia, renal insufficiency, anemia, bone lesions) to distinguish active from smoldering MM. However, overlap in populations defined by these algorithms is poorly characterized.

Objectives: To describe the overlap in the size and characteristics of active MM populations defined by published claims-based algorithms.

Methods: Using Optum© De-Identified Clinformatics® Data Mart Extended Socioeconomic data, we found patients aged 18+ with an index MM diagnosis (SNOMED 109989006/ICD-10 C90.0) between 01/2016–08/2018 that was preceded 30–180 days by the 1st MM diagnosis and ≥ 365 days continuous enrollment. As done in the literature, 4 algorithms were added to the base population to identify active MM: 1) 1+ MM treatment in 180 days after 1st diagnosis; 2) 2+ protein electrophoresis and 1+ immunoglobulin tests 180 days before the 1st diagnosis; 3) 1+ bone marrow biopsy or 2+ diagnostic tests before the 1st diagnosis with 2+ MM diagnoses 90 days before both; 4) 1+ diagnosis code for CRAB symptoms 180 days before the 1st diagnosis. We explored overlap between populations and compared standardized differences (SD) ≥0.2 in the proportion of prior diagnoses, drugs, procedures, and measurements.

Results: Of 10,387 patients in the base MM population, 10% had no active MM rule suggesting potential smoldering MM, 21% met only 1 active MM rule, and 10% met all active MM rules. The base population and the population defined by protein electrophoresis and immunoglobulin tests were similar, with SD <0.2 between all covariates. Populations defined by bone marrow biopsies/multiple diagnostic tests had a higher proportion receiving chemotherapies before the 2nd diagnosis than the base population. Populations defined by symptoms had more inpatient visits and condition codes, such as renal disease, but less treatment or diagnostic tests than the base population. There was little overlap between populations defined by bone marrow biopsy/early diagnostic tests and by CRAB symptoms.

Conclusions: Treatment, tests, and symptoms are proxies for distinguishing active from smoldering MM in claims but identify different underlying MM populations. When combining algorithms to isolate active MM, researchers should ensure that they are not integrating populations with different clinical characteristics.

146 | Association of in-Hospital Bleeding Events with subsequent infection and mortality among patients undergoing cancer-directed surgeries in English inpatient hospitals

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Background: Patients undergoing cancer-directed surgeries are at risk for bleeding events.

Objectives: To evaluate the incidence of in-hospital bleeding events, and their association with subsequent in-hospital infection and in-hospital mortality, among patients undergoing cancer-directed surgeries in English inpatient hospitals.

Methods: We conducted a retrospective, observational cohort study using hospital discharge data from English hospitals (Hospital Episode Statistics [HES] database) linked to electronic health records (Clinical Practice Research Datalink [CPRD]). We selected patients aged ≥18 years who underwent selected cancer-directed surgeries between January 2010 and February 2016: hysterectomy, low anterior resection (LAR, rectal), lung (transplant & resection), mastectomy, and prostate (prostatectomy & resection). The primary independent variable was occurrence of in-hospital bleeding events (diagnosis of hemorrhage and haematoma complicating a procedure or reopening/re-exploration and surgical arrest of postoperative bleeding). The primary outcomes were in-hospital infection (composite of wound infection, cellulitis, sepsis, transfusion-related infection, urinary tract infection, and pneumonia) and in-hospital mortality, each occurring during or after the surgery. We carried out multivariable logistic regression models to compare the study outcomes between patients with vs. without bleeding events, adjusting for baseline patient and procedural characteristics.

Results: The study included 26,438 cancer-directed surgeries (hysterectomy: 6,092; LAR: 2,957; lung: 1,539; mastectomy: 12,806; prostate: 3,044). Incidence proportions of bleeding events varied by surgical site

(hysterectomy: 1.9%; LAR: 2.9%; lung: 1.8%; mastectomy: 1.5%; prostate: 1.0%; overall: 1.7%). Overall, the incidence proportions of infection and mortality were higher among patients with bleeding events (infection: 12.67% vs. 3.36%, $p < 0.0001$; death: 2.89% vs. 0.37%, $p < 0.0001$) as compared with those without bleeding events. In multivariable analyses, bleeding events were associated with higher odds of subsequent infection (adjusted odds ratio [AOR] = 3.50, 95% Confidence Interval [CI] = 2.55–4.83) and mortality (AOR = 6.25, 95% CI = 3.39–11.53).

Conclusions: Among patients undergoing cancer-directed surgeries, bleeding events were associated with increased risks of subsequent infection and mortality, and therefore the prevention and management of such events may lead to improved patient outcomes.

147 | The incidence of hematologic cancers after breast cancer. A 35-year population-based cohort study in Denmark

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Background: Breast cancer survivors may have increased risk of new primary hematologic cancer, due to shared risk factors or breast cancer-directed treatments.

Objectives: To examine the incidence of hematological cancers among breast cancer survivors compared with the general population.

Methods: We used the Danish Cancer Registry to ascertain a cohort of all Danish women aged 18 years or older who were diagnosedwith incident non-metastatic breast cancer between 1978 and 2013 and who were alive and cancer free four months after their breast cancer diagnosis (n = 93,620 women). We followed the women until first new primary cancer of any type, death, emigration, or end of follow-up (30 November 2013). We computed standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (95% CI) as measures of the relative risk of hematologic cancers comparing hematologic cancers observed in breast cancer survivors with that expected in the general population.

Results: Overall, we observed 607 cases of hematologic cancer compared with an expected 575 cases corresponding to a SIR of 1.06 (95% CI 0.97–1.14) in a median follow-up of 6.4 years. We observed increased risk of myeloid leukemia (SIR 1.60; 95% CI 1.32–1.91), evident from one year after breast cancer diagnosis and persisting until 10 years of follow-up. The increased risk of myeloid leukemia was highest in women aged 18–49 years (SIR 2.36; 95% CI 1.54–3.46). Risk of myeloid leukemia was increased irrespective of chemotherapy or radiotherapy but was highest among women treated with chemotherapy (SIR = 2.54, 95% CI 1.64–3.75). The risk of non-Hodgkin lymphoma, the most frequently observed hematologic cancer, was similar to that in the general population (SIR 1.03; 95% CI 0.92–1.14), but the risk of lymphoid leukemia was lower in breast cancer survivors (SIR 0.75; 95% CI 0.59–0.92).

Conclusions: Our observed increased risk of myeloid leukemia among breast cancer survivors may be partly due to adverse effects of breast cancer-directed treatment. The potential mechanism underlying the decreased risk of lymphoid leukemia in breast cancer survivors is intriguing and warrants further investigation.

148 | Safety event rates in large claims-based cohorts of advanced/metastatic cancer patients after initiation of systemic therapy and immunotherapy

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Background: Healthcare claims databases are a source for real-world evidence and safety evaluation in oncology, but their use has been limited by lack of clinical information, such as cancer stage. We previously used claims data linked to cancer registries and machine learning methods to build and validate algorithms to predict advanced or metastatic (a/m) stage in five cancer types. In this study we aim to assess rates of pre-defined safety events in a population of a/m cancer patients identified based on these algorithms.

Objectives: To estimate safety event rates in five cohorts of a/m stage cancer: ovarian cancer (OC), urothelial carcinoma (UC), gastric adenocarcinoma (GC), Merkel cell carcinoma (MCC), and non-small cell lung cancer (NSCLC).

Methods: This cohort study was conducted in the HealthCore Integrated Research Database (HIRD), which contains claims data from across the US restricted to 2010–2018. We applied the previously defined algorithms to the HIRD to define five cohorts of a/m cancer. Cohort characteristics were described at a/m diagnosis and incidence of 62 pre-specified, fatal and non-fatal safety events were described after initiation of any systemic anticancer therapy including immunotherapy.

Results: Algorithm-defined a/m patients resulted in the following cohorts: 12,659 OC, 1,401 UC, 6,253 GC, 625 MCC and 38,451 NSCLC patients. The majority of patients in each cohort were de novo a/m, but a subset was diagnosed at early stage and progressed to a/m stage: from 3.3% for OC to 23.1% for UC with a mean time to a/m ranging from 245 to 470 days. Between 35% (MCC, UC) and 60–65% (GC, OC, and NSCLC) of patients received any systemic anticancer therapy during follow-up (most commonly alkylating agents). Most frequent safety events, regardless of causality to treatment, included infusion-related reactions, serious infections, nausea and vomiting, abdominal pain, and anemia (nearly all >20 events per 100 person-

years in all cohorts). In the subgroups of patients initiating immunotherapy (>5,000 overall) rates were similar or varied modestly compared with those after any anticancer therapy.

Conclusions: Using large cohorts of a/m cancer patients identified through predictive algorithms in claims data, this study found high rates of safety events, as expected in this population. The rates of selected safety events did not differ widely for users of immunotherapy compared to any systemic therapy.

149 | Association of Continuity of Care & Mortality for breast cancer patients with comorbidities

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Background: Breast cancer patients with comorbidities have high mortality risk and need to see multiple healthcare providers.

Objectives: To examine the association of continuity of care (COC) & mortality for breast cancer patients with comorbidities.

Methods: A retrospective cohort study of newly diagnosed female breast cancer patients (n = 57,578) with comorbidities (hypertension, hyperlipidemia, and diabetes) was conducted using SEER-Medicare data (2006–2014). The primary outcome was all-cause mortality (assessed annually for up to 5 years). COC index, a validated measure accounting for both the frequency and dispersion of healthcare provider visits, was measured yearly with a scale of 0 (dispersed) to 1 (concentrated) in five ways: Specialty COC (unique specialist groups: Primary Care Physicians (PCP), Oncologists, and Other specialists (Other)), Individual COC (all individual providers regardless of specialty), PCP COC (all individual PCP), Oncologist COC (all individual Oncologists), and Other COC (all individual Other). Cox proportional-hazards models estimated the hazard ratio (HR) of all-cause mortality associated with COC quartile.

Results: The average scores increased slightly across the study period for all five COC Indices (p < 0.05) Patients with stage IV breast cancer had the highest Specialty COC, Individual COC, and Oncologist COC than others (p < 0.05). Patients with 3 comorbidities had the highest PCP COC than others. Patients' crude mortality rate decreased with survival time and negatively associated with advanced tumor stages and more comorbidities (p < 0.05). Patients had high continuity of care based on Specialty COC (4^{th} vs. 1^{st} quartile, HR 1.45, 95%CI 1.33–1.58) and Oncologist COC (3^{rd} vs. 1^{st} quartile, HR 1.50, 95%CI 1.27–1.78) had higher mortality risks compared with those who had low COC. However, patients had high continuity of care based on Individual COC (4^{th} vs. 1^{st} quartile, HR 0.54, 95%CI 0.50–0.59), PCP COC (4^{th} vs. 1^{st} quartile, HR 0.35, 95%CI 0.31–0.39), and Other COC (4^{th} vs. 1^{st} quartile, HR 0.37, 95%CI 0.33–0.42) had lower mortality risks compared with those who had low COC.

Conclusions: This study examined the association between COC and mortality risk for breast cancer patients. Higher Individual, PCP, and Other COC levels were related to lower mortality risk. Higher Specialty and Oncologist COC levels were related to higher mortality risk, which might be confounded by uncontrolled disease severity factors. COC should be considered carefully when building the models of coordinated care and may help to improve the quality of care for cancer survivorship.

150 | The association between partner bereavement and first diagnosis and mortality of melanoma: Population-based cohort study

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Background: Partnership status may be important in the early detection of melanoma, and consequently in improved survival. However, we do not know whether the death of a partner affects the incidence and mortality of melanoma.

Objectives: To evaluate the association between partner bereavement and 1) first diagnosis of melanoma and 2) mortality in patients with melanoma.

Methods: We conducted two cohort studies using routinely collected data from Clinical Practice Research Datalink between 01/01/1997 and 31/07/2017. Study 1: A matched cohort study comparing incidence of first melanoma diagnosis between bereaved and matched (on age, sex and general practice) non-bereaved subjects. We used Cox regression, stratified by match set to estimate hazard ratios (HR). Study 2: A cohort of individuals with melanoma who were part of a couple and were eligible for linkage with Office for National Statistics (ONS) death registration data. We used Cox regression to estimate the risk of death (melanoma-specific and all-cause mortality) in those whose partner died compared to those whose partner was alive (partner bereavement defined as a time-varying variable). As a sensitivity analysis, we repeated the analysis in Study 2 for all-cause mortality without restricting to those with ONS linkage. All analyses were adjusted for Charlson Comorbidity Index, smoking status, body mass index, alcohol consumption and socioeconomic status. Missing data were handled by complete case analysis.

Results: In Study 1, we included 150,547 bereaved and 1,306,385 matched non-bereaved subjects. We observed a lower risk of incident melanoma (HR: 0.86; 95% CI: 0.79–0.94) post-bereavement in the bereaved compared with non-bereaved during the entire follow-up. In Study 2, we included 3,233 patients with melanoma. We found some evidence of an increased risk of all-cause mortality (HR: 1.23; 95% CI: 0.98–1.54) but little evidence of any increased risk of melanoma mortality (HR: 1.28; 95% CI: 0.88–1.86) associated with bereavement, possibly due to limited power. In the sensitivity analysis, we confirmed the

increase in all-cause mortality associated with bereavement (HR: 1.31; 95% CI: 1.15–1.50) among 8,373 patients with melanoma.

Conclusions: We found a decreased risk of melanoma diagnosis, but increased mortality associated with partner bereavement. These findings may be partly explained by delayed detection as a result of the bereaved not having a partner to notice skin changes. Results from a parallel study using Danish registries, including information on melanoma stage, are pending and will be presented.

151 | Incidence and trends of melanoma skin cancer in the United States, 1999–2016

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Background: Cutaneous melanoma is the sixth most common malignancy in U.S. While data from the Surveillance, Epidemiology and End Results (SEER) program are essential to incidence estimations of melanoma, under-reporting and delays in reporting have remained major limitations. Surveillance is hindered by the absence of melanoma on states' reportable disease list and possible omission of outpatient diagnoses from hospital registries. Thus, the exact incidence of melanoma has not been accurately known.

Objectives: To determine melanoma incidence and trends from 1999 to 2016 in a nationally representative sample of the US.

Methods: New melanoma cases among adults aged ≥20 years were identified from the National Health and Nutrition Examination Survey (NHANES), 1999–2016. Crude and age-adjusted incidences of melanoma and 95% CIs were estimated by survey year cohorts (1999–2006 and 2007–2016) based on the 2000 US standard population. Sex and age-stratified longitudinal trends were evaluated in age and sex-adjusted regression models. Statistical analyses accounted for complex survey design, including examination sample weight, and adjusted for nonresponse. Sensitivity analyses included unadjusted modeling and modeling adjusted for sex, age or different age groups. A 2-sided *p*-value of.05 was used to determine statistical significance.

Results: Among 47,172 adults and 21,192 non-Hispanic whites from 1999–2016, the overall age-standardized incidences of melanoma per 100000 persons were 76.9 (95% CI: 46.2–107.7) and 97.6 (95% CI: 56.0–139.3), respectively. The median age at first melanoma diagnosis was 70.7 (mean = 67.1, IQR = 57.6–79.6 years). The incidence was higher in men than in women (94.3 vs 50.5 per 100000 persons, $p = .04$) and increased with older age ($p < .001$). Between 1999–2006 and 2007–2016, the incidence of melanoma was significantly higher in those older than 70, 75, and 80 ($p \leq .02$). Growths in incidence were also observed in overall population, men, women, and by approximately 40% among those older than 70. The results of sensitivity analyses showed similar increasing trends.

Conclusions: Our incidence rates for all melanoma were high, particularly in the elderly. Our findings of risk factors for melanoma confirmed findings of previous studies. From 1999 to 2016, melanoma incidence substantially increased among those older than 70, a concerning observation given the aging US population. As understanding susceptible groups help tailor public health interventions, our study provided an updated depiction of melanoma incidence and trends in U.S.

152 | Characteristics of patients with small cell lung cancer in the real-world setting: A systematic review

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Background: Patients with poor performance status (PS) ≥2 are generally underrepresented in clinical trials. Describing patients' characteristics outside clinical trials setting would help better characterize unmet needs.

Objectives: To systematically review and describe characteristics of SCLC patients, overall and according to sub-types; extensive stage (ES) and limited stage (LS).

Methods: A systematic review of observational studies was conducted using MEDLINE and Embase databases between January 1998 and October 2018. Pragmatic searches of the gray literature were conducted to identify additional sources. Studies reporting epidemiological data on SCLC were independently screened, adjudicated and data were abstracted by two assessors, with conflicts resolved by a third.

Results: Of the 2,418 sources identified, 394 were reviewed in depth and 140 were retained. An additional 28 sources were identified through pragmatic searches yielding a total of 168. Median age at diagnosis (reported in 32 studies) ranged from 54 to 74 years. Sex distribution was reported in 86 studies, with a male predominance irrespective of stage. Eastern Cooperative Oncology Group PS was reported in 30 studies. The majority of studies were hospital-based (n = 28, 93%) and data mainly originated from medical records or chart review (22, 73%). PS was assessed at baseline or at the time of diagnosis in 26 studies. Twenty-three (77%) studies reported poor PS status for >25% of the SCLC population, with six reporting poor PS in ≥50% of the SCLC population. The proportion of SCLC patients with poor PS ranged from 14% to 88%. Findings were heterogeneous across studies due to the variability in thresholds used to define the categories, study setting and inclusion of both LS- and ES-SCLC patients for reporting. For studies reporting PS by stage (n = 4), the proportion of patients with poor PS ranged from 13% to 53% in ES-SCLC and 11% to 12% in LS-SCLC.

Conclusions: A significant percentage of patients with SCLC outside clinical trials present with a poor PS. LS-SCLC patients have a better PS. Prevalence of poor PS was higher for ES-SCLC and the reported figures are higher compared to non-small cell lung cancer.

153 | Incidence estimates and trends of non-melanoma skin cancer in the United States, 1999–2016

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Background: As the most common malignancy in the United States, skin cancer is associated with significant morbidity and healthcarecosts. Non-Melanoma Skin Cancer (NMSC), including basal cell carcinoma and squamous cell carcinoma, accounts for the majority of skin cancer cases. Due to sparse reporting to national cancer registries, the exact incidence of NMSC is unknown. Recent estimates primarily relied on county-specific electronic medical records and Medicare databases, posing limitations to application to the general US population.

Objectives: To investigate the incidence and trends of NMSC from 1999 to 2016 in a US nationally representative sample.

Methods: We identified new NMSC cases among adults aged ≥20 years in the National Health and Nutrition Examination Survey (NHANES). The crude and age-adjusted incidences of NMSC and 95% CIs were estimated. Further analyses stratified incidence by sex, race/ethnicity, age groups, and survey year cohorts (1999–2008 and 2009–2016) based on the 2000 US standard population. Age and sex adjusted regression models were applied to investigate longitudinal trends. Race/ethnicity was also examined for race-specific patterns. Statistical analyses were accounted for the complex survey design including examination sampling weights, which adjusted for nonresponse, and a 2-sided *p*-value of.05 for statistical significance. Sensitivity analyses including unadjusted modeling, modeling adjusted for sex only, age only, modeling with different age groups, and a stricter NMSC definition were performed.

Results: Among 47,172 adults and 21,192 non-Hispanic whites from 1999–2016, the overall age-standardized incidence of NMSC per 100000 persons was 319.5 (95% CI: 248.3–390.7) and 423.3 (95% CI: 327.1–519.5), respectively. The incidence in men was significantly higher compared to that in women (394.1 vs 258.5, $p = .02$). In all groups, incidence rose with age ($p < .001$). From 1999–2008 to 2009–2016, the overall incidence of NMSC significantly increased from 232.2 to 414.5 ($p = .01$). Rising incidence was also observed among women and those above 70, 75, and 80 years of age ($p \leq .02$). Similar trends were also found through sensitivity analyses ($p < 0.05$).

Conclusions: Over the study period 1999–2016, the incidence of NSMC nearly doubled in all adults, non-Hispanic whites, women, and among those 70 years and older, a concerning observation given the aging population. Our study findings provided an updated understanding of NMSC incidence in the US general population and susceptible subgroups. The observed rising incidence called for greater improvement in prevention.

154 | Real world treatment patterns, adverse events and healthcare resource utilization and costs among chronic lymphocytic leukemia (CLL) patients in the US

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Background: Treatment options for CLL have expanded in recent years, but few studies provide real-world data on treatment patterns and outcomes associated with these agents.

Objectives: To evaluate treatment patterns, adverse events (AEs), healthcare resource utilization (HCRU), and costs associated with CLL-directed therapy in patients with CLL.

Methods: This retrospective study used medical and pharmacy claims from the Optum Research Database to identify commercially insured and Medicare Advantage (MA) enrolled adults. Patients included had CLL (≥ 2 medical claims ≥7 days apart between July 1, 2012 to May 31, 2017), at least 1 claim for systemic CLL-directed therapy and continuous enrollment for 12 months prior to (baseline period) and ≥ 1 month after the first observed CLL-directed therapy (index date). Patients receiving CLL therapy in the baseline period or stem cell transplantation in the entire study period were excluded. Up to 3 lines of therapy (LOT) were captured. Cohorts based on the most common regimens received, regardless of LOT sequence, were created. Potential treatment-related AEs were identified by ICD-9 and ICD-10 diagnosis codes on claims. All-cause and AE-related healthcare resource utilization and costs (per patient per month (PPPM)) were examined. All analyses were descriptive.

Results: A total of 3292 patients with CLL met all study criteria (65% MA enrollees; 35% commercially insured). Mean age was 71 years (SD 11) with a baseline Charlson comorbidity index score of 3.5 (SD 1.9). Overall, 31% of patients had ≥2 LOTs and 10% had ≥3 LOTs. The most common regimens (excluding rituximab (R) maintenance therapy) observed by LOT were; bendamustine + R (23%) in LOT1, ibrutinib (22%) in LOT2 and ibrutinib (17%) in LOT3. Overall, 4,509 LOT periods (LOT1-LOT3) were observed, 3177 of these were the 5 most common treatment regimens: R (excluding maintenance therapy) (30%); bendamustine + R (28%); ibrutinib (20%); obinutuzumab ± chlorambucil and chlorambucil only (14%); and cyclophosphamide + fludarabine + R (8%). The most common AEs associated with these treatments were anemia (34%), hypertension (33%) and infection (32%). AEs associated with the highest mean

PPPM costs were renal failure ($14,237), stroke ($8,037), myocardial infarction ($6,976) and neutropenia ($6,787).

Conclusions: This study shows that occurrence of AEs in patients with CLL receiving systemic therapy in the real-world setting is substantial and associated with significant healthcare cost. The economic burden associated with AEs underscores the need for treatments with fewer AEs.

155 | Risk of primary urological and genital cancers following incident breast cancer: A Danish population-based cohort study

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Background: Screening programs and improved treatments have increased the prevalence of long-term breast cancer survivors. Chemotherapy, radiation, and anti-hormonal therapies for breast cancer may increase the risks of subsequent urological and genital cancers.

Objectives: To examine the risk of primary urological and genital cancers in patients with a history of breast cancer and to compare this cancer risk with that of the general population.

Methods: Using population-based Danish medical registries, we conducted a nationwide population-based cohort study of female patients (>18 years) diagnosed with primary breast cancer and restricted to patients with localized cancer or regional spread during 1978–2013. We followed them for any subsequent urological or genital cancer registered in the Danish Cancer Registry. We computed cumulative incidences, accounting for the competing risk of death. As relative risk measure, we computed standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) as the observed number of cancers relative to the expected number based on national incidence rates by age (5-year intervals) and calendar year (5-year intervals).

Results: Among 96,374 female patients with a history of breast cancer (median age 61 years), we observed 1397 genital cancers and 538 urological cancers during a median follow-up of 6.1 years. The cumulative incidence was 1.3% for any genital cancer and 0.4% for any urological cancer after 10 years of follow-up. SIRs were increased for cancers of the uterus (1.27, 95% CI: 1.17–1.37) and ovary (1.39, 95% CI: 1.27–1.51), but approximated unity for cancers of the external female genitalia (0.97, 95% CI: 0.73–1.28), vagina (1.31, 95% CI: 0.80–2.02), cervix (0.78, 95% CI: 0.66–0.92), kidney (0.98, 95% CI: 0.83–1.15), renal pelvis (1.20, 95% CI: 0.86–1.64), ureter (0.92, 95% CI: 0.42–1.76), and urinary bladder (1.13, 95% CI: 1.02–1.26). The SIR estimates remained largely unchanged when restricting to cancers occurring after 12 months of follow-up for all types of cancer.

Conclusions: Breast cancer survivors had higher risks of cancers of the uterus and ovary than expected, possibly related to tamoxifen therapy or the BRCA genotype. Although the absolute risks were relatively low, our findings merit increased attention to these cancer types during clinical follow-up of patients with a history of breast cancer.

156 | Hysterectomy utilization among newly diagnosed endometrial cancer patients by body mass index category: A real-world analysis using a claims and electronic health record database

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Background: For endometrial cancer (EC), laparoscopic hysterectomy (LH) is an effective, minimally invasive surgical treatment; however, this approach may not be recommended for obese patients due to increased risk for complications.

Objectives: The aim of this study was to measure the rates of LH and subsequent ER visits and rehospitalizations among EC patients stratified by body mass index (BMI) categories.

Methods: This retrospective study utilized insurance claims linked to electronic health record (EHR) data contained in the IBM MarketScan Explorys Claims-EHR Data Set. Newly diagnosed EC patients (1/1/2007–6/30/2017) with continuous enrollment during a 12-month baseline and 6-month follow-up period were selected. Patients were stratified into four BMI subgroups based on baseline BMI on the EHR: normal or underweight (BMI <25), overweight (BMI 25- < 30), obese (BMI 30- < 40), morbidly obese (BMI >40), and were required to have had a hysterectomy within the follow-up period. Emergency room visits and rehospitalization within 30 days of hysterectomy were measured.

Results: A total of 1,090 newly-diagnosed EC patients met the selection criteria, of whom, 16% were normal/underweight, 19% were overweight, 39% were obese, and 26% were morbidly obese. The proportion of patients receiving LH increased as BMI category increased: 53% among normal/underweight, 59% among overweight, 59% among obese, and 63% among the morbidly obese. Among those who received LH, rates of ER visits or rehospitalizations were lower than those receiving non-LH hysterectomy across all BMI strata, including the obese (11% in LH vs. 19% in non-LH) and morbidly obese (9% in LH vs. 15% in non-LH).

Conclusions: This real-world analysis shows that LH is utilized in a high proportion of morbidly obese EC patients, despite that it is frequently deemed infeasible in this patient population. Although the rate of ER visits and rehospitalization is lower among LH patients than those undergoing traditional hysterectomy across all BMI strata, the rates for these costly rehospitalizations are still burdensome and further research is needed to determine the optimal patient population to receive LH.

157 | Risk of cancer in patients with psoriasis/psoriatic arthritis: A population-based study in the province of British Columbia

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Background: Psoriasis (PsO) is a relapsing chronic autoimmune disease of the skin. Up to one-third of patients (pts) also develop inflammatory arthritis, known as psoriatic arthritis (PsA). PsO/PsA, like other forms of chronic inflammatory arthritis, are often associated with complications such as cardiovascular disease and infections. However, data on the risk of cancer in pts with PsO/PsA at population level are limited.
Objectives: To assess the risk of cancer in pts with newly diagnosed PsO/PsA at the population level.
Methods: We created a population-based matched retrospective cohort of pts with PsO/PsA diagnosed between January 1, 1997 and December 31, 2012 using administrative health data from British Columbia, Canada. We identified all incident cases of PsO/PsA and an equal number of controls matched on sex, age and calendar year. PsO/PsA cases met ≥1 of the following: 1 diagnostic code for PsO/PsA by a rheumatologist/dermatologist; ≥2 diagnostic codes for PsO/PsA, ≥2 months apart in a 2-year period by a non-rheumatologist/dermatologist; or ≥ 1 hospitalization with diagnostic code for PsO/PsA. We evaluated incident cancers during follow-up from the Cancer Registry in both cohorts. Adjusted risk of cancers was estimated using a generalized estimating equation extension of multivariate Poisson regression models.
Results: We identified 81,568 incident cases of PsO/PsA (mean age 48.5 years [SD 17.8], 51.5% female). Individuals with PsO/PsA were at significantly higher risk of being diagnosed with 8/41 types of cancer examined, including eye and orbit (4 fold; incidence rate ratio [IRR] 4.25 [95% CI: 1.21, 14.91]); female genital other than cervix uteri, corpus uteri and ovary (3 fold; IRR 2.57 [95% CI: 1.55, 4.25]); non-melanoma skin (2 fold; IRR 1.82 [95% CI: 1.54, 2.14]); and prostate (males; 1.1 fold; IRR 1.12 [95% CI: 1.01, 1.25]). Incidence of rectal (IRR 0.79 [95% CI: 0.64, 0.98]) and colon (IRR 0.84 [95% CI: 0.72, 0.99]) cancer was lower among pts with PsO/PsA relative to the non-PsO/PsA cohort.
Conclusions: This general population-based study demonstrates that pts with PsO/PsA have an increased risk of several types of cancer, and a decreased risk of rectal and colon cancer. This association highlights the need to further explore potential risk factors and pathways that contribute to these complications.

158 | Epidemiology of cholangiocarcinoma in adults with type 2 diabetes in the United Kingdom clinical practice research datalink

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Background: Cholangiocarcinoma (CCA) and other bile duct tumors are rare malignancies; however, CCA accounts for 10–20% of all liver cancers and 3% of all gastrointestinal cancers. Recently, metabolic syndrome has been considered as a risk factor for CCA, but the epidemiology of CCA in patients with type 2 diabetes mellitus (T2DM) is not well characterized.
Objectives: To calculate the incidence and prevalence rates of CCA in adults with T2DM compared to general population without diabetes in the U.K.
Methods: Electronic medical records of >17 million adults (≥18 years old) enrolled in the U.K. Clinical Practice Research Datalink (CPRD) between January 2007 and April 2018 were used to calculate the incidence (per 100,000 person-years) and prevalence (in %) of CCA among adults with T2DM and adults without diabetes. Read diagnosis codes were used to define CCA and T2DM. Results were stratified by gender, age groups, and body mass index (BMI) categories of (in kg/m2) <18.5 (underweight); 18.5–24.9 (healthy weight); 25.0–29.9 (overweight); 30.0–34.9 (obese); 35.0–39.9 (severely obese); and ≥ 40.0 (morbidly obese).
Results: During the analysis period, a total of 502,615 adults with T2DM and 16,628,872 adults without diabetes were followed. The incidence rate (per 100,000 person-years) of CCA among patients with T2DM was 11.0 (95%CI = 10.0–13.0), and in those without diabetes was 1.0 (95%CI = 1.0–2.0). Corresponding prevalence rates were 0.13% and 0.02%, respectively. There was no difference in the epidemiology of CCA between men and women with T2DM. The rates were increasing with age: incidence (18–44 years, 2.0; 45–54 years, 6.0; 55–64 years, 8.0; 65–74 years, 20; and ≥ 75 years, 17); prevalence (18–44 years, 0.02%; 45–54 years, 0.05%; 55–64 years, 0.08%; 65–74 years, 0.18%; and ≥ 75 years, 0.16%). Unlike general population, where rates increased by BMI, the rates were bimodal among those with T2DM, where higher rates observed in underweight and overweight patients: incidence (underweight, 20; healthy weight, 10; overweight, 12; obese, 10; severely obese, 10; and morbidly obese, 10); prevalence (underweight, 0.34%; healthy weight, 0.16%; overweight, 0.14%; obese, 0.11%; severely obese, 0.10%; and morbidly obese, 0.09%).

Conclusions: Compared to general population, patients with T2DM have markedly higher incidence and prevalence rates of CCA.

159 | Risk of primary gastrointestinal cancers following incident breast cancer: A Danish population-based cohort study

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Background: Development of new primary malignancies among breast cancer patients may be a public health problem, as the number of breast cancer survivors is growing.

Objectives: To examine the risk of primary gastrointestinal cancers in female patients (>18 years) with breast cancer and to compare this cancer risk with that of the general population. Such data may provide insight into the clinical course following breast cancer and inform screening guidelines for this population.

Methods: Data from the Danish Cancer Registry were used in this nationwide population-based cohort study of all patients with primary breast cancer with localized cancer or regional spread (1978–2013). The outcome measures were subsequent occurrence of gastrointestinal cancers. We calculated absolute cancer risks, accounting for the competing risk of death. As a measure of relative risk, we computed standardized incidence ratios (SIRs), as the observed number of cancers relative to the expected number based on national incidence rates by age (5-year intervals) and calendar year (5-year intervals).

Results: A total of 96,374 female patients with breast cancer (median age, 61 years) were identified. During a median follow-up of 6.1 years, 2,205 new primary gastrointestinal cancers were recorded. The cumulative incidence of any gastrointestinal cancer was 0.1% after 6 months, increasing to 1.9% after 10 years. There were weak positive associations with esophageal cancer [SIR, 1.19, 95% confidence interval (CI): 0.96–1.47], stomach cancer [SIR, 1.35, 95% CI: 1.17–1.55], cancer of the small intestine (SIR, 1.19, 95% CI: 0.81–1.69), and anal cancer (SIR, 1.24, 95% CI: 0.92–1.65). No meaningful associations were found with colon cancer (SIR, 1.04, 95% CI: 0.98–1.11), rectal cancer (SIR, 1.06, 95% CI: 0.97–1.17), pancreatic cancer (SIR, 1.07, 95% CI: 0.96–1.20), or bladder and biliary tract cancers (SIR, 0.92, 95% CI: 0.73–1.15). Slightly reduced risk was observed for liver cancer (SIR, 0.68, 95% CI: 0.50–0.90). The SIR estimates were largely unchanged when restricting to cancers occurring beyond 1 year.

Conclusions: Breast cancer was not associated with increased risk of gastrointestinal malignancies and thus no additional screening is warranted for breast cancer survivors.

160 | International comparison of cancer burden and Medicaloutcomes between 11 Asian countries and 23 cancer types(2018): A linear Mutilevel model analysis

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Background: Cancer is the most serious of the global burden of disease, and it is becoming the top of the leading causes of death. Understanding the current state of the cancer epidemic in a country's region benefits the rational resource allocation of health care in the country. However, only a few studies have explored the variation of cancer disease burden and medical outcomes between countries and cancer types in Asia.

Objectives: Focusing on countries in Asia, this study aims to explore the diversities of the cancer epidemics between countries, and the associations between economic/geographical factors these cancer epidemics. In addition, we also analyzed the variations of the cancer epidemics between cancer types by using both descriptive and inferential statistics.

Methods: The epidemic data of 23 cancer types among 11 Asian countries was acquired from Cancer Today, part of GLOBOCAN 2018 project, produced by the International Agency for Research on Cancer (IARC). We collected the prevalence (represent the disease burden) and calculated the mortality to incidence ratios (MIRs) (represent the medical outcomes). Descriptive statistic and the box plot were applied to show the variations of prevalence and MIRs between countries and cancer types. Linear Multilevel Model (LMM) was used to estimate the associations between multilevel factors (gender, cancer types, geographic area and economy level) and disease burden and medical outcomes.

Results: Among Asian countries, South Korea and Singapore had the largest variations in cancer prevalence and MIR. High-income countries (Japan, Korea, Singapore) had lower MIRs significantly, while no significant association between economic level and prevalence was found. Both prevalence and MIRs were not much different between geographic areas. Among all cancer types, endocrine cancer had the largest variation in prevalence, and head and neck cancers had the greatest variation in MIRs. The prevalence was significantly higher for digestive and reproductive cancers, and the MIRs of respiratory cancers were significantly higher.

Conclusions: This study compared the differences between Asian countries by analyzing the latest cancer epidemiological data in the world, and explored the correlation between cross-level factors and disease burden/medical outcomes. The results can be used as a

reference for future national cancer prevention and treatment related policy planning and development.

161 | Use of claims and electronic medical data to describe care pathway for newly-diagnosed colorectal cancer patients

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Background: Real-world data sources can be used to assess the feasibility of a proposed study design and inform changes that could minimize disruptions and burden to participating patients and investigators.
Objectives: The primary objective is to evaluate the use of real-world data to describe the care pathway of newly-diagnosed colorectal cancer (CRC) patients from colonoscopy to first treatment (eg., chemotherapy, surgery). The secondary objective is to assess for a correlation with time to first treatment and severity of disease.
Methods: This research analyzed a combination of disparate but linkable data sources to describe the care pathway from the time of colonoscopy to first treatment for adult CRC patients diagnosed within the US. The study utilized an encrypted anonymized patient key that links the patient activities across all data sources to ensure individual patient-level data is anonymous and protected consistent with US HIPAA rules. US outpatient medical and prescription data linked to electronic medical records were used. Patients age 18 or older who were diagnosed with CRC in the period June 2015 to June 2018 as defined by diagnosis codes for colorectal cancer diagnosis and with colonoscopy prior to or at diagnosis and a treatment post diagnosis were included. First treatment was defined as first recorded claim/prescription for any of first-line chemotherapy or surgical intervention. The care pathway was described in terms of type of procedures done concurrently with colonoscopy and types of treatment at time colonoscopy and within subsequent weeks.
Results: Over 9000 patients with evidence of CRC diagnosis were identified within the claims and medical data set. Of these patients, a final dataset of 1865 patients were selected based on evidence of endoscopy within 6 mos prior to diagnosis, availability of data for first line of treatment, and excluded patients without a diagnosis date or with Stage III or IV disease without prescription data. Within the final dataset, 6 care pathways characterizing types of tests and surgical procedures were identified from time of diagnosis to first treatment among Stage I - IV patients.
Conclusions: Using a combination of US claims and medical data from a discrete population of patients with colorectal cancer identified based on data completeness and diagnosis and procedures codes, it is possible to identify and define care pathways based on disease stage. This information can be used to optimize real-world protocols that maximize the likelihood of identifying eligible patients and minimize the burden of study participation to patients and investigators.

162 | Lymphovascular invasion: Strong factor in AA

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Background: Although node-negative disease is the major prognostic factor for survival in ampullary adenocarcinoma (AA), a subgroup of patients experience cancer death. There is strong evidence that the presence of lymphovascular invasion (LVI) can suggest occult micrometastases and therefore could identify at risk node-negative patients in gastric and colon cancers, however its importance in AA still unknown.
Objectives: To assess the hazard of LVI in overall survival (OS) of patients who underwent duodenopancreatectomy (PD) for a node-negative AA.
Methods: We performed a retrospective multicenter study of patients who underwent PD for node-negative AA between 2002 and 2011 in Lima, Peru. Pathological reports were reviewed for all patients. Survival curves were calculated using the Kaplan–Meier method form post-surgery until the death for any cause and the relation with ILV presence. Bivariate and multivariable analysis was performed using Cox regression analysis. Crude and adjusted Hazard Ratios (HR) con 95% Confidence Intervals (CI) were computed.
Results: 144 patients were included from the most important national hospitals in Peru. LVI was present in 54 patients (37%). Demographic and pathologic characteristics were similar between patients with and without LVI. Risk of LVI increased with T stage (T1, 14%; T2, 31%; T3, 47% and T4, 73%; $p = 0.002$). Patients with LVI had a shorter median OS (31 months) in comparison with patients without LVI (60 months; $p < 0.001$). On multivariable analysis, LVI (HR = 2.54, 95% CI 1.37–4.571; $p = 0.003$) was significantly associated with instantaneous risk of death.
Conclusions: In this study, LVI was a factor associated with higher instantaneous risk of death in patients who underwent PD for a node-negative AA. This result represents a potential evidence that LVI could identify node-negative AA patients with shorter survival who could benefit from adjuvant therapy.

163 | Survival and prognostic factors in patients with small cell lung cancer: A systematic review of observational studies

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Background: With limited advances in the management of small cell lung cancer (SCLC) within the past thirty years, SCLC still imposes a substantial burden. Identification of prognostic factors will help to optimize the development of appropriate treatment strategies.

Objectives: To systematically review and describe survival and prognostic factors in SCLC.

Methods: A systematic review of observational studies was conducted using MEDLINE and Embase over the period 01 January 1998–17 October 2018. Pragmatic searches of the gray literature, including conference abstracts and proceedings, were also conducted to identify additional sources. Search outputs were independently screened, adjudicated and abstracted by two assessors independently, with conflicts resolved by a third.

Results: Of the 2,418 sources identified in the literature, 394 were retained for full text review, out of which 140 were included. In addition, 28 were identified through pragmatic searches yielding a total of 168 sources. Data mainly originated from Asia-Pacific (51; 42.2%), North America (30; 24.8%) and Europe (29; 24%). Eight different measures of survival were used across 121 studies (102 overall, 40 limited stage [LS]-SCLC and 42 extensive stage [ES]-SCLC): median overall survival (OS) was the most commonly reported, followed by 1- and 5-year survival rates. A total of 71/102 (69.6%) studies on SCLC, 19/40 (47.5%) on LS-, and 17/42 (40.5%) on ES-SCLC reported median OS. In SCLC, the median OS ranged from 4.6 to 29.1 months, while it ranged from 10 to 47 months in LS-SCLC and from 4 to 14.2 months in ES-SCLC. Survival trend was reported in three studies using data from SEER registries with a general trend towards an increase in survival rate when 2- and 5-year survival rates were reported. When reported (one source), no improvement in OS trend was noted. Chemotherapy, radiation therapy, prophylactic cranial irradiation, performance status, age and sex were among prognostic factors identified in both stages of SCLC.

Conclusions: SCLC survival rate is low yet variable with significantly lower rates in ES-SCLC and minimal changes in survival trend. Significant variability exists in measurement and reporting SCLC survival and survival trend, thus hampering comparability of findings, syntheses of findings and clinical decision-making.

164 | Trends and factors associated with asthma among U.S. prostate cancer patients in 2007–2014

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Background:

Objectives: To examine trends in the prevalence of and identify factors associated with asthma among prostate cancer patients, and treatment patterns among patients with concurrent asthma and prostate cancer.

Methods: A retrospective, cohort analysis was used to identify newly diagnosed prostate cancer patients (n = 107,285) from the 2007–2014 Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Prostate cancer patients were identified as primary site cancer by using ICD-9 code (185) and ICD-O site code (619). Asthma was identified using ICD-9 codes (493) in 12 months before the initial prostate cancer (index date) and the 'Asthma First Ever Occurrence Date' flag in the master beneficiary summary file among prostate cancer patients and non-cancer patients (comparison group). Prostate cancer and asthma treatments were examined in 12 months post-index period. Simple linear regression models were applied to test annual prevalence trends in asthma among prostate cancer patients and non-cancer comparison group. Multivariable logistic regression model was used to identify factors associated with asthma among prostate cancer patients. Statistical significance was set at $P < 0.05$.

Results: Annually, about 17% of prostate cancer patients had asthma comparing with 15% in non-cancer patients from 2007 to 2014. The annual trend in prevalence of asthma was stable (trend $P = 0.61$). The top three prostate cancer management strategies in the 1st year after cancer diagnosis were Active Surveillance (14.01% vs. 17.15%), ADT only (29.74% vs. 24.01%), and ADT plus surgery (8.91% vs. 11.74%) among prostate cancer patients with and without asthma, respectively. The most frequently used asthma treatment was inhaled corticosteroids (65.58% vs. 79.23%) among asthma patients with and without prostate cancer, respectively. Prostate cancer patients who also had comorbid asthma were more likely to be associated with older age, non-Hispanic black, not married, in stage IV prostate cancer, and with two or more comorbidities.

Conclusions: This study identified a stable trend in comorbid asthma among U.S. prostate cancer patients. Treatment patterns for prostate cancer were similar between prostate cancer patients with and without asthma. Understanding burden of and factors associated with asthma helps practitioners better identify patient's needs and improve clinical decision making in treatment selection for prostate cancer patients with comorbidities. Future studies need to investigate how cancer and asthma treatments affect clinical outcomes for patients with prostate cancer and comorbid asthma.

165 | Age and race as determinants for surgical treatment of fibroids: A retrospective analysis of a large United States electronic health record database

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Background: Fibroids are benign, often asymptomatic tumors of the uterus that occur in about 80% of women in the United States by the age of 50, with age and race being important epidemiological risk factors. Apart from medications, treatment options may include surgery based on severity of symptoms.

Objectives: The objective of the present study was to assess said risk factors in fibroid patients and their impact, if any, on surgical rates.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All visits, including inpatient (females, age ≥ 18 years), between 2012 and 2016 with a principal ICD9/10 diagnosis of fibroids were included in the analysis. Surgical procedures were identified based on relevant ICD-9 and CPT codes.

Results: The study included 364,384 fibroid-related patient visits. Intramural fibroids were present in 9.3% of visits, while 5.1% had submucosal fibroids. Majority of visits were in the age group of '36–65 years' (81.1%), while 45.7% were Caucasian, closely followed by African-American (38.5%). However, when compared to the total patient visits in the database for each race, African-American women had a higher number of fibroid-related visits as compared to Caucasian women (0.8% vs. 0.2%). As for surgical rates, 15.9% of visits underwent surgery with rates differing slightly across age groups (12.1% in the 18–36 age group, 16.7% in the 36–65 age group, and 14.2% in the >65 age group). From the subset of patients undergoing surgery, 21.2% were Caucasian, followed by Hispanic (13.5%).

Conclusions: The results of the study show a higher prevalence of fibroid-related visits in African-American women compared to other races. Surgical rates were similar across different age groups, with Caucasian women showing a higher surgical treatment rate as compared to other races.

166 | Dynamic assessment of stroke risk among patients with atrial fibrillation in Japan - evidence from J M D C Inc database

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Background: Stroke risk scores, often used to guide stroke prevention therapy among patients with atrial fibrillation (AF), may vary over time. A recent study among newly-diagnosed AF patients in a Taiwanese population found the 1-, 2-, and 7-year cumulative incidence of an increase in CHA_2DS_2-VASc scores among both men and women to be approximately 16%, 25%, and 49%, respectively (Chao et al., Ann Intern Med. 2019). The generalizability of these findings to other Asian populations is unknown.

Objectives: To investigate the incidence of an increase in CHA_2DS_2-VASc scores to ≥1 (men) or ≥ 2 (women) among newly-diagnosed AF patients in Japan.

Methods: This retrospective study used claims data from the JMDC Inc. database between 1/1/2005 and 5/31/2018. OAC treatment naïve adults (≥18 years) with ≥1 AF diagnosis between 1/1/2007 and 5/31/2017 were identified. The first day of the month (index month) of the AF diagnosis was set as the index date. Patients were required to have ≥12 months of continuous enrollment and no diagnosis of AF prior to the index date. Baseline CHA_2DS_2-VASc scores were calculated using all observable records from 1/1/2005 until the end of the index month; only patients with a score of 0 (men) or 1 (women) were retained. Patients were followed from the index date until an observed incident score increase or were censored at the start of OAC therapy or the end of eligibility/data, whichever came first. Cumulative incidence curves for the increase in CHA_2DS_2-VASc scores were estimated for men and women separately using the Kaplan–Meier method. All statistical analyses were performed using the Instant Health Data platform (BHE, Boston, MA, USA).

Results: A total of 1,768 newly-diagnosed AF patients met all inclusion and exclusion criteria. The mean (SD) age was 44.6 (11.4) years and 31.1% were female. The mean duration of follow-up was 27 months. Among men, the cumulative incidence of an increase in CHA2DS2-VASc scores at 1, 2 and 7 years was 31% (95%CI: 29%–34%), 45% (42%–48%), and 74% (70%–78%), respectively. Among women, corresponding estimates at 1, 2 and 7 years were 22% (95%CI: 18%–25%), 32% (28%–36%), and 60% (50%–68%). The cumulative incidence of an increase in stroke risk was higher among men (log-rank test $p < 0.0001$).

Conclusions: Japanese patients with newly-diagnosed AF experienced increases in CHA_2DS_2-VASc scores over time, with the largest increases occurring among men. The increase in risk observed in this study exceeded those found in a Taiwanese AF cohort in the prior analysis. Our results confirm that the re-evaluation of stroke risk among AF patients should be carried out regularly.

167 | Incident unrecognized myocardial infarction among people with Dysglycemia: An opportunity for prevention

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Background: Up to 45% of initial myocardial infarctions (MI) are unrecognized (UMI), which is problematic since they are asymptomatic and are often only detected during a routine electrocardiogram (ECG), post-event. This delayed diagnosis may postpone necessary medical management of risk factors for the prevention of future MI. The risk for subsequent events following UMI is similar to MI placing these individuals at particularly high risk. This is especially problematic among people with diabetes and prediabetes who are already at high risk for these events.

Objectives: Our objective was to determine if there was a difference in the incidence of UMI between those with diabetes or prediabetes and their subsequent treatment for cardiovascular (CVD) risk factors, specifically hypertension and hyperlipidemia.

Methods: Data from two cohort studies, the Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Studies (CHS), were pooled and analyzed (n = 17623 people with diabetes or prediabetes). Thirteen years of follow-up data were available. CHS was an observational study in adults 65 years or older undergoing annual

exams from 1989–1999 with subsequent phone follow-up. ARIC individuals were aged 45–64 and were examined every three years through 2013. Definitions: UMI was determined according to Minnesota Codes on ECG, prediabetes: fasting glucose 100–125 mg/dL, diabetes > = 126 mg/dL or treatment for diabetes, hypertension: > = 140/90 mmHg, and hyperlipidemia: LDLc> = 100 mg/dL.

Results: The population consisted of 9,567 (54%) with diabetes and 8,056 (46%) with prediabetes. The mean age was 64 and 55 years respectively. Approximately half the population in both groups were female and three-fourths were white. There were 210 UMI events: 0.88% of those with diabetes had UMI while 1.56% of people with prediabetes experienced UMI. Significant predictors of UMI were prediabetes, male sex, older age, and history of hypertension. Among those who did not experience UMI, but had a history of hypertension or hyperlipidemia, people with diabetes were 60% more likely to be treated for hypertension and 68% more likely to be treated for hyperlipidemia compared with people with prediabetes. These treatment differences were statistically significant ($p < 0.0001$).

Conclusions: Despite the higher risk for UMI among prediabetes, those with diabetes were more likely to be treated for hypertension and hyperlipidemia. This may indicate a lack of awareness for the high risk for UMI in prediabetes and the need for risk factor treatment for primary prevention of coronary events in this population.

168 | Sex disparities in cardiovascular risk and risk factor Management in Type 2 diabetes: A population-based study of the clinical practice research datalink

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Background: Historically, women developing type 2 diabetes (T2DM) have experienced a 27–50% greater increase in their risk for cardiovascular disease (CVD) than men developing T2DM.

Objectives: With recent changes in UK clinical practice for diabetes care, we aimed to determine if this gender disparity persists in contemporary data and if any disparity could be explained by gender biases in diabetes management.

Methods: Using the Clinical Practice Research Datalink (CPRD) linked to hospital admission and death data, we identified 79,985 people with incident T2DM between 2006–2013 and 386,547 age-sex-practice-matched controls without diabetes. The primary endpoint was the first record of fatal and non-fatal myocardial infarction, stroke or cardiovascular death, identified from primary care, hospital and death records. Sex-stratified Cox models were used to assess cardiovascular risk.

Results: Compared to women without T2DM, women with T2DM had a higher cardiovascular event risk (adjusted HR 1.20 [95% CI 1.12–1.28]) with similar corresponding data in men (HR 1.12 [1.06–1.19]) leading to a non-significant 7% excess relative risk in women (risk ratio 1.07 [0.98–1.17]). However, some important sex differences in the management of risk factors were observed. Compared to men with T2DM, women with T2DM were more likely to be obese, hypertensive and have hypercholesterolaemia but were less likely to be prescribed statins and ACE inhibitors, especially if they had CVD. In T2DM subgroups with CVD, women were less likely to receive antiplatelet agents than men.

Conclusions: Compared to men developing T2DM, women with T2DM do not have a significantly higher relative increase in CVD risk, but ongoing sex disparities in prescribing should prompt heightened efforts to improve the standard and equity of diabetes care. Particular attention is required for women with abnormal cardiovascular risk factors, who may be receiving suboptimal preventative care.

169 | Trend in 3-day, 7-day and 30-day heart failure readmission rates from 2010 To2015 in the Nationwide readmissions database

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Background: Thirty-day readmission among heart failure patients has been used as a quality measure in the Hospital Readmission Reduction Program (HRRP) and are tied to financial penalties for hospitals by the Centers for Medicare and Medicaid Services (CMS). Although 30-day readmission rates have been widely used to evaluate hospital performance, there have been many concerns about the validity of the metric, including the choice of the 30-day interval.

Objectives: This analysis evaluated the trends in 3-day, 7-day, and 30-day readmissions for heart failure in Medicare beneficiaries between 2010 to 2015 to determine how this policy has influenced hospital quality.

Methods: The Nationwide Readmission Database (NRD) from 2010 to 2015 was used which contains a national sample of hospital discharges and readmissions. Patients aged ≥65 years-old with a primary diagnosis of HF and Medicare insurance during January to November each year were included. We excluded patients who died during index hospitalization, were transferred, discharged against medical advice, and with missing data. The measures of interest were 3-day, 7-day, and 30-day unplanned, all-cause readmissions as a proportion of index admissions. Multiple index admissions per patient were considered but could have only one readmission. The second outcome of interest was the relative reduction in the proportion of readmissions. Adjusted readmission rates were calculated for each year controlling for patient demographic, hospital, and clinical characteristics between years using hierarchical logistic regression models. Cochran-Armitage Trend Tests were used to assess the trend in adjusted readmission rates between years.

Results: Overall trends showed a decreased readmission rate between 2010 and 2015 and was statistically significant for trend ($P < 0.001$) for each readmission interval: 23.1% to 20.8% (30-day); 7.6% to 6.6% (7-day); and 3.4% to 2.9% (3-day). Relative percent reduction in readmission rates in 2015 versus 2010 were 9.9% for 30-day interval, which was a lower reduction compared to 13.9%, and 14.9% for 7-, and 3-day intervals.

Conclusions: We found that shorter readmission intervals (3-day and 7-day) had larger relative reductions since the introduction of financial penalties compared to 30-day readmissions. The findings support the assertion that hospitals may be disincentivized by metrics they cannot influence or that further innovation is needed to differentiate and intervene on factors that drive shorter versus longer term readmissions.

170 | Incidence of post-operative acute myocardial infarction among adults undergoing elective spinal fusion, Total hip and Total knee arthroplasty

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Background: Acute myocardial infarction (AMI) is one of most serious complications after elective spinal fusion surgery (SF), total hip arthroplasty (THA), and total knee arthroplasty (TKA). There is scarce data on the incidence of AMI in these populations, particularly in high-risk sub-populations and after 30 days post-operation.

Objectives: To estimate incidence rates (IRs) of AMI among adults undergoing elective SF, THA, and TKA in different post-operative periods and characterize high-risk sub-populations in the United States.

Methods: We conducted a retrospective cohort study using a longitudinal EHR database (Optum EHR) from January 1, 2007 to June 30, 2018. Patients aged 18 to 85 years undergoing elective SF, THA, or TKA were identified. ICD codes were used to identify SF, THA, TKA, AMI, and selected clinical characteristics. IRs and 95% confidence intervals (CIs) were estimated in the following windows: surgical hospitalization, 10, 30, 90, 180, and 365 days post-operation.

Results: 67,327 SF patients, 88,284 THA patients, and 168,785 TKA patients were eligible for the study. There were more whites (>88%) across all surgical types, more females undergoing THA (53%) and TKA (59%), and more males undergoing SF (57%). The median age at the index date was 59, 65, and 66 years for SF, THA, and TKA, respectively. The IR of AMI after SF, THA and TKA per 1000 person-years decreased consistently from 295.96, 280.37, and 231.85 during surgical hospitalization to 12.77, 11.61, and 10.20 $\leq$ 365 days post-operation, respectively. The IR of AMI was higher among patients who were older, male, with longer hospital stays (LHS), had a history of MI, and had a history of diabetes across three types of surgery at each widow. The LHS could be a result of AMI. Racial differences were also observed. The IR of AMI was higher among blacks in TKA at each window and in SF up to the 90 days post-operation while the IR of AMI was higher among whites in THA at each window. Additionally, SF and TKA patients with the same day revisional surgery had higher IRs of AMI at each window and during surgical hospitalization, respectively. Patients with exiting permanently implanted devices/prostheses had a higher IR of AMI in THA and TKA at each window.

Conclusions: Our study showed the IRs of AMI in patients undergoing elective SF, THA, or TKA were highest during surgical hospitalization and attenuated over 365 days post-operative periods. Furthermore, we identified some high-risk sub-populations. Further studies are warranted to confirm these findings by controlling confounding and identifying effect modifiers.

171 | Evaluating the Charlson and Elixhauser comorbidity index to predict acute cardiovascular disease survival for 1 to 5 years in Korean National Health Insurance Cohort

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Background: The Charlson comorbidity index (CCI) and Elixhauser comorbidity index (ECI), which are commonly used as adjusting methods for Korean comorbidity, have been developed for specific patients and diseases in the United States and Canada. Therefore, it would not be appropriate for the Korean population and disease structure.

Objectives: To identify the survival aspects of acute myocardial infarction (AMI) or Stroke patients for 1 to 5 years according to the comorbidity levels and evaluate whether the Charlson comorbidity index (CCI) and Elixhauser comorbidity index (ECI) is a good predictor compared to other predict factors in Korean claims database.

Methods: This study identified 11,281 patients aged 20 or older who were diagnosed with acute myocardial infarction (AMI) or stroke between 2006 and 2010 in korean national health insurance cohort. Using the Kaplan Meier Curve, we described the survival aspects of patients according to comorbidity index level of CCI and ECI. And we selected key variables for predicting survival well among 10 factors including CCI and ECI through the hazard ratio (HR) of cox regression. The factors are age, sex, inpatient course, insurance type, inpatient history, hospital level, operation status, severity of disability,

medication use for cardiovascular, CCI or ECI. We evaluate model discrimination by the area under the receiver-operating curve (AUC).

Results: Age, medication use for cardiovascular and comorbidity index were selected as the 3 key variables that affect to survival prediction. In the 1-year survival, a base model (age, sex) AUC was 0.660, and after the addition of CCI, discrimination was increased but did not outperform(0.686). On the other hand, the significant increase occurred after adding the medication use(0.747) on base model. In the 5-year survival, AUC was also increased over the base model(0.715) after addition of CCI(0.737), but addition of medication use on the base model made a much greater increase(0.772). This result was almost near to the model discrimination with 3 major predictors and sex(0.786) or with all 10 predict factors(0.780). The ECI result patterns were similar to above and the discrimination was slightly higher than CCI but not significantly different.

Conclusions: The CCI and ECI are not sufficient to predict survival in Korean claims database. Especially it needs to be improved for better predicting the short-term survival within 1-year.

172 | Identification of incident atrial fibrillation patients using health claims database

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Background: Atrial fibrillation (AF) is the most common arrhythmia among adults in the United States (US).

Objectives: To examine variation in treatment associated with different approaches to incident AF identification using health claims database.

Methods: We used the 2010–2016 IBM MarketScan® Commercial Database. We used multiple approaches to identify incident AF, and examined variation in treatment use in the first year post-diagnosis. The approaches differed in terms of the underlying diagnosis criteria (i.e., identification using multiple visits versus single visit), prior pharmacotherapy (i.e., identification with prior oral anti-coagulant use versus without prior oral anticoagulant use), and baseline pre-incident diagnosis period (i.e., one year versus two-year). For the first approach, patients aged 20–64 years with at least two visits with primary diagnosis of AF (with the first visit classified as 'index diagnosis') within three months and continuous enrollment for a least one-year pre-index and post-index visits were included. Patients who had a primary or secondary diagnosis of AF or had filled an AAD in the 12 months pre-index period were excluded. For the second approach, we included patients aged 20–64 years with at least one primary diagnosis of AF and continuous enrollment for a least 24 months pre-index and 12 months post-index diagnosis. Patients who had any diagnosis of AF or had filled an AAD or an oral anticoagulant in the 24 months pre-index period were excluded.

Results: For the first approach for AF identification, 77,207 patients met inclusion criteria. Mean age was 53.9 years, 66.8% were male. Almost 30.0% of patients had been trialed on at least one anti-arrhythmic drug (AAD) and 46.3% on an oral anticoagulant, 24.4% had been cardioverted, and 7.1% of patients underwent ablation in the 12-months post-incident diagnosis period. For the second approach for AF identification, 87,758 patients were identified. The mean age was 53.2 years and 61.1% were male. Almost 22% of patients had been trialed on AAD and 28% on an oral anticoagulant, 16.0% had been cardioverted, and 4.5% had ablation in the 12-months post-incident diagnosis period.

Conclusions: Variation in inclusion/exclusion by diagnosis criteria, baseline enrollment, and baseline pharmacotherapy led to variation in outcomes assessment. The rate of treatment was lower for patients in the second approach, which could be because of identification of transient AF patients, as this approach relied on identification using single medical visit. Further research is needed to better understand AF phenotyping using health claims database.

173 | Incidence and prevalence of systolic and diastolic heart failure among obese patients with type 2 diabetes in the United States

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Background: Obesity and diabetes are known risk factors for heart failure; however, the epidemiology of heart failure by type in obese patients is not well characterized, especially among patients with type 2 diabetes mellitus (T2DM).

Objectives: To estimate the incidence and prevalence of heart failure by type among obese patients with and without T2DM.

Methods: Between 2007–2017, an analysis of the U.S. Truven Health MarketScan claims database was performed to calculate the incidence and prevalence rates of heart failure in obese T2DM patients compared to obese general population without diabetes. Rates were stratified by type of heart failure, including systolic (with reduced ejection fraction__HFrEF) and diastolic (with preserved ejection fraction__HFpEF). Obesity, diabetes, and heart failure were defined by corresponding inpatient and outpatient ICD-9/10-CM diagnosis codes.

Results: During the analysis period, >12 million obese patients were included (mean age 43 years; 63% females), corresponding to >2 million with T2DM (mean age 53 years; 58% females), and > 9 million without diabetes (mean age 40 years; 65% females). Incidence (per 100 person-years) and prevalence rates of heart failure for corresponding populations were: overall (112.7; 6.1%); T2DM (238.7; 15.7%); and general population (76.9; 3%). Corresponding rates for HFrEF: overall (29.9; 1.4%); T2DM (59.9; 3.9%); and general

population (19.2; 0.6%), and for HFpEF: overall (43.8; 1.8%); T2DM (92.8; 5.3%); and general population (24.4; 0.7%). Obese men with T2DM had higher rates of heart failure than women (incidence = 164.2 vs. 89.1; prevalence = 7.3% vs. 5.4%). Incidence rates of both heart failure types were higher in obese men with T2DM compared to women (HFpEF, 53.9 vs. 39.1; HFrEF, 50.1 vs. 20.4). There was no difference in prevalence rates (HFpEF, 1.9% vs. 1.8%; HFrEF, 2.1% vs. 1.1%). The rates of any heart failure were increasing with age among obese T2DM patients (18–44 years old, 47.9 and 1.9%; 45–54 years old, 120.6 and 5.7%; 55–64 years old, 188.2 and 10%; 65–74 years old, 287.5 and 20.7%; and ≥ 75 years old, 444.2 and 37.1%). Corresponding rates by race were: any heart failure (Whites, 128.2 and 11.7%; Blacks, 118.3 and 10.8%; and Hispanics, 50.7 and 2.6%); HFpEF (Whites, 54.9 and 3.8%; Blacks, 56.3 and 3.8%; and Hispanics, 23.5 and 0.8%); and HFrEF (Whites, 30.2 and 2.6%; Blacks, 36.2 and 2.9%; and Hispanics, 11.8 and 0.6%).

Conclusions: Incidence and prevalence rates of heart failure, especially diastolic (HFpEF) type, were higher in obese patients with T2DM compared to obese general population.

174 | Risk factors for post-ablation early and late symptomatic recurrence of atrial fibrillation: Findings from a real world database study

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Background: Catheter ablation is a mainstay treatment for drug refractory atrial fibrillation (AFib), but recurrence can occur after initially successful ablation. Identifying risk factors for post-ablation recurrence may help develop effective strategies to reduce recurrences.

Objectives: To identify risk factors for early and late symptomatic recurrence in real-world settings.

Methods: A retrospective cohort study was conducted in patients undergoing cardiac ablation for AFib during 2011–2016 using the MarketScan® Commercial Database. Symptomatic recurrence was defined as a composite of AFib-related inpatient readmission, cardioversion and repeat ablation in an inpatient or outpatient setting. Multivariable logistic regression was used to evaluate the association between patient characteristics (assessed in the year pre-index ablation [baseline]) and risk of early symptomatic recurrence during the first 3 months post-index ablation. Multivariable Cox models were used to evaluate the association for late symptomatic recurrence (4–12 months).

Results: Of the 14,239 study patients (median age, 57 years; male, 74%), 18% had early symptomatic recurrence post ablation. In multivariable analyses, baseline characteristics that were significantly associated with a lower risk of early symptomatic recurrence were age < 50 years, inpatient service setting, presence of AFib and other arrhythmia, use of antiarrhythmic drugs, and later calendar years of index ablation. Baseline characteristics that were significantly related to a higher risk of early symptomatic recurrence were hypertension, sleep apnea, obesity, valvular heart disease, cardiomyopathy, and use of ≥2 (vs 1) different anticoagulants. Freedom from early symptomatic recurrence during the first 3 months and baseline characteristics including later calendar years of index ablation, presence of AFib and other arrhythmia, and Northeast/South regions were significantly related to a lower risk of late symptomatic recurrence. The hazard ratio comparing patients without vs with symptomatic recurrence during the first 3 months was 0.42 (95% confidence interval: 0.39–0.46) for late symptomatic recurrence. Baseline inpatient service setting, valvular heart disease, use of ≥2 (vs 1) different anticoagulants, and North Central region were significantly related to a higher risk of late symptomatic recurrence.

Conclusions: Cardiometabolic comorbidities were associated with risk of early and late symptomatic recurrence. Early symptomatic recurrence was strongly related to late symptomatic recurrence.

175 | Epidemiology of non fatal major adverse cardiovascular events in children with diabetes

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Background: Unlike adult population, the epidemiology of non-fatal major adverse cardiovascular events (MACE) in children with diabetes is not well characterized.

Objectives: To estimate the incidence and prevalence rates of non-fatal MACE in children with diabetes.

Methods: Records of patients enrolled in Truven MarketScan database between 2015–2016 were analyzed for children (aged <18 years) with and without diabetes. The primary outcome of non-fatal MACE was measured as a composite of myocardial infarction (MI), stroke, hospitalization for transient ischemic attack (TIA), hospitalization for unstable angina (UA), or revascularization procedures (RP). Prevalence rates in percentages and incidence rates per 100 person-years (PY) were estimated and stratified by age, gender, and diabetes type (T1D and T2D) and compared to those without diabetes.

Results: During the analysis year, >6 million children were identified, including 32,256 with diabetes (T1D = 16,959 and T2D = 7,963), and 6,697,362 without diabetes. Children with diabetes had 3-times the prevalence and twice the incidence of MACE than those without diabetes (prevalence, 0.3% vs. 0.1%; incidence, 0.12 vs. 0.05 per 100 PY). Children with T2D had higher rates than those with T1D (prevalence, 0.4% vs. 0.2%; incidence, 11 vs. 2.79 per 100 PY). There was no difference in prevalence by gender, but boys with diabetes had higher incidence (0.14 vs. 0.1 per 100 PY). Children with diabetes <6 years had higher rates (prevalence, 0.9%; incidence, 0.44 per 100 PY) than those aged 6–12 years (prevalence, 0.2%; incidence, 0.08

per 100 PY) or 13–17 years (prevalence, 0.3%; incidence, 0.11 per 100 PY). Stroke contributed to the majority of MACE, with rates in children with T2D higher than those with T1D (prevalence, 0.3% vs. 0.1%; incidence, 5.51 vs. 2.03 per 100 PY). Adults with diabetes had MACE prevalence and incidence of 6.6% and 3.89 per 100 PY.

Conclusions: Children with diabetes, particularly T2D, are at risk for non-fatal MACE; however, less than adult counterpart population. Therefore, cardiovascular outcome studies in pediatrics might not be feasible.

176 | Embolic events and unmet Therapeutical need for coronary and peripheral arterial disease

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Background: Despite a decline in vascular mortality over past decades, atherosclerosis remains the number one cause of death worldwide.
Objectives: To assess prevalence of coronary and peripheral arterial disease (CAD and PAD) in the Netherlands, embolic event rates and risk factors.

Methods: Within a cohort of patients diagnosed with CAD and/or PAD prior to July 2015, embolic event rates after diagnosis were assessed using data from the PHARMO Database Network. Furthermore, a nested case–control study was performed to assess risk factors for embolic events.

Results: Of 41,163 patients, 26,306 had CAD-only, 11,518 PAD-only and 3,339 polyvascular disease. In 2015, respective prevalences were 27, 12 and 3.7 per 1000 persons. Comparing embolic event rates in the first year after diagnosis with next years, rates declined from 34 to 20 per 1000 person years (PY) for CAD-only and 73 to 35 per 1000 PY for PAD-only. Most frequent embolic events were myocardial infarction, stroke, transient ischaemic attack and acute limb ischaemia. Risk factors for embolic events included history of embolic events, time between diagnosis and event, smoking, diabetes and revascularisation. Anti-thrombotic drugs were preserved for patients with highest risk.

Conclusions: The decreasing risk of embolic events after diagnosis confirms what is already known and indicates that treatment reduces risk over time. Nevertheless, the association between specific drugs and embolic events shows that current treatment options are insufficient to eliminate excess risk. To lower the risk of embolic events among patients with CAD and/or PAD this unmet medical need has to be addressed.

177 | Glycemic control from 2013 to 2016 among US adults with type 2 diabetes: A National Estimate Stratified on age, eGFR category and comorbidities

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Background: The adequacy of adherence to ADA's guidelines, as reflected in glycemic control, has not been assessed among US adults with type 2 diabetes (T2D) by different risk factors, such as age, cardiovascular diseases (CVD), obesity and chronic kidney disease (CKD).
Objectives: To assess glycemic control (measured by HbA_{1C}) among US adults with T2D, overall and stratified by age, eGFR categories and presence/absence of overweight/obesity and CVD.
Methods: Using the National Health and Nutrition Examination Survey (NHANES) 2013–2016 data, we conducted a cross-sectional analysis of an adult sample with T2D, aged≥18 years. T2D was defined as diagnosed T2D (self-reported provider diagnosis) and undiagnosed T2D (FPG ≥126 mg/dL or $HbA_{1c} \geq 6.5\%$ without self-reported diagnosis). Participants who started insulin within a year of T2D diagnosis, or were pregnant at the time of interview were excluded. CVD was defined based on self-reported interview data on a broad range of health conditions—congestive heart failure, coronary heart disease, angina, stroke, or heart attack. GFR categories were based on eGFR, calculated using the CKD-EPI equation. The classification of overweight/obesity was based on measurement of Body Mass Index. HbA_{1c} measures were aggregated to 4 levels: <7%, 7- < 8%, 8- < 9%, and ≥ 9%. Glycemic control rates were calculated as the proportion of T2D patients within each pre-specified HbA_{1c} levels, overall and in each pre-specified subgroup. Appropriate sample weights were used to provide a national estimate.
Results: The NHANES 2013–2016 sample included a total of 1,705 adults with T2D, yielding a national projected population estimate of 27.1 million. The overall glycemic control rate, defined as $HbA_{1c} < 7\%$, was 51.9%. Among T2D aged 45–64 years, 46.6% had an $HbA_{1c} < 7\%$; while 60.3% of T2D aged ≥75 years had an $HbA_{1c} < 7\%$. Among T2D with renal impairment, the glycemic control rate was similar across eGFR categories, remaining at above 50%. Among T2D with comorbidities, glycemic control rate ranged from 48.5% for those with both obesity and CVD to 69.5% for those with CVD only. It is worth noting that 14.8% of T2D had an $HbA_{1c} \geq 9\%$, with 22.7% among aged 18–44 years and 20.3% among those with eGFR >90 ml/min/1.73m^2.
Conclusions: Our findings provide national estimates of glycemic control from 2013–2016 among US adults with T2D by different risk factors. Despite the approval of many new anti-diabetic medications, the proportion of patients achieving glycemic control targets has not improved, with only about 50% at HbA_{1c} goal of <7%, ranging from 47–70% depending on risk factors.

178 | Variation in polycystic ovary syndrome patient characteristics by body mass index: A real-world analysis using a claims and electronic health record linked database

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Background: Polycystic ovary syndrome (PCOS) is characterized by hormonal imbalances which often manifest as both endocrine and metabolic-related comorbidities, including obesity.

Objectives: The aim was to describe PCOS patients in terms of clinical characteristics, medication utilization, and healthcare costs stratified by body mass index (BMI) categories.

Methods: This retrospective, observational study utilized claims linked to electronic health record (EHR) data contained in the IBM MarketScan Explorys Claims-EHR Data Set. Patients with at least one diagnosis for PCOS (ICD-9-CM 256.4; ICD-10: E282; SNOMED: 69878008) from 1/1/2007 through 6/30/2017 were selected. Patients were required to be continuously enrolled in the database, and with no evidence of pregnancy, during the 12-month observation period (6 months before and after the PCOS diagnosis). Clinical characteristics, medication utilization, lab results and all-cause healthcare costs were described. Patients were stratified into four BMI subgroups: normal or underweight, overweight, obese, and morbidly obese.

Results: A total of 4,142 PCOS patients met the selection criteria, of whom, 16% were normal or underweight, 17% were overweight, 40% were obese and 27% were morbidly obese. The mean age was 32 years. Approximately 22% of morbidly obese patients were diagnosed with type 2 diabetes, compared to 13%, 7% and 3% in the obese, overweight and normal/underweight subgroups, respectively. Acne was more often diagnosed in the lower weight patient subgroups (normal/underweight 22%; overweight 15%; obese 11%; morbidly obese 6%). Cardiovascular conditions were rare. Oral contraceptives were more commonly utilized in the lower BMI categories, while opioids and nonsteroidal anti-inflammatory drugs were more common in higher BMI categories. HbA1c levels did not differ between BMI categories. Mean and median total healthcare costs were highest in the morbidly obese patients.

Conclusions: This descriptive analysis provides real-world evidence of the variation in the clinical and economic burden of PCOS based on the presence of comorbid obesity. Further research is needed into the impact of obesity on comorbidity disease management, treatment and healthcare costs among women with PCOS.

179 | A comparison of the burden and characteristics of incident type 2 diabetes mellitus cases in HIV and non-HIV cohorts within a US claims database

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Background: Antiretroviral therapy (ART) has been associated with increased risk for glucose metabolism disorders, including Type 2 diabetes mellitus (T2DM). However, the burden of T2DM in HIV vs non-HIV patients is not well studied. Additionally, comorbidities and comedications may also contribute to T2DM onset or complicate T2DM management, and merit further study.

Objectives: To compare the incidence of T2DM between HIV and non-HIV cohorts. Comorbidities, comedications, and treatment of incident T2DM cases were compared. Additionally, ART use in the HIV cohort was studied.

Methods: This is a retrospective, longitudinal study using Optum™ Clinformatics™ claims data from 1/1/2012 to 12/31/2016. Estimates of annual T2DM incidence were calculated using HIV vs non-HIV age and gender 1:3 matched cohorts. Demographics, comorbidities, and comedications were evaluated in the 12 months prior to an incident T2DM claim. T2DM complications and medication, as well as ART use were evaluated 0–90 days after an incident T2DM claim. A GSK funded study.

Results: Commercially insured patients with HIV had a higher incidence of T2DM during years 2012–2016 (n = 1,121, range 3.2–5.6 cases per 100 person-years), compared to those without HIV (n = 3,363, range 2.2–2.7 cases per 100 person-years). In the 12 months prior to T2DM diagnosis, HIV patients were more likely to have chronic liver disease (2.2% vs 0.6%, $p < 0.0001$), chronic kidney disease (3.5% vs 0.9%, $p < 0.0001$), hepatitis B (5.1% vs 0.1%, $p < 0.0001$) and hepatitis C (4.4% vs 0.2%, $p < 0.0001$), while non-HIV patients were more likely to be classified as obese (16.4% vs. 7.3% $p < 0.0001$), and have hypertension (34.9% vs. 26.8%, $p < 0.0001$) compared to HIV patients. In the 90-day period after T2DM diagnosis, no significant differences were observed between the proportions of HIV vs non-HIV patients receiving diabetes therapy (58.5% vs, 60.8%, $p = 0.2$), but HIV patients were more likely to experience T2DM complications (39.5% vs 33.6%, $p = 0.0004$). Among HIV patients with incident T2DM, 86.8% had received treatment with ART prior to T2DM diagnosis and 83.3% were being treated with ART 0–90 days after diagnosis.

Conclusions: The incidence of T2DM was higher in HIV patients than non-HIV patients, and similar proportions of these incident T2DM cases received diabetes therapy in both cohorts. T2DM patients with HIV had a higher prevalence of chronic conditions, such as chronic liver and kidney disease, and/or infectious diseases, such as hepatitis B. In contrast, T2DM patients without HIV were more likely to have comorbidities reflecting lifestyle risk factors.

180 | Potassium trajectories and predictors for repeated hyperkalemia in high-risk patients: A population-based cohort study

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Background: Hyperkalemia (HK, defined as blood potassium >5.0 mmol/L) is associated with cardiac arrhythmias and increased mortality. HK is often considered a transient condition, but some patients may be susceptible to repeated HK.

Objectives: To examine potassium trajectories and predictors for repeated HK among high-risk patients after a first HK event.

Methods: We used Danish population-based registries to identify all patients with first-time renin angiotensin system inhibitor (RASi) prescription, chronic kidney disease (CKD), or chronic heart failure (CHF) in Northern Denmark (population, 1.8 million), during 2000–2012. For patients with a first HK event, potassium trajectories over the following 6 months were examined. Predictors associated with repeated HK (defined as a second potassium test >5.0 mmol/L within 6 months after the first HK event) were assessed.

Results: Overall 262,375 first-time RASi users, 157,283 incident CKD patients, and 14,600 incident CHF patients were included. Of these 41,818 (16%), 43,845 (28%), and 5,634 (39%) patients, respectively, had a subsequent HK event. Of patients with a first HK event, repeated HK within 6 months occurred in 37% of RASi users, 40% with CKD, and 49% of patients with CHF. Predictors of repeated HK included severe HK at baseline, low baseline eGFR, diabetes, and spironolactone use. In all cohorts, the median potassium levels declined over 2–4 weeks after a first HK event, but reverted to levels higher than before the first HK event in those who had repeated HK, with the highest 10% of recorded potassium measurements each week staying above 5.0 mmol/L.

Conclusions: Repeated HK was common among the explored patients. The potassium values in the trajectory for patients with repeated HK were markedly higher than the values in the trajectory for patients with only a single HK event. The first HK event was an indicator of subsequent increased median potassium levels. Repeated HK predictors may identify patients likely to benefit from intensified monitoring and intervention for HK.

181 | Prevalence and Management of Dyslipidaemias in adult renal transplant recipients attending nephrology Clinic at a Tertiary Hospital in Kenya

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Background: Dyslipidemia is a common cause of cardiovascular morbidity and mortality among renal transplant recipients. Management of dyslipidemia in these patients is complicated by concerns over safety of statins due to drug interactions.

Objectives: This study aimed to assess the predictors and management of dyslipidemia in Renal Transplant recipients attending clinic in a tertiary hospital in Kenya.

Methods: A cross-sectional study was conducted a Kenyatta National Hospital, a leading referral hospital in Nairobi, Kenya. Adults (≥ 18 years) patients who had received a renal transplant at least 3 months before the date of recruitment into the study and on follow up at the renal transplant clinic were eligible for the study. Those who met the inclusion criteria were consecutively selected and interviewed using a structured questionnaire and data was abstracted from their medical files. Descriptive, bi-variable analysis and logistic regression was done using STATA version 13.

Results: 110 adult renal transplant recipients were recruited into the study. The mean age of the participants was 43.4 ± 13.4 with a male gender predominance at 64% (n = 70). The prevalence of dyslipidemia was 72%. The most prevalent types were elevated LDL-C and elevated non-HDL-C each at 44%. Only 12% of the participants were on a statin and atorvastatin was the most commonly used at 10%. Lifestyle modification strategies used by participants included dietary modification (30%), physical activity (64%), weight reduction (58%), smoking cessation/abstinence (99%) and limitation of alcohol intake (99%). Weight gain (P = 0.003), dietary modification (P = 0.001) and physical activity (P = 0.04) were significantly associated with dyslipidemia. Dietary modification (P = 0.004) was the only independent predictor of dyslipidemia.

Conclusions: The prevalence of dyslipidemia was high and the most prevalent types were elevated LDL-C and Elevated non-HDL-C. The use of statins and Lifestyle modification strategies for the management of dyslipidemia was low.Dietary modification, physical activity, obesity weight gain and time on dialysis before transplant were significant predictors of dyslipidemia.

182 | Temporal trajectories of complications of type 2 diabetes mellitus

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Background: Type 2 diabetes mellitus (T2DM) is rapidly becoming a global pandemic. Moreover, people with T2DM are at increased risk of many complications, such as hypertension, dyslipidemia, and cardiovascular diseases, due to their interconnected mechanisms. While many studies have examined complications of T2DM, few attempts have been made to understand complication trajectories over time.

Objectives: To analyze temporal patterns of T2DM complication progression, we constructed diagnosis trajectories using data from the National Health Insurance Service (NHIS) cohort, which sampled approximately 2% of the Korean population from 2002 to 2013.

Methods: We classified patients as having T2DM if they had one relevant ICD-10 code (E11-E14). To account for confounding factors, controls (without T2DM) were matched according to age, gender, and hospital discharge week in a ratio of one case to four controls.

We constructed T2DM trajectories using the following steps: (1) we used the relative risk (RR) and *p*-value from Fisher's exact test to measure the significance of first complications of T2DM (T2DM → D1); (2) associations with second and third complications were defined similarly and we combined pairs with overlapping diagnoses (*i.e.*, T2DM → D1 → D2 and T2DM → D2 → D3 were combined to yield T2DM → D1 → D2 → D3); and (3) finally, we identified the frequency and duration of the progression of each trajectory.

Results: The NHIS sample cohort contained 1,111,007 patients and 23,829,621 incidence cases. Overall, 214,817 patients were considered to have T2DM and there were 859,207 matched controls. There were 1,393 distinct complications after T2DM, of which only 96 had a significant temporal relationship with T2DM (T2DM → D1). From the T2DM patient dataset, we identified 133,632 pairs (D1 → D2) of diagnoses, of which 16,268 were significant. These directional pairs were then combined into longer trajectories consisting of four diagnoses, including T2DM (T2DM → D1 → D2 → D3). The top 50 most frequent trajectories include highly reliable patterns, such as "Type 2 diabetes mellitus → Polyneuropathy in diseases classified elsewhere → Retinal disorders in diseases classified elsewhere → Gastro-esophageal reflux disease", which confirms that our trajectories reflected the complications after T2DM in temporal terms.

Conclusions: We constructed dependable T2DM trajectories that have predictive potential for future research, should contribute to achieving precision medicine, and will uncover many links among complications that hitherto have been unclear.

183 | Incidence and prevalence of gastrointestinal stenosis and obstruction in patients with diabetes in the United States

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Background: The epidemiology of gastrointestinal (GI) stenosis and obstruction in patients with diabetes mellitus (DM) is not well characterized in the medical literature.

Objectives: We estimated the incidence and prevalence of GI stenosis and obstruction in this population in US.

Methods: The Truven Health MarketScan database was used to create 2 person-time cohorts of adults (≥18 years) with DM and general population between 2015–2016. Diagnosis and procedure codes denoting to GI stenosis and obstruction were used to identify the condition of interest. Patients with GI obstruction events related to neoplasms, neonatal, congenital, pregnancy, foreign body, or food were excluded. Point prevalence (%) and incidence (per 100 person-years) rates were estimated for both cohorts, and stratified by age, gender, and (for DM cohort) by DM type (T1DM and T2DM).

Results: During the study period, >4 million patients with DM were identified (2% T1DM and 43% T2DM). Patients with DM have 3-times the rates of GI stenosis and obstruction compared to general population (prevalence = 9.3% vs. 2.8%; incidence [95%CI] = 1.97 [1.96–1.99] vs. 0.71 [0.70–0.71]). Patients with T2DM have higher rates than those with T1DM (prevalence = 8.4% vs. 2.6%; incidence [95%CI] = 4.05 [3.99–4.10] vs. 0.57 [0.51–0.63]). Compared to men, women with T2DM have higher prevalence rates; however, incidence rates of GI stenosis and obstruction do not appear to be much different (prevalence = 7.7% vs. 9.1%; incidence [95%CI] = 4.11 [4.03–4.19] vs. 3.99 [3.91–4.07]). Rates in those with T1DM did not show differences between genders, and all patients were in 18–44 years age group. Among patients with T2DM, prevalence rates appear to significantly increase with age, albeit incidence rates showed modest rise. The highest prevalence rates were observed in the elderly (18–44 years = 4.5%; 45–54 years = 6.4%; 55–64 years = 8.0%; 65–74 years = 12.1%; and ≥ 75 years = 16.1%).

Conclusions: Patients with DM, especially T2DM, have high rates of GI stenosis and obstruction and should be considered as a comorbidity during T2DM management.

184 | A snapshot of characteristics recorded in electronic medical Records of Women with polycystic ovary syndrome in TriNetX within two years of diagnosis

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Background: Polycystic ovary syndrome (PCOS) is a multifactorial disorder that affects approximately 10% of women of childbearing age. There is considerable interindividual variation in presentation thus making the condition difficult to diagnose.

Objectives: To describe demographic characteristics, medications, and labs in electronic medical records of women with PCOS in the United States within two years of diagnosis.

Methods: TriNetX, a global federated research network, which contains electronic medical record data of up to 47 million US patients in 39 large healthcare organizations, predominately in [the USA] was used to identify women with PCOS (ICD-10 code E28.2) and gather descriptive statistics on associated variables within two years of a PCOS diagnosis. The analytics associated with this abstract were performed on February 07, 2019.

Results: Of the 24,801,671 women on the network, there are 164,709 (0.66%) with PCOS with a mean age of 35 years. Sixty-four percent are white, 11% are black, 3% are Asian and the other are of unknown race. The top 3 diagnoses recorded were: 1) factors influencing health status and contact with health services (47%), which included encounters for special examinations (*n* = 49,233), 2) endocrine, nutritional and metabolic disorders, (46%), which included diabetes (*n* = 10,872) and obesity (*n* = 27,710), and 3) symptoms, signs, and abnormal clinical findings, not elsewhere classified (38%), which included malaise/fatigue(*n* = 9,313) and headache (*n* = 8,390). Top 3 medication classes prescribed were: hormones/synthetics (*n* = 57,842; 38%), central nervous system medications (*n* = 48,125; 32%), and dermatological agents (*n* = 43,983; 29%). The most prescribed medications under these

respective classes were: blood glucose regulation agents (*n* = 25,916; 17%), analgesics (*n* = 32,870; 22%) and sodium chloride (*n* = 18,659; 12%). Lab procedures performed included: hemoglobin (*n* = 45,558; 30%), creatinine (n = 45,449; 30%), hematocrit (n = 43,076; 28%), erythrocyte mean corpuscular volume (*n* = 42,699; 28%) and platelets (n = 42,151; 28%). Body Mass Index (BMI) was also measured (n = 57,229; 38%). The mean BMI was 35.03 kg/m^2 with a standard deviation of 9.54.

Conclusions: Characteristics and diagnoses within 2 years of a PCOS diagnosis in women include: white race, diabetes, obesity, fatigue and taking blood regulation agents. These characteristics and lab procedures such as hemoglobin and creatinine can aid physicians on diagnosing women with PCOS when taking into account other factors in relation to a woman's health.

185 | Comparison of health outcomes in diabetic and non diabetic patients undergoing maintenance Haemodialysis

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Background: End stage renal disease and diabetes are diseases that are associated with significant decrease in health related quality of life. Epidemiological studies have shown that combination of ESRD and diabetes leads to increased risk of cardiovascular events and shorter life expectancy in this group of patients.

Objectives: The aim of this study was to compare the HRQoL in diabetic and non diabetic patients undergoing MHD, to provide comprehensive patient education and assess the effect of patient education on HRQoL, and to assess the factors affecting HRQoL in diabetic and non diabetic patients undergoing MHD.

Methods: This eight months prospective interventional study conducted in the dialysis unit included maintenance hemodialysis patients. The kidney disease quality of life (KDQoL™-36) questionnaire was administered to the patients at the baseline, first follow up and second follow up. Comprehensive patient education was provided at baseline and re-in forced at third month and at sixth month during the study period. Responses of the patient to the questionnaire were compared between baseline and two follow ups for all patients and between diabetic and non diabetic patients. KDQoL mean scores were compared using student's t test andthe factors affecting the QoL were assessed by using chi square test.

Results: A total of 89 patients were enrolled into this study and 69 were followed up. Males comprised majority of the patient population where diabetics were 87% and non diabetics were 79%. The mean age of the study population was 46 ± 12 years. It was observed non diabetic patients had better HRQoL than diabetic patients undergoing MHD. An improvement in HRQoL during the follow up period was observed in the patients after providing with patient education compared to the baseline scores. Male gender (p = 0.032), education less than or equal to high school (p = 0.049), presence of history of smoking and alcoholism (p = 0.031) and less than three years of dialysis history (p = 0.035) were the factors found to have significant influence on the HRQoL. Other factors found associated with lower HRQoL scores were presence of comorbid diabetes mellitus, age more than 50 years, unemployment and more than five medications.

Conclusions: Non diabetic patients had better HRQoL when compared to diabetic patients undergoing MHD. Implementation of clinical pharmacy services in dialysis units can improve HRQoL among the patients undergoing MHD. Better patient care can be provided by health care professionals focusing on the factors contributing to lower HRQoL among patients undergoing MHD.

186 | Identification of medical complications and real-life Care of Familial and Multifactorial Chylomicronaemia Syndromes: The Esthym study

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Background: The absolute risk of complication and the health impact of multifactorial hyperchylomicronemia (MCS) and familial hyperchylomicronemia (FCS) syndromes are poorly understood in real life, whereas conventional treatments are poorly effective.

Objectives: To understand the management of FCS and MCS and to identify the occurrence of complications.

Methods: 30 FCS and 124 MCS patients, with genetic documentation, followed between 2006 and 2016 in France, were identified in hospital records. Individual hospital data were linked to the national claims data (SNDS, health care utilization). Disease management and occurrence of complications were described during a median follow-up time of 9.8 years, leading to 1509 patient year of follow-up.

Results: Mean age was higher in the MCS group (45.0 ± 12.4 years) than in the FCS group (34.1 ± 13.3 years, p < 0.0001). The sex ratio was towards females in the FCS group (0.67), while it was towards males in the MCS group (2.1) (p = 0.049). During the study period, 50.0% of FCS patients had ≥1 acute pancreatitis, compared with

20.2% in the MCS group (p < 0.0001). In addition, the mean number of hospitalizations for acute pancreatitis was 9.3 in the FCS group, compared to 2.1 in the MCS group (p < 0.0001). By contrast, hospitalizations for cardiovascular conditions were more frequent in MCS than in FCS patients (25.0% versus 6.7%, $p = 0.03$).

Conclusions: The incidence of acute pancreatitis was higher in FCS than in MCS patients. The incidence of ischemic cardiovascular conditions was higher in MCS. These data illustrate the severity of these two orphan conditions (prevalence of about $2/10^6$ for FCS and $1/10^4$ for MCS).

187 | Thyroid disease: A retrospective analysis of a large United States electronic health record database

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Background: Thyroid is an endocrine (ductless) gland that secretes Thyroid hormone, which enables various metabolic reactions. Disruptions to this secretion, either over or under secretion are the hallmarks of Thyroid disease. Approximately 20MM Americans are reported to have a thyroid disease, with more than 12% of the U. S. population estimated to develop a thyroid condition during their lifetime.

Objectives: The objective of the present study was to identify types of thyroid disorders and asses comorbid conditions presented in this population.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All patient visits (age $\geq$ 18 years) between 2014–2018 with an ICD9/10 diagnosis of thyroid disease were included in the analysis. Thyroid disorder types were defined based on ICD9/10 diagnosis codes (Thyroid cancer, Hypothyroidism, Hyperthyroidism, Goiter, Other thyroid diseases) following medical review. Comorbid conditions were identified by corresponding ICD9/10 diagnosis codes.

Results: Over 1.1MM patients with thyroid disorders were identified in the database, with a total number of 2.8MM visits. Hypothyroidism (64.1%) and Goiter (20.2%) were the most commonly seen types of thyroid disorders. Most patients were females (78.9%), with 9 out 10 thyroid patients over 36 years old. Several comorbidities were presented in the study population, with dyslipidemia (20.0%) and cardiovascular conditions such as atrial fibrillation (5.6%) and coronary heart disease (4.6%) being the most prominent.

Conclusions: This real-world large database analysis provides insights on different types of thyroid disorders, patient demographics and comorbid conditions presented in thyroid patients.

188 | Prevalence of chronic kidney diseases in patients with diabetes mellitus in the Middle East: A systematic review and meta-analysis

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Background: Diabetes mellitus is a major risk factor for chronic kidney diseases (CKDs). Chronic kidney diseases increase the risk of morbidity and mortality as a result of cardiovascular complications and may progress to end-stage renal diseases. The prevalence of CKDs in patients with diabetes mellitus in the Middle East region is unclear.

Objectives: This review aims to review the existing literature on the prevalence of CKDs in patients with diabetes mellitus in the Middle East region.

Methods: Medline, EMBASE and Cochrane Review databases were searched for relevant studies up to January 2019. The search strategy was conducted using both keywords and MeSH terms. Following PRISMA guidelines, two reviewers independently screened articles, extracted data and assessed the quality of the included studies. Randomized controlled trials (RCTs) and observational studies including patients from all age groups, and any study design related to the prevalence of CKDs in patients with diabetes mellitus were included in the review. Pooled estimate for the prevalence of CKDs in patients with diabetes were calculated using random effect models with 95% confidence intervals (CI).

Results: A total of 489 citations were identified of which only 3 studies matched our inclusion criteria and were included in this review. The three studies were of an observational study design (two retrospective and one prospective study), covering a total of 57,122 patients with type 2 diabetes mellitus aged 25 years and above. The pooled estimate of the prevalence of CKDs in patients with diabetes mellitus was 25.4% (95% CI, 8.1–42.8).

Conclusions: The findings of this review highlighted that there is a lack of studies on the prevalence of CKDs in patients with diabetes mellitus in the Middle East region. Further epidemiological studies are required to investigate the prevalence of CKDs among patients with diabetes mellitus.

189 | Incidence and time course of surgical complications by cancer stage and site among Medicare patients undergoing elective colorectal resection for cancer: An analysis of the SEER-Medicare database

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Background: Anastomotic leak, infection, and bleeding are serious surgical complications among patients undergoing resection for colorectal cancer which may initially present during hospitalization or after discharge.

Objectives: We describe the incidence and time course of these complications by cancer stage and site among Medicare patients undergoing elective resection for colorectal cancer.

Methods: We selected stage 1–4 colorectal cancer patients diagnosed in 2009–2013 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Database who were aged ≥66 years, admitted for elective resection of the primary site (considered the index admission) and enrolled in fee-for-service Medicare Part A&B for 1 year before surgery. By cancer stage and site (colon, rectum), we used the Kaplan–Meier method to calculate unadjusted cumulative incidence proportions of the complications for the period spanning from the index admission through 90 days post-discharge. We used multivariable Cox regression to quantify the association of cancer stage and site with the rate of each complication, adjusting for patient and provider/hospital characteristics.

Results: The eligible study sample included 16,997 patients (median age = 76 yr; 53.3% female). The 90d unadjusted cumulative incidence proportions of complications were as follows: anastomotic leak (stage 1–4: 14.9%, 14.1%, 14.9%, 15.4%; colon = 14.0%, rectum = 18.3%); infection (stage 1–4: 10.0%, 10.5%, 11.7%, 14.8%; colon = 9.8%, rectum = 18.0%); bleeding (stage 1–4: 14.1%, 17.1%, 17.3%, 16.1%; colon = 15.3%, rectum = 20.7%). With respect to timing, across the stages and sites 74–85% of 90d anastomotic leak was diagnosed during the index admission, 34–45% for infection, and 65–71% for bleeding. In multivariable analyses, cancer stage was not significantly associated with anastomotic leak; however, stage 4 cancer was associated with the highest rate of infection (HR = 1.26 vs. stage 3, $P < 0.01$), whereas stage 1 cancer was associated with the lowest rate of bleeding (HR = 0.85 vs. stage 3, $P < 0.01$); rectal resection was significantly associated a higher rate of anastomotic leak (hazard ratio [HR] = 1.26, $P < 0.01$), infection (HR = 1.64, $P < 0.01$), and bleeding (HR = 1.25, $P < 0.01$) in comparison with colon resection.

Conclusions: Among Medicare patients undergoing colorectal resection for cancer, anastomotic leak rates were high regardless of anatomic site, and significant complications continue to accrue over time for colorectal cancer patients after the index surgery.

190 | Relative Hazard of chronic kidney disease among patients with inflammatory bowel disease varies by age

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Background: The risk of chronic kidney disease (CKD) among patients with inflammatory bowel disease (IBD) is uncertain, with prior studies inconsistently demonstrating increased risk and association with 5-aminosalicylates (5-ASAs).

Objectives: To calculate the relative hazard of IBD for development of CKD and to determine whether IBD medications are associated with estimated glomerular filtration rate (eGFR) decline.

Methods: This retrospective cohort study analyzed patients enrolled in the United Kingdom's The Health Improvement Network. Patients who were diagnosed with IBD during follow-up were matched to up to 4 age-, sex-, and practice-matched controls. The relative hazard of IBD for CKD was calculated using a Cox model adjusted for risk factors for CKD (smoking, coronary artery disease, hypertension for at least two years, peripheral artery disease, stroke, diabetes, and systemic lupus erythematosus) and number of healthcare visits. The outcome of CKD was ascertained using eGFR measurements and diagnostic codes. Because the manifestations of IBD change with age, an interaction term between IBD and age was incorporated into the Cox model using quadratic splines with a knot at age 60. In a second analysis, medication risk factors for eGFR decline among patients with IBD were evaluated using a longitudinal model fit through a generalized estimating equation. Patients were considered exposed to a medication if they received it in the 60 days prior to eGFR measurement.

Results: 17,807 patients with IBD during were identified, and they were matched to 66,929 controls. The age-standardized incidence rates were 131.4 per 100,000 person-years (95% CI 123.0–140.2) and 104.6 per 100,000 person-years (95% CI 100.7–108.7) for persons with IBD and controls respectively. After controlling for risk factors associated with CKD, IBD was associated with development of CKD from ages 16 to 81, with the adjusted hazard ratio declining monotonically from aHR 7.61 (95% CI 2.51–23.00) to aHR 1.15 (95% CI 1.02–1.31) with increasing age. In the longitudinal analysis of eGFR change among patients with IBD, exposure to 5-ASAs and methotrexate were not associated with an increase or decline in eGFR (−0.04 mL/min/1.73 m^2, 95% CI -0.17 - 0.09 and 0.29 mL/min/1.73 m^2, 95% CI -0.07-0.66, respectively). Azathioprine was associated with small improvement in eGFR (0.32 mL/min/1.73 m^2, 95% CI 0.16–0.48).

Conclusions: The hazard ratio of IBD for development of CKD declines with increasing age and common IBD medications are not associated with declines in eGFR. The mechanism of the IBD-CKD association should be the subject of future research.

191 | Risk and prognosis of primary liver, gallbladder, bile duct, and pancreatic cancer after a negative CT scan: A Danish population-based Nationwide cohort study

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Background: Computed tomography (CT) scans play a key role in ruling out and detecting primary liver, gallbladder, bile duct, and pancreatic (LGBP) cancers. The sensitivity of CT scans for detecting LGBP cancers is proven to be high. However, the risk of a LGBP cancer diagnosis after a negative CT scan remains unknown.

Objectives: We aimed to investigate the risk of LGBP cancers detected after a negative CT scan compared with the risk of these cancers in the general population and to evaluate the prognosis among patients with post-CT detected LGBP cancers compared with patients whose LGBP cancers were diagnosed during a first-time CT scan.

Methods: We conducted a nationwide population-based cohort study during 2002–2013 using Danish health registries. We identified all patients with a first-time abdominal contrast-enhanced CT scan who were not diagnosed with a LGBP cancer during the three months following this scan. We then followed these patients from three months post-scan until a first diagnosis of post-CT detected LGBP cancer, death, emigration, or for three years. As an absolute risk measure, we computed cumulative incidence proportions considering death as a competing risk. We then calculated age-, sex-, and calendar-period standardized incidence ratios (SIRs) for a LGBP cancer as a measure of the relative risk. We evaluated survival among all patients with a CT scan and a diagnosis of a LGBP cancer regardless of the timing of the diagnosis. Patients were followed from their diagnosis of a LGBP cancer to death, emigration, or end of study. We calculated survival probabilities and crude and adjusted mortality rate ratios (MRRs), comparing LGBPs detected after a scan with LGBPs diagnosed at the time of a scan.

Results: We observed 687 post-CT detected LGBP cancers among 154,405 patients recorded as having a contrast-enhanced CT scan of the abdomen. The absolute risk of LGBP cancers among patients with a negative CT scan was 0.44% [95% confidence interval (CI):0.40–0.48] during three years of follow-up, corresponding to a relative risk of 2.11 (95% CI:1.83–2.43). The relative risk was substantially increased during the first three to six months after the CT scan [SIR = 9.46 (95% CI: 8.05–11.04)]. Five-year survival was 9.5% (95% CI:6.8–12.7) for post CT-detected LGBP cancers and 6.4% (95% CI:5.2–7.8) for cancers diagnosed at a first-time scan. The adjusted MRR was 0.88 (95% CI:0.80–0.97).

Conclusions: Although the absolute risk was low, patients with a negative CT scan had an increased relative risk of a LGBP cancer. Prognosis was poor regardless of diagnosis time.

192 | Progression from metabolic syndrome to non-alcoholic fatty liver disease: Analyses in an E.M.R-claims database

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Background: Non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease, is increasing alongside known risk factors like metabolic syndrome (METS).

Objectives: This study used the IBM MarketScan Explorys Claims-EMR Dataset to explore progression to NAFLD in METS patients.

Methods: Adults with METS (ICD-9:277.7; ICD-10:E88.1) were identified and stratified by NAFLD risk. The first METS diagnosis served as the index date; continuous eligibility for 6 months prior and 24 months following index was required. Patients with baseline diagnoses of NAFLD or diagnoses of alcohol dependence, hepatitis, liver or metastatic cancer,or biliary cirrhosis at any time were excluded. High (HR) and low (LR) NAFLD risk groups were defined at index based on evidence of any of the following: BMI > = 25, AST or ALT > = 30, diabetes, a liver biopsy, or bariatric surgery. Clinical characteristics and the incidence of NAFLD were compared between groups.

Results: The sample included 21,186 patients with METS; 40% of the sample (8,518) was classified as having a high risk of NAFLD. HR patients were older (54.9 v. 50.7) and more likely to be male (43.4% v. 37.8%) compared to LR patients, $p < 0.001$. A higher proportion of HR patients (6.9% v. 3.9%) progressed to NAFLD and within a shorter time (253 v. 316 days) than LR patients. Clinically, progressors were more likely to have elevated liver enzymes, low HDL, hypertension, hyperlipidemia, diabetes, and obesity at baseline compared to non-progressors. Progression to NAFLD also resulted in a ~3-fold increase in annual healthcare costs over the study period compared to METS alone.

Conclusions: Within a population of METS patients, some patients remain at higher risk of NAFLD. Identification and treatment of METS patients with elevated NAFLD risk may help to delay the onset of chronic liver disease, improve outcomes, and mitigate increasing costs of care.

193 | Epidemiology and characteristics of patients with hepatocellular carcinoma and Care in the United States

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Background: The incidence of liver and intrahepatic bile duct cancer, of which hepatocellular carcinoma (HCC) accounts for 72.7%, has doubled from 1992 to 2014 in the United States (US).

Objectives: This non-interventional, cross-sectional study aimed to examine the latest epidemiology of HCC by analyzing 2 large US databases.

Methods: The IBM MarketScan (IBM-MS) and Surveillance, Epidemiology, and End Results-National Program of Cancer Registries (SEER-NPCR) databases were analyzed separately. Patients (age $\geq$ 18 years) with HCC as the primary cancer who were covered by employer-provided commercial or Medicare supplemental insurance were identified from the IBM-MS database using International Classification of Diseases, Ninth and Tenth Revision (ICD-9/10) codes. Index diagnosis

was defined as the first eligible HCC diagnosis within the study period (Jan 2012-Sep 2017) and no other HCC diagnosis in the prior 12 months. Comorbidities, performance status, distribution of patients, and treatments received were described. In SEER-NPCR (Jan 2010-Dec 2014), a nationally representative patient sample was analyzed to describe the incidence and mortality of patients with HCC.
Results: A total of 8150 and 119,927 patients were identified in IBM-MS and SEER-NPCR, respectively. Patients were predominately male in both databases (IBM-MS: 72%; SEER-NPCR: 75%). The HCC incidence rates among the IBM-MS cohort were 5.9, 5.5, 4.9, and 4.7 per 100,000 person-years in 2013, 2014, 2015, and 2016, respectively. The downward trend in the HCC incidence rate post-2013 for this population coincided with the drop in HCC incidence rate from 2013 to 2014 in SEER-NPCR. Among the IBM-MS cohort, 6%, 36%, and 59% of patients had hepatitis B, hepatitis C, and cirrhosis at index diagnosis, respectively. Most patients (88%) were considered to have good performance status (defined as without any hospice, hospital bed, oxygen use, etc.) at index diagnosis. Embolization and chemo/targeted therapies were the most common treatments received by patients irrespective of the disease stage (31% and 12%, respectively) and in patients with metastatic HCC (19% and 18%, respectively). Approximately 44% of the index HCC diagnosis occurred in hospital outpatient settings, 31% in inpatient settings, and 23% in physician offices.
Conclusions: This study identified the recent epidemiologic changes in patients with HCC and characterized their comorbidities in a commercially insured and a US representative population. These epidemiologic data may be important considerations for US payers making coverage policies for patients with HCC.

194 | SALT-II: Study of acute liver transplantation in France

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Background: A previous study (SALT) looked at all liver transplantations in 7 countries in Europe over 3 years (2005–2007). SALTII is a continuation of SALT, in France, over 2008–2013.
Objectives: To estimate the event rates for drug-associated acute liver failure leading to registration for transplantation (ALFT).
Methods: All ALFT without identified clinical cause were retrieved from the 22 French liver transplant centers from 2008 to 2013. Clinical information and previous drug exposure were abstracted by trained assistants and validated by the Centre director. Previous exposure was considered within 30 days before onset of liver symptoms. Cases were classified in acute drug overdose (voluntary or not), drug-exposed, or non-exposed ALFT. Exposed cases were compared to national exposure data from EGB, the 1/97thpermanent representative sample of SNDS, the National healthcare database system. Rates are given as cases per million patients (MPt) and per million patient-years (MPY).
Results: Over 6 years in 66 million persons, 246 cases of ALFT were identified, of which 132 were acute drug overdoses, 82 had been exposed to non-overdose drugs, and in 32 no drug exposure was found. Cases were female for 73, 55 and 59% respectively, mean age was 37, 44, and 42 respectively, and 59%, 77% and 87% were transplanted. The drug most commonly found in overdose was paracetamol (96%), followed by anxiolytics (33%), antidepressants (22%), hypnotics 15%, as well as opioids and antipsychotics. 43% of paracetamol overdoses were non-intentional. For non-overdose ALFT, the most commonly found drugs were paracetamol (43%), antimycobacterials (AMB, 20%), direct acting antiretrovirals (ARV, 15%), antidepressants (16%), anxiolytics (13%), antiepileptics (13%), as well as NSAIDs (10%), lipid-lowering agents (10%), and antithrombotic agents (10%). Event rates were highest for AMB with 75/MPt and 63 per MPY, followed by ARV (2.5/MPt, 1.65/MPY). Non-overdose paracetamol was 0.74/MPt, 0.22/MPY, NSAIDs 0.2/MPt, 0.07/MPY; Antiepileptics were 2/MPt, 0.88 per MPY, antidepressants 1.15/MPt and 0.44/MPY.
Conclusions: Most drug-associated ALFT were related to overdoses, especially of paracetamol. The highest ALFT risk for non-overdose drugs was by very far with antimycobacterials, followed by ARV, antiepileptics and antidepressants. Paracetamol was present in 43% of non-overdose ALFT. These results parallel those for hospital admissions for non-transplant acute liver injury (EPIHAM), presented elsewhere in this meeting.

195 | Blood lipids and risk of dementia in a cohort of 1.8 million people followed over two decades

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Background: The association between lipids and dementia is inconsistent.
Objectives: To investigate the association between lipid measurements and the incidence of dementia,
Methods: We conducted a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD). We included people aged > = 40 years old with a first total cholesterol (TC) measurement between 1992 and 2009 we also identified a subset of people with measurements of triglycerides (TGs) and high-density lipoprotein cholesterol (HDL-C) while low-density lipoprotein cholesterol (LDL-C) was calculated. We excluded people with a prior record of dementia diagnosis. Patients were followed until a record of dementia diagnosis death, change of general practice, or last data collection. Using Poisson regression, we estimated rate ratios to compare five categories of each lipid fraction, adjusting for age, sex, calendar year, smoking

and alcohol status, body mass index, a history of diabetes, cardiovascular diseases, COPD, and antihypertensives and lipid-lowering agents overall and by age at first measurement (<65 or ≥ 65 years old) and length of follow-up (<10 years or ≥ 10 years).

Results: In our cohort of 1,853,954 eligible people with a first TC measurement (median baseline age 59 years, male sex 48.9%, median follow-up 7.4 years), 49,416 people received a recorded diagnosis of dementia during follow-up, providing an incidence rate of 3.5 per 1,000 person-years. Overall, there was no association between TC level and dementia. In a patients with TC measurement in midlife (i.e. at <65 years old) and follow-up >10 years, there was a strong positive association between TC level and dementia: adjusted rate ratios (95% CIs) were 1.26 (1.01–1.58), 1.36 (1.09–1.68), 1.48 (1.19–1.85), and 1.53 (1.22–1.93) in the 2nd, 3rd, 4th, and highest group, respectively. A similar pattern was observed for LDL-C, while there was no association between TGs or HDL and dementia. Simulation accounting for the influence of unmeasured apoE4 variant did not materially change the estimates.

Conclusions: This single large study explains the conflicting results of previous studies on the association between lipid measurements and risk of dementia. TC and LDL measured in midlife were associated with the incidence of dementia after 10 years.

196 | Suicidal behaviors in patients diagnosed with multiple sclerosis (MS): A study in the UK clinical practice research datalink (CPRD) GOLD

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Background: Suicides among multiple sclerosis (MS) patients, though rare, are more common than among non-MS patients. However, there is limited information on other suicidal behaviors (including attempts and ideation) among MS patients.

Objectives: To estimate the prevalence and incidence of suicidal behavior in patients with MS and compare them to matched non-MS patients.

Methods: We conducted a cohort study in the UK Clinical Practice Research Datalink (CPRD) GOLD. Each MS patient diagnosed from 2001–2015 with ≥1 year of pre-diagnosis history was matched with non-MS patients of comparable age, sex, general practice and record history length before cohort entry (MS diagnosis or matched date) and general practice. We compared prevalence of suicidal behaviors and risk factors before cohort entry using chi-square tests. Using Byar's method, we calculated incidence rates (IRs) and incidence rate ratios (IRRs) with 95% confidence intervals (CIs) of suicidal behaviors after cohort entry.

Results: 6932 MS patients were identified and compared with 68,526 non-MS patients (female, 70%; median age at cohort entry, 43 years). Before cohort entry, 113 (1.6%) MS patients and 934 (1.4%) non-MS patients had a history of suicide attempt or ideation (p = 0.07). 279 (4.0%) MS patients and 2570 (3.8%) non-MS patients had a history of intentional self-harm or drug overdose (p = 0.25). During a median follow-up of 5 years, 5 MS patients and 41 non-MS patients died by suicide or made suicide attempts. The IRs per 10,000 person-years (PY) of any suicidal behavior (suicide death, attempt or ideation) were 11.4 (8.4–15.1) for MS patients and 7.8 (7.0–8.8) for non-MS patients [IRR 1.45 (1.04–1.97)]. Among patients with no history of suicidal behavior or risk factors before cohort entry, the IRs of suicidal behaviors were 8.9 (6.3–12.4) for MS patients and 5.3 (4.6–6.1) for non-MS patients [IRR 1.67 (1.14–2.38)]. IRs and IRRs were higher among males and patients age < 40 years in both analyses.

Conclusions: In the UK CPRD GOLD, MS patients had a similar prevalence of suicidal behavior before MS diagnosis as matched non-MS patients before their matched date. After MS diagnosis or matched date, suicide and suicide attempts were rare. Rates of any suicidal behavior were increased in MS compared to non-MS patients after diagnosis, with the strongest risk among males and patients age less than 40.

197 | Incidence of venous thromboembolic events among amyotrophic lateral sclerosis patients in a United States health insurance claims database

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Background: Reduced mobility in ALS patients is hypothesized to increase risk of venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE). Few small, single-center studies have investigated the risk of VTE in ALS patients. Given the high morbidity and mortality associated with VTE, further understanding of risk in ALS may inform clinical care.

Objectives: Estimate the incidence of VTE in amyotrophic lateral sclerosis (ALS) patients compared to non-ALS controls.

Methods: Patients were identified from a US health insurance claims database, Truven Health MarketScan®, between 2012 and 2018. ALS was defined as patients age ≥ 18 years with ≥2 ALS claims ≥27 days apart with ≥1 claim(s) from a neurologist visit or ≥ 1 ALS claim(s) and a prescription for Riluzole or Edaravone. Each ALS case was matched to 5 controls without ALS on age and gender. VTE was defined as ≥1 claim(s) for VTE and ≥ 1 anticoagulant prescription(s) or VTE related procedure(s) within 7 days of VTE claim date. Incidence rates were reported per 1,000 person-years (PYs). Hazard ratios (HR) and 95% confidence intervals (95% CIs) were estimated using Cox's proportional hazards model.

Results: Among 3,078 ALS subjects and 15,390 controls, incident VTE occurred in 70 ALS subjects (2.3%) and 47 controls (0.3%). Incidence rates of VTE were 18.2 per 1,000 PYs in ALS cases versus 2.5 in controls with a HR of 7.1 (95% CI: 4.9, 10.2). Median time from initial ALS claim to first VTE was 7 months (range: 0.4, 58 months).

Conclusions: Consistent with previous studies, a higher incidence of VTE was observed in a large sample of ALS patients from across the US compared to matched controls. The markedly increased risk underscores the importance of preventive efforts and careful monitoring for DVT and PE in ALS patients.

198 | Risk factors for suicide and suicide attempts among patients with treatment resistant depression: A population based nested case–control study

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Background: The risk for suicide is markedly elevated in treatment resistant depression (TRD) compared to other patients with depression. However, risk factors for suicide and attempted suicide have not been investigated in this clinical population.

Objectives: To investigate risk factors for suicide and attempted suicide in TRD, utilizing a pharmacoepidemiological definition of TRD for use in Swedish health register data.

Methods: A cohort of 119,407 antidepressant treated patients >18 years diagnosed with depression in specialized health care 2006–2014 were identified in Swedish register data. Patients who started a third sequential AD treatment during the same depressive episode were classified with TRD. Among these, a nested case–control study was performed, where each identified case of suicide or attempted suicide were matched to three controls by age, sex, time from depression diagnosis to TRD and time since TRD. Sociodemographic and clinical risk factors from the literature were assessed using univariable and multivariable conditional logistic regression analyses.

Results: Of the 15,631 patients identified with TRD (58% women), 178 (1.1%) died by suicide and 1,242 (7.9%) experienced a suicide attempt during follow-up. In multivariable analyses, a suicide attempt was associated with an elevated risk of suicide within 1 year (aOR 8.8, 95% CI 4.5–16.9), and if over a year ago (aOR 3.6, 95% CI 1.9–6.7). Higher education increased the suicide risk compared to lower education (aOR 1.7, 95% CI 1.02–2.8). Factors associated with attempted suicide were: previous suicide attempt (aOR 5.1, 95% CI 4.0–6.5 within 1 year; aOR 2.5, 95% CI 2.0–3.1 over a year ago), substance use (aOR 2.6, 95%CI 2.2–3.1), anxiety disorder (aOR 1.3, 95% CI 1.1–1.5), personality disorder (aOR 1.9, 95% CI 1.5–2.3), recurrent depression (aOR 1.2, 95% CI 1.01–1.5 within 1 year; aOR 1.4, 95% CI 1.1–1.7 thereafter), and somatic comorbidity (aOR 1.4, 95% CI 1.2–1.7). Results were similar when stratified by age and sex. In a separate analysis performed only on the 93 suicide cases without any history of suicide attempts in the registers, substance use emerged as an independent risk factor (aOR 2.1, 1.2–3.6).

Conclusions: Suicide attempts, especially if recent, are strong risk factors for completed suicide in TRD. Several established risk factors for suicide attempts among patients with MDD were identified also in TRD.

199 | Early signs of bipolar disorder in a UK primary care patient cohort

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Background: Bipolar Disorder (BD) is a serious mental illness characterized by mood instability. Delay in diagnosis is typically between 6–10 years with many experiencing persistent untreated symptoms and potentially poorer outcomes such as poor social adjustment and high prevalence of coexisting cardiovascular, endocrine/metabolic or neurological conditions. There is no agreed strategy for improving early identification and treatment of BD.

Objectives: To identify signs of emerging Bipolar Disorder, including prior mental illness symptomatology and diagnoses, psychotropic medication prescribing and health service engagement.

Methods: The Clinical Practice Research Datalink (CPRD) is an anonymised primary care electronic patient record database with linkage to secondary data. Adult incident BD diagnoses made during years 2010–2017 inclusive were extracted using Read and ICD-10 codes. Matching by age, gender and GP practice was applied using 1:20 ratio of case:comparators without BD. Extracted health events prior to index date included other mental illness diagnoses, prescriptions (antidepressants, antipsychotics, benzodiazepines, Z-drugs, mood stabilizers, pregabalin, gabapentin, strong opioids), substance abuse, self-harm/suicidal ideation, mood swings, sleep disturbance and service interactions (face-to-face consultations, missed appointments, A&E presentations, referral to mental health services). Annual episode incidence for cases and comparators and odds ratios of cases presenting with each health event prior to index date were reported.

Results: There were 2,366 incident BD cases and 47,138 comparators (median age 40 years, 60.5% females). Cases had higher incidence of depression, schizophrenia, personality and anxiety disorders even 10 years before BD diagnosis compared to non BD comparators. Cases were 8 times more likely to have received 3 different categories of prescription 6 years prior to index date (OR: 8.4 [95% CI 6.8, 10.6]; $p < 0.001$). The number of face-to-face consultations was higher in all years prior to index date, with a median [IQR] of 8[15] for cases vs 4[9] for comparators, $p < 0.001$. At 5 years prior to BD diagnosis, cases were 5 times more likely to miss 6 scheduled appointments in a year compared to comparators.

Conclusions: Potentially useful signals to raise awareness in primary and specialist care include more than three psychiatric drug prescriptions during the same year, multiple GP attendances in one year, increasing frequency of non-attendance of scheduled appointments. Knowledge about these signs could aid earlier detection of the illness, leading to more timely and appropriate care.

200 | Parkinson disease psychosis prevalence, associated comorbidities, and mortality in the Medicare population

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Background: Parkinson disease psychosis is characterized by hallucinations or delusions, has a lifetime prevalence of over 50% among Parkinson disease (PD) patients, and is a leading cause of disability and nursing home placement. Unfortunately, studies have yielded conflicting results around the comorbidities and risk factors for PDP. This analysis evaluates one of the largest populations of PDP patients and determines the factors and outcomes associated with PDP.
Objectives: To characterize PDP patients in the Medicare database, determine comorbidities associated with the disease, and evaluate mortality compared with PD without psychosis.
Methods: A retrospective study evaluated the full Medicare claims database during a 4-year period from January 1, 2012, to December 31, 2015. PD patients were identified as patients having at least 1 claim for a diagnosis of PD and another confirmatory claim for PD at some point during the study period. PDP patients were identified as those with at least 1 psychosis diagnosis claim during the study period and at least 2 PD diagnosis claims, with at least 1 of those occurring before the first psychosis diagnosis.
Results: Overall, 106,893 PD patients were identified: 68,821 PD patients without psychosis (64.4%) and 38,072 PDP patients (35.6%). The PDP cohort was older, with a mean age of 81.9 years vs 78.7 years in the PD cohort ($P < 0.001$), and prevalence of PDP increased with age. The PDP cohort had more comorbidities, with a mean Charlson Comorbidity Index score of 4.14 vs 2.46 in the PD cohort ($P < 0.001$). The most common comorbidities in the PDP cohort with a prevalence greater than twice that of the PD cohort included: urinary tract infection, dementia, congestive heart failure, depressive symptoms, stroke, and pneumonia. Age-standardized mortality in the PDP cohort was also significantly higher than in the PD cohort, 28.2 vs 7.3 deaths per 100 patient years, respectively.
Conclusions: As patients with PD age, their likelihood of experiencing symptoms of psychosis increases. The increased patient morbidity and mortality associated with PDP, along with the increased prevalence of comorbidities in this population, suggests the need for the utilizations of treatments that can control these symptoms without worsening the other concurrent comorbid conditions experienced by these patients.

201 | The incidence of stroke among patients undergoing elective open posterior lumbar fusion procedures with multilevel instrumentation: A retrospective cohort study

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Background: Stroke is a rare but life-threatening complication of spinal surgery occurring in approximately 0.2% of adults undergoing posterior lumbar fusion procedures. However, data on the incidence of stroke among adults undergoing complex instrumented spinal surgery are limited.
Objectives: To estimate the incidence of stroke among adults undergoing elective open posterior lumbar fusions procedures with multilevel instrumentation (EOPLFPMI) in the United States.
Methods: A retrospective cohort study using a longitudinal electronic health record (EHR) database, Optum EHR, from January 1, 2007 to June 30, 2018 was performed. Patients aged 18 to 85 years with $\geq$183 days of enrollment in the database prior to undergoing EOPLFPMI were identified. EOPLFPMI, stroke, and selected clinical characteristics used for stratifications were defined based on International Classification of Disease codes. Patients were followed from the index date (i.e. the date of EOPLFPMI surgery) until the occurrence of stroke, death, loss to follow-up, or end of study period. Descriptive statistics were performed to describe patients' demographic and clinical characteristics; incidence proportions (IPs), incidence rates (IRs), and 95% confidence intervals (CIs) were estimated in the following risk windows: surgical hospitalization, 10, 30, 90, 180, and 365 days post-operation.
Results: A total of 43,287 patients were eligible for the study. The IP of stroke following EOPLFPMI ranged from 0.30% (95% CI: 0.25%, 0.35%) during surgical hospitalization to 1.14% (95% CI: 1.04, 1.24) $\leq$ 365 days post-operation; the IR of stroke following EOPLFPMI per 1000 person-years (PYs) decreased consistently from 227.99 (95% CI: 191.73, 271.12) during surgical hospitalization to 13.88 (95% CI: 12.70, 15.17) $\leq$ 365 days post-operation. Stratified analyses revealed that older patients and those with longer hospital stays had a higher incidence of stroke. However, the longer hospital stays could be a consequence of stroke. Racial differences were observed too (e.g., the IR of stroke $\leq$365 days post-operation per 1000 PYs was 20.86 among black patients and 13.48 among white patients).
Conclusions: The stroke incidences observed in our study are slightly higher than those reported in the literature; however, this discrepancy may be due to differences in the study population (e.g., complex

instrumented surgeries), follow-up period, and data source between our study and those in the literature.

202 | Incidence of depression, anxiety and self-directed violence in women with uterine fibroids

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Background: Depression and anxiety are commonly reported among women with uterine fibroids (UF). Further, women with depressive symptoms and diagnosed depression have a greater risk of UF than women without. Few studies have quantified the incidence of depression, anxiety and self-directed violence in women with UF.

Objectives: To evaluate the incidence of mental health disorders and self-directed violence in diagnosed UF patients.

Methods: Women aged 18–50 years with UF (*N* = 317,055) were identified in the Optum Clinformatics™ claims database from May 1, 2000 through March 31, 2018. UF was defined as ≥2 diagnosis claims for UF (ICD9 codes 218.X or ICD10 code D25.X; *N* = 89,066, 28%) or 1 claim preceded by ultrasonography 30 days prior (*N* = 227,989, 72%). Women with UF were age-matched 1:2 to women without UF, who had a claim for a general medical exam (*N* = 635,183). Depression and anxiety were defined by ICD9 and ICD10 diagnosis codes and/or prescription fills for antidepressants or antianxiety medications, respectively. In sensitivity analysis, these outcomes were defined using diagnosis codes only. Self-directed violence (suicide, suicide attempt, and intentional self-inflicted injury or self-harm) was defined by ICD9 and ICD10 diagnosis codes. Women with claims for depression, anxiety, self-directed violence or prescription fills for antidepressants and antianxiety medications at baseline were excluded. Cox proportional hazards models estimated the hazard ratio (HR) and 95% confidence interval (CI) between UF and each outcome, adjusting for demographics and comorbidities at baseline.

Results: Overall, the mean age was 41 (SD: 6) years. Women with UF compared to women without were more likely to be African-American (20% v 9%), have a history of hypertension (20% v 16%), infertility diagnosis (5% v 3%), and prior hysterectomy (4% v 1%) at baseline. The crude incidence rate (per 1000 patient-years) for depression (58.1 vs. 55.3), anxiety (75.6 vs. 64.4) and self-directed violence (0.6 vs. 0.4) were higher for women with UF compared to women without. The adjusted HRs (95% CI) comparing women with UF to women without were 1.06 (1.05–1.08) for depression, 1.16 (1.15–1.17) for anxiety, and 1.40 (1.24–1.58) for self-directed violence. The HRs were not appreciably different when depression and anxiety were defined by diagnosis codes only.

Conclusions: Women with diagnosed UF have an elevated risk of diagnosed depression, anxiety, and self-directed violence. Because comorbid mental illness may affect treatment strategies, identifying women at risk may improve patient-centered care.

203 | A landmark approach to estimate the incidence of malignancies in patients treated for multiple sclerosis

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Background: Long-term effect of drugs on malignancy risk is difficult to characterize due to the time lag between drug initiation and event onset. Considering the methodological challenge involved in the dynamic nature of the exposure period, a landmark approach allows to consider different exposure time.

Objectives: Implement a landmark approach for estimating the incidence of any malignancies (excluding non-melanoma skin cancer) in MS patients (pts) initiating immunomodulators (IM) or immunosuppressants (IS).

Methods: Data from the Danish Multiple Sclerosis Registry linked to the Danish Cancer Registry were used to identify adult pts with a diagnosis of MS between 1995–2015, at least one prescription for an IM or IS between 1995–2016 (first prescription as the index date), and ≥ 1 year of database history prior to the index date. Pts were followed until the first occurrence of: any malignancy, death, end of data collection or 31-Dec-16. Groups were categorized first based on drug taken at index, secondly based on drug taken continuously during 12, 24 or 48 months (landmark periods) with gaps less than 90 days allowed. The incidence rate (IR) of any malignancy per 100,000 person-years, with 95% confidence interval (95% CI), was calculated in each exposed group.

Results: At index, respectively 6,739, and 1,329 were identified in the IM only and IS only groups. By IM only at index, IR per 100,000 PY (95% CI) was 329.1 (284.8–373.4), median (q1-q3) follow-up (FU) of 9 (5–13) years. After landmark periods of 12, 24, 48 months, during which patients were continuously exposed to IM only, IR estimates respectively ranged from 337.0 (289.0–385.0), 359.2 (305.0–413.4), to 403.5 (334.1–472.8). As the landmark duration increased, the number of patients decreased, respectively 6,275, 5,531, and 4,264 pts. By IS only at index, IR per 100,000 PY (95% CI) was 383.5 (189.4–577.5), median (q1-q3) FU of 2 (1–3) years. After selecting pts continually exposed to IS only during landmarks of 12, 24 and 48 months, IR estimates respectively ranged from 478.7 (207.9–749.6), 382.1 (76.4–687.9), to 689.7 (137.8–1,241.6). Number of patients decreased for each increase in landmark duration: 1,077, 616 and 187 pts, respectively.

Conclusions: With various exposure duration and across treatment groups, the IR estimates overlapped. However, due to the lower

number of patients, the estimates in the IS groups were less precise. A strength of this method is the ability to obtain IR estimates for variable length of continuous exposure. A limitation is the decrease of the number of patients, while the duration of the landmark increased, especially in the IS group.

204 | Description of treatment resistant depression in France, from the French Nationwide claims database

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Background: Treatment Resistant Depression (TRD) is a serious health hazard worldwide, which results in significant impairment, increased morbidity and high costs for society. To date, the global epidemiological situation and the clinical characteristics of TRD patients are poorly understood, especially in France.

Objectives: To estimate annual incidence and prevalence of TRD in France, and patient characteristics, from the nationwide claims database SNDS (*"Système National des Données de Santé"*).

Methods: We identified all adult patients (≥ 18 years) with a TRD episode between January 1, 2012 and December 31, 2014 in EGB ("*Échantillon généraliste des bénéficiaires*"), the 1/97 permanent random sample of SNDS. After exclusion of any psychotic disorders, Parkinson's disease, dementia or bipolar affective disorders, a TRD episode was defined as the succession of 3 sequences of different antidepressants (AD), or a combination of an AD with a potentiator (lithium, antiepileptic drugs, antipsychotic drugs or thyroid hormones) over a period of 3 months, with at least 3 weeks of treatment between each AD and with a Medication Possession Ratio ≥ 80%. TRD patients should not have had any AD dispensing or hospitalization for depression within the 6 months preceding the first AD dispensing (*i.e.* initiation date). The incidence rate was estimated yearly from 2012 to 2014 then averaged. The prevalence was estimated according to a Gamma parametric function using treatment duration and a 30-year prediction.

Results: Between 2012 and 2014, 700 patients were identified in EGB with a TRD episode. The mean age was 47.4 years; 52.7% were women, 694 had only one episode and 6 had 2 episodes. The median duration of a completed TRD episode was 5.4 months. The annual incidence of TRD was estimated at 5.8 per 10 000 persons, and the annual prevalence at 25.8 per 10 000 persons.

Conclusions: From the event rates we found, TRD may be amenable itself to further analyses, including analysis of treatment trajectories and comparative effectiveness in the full national database.

205 | Revisiting multiple sclerosis prevalence in the 21st century: Exploration based on a large representative real-world cohort in the United States

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Background: Recent estimates from claims databases more than double the widely reported prevalence of multiple sclerosis (MS) in the United States (estimated at 400,000 or approximately 123 per 100,000), prompting the creation of a national surveillance registry. In the meantime, quantifying the disease burden and characteristics of patients with MS is critical for the diagnosis and management of this heterogeneous, debilitating disease.

Objectives: To estimate the prevalence of MS in the US using a large, representative database of patients with linked electronic medical record (EMR) and claims data.

Methods: The OM1 Data Cloud collects, links, and leverages structured and unstructured data, including extensive clinical and claims data on patients from multiple payers seen in a variety of provider practice types across the US with data from 2013 through the present. An ongoing, continuously enrolling cohort of MS patients who are prospectively followed was developed using a conservative case definition for MS based on diagnosis and medication codes. Prevalence was estimated based on the number of adult patients ≥18 years in the MS cohort over the total adult patients in the OM1 Data Cloud from 2013 to 2018.

Results: Of the 195 million adult patients in the OM1 Data Cloud, approximately 591,000 patients met the case definition for MS and were included in the MS cohort for a prevalence of 303 per 100,000 patients. The average age of patients was 55 years (SD 13.8) and 75% of patients were female. Prevalence was higher in the Midwest and North census regions (339 and 319 per 100,000, respectively) than in the West and South (293 and 286 per 100,000, respectively). Approximately 30% of patients had a history of treatment with at least one disease-modifying therapy (DMT) and 5% had more than one. Of patients overall, the most common DMTs were glatiramer acetate (10%), interferon beta 1a (7%), and dimethyl fumarate (6%).

Conclusions: The prevalence of MS in the OM1 Data Cloud is more than double commonly referenced estimates. This finding is important for planning the provision of healthcare services and motivating the development of novel therapies. Given that less than one-third of patients received DMTs, further investigation into patterns of treatment use to understand unmet clinical need is warranted.

206 | Odds of discharge to substance abuse treatment or psychiatric care after hospitalization for alcohol or drug poisonings, Maryland 2016

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Background: Hospitalizations involving alcohol- and drug- related poisonings continue to be a pressing public health issue. Poisonings, particularly those associated with suicide, often indicate a need for additional psychiatric or substance related care.

Objectives: To identify the predictive variables for discharge to psychiatric or substance use care following hospitalizations involving alcohol- and drug-related poisonings.

Methods: This cross-sectional study identified alcohol and drug-related poisoning hospitalizations from a 100% sample of 2016 Maryland Health Services Cost Review Commission (HSCRC) data. Alcohol and drug-related poisonings were defined as events with ICD-10-CM diagnostic codes for poisonings involving alcohol, heroin, opioids, marijuana, cocaine, psychotropics, and hallucinogens. Chi-square tests compared demographic characteristics among individuals who were and were not discharged to psychiatric or substance use rehabilitation facilities after alcohol or drug-related poisonings. Adjusted logistic regression was used to determine the association of predictive variables with discharge to psychiatric or substance use treatment facilities among individuals with alcohol or drug-related hospitalizations.

Results: In 2016, 9,952 of the 622,397 hospitalizations in Maryland involved alcohol- or drug- related poisonings; 518 (5.2%) of hospitalizations involving alcohol and drug-related poisoning were discharged to psychiatric or substance use facilities. Relative to alcohol and drug-related poisoning individuals not discharged to these facilities, poisoned individuals who did receive this additional care were younger (mean 43.6 vs. 55.4 years, $p < 0.01$), single (80.3% vs. 76.2%, $p < 0.01$), and white (74.3% vs. 62.4%, $p < 0.01$). In our adjusted model, events involving suicidal intent had increased odds of discharge to psychiatric or substance use care (OR: 20.38 (95% CI: 16.1–25.2) compared to individuals with unintentional or not otherwise stated (NOS) intent.

Conclusions: Care after hospitalization plays an important role in preventing recurrent alcohol- and drug- related harms across the lifespan. More research regarding discharges to psychiatric or substance abuse treatment facilities and its effect on outcomes overall and among vulnerable groups is warranted.

207 | Visit adherence and visual acuity in wet macular degeneration

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Background: The effect of missed appointments for anti-VEGF treatment for age-related macular degeneration (AMD) on visual acuity (VA) is unknown. We performed a secondary analysis of the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT) study to evaluate the association between patient's visit adherence to clinical trial visits and VA in AMD patients.

Objectives: To determine if visit adherence is related to visual outcomes in wet AMD patients.

Methods: The publicly available CATT data files were reviewed to characterize visit adherence. The 2-year CATT study protocol required a visit every 4 weeks (every 28–35 days, 26 total). Visit adherence was measured in 4 ways: average number of days (avg days) between each visit, longest duration in days between visits, total number of missed visits, and visit constancy (the tally of 3-month periods with at least 1 visit attended). Average and maximum days between visits were also categorized as being "on time"(28–35 days), "late"(36–60 days), and "very late"(>60 days). The primary outcome was change in ETDRS visual acuity (VA) between the baseline study visit and the last visit. Nonparametric univariate tests, linear and multivariate regression models were applied to analyze the association between visit adherence parameters and change in VA, controlling for age, gender, and baseline VA.

Results: 1,173 CATT patients had complete visit data. Mean (standard deviation [SD]) number of missed visits was 2.7(±3.7). 1,088(93%) patients had complete visit constancy over the length of the study period. Avg days between visits were 38.2[SD ± 31.8] days; when categorized, 966(82.3%) patients were classified as "on time," 125 (10.7%) were "late," and 82 (7.0%) were "very late." These groups averaged +3.0, −1.1, and − 0.9 letter change in vision, respectively. The longest duration between two visits ranged from 29 to 667 days (84.8[±118.6] days).Increasing number of missed visits and longest duration between visits were significantly associated with decreasing final visual acuity($p < 0.02$ for both). Patients whose average visit interval were "late" and "very late" were also more likely to have worse vision($p < 0.001$). This remained true even after controlling for baseline vision, gender, age, drug, and treatment frequency in multivariate regression modeling. Visit constancy and avg days between visits were not associated with VA.

Conclusions: Visit adherence contributes to visual acuity outcomes in AMD.

208 | Do Parents' mental disorders affect child behaviour via home environments, and/or Parents' education? A mediation analysis

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Background: Children of parents with mental disorders, e.g. schizophrenia (SZ), bipolar disorder (BP), are exposed to numerous

environmental risk factors and may face different developments and behavioral problems. These problems may also link to their home environments (HEnv) and/or parents' education (PEdu) that act as mediators. Classical statistical methods (e.g. linear regression) are widely applied to study such problems in psychiatric epidemiology. However, research on this area using mediation analyses is not widely studied.

Objectives: We aimed to investigate the association of parents' mental disorders and child behaviour when home environments and/or parents' education act as mediators.

Methods: We used data from the Nationwide Danish High Risk and Resilience Study - VIA7 cohort. The study sample was 522 in which 202 7-year-old children living with their parents diagnosed with SZ, 120 children living with their BP parents and 200 control children living with their parents who did not have a diagnosis of SZ or BP. The outcome was considered as child behaviour checklist school-age version (CBCL) and the HEnv and PEdu were considered as mediators. We analyzed data using different statistical models including parallel and serial mediation models and the analyses were also stratified by sex of the children.

Results: Our mediation analyses showed that the total effects of parents' mental disorder, BP and SZ, as compared to the control group on the CBCL was 6.50 [2.15, 10.85] and 9.96 [6.22, 13.69], respectively. When considering both mediators simultaneously (serial mediation model), there was a significant indirect effect of SZ and BP vs. control on the CBCL through HEnv and PEdu. Here, 34% total effects for BP and 43% total effects for SZ on the CBCL were accounted by both mediators. For male children, the mediators could account for 32% and 39% of the total effect of the BP and SZ on the CBCL and for female children, they accounted for 42% and 59% of the total effect of the BP and SZ on the CBCL, respectively.

Conclusions: Our analyses show that the mediation analysis is an essential tool to find out actual causal association in a complex study in psychiatric epidemiology. Hence, we conclude that an adequate home environments and/or parents' education are significant mediating factors for child behaviour, which is more vital when either one of the parents is mentally sick.

209 | Epidemiology of radiation retinopathy in the United States

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Background: Radiation retinopathy (RR) can cause devastating vision loss in patients undergoing radiation for head and neck malignancies. Incidence, prevalence, and patient characteristics of RR have not been well established in the general population of the United States (US).

Objectives: To estimate incidence and prevalence of RR in a representative US patient population using large commercial medical claims databases, and to describe the demographic and clinical characteristics of patients at first RR diagnosis.

Methods: A cohort of adult patients were retrieved from the Truven MarketScan Commercial and Medicare Supplemental Database during 2013/01/01–2017/12/31. To be eligible for the study, patients must be enrolled for at least 6 months during the study period. Cases of RR were ascertained through an integrated algorithm that is composed of a sequence diagnosis of head and/or neck cancer; treatment with radiation; and diagnosis of retinopathy. Only the first occurrence of RR was counted. Age-sex stratified prevalence was calculated and directly standardized to the 2017 US population. Incidence rate was defined and calculated as the number of new cases divided by person-years. Demographics, treatment characteristics and comorbidities among RR patients were described.

Results: A total of 52,865,903 patients were eligible for the analysis, with a median age of 43 years (range: 18–119 years) and females comprised 53% of the total. Among these patients, 3,171 (6.00/100,000) patients were identified as RR cases. The age-sex standardized prevalence of RR by the US Census population was 7.74/100,000 in 2017. The incidence rate of RR was 3.37/100,000 person-years. The median age at RR diagnosis was 60 years and 60% were males. The median interval between the first oncology radiation treatment and the first occurrence of RR was 4.3 months. Patients had received an average of 11 radiation treatment before the first occurrence of RR. Among the RR patients, the most common comorbidities were diabetes (13.2%), chronic pulmonary disease (12.8%), cerebrovascular or cardiovascular disease (11.1%), and liver disease (4.0%).

Conclusions: This study characterized the epidemiology of RR patients using a large medical claims database in the US. The MarketScan databases include employer-sponsored active employees, dependents, and retirees and therefore may not be representative of the national population. The algorithm for RR identification was developed based on claims data and clinician experience; however, future studies with medical chart review are needed to further validate this algorithm.

210 | Eye color and risk of ocular melanoma in patients with glaucoma - a Swedish register study combining data from the Swedish police Authority's register on passport applications and National Health Registers

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Background: Data on the association between glaucoma and risk of ocular melanoma (OM) are scarce with conflicting results. Individuals with light eye color are at higher risk of developing OM. However, the association between eye color and OM in individuals with glaucoma have not previously been studied. Topical prostaglandins might increase the risk of OM, but studies show conflicting results. In previous studies data on eye color have been obtained by visual inspection of the eye. The availability in Sweden of register data on eye color that

can be linked via the personal identifier to other national health registers makes it possible to study the association between eye color and OM in a real-world setting.

Objectives: To examine the association between light eye color and OM in patients with glaucoma.

Methods: A case–control study using linked data from national health registers and the Swedish Police Authority's register with information on passport applications. The study population consisted of individuals filling at least one prescription of topical drugs for glaucoma treatment during the period 1 July 2006–2012. Individuals who developed OM were selected as cases. Controls without OM were selected from the general population. Cases and controls were matched (1:3) on age, sex and region of residency. Data on eye color were manually retrieved from passport applications during the period 1964–1989. Eye color was categorized as light (blue, gray) and other (green, mixed, brown). Adjusted odds ratio (aOR) with 95% confidence interval (CI) was calculated by a conditional logistic regression, adjusted for sun exposure (geographical region).

Results: We identified 44 cases and 132 controls, and obtained data on eye color for 78% of the individuals. Among the cases, 73% had light colored eyes, 16% had other eye colors, while 11% had no information on eye colors (no passport application in the available period). For the controls, 58% had light colored eyes, 16% had other eye colors and 26% had no information on eye colors. The aOR for the risk of OM was 1.95 (95% CI 0.92–4.11) when comparing light colored eyes with other eye colors.

Conclusions: We found a slightly and imprecise increased risk of OM associated with light colored eyes in patients with glaucoma. The study confirmed that linkage to the Swedish Police Authority's register was possible and that information on eye color could be obtained for a high proportion of the individuals.

211 | Incidence of depression, anxiety and self-directed harm in women with endometriosis

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Background: In cross-sectional studies, women with endometriosis (EM) have a high prevalence of anxiety and depression. However, prospective studies assessing the relationship between EM and subsequent comorbidities are limited.

Objectives: To evaluate the incidence of diagnosed mental health disorders and self-harm in women with clinically recognized EM.

Methods: Women aged 18–50 years with EM (*N* = 2,101) were identified in the Optum Clinformatics™ commercial insurance claims database from May 1, 2000 through March 31, 2018. EM was defined as ≥2 diagnosis claims (ICD9 codes 617.X or ICD10 codes N80.X; 10%) or 1 claim preceded by laparoscopy 30 days prior (90%). Women with EM were age-matched 1:2 to women without EM but had a claim for a general medical exam (*N* = 4,232). Depression and anxiety were defined by ICD9 and ICD10 diagnosis codes and/or prescription fills for antidepressants or antianxiety medications, respectively. In sensitivity analysis, these outcomes were defined using diagnosis codes only. Self-directed violence (suicide, suicide attempt, and intentional self-inflicted injury or self-harm) was defined by ICD9 and ICD10 diagnosis codes. Women with claims for depression, anxiety, self-directed violence or prescription fills for antidepressants and antianxiety medications at baseline were excluded. Cox proportional hazards models estimated the hazard ratio (HR) and 95% confidence interval (CI) between EM and each outcome, adjusting for demographics and comorbidities at baseline.

Results: The mean age was 38 (SD: 7) years and 63% of women were Caucasian. Women with EM compared to women without were more likely to have a history of opioid use (65% v 36%), hysterectomy (49% v 1%), infertility diagnosis (13% v 5%), low back pain (27% v 20%), migraines (9% v 6%) and asthma (10% v 7%) at baseline. The incidence rate (per 1,000 patient-years) among women with EM was 81.8 for depression, 98.5 for anxiety and 1.0 for self-harm, using diagnosis and/or prescription claims and 39.2 for depression and 35.7 for anxiety, using diagnosis claims only. The adjusted HRs (95% CI) comparing women with EM to women without were 1.6 (1.4–1.8) for depression, 1.7 (1.5–1.9) for anxiety, and 2.1 (0.6–7.6) for self-directed harm. Results were similar when outcomes were defined using diagnosis claims only.

Conclusions: Women with clinically recognized EM were more likely to develop depression and anxiety than women without EM. Rates of self-directed harm were low but higher among EM patients. Because comorbid mental illness may affect treatment strategies, identifying women at risk may improve patient-centered management.

212 | Epidemiology of acute medical events in a cohort with a rare neurodegenerative disease, progressive Supranuclear palsy, after diagnosis

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Background: Acute medical events in persons with Progressive Supranuclear Palsy (PSP), a rare debilitating neurodegenerative disease, have not been systematically examined outside small clinic samples. Understanding their incidences occurring in a real world setting and risk factors help inform strategies to improve patients' quality of life.

Objectives: To determine the frequency, onset, and potential risk factors for select acute medical events after a diagnosis of PSP.

Methods: This cohort study included patients with a first diagnosis of PSP [ICD-10 G23.1], within the interval 1/1/2010 to 12/31/2017,

aged ≥40 years, both sexes, within electronic medical records databases sourced by Disease Analyzer (IQVIA) from general practitioners and internists providing community care in Germany, and having at least 365 days of observation before diagnosis. Five acute medical events were selected, based on the age and disability present in this patient population, determined from at least one day after the PSP diagnosis. Rates were examined by sex, age group (<65, 65+ years) and a prior diagnosis of Parkinson's disease (PD) (yes/no). Person-time in years was computed from the PSP diagnosis date to the first date of each acute medical event or to the last activity in the database divided by 365.25 days. Incidence rates, 95% confidence intervals, time to event probabilities calculated with the product-limit method, and their significance were computed using SAS.

Results: The cohort of 115 patients had mean age at diagnosis of 73.7 years, were 54.8% male, and 63.5% had prior diagnosis of Parkinson's disease (PD). After the diagnosis of PSP, the overall incidence rates of acute respiratory infection (ARI), falls, hospitalization for any cause, suicidality, and thrombosis were 15.5, 23.8, 26.1, 3.0, and 3.0 per 100 person-years, respectively. In subgroup analysis, the relative risk (RR) of ARI was higher among those with a prior PD diagnosis (RR = 2.33, 95% CI: 1.01–5.95, p = 0.05) compared to those without a prior PD diagnosis. The RR of suicidality among males was higher than females (RR = 4.76, 95% CI: 0.66–113.4, p = 0.069). Suicidality is seen in males with approximately 5% probability within one year after diagnosis. Age group did not predict any of the acute medical events.

Conclusions: The rates of selected acute medical events after a PSP diagnosis are high. While some of these acute medical events, such as falls, could be a symptom of the disease itself, prior diagnosis of PD or gender could influence their occurrence. Awareness of the rates of these events may inform strategies for their prevention.

213 | Predictors of in-hospital psychiatric care among alcohol- and drug- related hospitalizations in Maryland, 2016

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Background: Alcohol- and drug- related hospitalizations continue to be a pressing public health issue. Psychiatric disorders are of concern among patients involved in alcohol- or drug- related hospitalizations, as they are associated with increased risk for substance-related adverse events, including overdose.

Objectives: To identify the predictive variables for receiving psychiatric care during alcohol- and drug-related hospitalizations.

Methods: This cross-sectional study identified alcohol- and drug-related hospitalizations from a 100% sample of 2016 Maryland Health Services Cost Review Commission (HSCRC) data. Alcohol and drug-related hospitalizations were defined as events with ICD-10-CM diagnostic codes for abuse, dependence, or poisonings involving alcohol, heroin, opioids, marijuana, cocaine, psychotropics, and hallucinogens. Chi-square tests compared demographic characteristics among individuals who did and did not receive in-hospital psychiatric care. Adjusted logistic regression was used to determine the association of predictive variables with receipt of in-hospital psychiatric care.

Results: In 2016, 77,293 of the 622,397 hospitalizations in Maryland involved alcohol or drugs; 14,404 (18.6%) received in-hospital psychiatric care. Those who received in-hospital psychiatric services, relative to individuals not receiving psychiatric care were younger (mean 39 vs. 50 years, p < 0.01), single (86.1% vs. 74.1%, p < 0.01), and associated with a principal diagnosis of mental or behavioral disorder (98.6% vs. 17.3%, p < 0.01). In our adjusted model, events involving adults older than 25 had decreased odds of receiving psychiatric care (OR range: 0.38 (95% CI: 0.2–0.7) age 26–34 to 0.09 (95% CI: 0.04–0.2) age 65 and older) compared to individuals 18 or younger (age 19–25 non-significant OR 0.78 (95% CI: 0.4–1.5). Events involving patients who were married have 0.5 times (0.4–0.7) the odds of psychiatric care compared to those involving single patients. Gender and race were found to be non-significant with males having 1.0 times (95% CI: 0.8–1.3) the odds and African Americans having 1.2 times (95% CI: 0.8–1.5) the odds of psychiatric care compared to females and to whites, respectively.

Conclusions: Mental health plays an important role in recurrent alcohol- and drug- related harms across the lifespan, but especially in younger patients. More research regarding in-hospital psychiatric intervention and its effect on outcomes overall and among vulnerable groups is warranted.

214 | Identifying psychosis in patients with dementia: Not a hallucination or delusion, the challenge really exists

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Background: Psychosis is common in advanced Parkinson's disease and in some dementias, such as Alzheimer's disease. Antipsychotics are commonly used to treat psychosis associated with dementia, although the FDA issued a black box warning of mortality risk in these patients. Assessing the risk of mortality associated with antipsychotics requires correct identification of patients with psychosis, which may be challenging, particularly in automated health care databases where diagnosis code algorithms are used.

Objectives: To identify coding algorithms used to identify patients with psychosis associated with dementia in recent literature.

Methods: A targeted literature review, from 2008 to date, was conducted in PubMed to identify code algorithms used to identify psychosis associated with dementia in studies assessing the mortality risk among these patients treated with antipsychotics.

Results: Of 324 records identified in our search strategy, 32 articles were selected for review. Of them, 28 articles were excluded because they relied on medication use and 2 were excluded because they

identified psychosis using patient-reported questionnaires. Two included studies conducted in the US identified psychosis using the following ICD-9-CM codes: 293.81–2, 297.0–3, 297.8–9, 298.0–4, 298.8–9, 368.16, and 780.1. We expanded our search by conducting a literature search in PubMed to identify studies assessing the epidemiology of psychosis in dementia. We identified 3 additional articles: 1 US study defined psychosis with the presence of one of the following ICD-9-CM codes: 780.1, 292, 292.1, 293.81–2, 297, 298.3–4, 301.0. Another study conducted in Taiwan identified psychosis with ICD-9 codes 295.00–298.9, and 299.10–11. A third US study used the definition: ≥ 1 medical claim with a diagnosis of psychosis (298.0, 298.1, 298.4–298.9), hallucinations (293.82, 368.16, 780.1), or delusions (293.81, 297.1).

Conclusions: The majority of studies analyzing mortality in patients with dementia treated with antipsychotics did not identify psychosis with diagnosis codes, and most did not account for delirium or agitation. Only five studies used coding algorithms to identify psychosis in patients with dementia. Most of these studies used similar codes to identify hallucinations (293.82 and 780.1) and delusions (293.81 and 297). However, these studies also included different, including nonspecific, codes to identify psychosis. A validated coding algorithm updated to ICD-10-CM to identify psychosis related with dementia is recommended.

215 | Sociodemographic and clinical risk factors of treatment-resistant depression: A Danish populations-based study

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Background: Knowledge of risk factors of Treatment-Resistant Depression (TRD) contribute to understanding the underlying mechanisms and to identify patients at risk. Several studies have investigated this matter, however, there are still caveats in our current understanding of how different risk factors associate with TRD.

Objectives: To determine how potential sociodemographic and clinical risk factors associates with TRD.

Methods: We included all citizens in Denmark diagnosed first time with depression at a hospital, either as in- or outpatient, between 1 January 1996 and 31 December 2014. The patients were identified in the Danish National Patient Registry using the international Classification of Diseases, Tenth Revision (ICD-10 codes), codes F32 and F33. We excluded patients with either a comorbid diagnosis of manic episode (ICD-10: F30), bipolar disorder (ICD-10: F31), persistent mood disorder (ICD-10), other or unspecified mood (affective) disorders (ICD-10: F38 and F39) or a comorbid schizophrenia spectrum disorder (ICD-10: F20). A total of 208,625 patients were followed for development of TRD within 12 months after diagnosis. TRD was defined as two shifts in antidepressant treatment. Patients' redemption of prescriptions for antidepressant medication were identified in the Danish National Prescription Registry by Anatomic Therapeutic Chemical (ATC) classification system codes (N06A). Potential sociodemographic and clinical risk factors were identified in nation-wide registries. Data were analyzed using Cox Proportional Hazard Regression and Fine-Gray model for competing mortality risk.

Results: 14.1% of patients developed TRD corresponding to an incidence rate of 164.31 per 1,000 person years (95% CI, 162.5–166.2). Indicators of disease severity (type of depression, depression severity, type of patient, type of contact) were the strongest risk factors. Disadvantaged socioeconomic conditions, stressful life events, comorbid anxiety (adjusted HR 1.21 (CI 95%, 1.14–1.30)), insomnia (adjusted HR 1.29 (CI 95%, 1.08–1.55)) and migraine (adjusted HR 1.40 (CI 95%, 1.14–1.71)) as well as use psychotropic drugs were also associated with higher rates of TRD.

Conclusions: We tracked patients who did not benefit from standard treatment, and showed that besides indicators of disease severity, other important risk factors are those related to social conditions, stressful life events as well as anxiety, insomnia, migraine and the use of psychotropic drugs.

216 | Confounding variable capture in large healthcare administrative claims databases: A trend analysis in the sentinel system

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Background: Several variables such as smoking, obesity, and drug abuse are traditionally considered important confounders in post-marketing observational studies, yet are often underreported due to limitations of administrative claims data.

Objectives: To conduct a trend analysis to determine how well selected confounding variables are captured in the Sentinel Distributed Database (SDD), from 2007 through 2017.

Methods: We analyzed healthcare billing data from 17 Data Partners contributing to the SDD. Descriptive analyses were conducted to examine the prevalence and incidence of five confounding conditions, including smoking, obesity, overweight, alcohol abuse or dependence, and drug abuse or dependence, identified by diagnosis, procedure, and dispensing codes. Eligible members were required to be continuously enrolled in health plans with medical and pharmacy coverage for ≥365 days before the date of first recording of a confounder of interest during the study time. For incidence estimates, eligible members cannot have evidence of the confounder of interest in the prior

365 days. The proportion of enrollees with at least 1 claim for each confounder was calculated, stratified by age, sex, and calendar year.

Results: The number of eligible beneficiaries in the SDD increased from 15 million in 2007 to the highest of 67 million in 2016. During 2007–2017, the estimated prevalence of obesity increased 1.9-fold from 69 to 197 per 10,000 eligible members, paralleled by a 2.5-fold increase in overweight from 22 to 78 per 10,000. The prevalence of smoking increased 82% from 65 to 118 per 10,000. For alcohol abuse or dependence, this increase was 50%, from 14 to 21 per 10,000. The prevalence of drug abuse and dependence increased 67% (from 6 to 10 per 10,000) over the same time. Similar increasing trends were noted in the incidence of confounding condition estimates. The transition of the ICD coding system in 2015 does not seem to change the increasing trend of prevalence and incidence estimates. For smoking, obesity, and overweight, prevalence and incidence increased as a function of age. For alcohol and drug abuse, the highest prevalence and incidence were observed among subjects aged 44–64 and 18–43 years.

Conclusions: A continuous increase in the recording of confounding conditions in claims data was observed; though low prevalence suggests these conditions remain inadequately documented in US claims. Future studies should evaluate whether this represents an actual improved recording of these conditions or an increase in the underlying prevalence of these conditions or a combination of these factors.

217 | The comparison of medical records and claims for Oral anti cancer agents

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Background: Healthcare claims databases like Medicare Part D are increasingly being used for drug utilization research. Such use of administrative claims data for pharmacoepidemiologic studies of oral anti-cancer agents may be affected by misclassification bias due to disagreement between administrative claims and electronic medical records.

Objectives: To determine the rate of concordance between electronic medical records and Medicare Part D claims for use of oral anti-cancer agents.

Methods: Medicare Part D claims were linked with electronic medical records for selected patients treated at The University of Texas MD Anderson Cancer Center (MDACC), Houston, Texas via the Texas Cancer registry. Patients aged 65 or more treated at MDACC with at least 1 Medicare Part D claim and continuous enrollment in Medicare for at least 12 months during the study period of Jan 2007 to Dec 2012 were included in the study. The use of any oral anti-cancer agent was extracted from the MDACC electronic health record (EHR) through retrospective chart review of clinic notes, medication lists, and pharmacy records. The Medicare Part D event files were used to identify claims for oral anti-cancer drugs for each patient. EHR and Part D concordance rates were ascertained after matching drug name and requiring overlapping treatment dates.

Results: The study sample consisted of 419 medication records for 170 patients. There were 23 different oral anti-cancer drugs evaluated. Bicalutamide, anastrozole and capecitabine were the most frequently used drugs. The overall percent agreement between the two datasets was 67.5%, where 106 claims were yes/yes and 177 claims were no/no for both datasets. The percent disagreement was 32.5%, where (n = 75) 17.9% claims found in Part D were not in the EHR and (n = 61)14.6% drugs were found in the EHR and not in Part D. The kappa statistic was found to be 0.33, with 95% confidence limits of 0.24 to 0.43.

Conclusions: There was moderate concordance between electronic medical records and Medicare Part D event files for oral anti-cancer agents. This has important implications for the ability to use Medicare Part D data to identify oral anti-cancer utilization and study toxicity patterns. A limitation of this study was the inability to measure the reasons for disagreement. Missing claims for the drug may be due to use of drug discount programs or obtaining medications from a source other than Part D. Missing medical records may be due to incorrect medication documentation or treatment outside of MDACC. Further work is needed to verify concordance for individual anti-cancer agents in specific populations.

218 | UK electronic health records (EHR) databases: Expanding primary care coverage with clinical practice research datalink (CPRD) aurum

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Background: For 30 years, CPRD has been collecting General Practice (GP) primary care data for public health research from practices using one GP EHR system in the UK (contributing to the CPRD GOLD data resource). To expand sample size, geographical coverage, and representativeness, CPRD has begun collecting data from practices using an additional GP IT system, and participating practices contribute to a new data resource, CPRD Aurum.

Objectives: To characterize the patients and GP practices in CPRD Aurum. To describe the data available in CPRD Aurum and standard linkages to additional national health and socioeconomic databases.

Methods: We describe the full cohort of patients available in CPRD Aurum, using the September 2018 build. In particular, we report the distribution of gender, age, geographical region, deprivation, and follow-up, for both current (alive and registered at actively contributing

practices) and all patients (including dead and transferred-out), and describe the types of data recorded.

Results: As of September 2018, CPRD Aurum contained routinely-collected data from 738 primary care GP practices in England. This included records for over 19 million patients, of whom 7 million were current. Current patients had a median follow-up of 9.1 years, of whom a quarter had over 20 years of follow-up (Interquartile range: 3.3–20.1) and were broadly representative of the English population in terms of age, gender, and deprivation (compared to Office for National Statistics data). Routinely collected data in CPRD Aurum includes information on demographics, diagnoses, symptoms, prescriptions, referrals, immunisations, lifestyle factors, and tests recorded by GPs or other practice staff. These are entered using nationally approved coding systems (Read, SNOMED, dm + d). Standard linkages to CPRD Aurum data include Hospital Episode Statistics (HES) databases as well as national mortality, cancer, mental health, and deprivation databases.

Conclusions: CPRD Aurum's strengths are its sample size (corresponding to 13% of the population of England), longitudinal follow-up, representativeness, and standard linkages to additional data resources.

219 | Leveraging heterogeneity of European healthcare data sources to estimate validity of case-finding algorithms in multi-database studies where a true gold standard is lacking: Strategy from the Emif project

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Background: European healthcare databases are heterogeneous in coding terminology, language, underlying health policies and data provenance. Some collect diagnoses from primary care practices (PC), others from inpatient care (INP) and/or death registries (DEATH). In multi-database studies, heterogeneity is commonly considered as a weakness.

Objectives: Leveraging heterogeneity of healthcare databases to estimate case-finding algorithms' sensitivity (SE) and positive predictive values (PPV) when a gold standard is not available.

Methods: We measured the incidence of acute myocardial infarction (AMI) as a test case. Five databases were considered: SIDIAP (Spain), HSD, ARS (Italy), PHARMO (Netherlands) and AUH (Denmark). HSD provided diagnoses from PC, SIDIAP and PHARMO from PC and INP, ARS and AUH from INP and DEATH. The Unified Medical Language System was used to project the AMI concept to local terminologies (ICD9CM, ICD10, ICPC, READ). Three standardized AMI-finding algorithms, *PC*, *INP* and *DEATH*, were created. In each database, cases were retrieved using all available algorithms. Cumulative incidence (CI) of AMI was estimated in 2012 among subjects aged 45+, with ≥2 years of look-back. Results were compared within and across databases. Based on previous validation studies: PPV of *INP* was 100% in AUH, and PPV of *PC* in HSD was 96.6%. To estimate the algorithms' SE and PPV in all databases, we made three assumptions: PPV = 100% for *INP*, SE = 100% for the combination *INP or DEATH*, cases retrieved from *PC* were true positives only if also found in *INP*.

Results: Study population was about 4 million subjects. CI (cases/10,000 persons) ranged between 7.8 and 24.8 for *PC*, 30.3 and 47.3 for *INP* and 8.9 and 9.4 for *DEATH*. Cases identified from two provenances overlapped partially. *INP* identified 28.9% and 30.5% of *DEATH* in ARS and AUH, and 44.7% and 44.1% of *PC* in SIDIAP and PHARMO, respectively. Based on our assumptions, conservative estimates of SE of *INP* were 83.4% in ARS and 77.5% in AUH; PPV of *PC* was 44.1% in PHARMO and 44.7% in SIDIAP. Assuming that SE of *INP* in SIDIAP and PHARMO was the average between ARS' and AUH's (80.5%), then conservative estimates of SE of *PC* in PHARMO and SIDIAP were 26.7% and 29.4%, respectively. The average between those two estimates, 28.1%, could be assumed to be SE of *PC* in HSD.

Conclusions: In multi-database studies, when *de novo* validation is not possible, existing information and assumptions can be exploited to provide a range of validity estimates and adjust study results to account for event misclassification.

220 | Use of claims profile review to guide retrieval of medical Records in an Observational Cohort Study

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Background: Medical record review provides clinical information that is not available in administrative claims data, and is commonly used to validate claims-based methods to identify outcomes. Limitations of

medical record review may include incomplete information obtained from a single site and low rate of response to record requests.

Objectives: Create a stepwise process to optimize case retrieval rate and completeness of clinical information necessary to adjudicate potential cancer cases identified using administrative claims data.

Methods: Cancer cases occurring between 10/1/2012 and 12/31/2017 were identified for a historical cohort study of patients 18–90 years of age receiving treatment for overactive bladder. A claims profile was created for each patient, consisting of a chronological listing of cancer-related encounters −30 days to +90 days of the first observed diagnosis. Using the claims profile, a nurse experienced in medical record review ranked up to three sites using criteria of physician specialty, place of treatment, and procedures performed. Next, the identified sites were outreached with medical record requests, with the highest priority site being the site most likely to have a record that could serve to validate the cancer (e.g., an oncologist encounter). Information from the medical records were consolidated into a single abstraction form reflecting relevant clinical information necessary for a panel of oncologists to adjudicate the case.

Results: A total of 1,100 cancer cases were identified for adjudication. After claims profile review, 2,960 sites were prioritized for medical record retrieval, and 65% (*N* = 1,931) of requested charts were retrieved. At least one chart was retrieved for 84% (*N* = 925) of cases identified from claims. Mean (SD) number of charts received for cases with at least one chart retrieved was 2.1 (0.4). Of the 925 patients, 74% (*N* = 683) had a physician note in their medical records confirming cancer and 62% (*N* = 569) had a biopsy or pathology report retrieved. Chart obtain rates were 69% (837/1,219) for charts assigned priority 1, 65% for priority 2 (627/960), and 60% (467/781) for priority 3.

Conclusions: The use of claims profile review and the identification of multiple sites for medical record retrieval resulted in a high overall case retrieval rate. The site prioritization resulted in retrieval of charts with relevant clinical information needed to adjudicate the case. This study benefited from use of an integrated team to design claims profiles and chart prioritization methodology as well as concise chart abstraction forms to organize key clinical information.

221 | The potential of German claims data to characterize real-world treatment patterns in cancer patients - the example of Crizotinib

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Background: As clinical trials are conducted under very controlled conditions (including highly selective populations), they often face problems of generalizability and only little is known about real-world treatment patterns after marketing approval. Claims data might be useful to characterize oncologic drug utilization in clinical practice.

Objectives: To explore the potential of German claims data for characterization of real-world treatment patterns in oncology, exemplified by patients treated with crizotinib which was approved for the 2nd or later line therapy of anaplastic lymphoma kinase positive non-small cell lung cancer in 2012 and for the respective 1st line therapy in 2015.

Methods: We used claims data from the German Pharmacoepidemiological Research Database (GePaRD) to identify patients with at least one crizotinib dispensation. Each individual was followed as long as possible, longest 2004 until 2015. We defined first line therapy as the first antineoplastic therapy (inpatient or outpatient) after a lung cancer diagnosis (ICD-10 C34) was coded. The subsequent therapies were then defined as second or later line therapy. We described patients with regards to age, sex, diagnosis codes for lung cancer and metastases, number of crizotinib prescriptions, as well as sequence of oncologic therapies.

Results: In total, 229 crizotinib patients were identified. The mean age at first crizotinib prescription was 58.1 years and 54.2% were women. Lung cancer was diagnosed in 96.5% of the patients and 87.8% of these patients had diagnosis codes for metastases within 6 months after the first lung cancer diagnosis recorded in GePaRD. The mean time between the first lung cancer diagnosis and the first crizotinib prescription was 16.9 months. The mean number of crizotinib prescriptions a patient received was 7.4. The minority of the patients (18.3%) received crizotinib as first line therapy, whereas the remaining ones (81.6%) received crizotinib as second or later line therapy. Overall, 83% of the patients received at least one other chemotherapy prescription during the study period. Only 13.5% of patients received another chemotherapy after crizotinib discontinuation.

Conclusions: Using GePaRD we found treatment patterns regarding crizotinib consistent with other studies and could provide detailed information on its utilization. The results underline the potential of German claims data for monitoring real-world oncologic drug utilization.

222 | Data sources for drug utilization research in Latin American (LatAm) countries

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Background: Cross-national comparisons (CNC) of drug use have been recognized as important in Drug Utilization Research (DUR). However, valid CNC studies can only be performed if data sources are available, accessible, and can deliver valid information to describe and measure the pattern, extent, and determinants of drug exposure in each individual country.

Objectives: To develop an inventory of available national drug utilization data in the Latin American (LatAm) region as potential data sources for DUR.

Methods: A network of health experts from 10 countries at the LatAm region (Argentina, Bolivia, Brazil, Chile, Colombia, Equator, Mexico, Nicaragua, Peru, Uruguay conducted a) a website search from government, academic, and private institutions and b) liaising with national data providers and academic experts in Pharmacoepidemiology (via on-line survey). Researchers independently screened eligible data sources. Possible divergences were analyzed by a third researcher. The data sources were characterized for accessibility, coverage (national, regional, municipality, organization multi-site) data provider (public health, private sector, both), type of data sources (wholesaler, pharmacy records, electronic health records, other) and setting (ambulatory, hospital, both). Descriptive analysis was performed.

Results: As a preliminary result, we identified 85 data sources for DUR in 10 LatAm countries. Brazil, Colombia and México leaded the available national. Fifteen (17%) out of the 85 data sources were publicly and conveniently accessible;49 (57%) were accessible with limitations (32 with access restricted by country specific legislation and 17 only accessible after a priori authorisation), and 21 (25%) lacked clear rules for data access. *About coverage, 77 (90%)* portrayed national data, *65 (76%) were of public sector origin, 30 (35%) were sourced from pharmacy records and 63 (74%) came from a hospital or ambulatory setting - with possible access to individual patient-level data*.

Conclusions: Those preliminary findings show that although a great number and a variety of data sources for DUR are available in LatAM,the accessibility is a major challenge. The procedures for researcher access to DUR data, should be transparent, feasible, affordable, protocol-driven. Linkage of DUR data to outcome data at the patient level could substantially improve governance of health care. Data collection is being undertaken in other LatAm countries in order to expand the inventory.

223 | Enrollment patterns and health in claims data for the commercially insured US population

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Background: It is often stated that duration of enrollment in administrative claims data - a correlate of duration of exposure and follow-up in medication safety or effectiveness studies - is potentially associated with patients' underlying health status. Such associations could result in limited representativeness of studied populations and biased estimates when clinical conditions and enrollment duration define cohort eligibility.

Objectives: To study if enrollment duration is associated with patients' health status in a commercial US healthcare claims database.

Methods: We used the IBM® MarketScan® Research Databases data from 2003–2016. We conducted a preliminary analysis among 16mil randomly sampled enrollees to evaluate enrollment patterns such as median duration, time trends, gaps, pharmacy benefits, and primary subscriber versus dependent. Then, to study the association of health status with enrollment length, we defined cohorts from the full dataset in specific calendar periods. Individuals entered the cohorts on completion of 6 months of continuous enrollment. We assessed demographics (year, age, insurance plan type, gender), clinical characteristics (diabetes with/without complications, coronary artery disease, renal disease), key health status measurements including Charlson Comorbidity index (CCI), and resource utilization (hospitalizations, office visits, dispensings) during a 6 m baseline period. We used

multivariable Cox models to estimate the association of enrollment duration with the measured characteristics.

Results: Nearly 90% of enrollees had only one enrollment period (median 947d). 8.8% had 2 periods of eligibility, the 1st was longer (medians length 517 and 426 d respectively), with a median gap of 1y. Results were similar for an allowable enrollment gap of 0d or 31d. In the multivariate analysis (estimates based on 04/2012 cohort), use of any drug (hazard ratio (HR) of enrollment discontinuation with 95% CI, 1.12 (1.12–1.13)), ER visit (1.09 (1.08–1.10)), and a CCI of either 3+ (1.17 (1.09–1.25)) or a CCI of 2+ (1.08 (1.02–1.13)) were associated with shorter enrollment. Older age, female gender, and outpatient visits were associated with longer enrollment durations. Moderately elevated health status was associated with longer enrollment in the univariate, but not in the multivariate models.

Conclusions: The association of certain non-severe diseases with enrollment duration varied across subgroups and was confounded by other factors. While these results should not be interpreted as a causal relationship, they serve to caution against assuming a simple association.

224 | Characterizing disease registries utilized for drug safety evaluation

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Background: Under the 21st Century Cures Act of 2016, the U.S. Food and Drug Administration began a program for evaluating use of real-world data (including registries) for real-world evidence generation fit for regulatory purposes. Characterizing disease registries provides the opportunity to better understand and optimize their use for regulatory safety surveillance.

Objectives: To characterize disease registries and unique contributions across three publicly available data sources used for identifying disease registries.

Methods: Studies that used existing disease registries to evaluate outcomes of patients receiving a drug and systematically collect adverse event data were identified through December 2018 using publicly available resources: PubMed, Embase, and ClinicalTrials.gov. Disease registries that examined drug safety among pregnant women were excluded. Registries were further restricted to those with U.S. participating sites. Studies were characterized using a standardized approach to assess pre-specified study and registry-level elements following manual extraction of information from qualifying registries. Using a semi-automatic approach, we applied open source natural language processing (NLP) tools to determine whether identified registries were included in existing drug labels archived in DailyMed.

Results: Of 36 studies (26 distinct disease registries) identified in the initial search, 11 (31%) used disease registries that included international populations in addition to US sites; one identified study was found in drug labels using NLP. Most studies (94%) were based on disease registries with clear objectives. Nearly all identified studies had additional objectives beyond drug safety; one evaluated safety as its sole objective. Forty-seven percent of studies comprised populations that had rare conditions. Over 80% of identified studies ascertained baseline health status, concomitant medications, and presented clear follow-up strategies. Adequate analysis plans and consideration of relevant covariates were described in greater than 20 studies; however, only 44% of studies indicated measures to account for missing data due to potential loss to follow-up. We observed variations in data completeness and type/granularity of information reported within each data source.

Conclusions: Initial results suggest that clear objectives, follow-up strategies, and inclusion of key covariates contribute to the utility of disease registries. This review highlights the need to improve patient retention efforts in studies and transparency of information for registries across resources.

225 | Non-small cell lung cancer (ALK+/EGFR+) data sources in Europe and Canada: A landscape study

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Background: Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases. Targeted treatments are in development for the ALK+/EGFR+ subtypes.

Objectives: This study aimed to identify and characterize fit-for-purpose ALK+/EGFR+ NSCLC data sources for the generation of real-world evidence.

Methods: A literature search using MEDLINE and Embase (01 Jan. 2012–23 Apr. 2018) as well as pragmatic searches of web sources were conducted. Data sources were identified using, as the search strategy, data requirements for real-world studies in this disease (e.g., diagnostic procedures, treatments, safety and effectiveness outcomes). For each data source identified, metadata were abstracted in a standardized data extraction form, including: availability of mandatory and optional data elements, codification, infrastructure and access policies, linkage capabilities with administrative claims databases. To obtain further information, an online questionnaire was administered to database custodians.

Results: A total of 74 unique data sources on ALK+ and/or EGFR+ NSCLC were identified: 72 covered ALK+ NSCLC patients, of which

40 also included data on EGFR+ NSCLC patients. Questionnaire to custodians led to the identification of two additional EGFR+ data sources, resulting in a total of 42 databases for EGFR+ NSCLC patients. Of the 72 ALK+ NSCLC sources, the majority originated from Europe (*n* = 65, 90.3%), followed by Canada (*n* = 5, 6.9%), and two (2.8%) covered both Europe and Canada. Most sources consisted of cohorts with *ad* hoc data collection (*n* = 23, 31.9%) or medical records (*n* = 11, 26.4%, 10 electronic and 1 paper-format). More than three quarter (*n* = 55, 76.4%) ascertained ALK+ diagnosis through genetic testing. Of the 42 EGFR+ NSCLC sources, 34 were disease-specific (81.0%) while the remaining (*n* = 8, 19.0%) covered the general population. For most sources, data collection was ongoing at the time of evaluation (*n* = 32, 76.2%). Linkage to medical charts or administrative claims were possible for 16 sources (38.1%). Based on the number of patients and the interest of custodians for potential collaboration, 41 data sources were considered fit-for-purpose for ALK+/EGFR+ NSCLC: 32 (78.1%) would allow the conduct of drug utilization studies and 29 (70.7%) provide longitudinal data on clinical outcomes allowing for the conduct of safety and effectiveness studies.

Conclusions: Several real-world data sources on ALK+/EGFR+ NSCLC have been identified throughout Europe and Canada. A formal feasibility assessment will need however to be undertaken prior to the implementation of a study and common data models.

226 | Assessment of the use of synthetic data to support the generation of real-world evidence in cancer in England

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Background: Real-world data (RWD) are commonly used to support drug development and to understand patients' characteristics and clinical effectiveness of care. Whilst the use of RWD in cancer is increasing, data sources remain subject to operational challenges related to data access and patient confidentiality. In England, a synthetic oncology dataset "Simulacrum" was developed to overcome these core challenges and make the data collected by the National Cancer Registration and Analysis Service (NCRAS) more accessible to researchers.

Objectives: To explore the potential of using the Simulacrum to refine real-world evidence (RWE) generation from the cancer data collected by NCRAS in England.

Methods: In 2018, we enhanced a process that employs the Simulacrum to conduct exploratory analyses and test methodological approaches. Our analytical queries were programmed in R using Simulacrum data. We tested, refined and validated R codes before being applied to the national cancer registry data. The distribution of patients and tumors were described.

Results: In our exploratory studies (on breast and lung cancers) run via this process, we extracted counts and tested queries in Simulacrum. Between 2013 and 2015, the Simulacrum included 1.45 million tumors (of which 136,249 [9.4%] were breast cancers) and 1.37 million patients with ≥1 cancers (of whom 132,800 [9.7%] were those with a breast cancer). When our code was applied to the real data, the national cancer registry database identified 1.46 million tumors (137,656 [9.4%] breast cancers) and 1.37 million patients with ≥1 cancers (133,627 [9.7%] patients with a breast cancer). All results from the actual data were certified as anonymous, and aggregated results were generated with no risk of patient identification.

Conclusions: Synthetic datasets, like Simulacrum, can be used as a framework to test and refine analytical codes and to support the generation of RWE in oncology, leveraging the data collected by NCRAS in England without the risk of patient identification. However, it should be noted that Simulacrum cannot be used as a standalone resource to generate scientific evidence.

227 | Health indicator recording in UK primary care electronic health records: Key implications for handling missing data

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Background: Clinical databases are increasingly used for health research; many of them capture information on common health indicators including height, weight, blood pressure, cholesterol level, smoking status, and alcohol consumption. However, these are often not recorded on a regular basis; missing data are ubiquitous.

Objectives: We described the recording of health indicators in UK primary care and evaluated key implications for handling missing data.

Methods: We examined the recording of health indicators in The Health Improvement Network (THIN) UK primary care database over time, by demographic variables (age and sex) and chronic diseases (diabetes, myocardial infarction, and stroke). Using weight as an example, we fitted linear and logistic regression models to examine the associations of weight measurements and the probability of having weight recorded with individuals' demographic characteristics and chronic diseases.

Results: In total, 6,345,851 individuals aged 18–99 years contributed data to THIN between 2000 and 2015. Women aged 18–65 years

were more likely than men of the same age to have health indicators recorded; this gap narrowed after age 65. About 60–80% of individuals had their height, weight, blood pressure, smoking status, and alcohol consumption recorded during the first year of registration. In the years following registration, these proportions fell to 10%–40%. Individuals with chronic diseases were more likely to have health indicators recorded, particularly after the introduction of a General Practitioner incentive scheme. Individuals' demographic characteristics and chronic diseases were associated with both observed weight measurements and missingness in weight.

Conclusions: Missing data in common health indicators will affect statistical analysis in health research studies. A single analysis of primary care data using the available information alone may be misleading. Multiple imputation of missing values accounting for demographic characteristics and disease status is recommended but should be considered and implemented carefully. Sensitivity analysis exploring alternative assumptions for missing data should also be evaluated.

228 | Quantifying the completeness of hospital episode information recorded in primary Care in England Using THIN-HES

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Background: The Health Improvement Network - Hospital Episode Statistics (THIN-HES) is an Electronic Medical Record (EMR) database containing linked, patient-level General Practice (GP) and hospital data from National Health Service patients in England. Hospital episodes, especially events like hospitalization and Accident & Emergency (A&E) visits, are often used as proxy for secondary care information within observational studies using primary care medical records.

Objectives: To quantify the completeness of recording of hospital episode information in primary care by comparing the distribution of A&E attendances and hospitalization between primary and secondary care.

Methods: In this retrospective EMR cohort study, completeness of primary care records was quantified for 01/01/2016–12/31/2016. The study population were patients in the THIN-HES database (*N* = 2,292,443; 162 GP practices), including both active (i.e. registered with a GP contributing data to THIN) and historic patients that passed data quality checks. Descriptive statistics on hospitalization and A&E records in primary and secondary care were calculated. Events were defined using THIN Read codes and HES variables. The following measures were reported: total number of records, number (%) of patients with a record in THIN-HES, mean number of records per patient, and mean number of records per patient with a record. As each patient had a THIN and a HES record, the McNemar's test of difference in paired proportions was used to compare the proportion of patients with a record in primary and secondary care.

Results: In primary and secondary care, the total number of records were reported for hospitalization [48355 vs. 786709, respectively] and A&E events [99372 vs. 759700, respectively]. The number of patients in primary and secondary care with records was also calculated for hospitalization [24738 vs. 336220, respectively] and A&E events [57720 vs. 454649, respectively]. The proportion of patients in THIN-HES with an A&E record was significantly lower in primary than secondary care ($p < 0.001$), [2.5% (n = 57720) vs 19.8% (n = 454649), respectively]. The proportion of patients in THIN-HES with a record for hospitalization was also significantly lower in primary than secondary care ($p < 0.001$): [1.1% (n = 24738) vs 14.6% (n = 336220), respectively].

Conclusions: The THIN primary care records did not accurately capture HES hospitalization and A&E events. Research should not rely on secondary care information recorded in primary care. Rather, robust secondary care data sources should be sought.
Recording practices may have changed since 2016.

229 | Development of an integrated research network to facilitate non-interventional research

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Background: Key success factors for high quality and timely research include methods for rapid identification, recruitment, and enrollment of "protocol-specified" patients, and engagement of study sites reflective of usual care community practice.

Objectives: To describe development of a research network based on an electronic health record (EHR) technology platform that connects providers and patients to researchers.

Methods: The potential scale of the research network comprises approximately 30,000 practitioners from small private US practices who collectively treat about 18 M patients (mostly "research naïve"). Practitioners are approximately evenly split between primary care physicians and specialists, and the network is compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Care rendered by providers is entered into EHRs using commonly accepted US coding conventions (e.g., ICD-10 for diagnoses, SNOMED codes, national drug codes [NDCs]); providers and support staff can also be contacted via EHRs to participate in research. Study-specific questions also can be added to the EHRs to collect additional data (e.g., quality-of-life, patient preference).

Results: The number of patients (or clinicians) who meet prespecified selection criteria operationalizable through EHRs can be ascertained rapidly (<5 days), with invitations for participation then sent to clinicians who treat "qualifying" patients (or who themselves qualify,

depending on study focus). Clinicians who opt in are contracted to participate in the research, and their qualifying patients are asked to provide informed consent. For patients who provide consent, their EHRs can be queried to develop "baseline" histories. Their EHRs can also be used to collect information during the study, thereby reducing the burden of participation on qualifying patients and their clinicians and minimizing the chance of data collection/transcription errors.

Conclusions: Our EHR-based research network represents real-world experience at small private practices that capture a relatively large segment of the US population. Three potential applications of the network have been identified for evaluation: (1) natural history studies; (2) risk evaluation and mitigation strategy (REMS) programs and evaluations; and (3) disease and product registries. Key parameters to evaluate will include response rates, time to identify and enroll patients and/or physicians, EHR- and participant-reported data quality and completeness, and study timelines and costs (versus non-network studies).

230 | Rare disease epidemiology: A Danish population-based program

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Background: The epidemiologic study of rare diseases is limited by difficulty in identifying sufficiently large cohorts of patients to evaluate demographic, clinical, or treatment characteristics or to determine outcomes or adverse events.

Objectives: To describe the system of large, longitudinal, population-based medical databases and biobanks in Denmark, which have been successfully utilized to investigate the prevalence of rare diseases as well as the health care resource use and clinical course of patients with rare diseases.

Methods: We provide an overview of Danish administrative and medical data sources that permit the identification and quantification of rare diseases and their outcomes. Examples of the capabilities of these data resources are illuminated through a listing of recent publications.

Results: In Denmark a tax-supported healthcare system guarantees medical care for residents. A unique identifier, assigned to all Danish residents at birth or immigration since 1968, allows linkage of national registry data on all hospital diagnoses, pathology and laboratory reports, and nearly 200 other health registries under the auspices of the Danish government. Virtually all Danish residents are included in these registries. Important variables include ICD diagnosis codes, treatments, examinations, prescriptions, laboratory tests, hospital outcomes, and vital status. The Danish population-based databases are essentially complete, and data entry is integrated into clinical practice with on-going quality control procedures in place, supporting long-term and multi-generational epidemiological research. The DNA of all persons born after 1981 is stored in the Danish National biobank, making it possible to study the impact of early biomarkers over the lifespan. Examples of cohorts created using linked datasets to examine disease prevalence, disease severity, health resource use, treatment patterns, outcomes (including thromboembolic events), and vital status include Prader-Willi Syndrome, systemic mastocytosis, X-linked hypohidrotic ectodermal dysplasia, and cold agglutinin disease among many others.

Conclusions: The nationwide Danish health care system incorporates uniform registration and coding, allowing for near-complete cohort ascertainment, including identification and complete follow-up of rare disease patient cohorts. The Danish research infrastructure is an exceptionally valuable resource for evaluating the epidemiology, demographic and clinical characteristics, treatments, outcomes, and prognosis of patients with rare diseases.

231 | The Zuellig pharma Korea consortium database - an on-site drug wholesales database for Pharmacoepidemiological studies using real-world data

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Background: Drug wholesales data are collected on-site, allowing for its quicker release for research and minimizing the drug use latency issue when compared to health insurance claims data. However, representativeness of drug wholesaler data have yet to be evaluated.

Objectives: To assess the value and representativeness of the Zuellig Pharma Korea Consortium (ZPK-C) database, which contains drug wholesales data collected in a weekly interval, for its prospective use as a data source for pharmacoepidemiology studies.

Methods: We conducted a descriptive drug utilization study by comparing the ZPK-C database to South Korea's nationwide health insurance claims database between 1 January 2016 and 30 September 2017. Therapeutic areas of interest were 13 antidiabetic and 10 antihypertensive products. Product-based analyses were conducted for each of the 17 provincial-level administrative regions of South Korea. For standardized comparison, the defined daily dose (DDD) was used to calculate DDDs per 100,000 inhabitants per day (DID). For each product, the DID proportion was calculated by dividing each provincial-level region's DID over the total DID of South Korea. The nationwide claims database was considered to be the gold standard. The ZPK-C database was considered to have regional

concordance and representativeness if the DID proportion of the health insurance claims database lied within the DID proportion's 95.0%, 97.5% or 99.0% confidence interval of the ZPK-C database.

Results: We found regional concordance between the ZPK-C and nationwide claims database in 12 and 13 regions (out of 17) for antidiabetic and antihypertensive products, respectively, of which, concordance was higher in rural regions than metropolitan regions. For the 13 antidiabetic products at the 95.0% confidence level (CL), ≥ 11/13 products showed concordance in three regions. Especially, at both 97.5% and 99.0% CLs, one region showed complete concordance for all 13 products. As for 10 antihypertensive products, six regions, double that of antidiabetic products, ≥ 8/10 products showed concordance, with three regions showing complete concordance in all 10 products. Throughout all CLs (95.0% to 99.9%), all 10 antihypertensive products showed concordance in three regions.

Conclusions: In particular regions of South Korea, the ZPK-C database was found to have very high regional concordance and therefore, representativeness. Thus, with further evaluation in other therapeutic areas, the ZPK-C database has shown potential as a valuable data source for future research.

232 | Real world evidence multi-database research in Europe: The EU-ADR Alliance

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Background: The EU-ADR Alliance was established in 2013 built on the results of the project "Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge". The network is based on the concept of federated databases, non-competition with its members, independence and scientific interest.

Objectives: The EU-ADR Alliance is a network of EU-based researchers and databases set up to conduct real-world evidence studies to evaluate drug safety in clinical practice, the effectiveness and safety of drugs in specific populations, drug utilization, and health outcomes research.

Methods: Initially, there were eight research centres from five EU countries (the Netherlands, UK, Denmark, Italy and Spain) participating in the EU-ADR Alliance, and the network is progressively expanding to new databases and countries. Source data are routinely collected data from electronic health records (primary care databases, dispensing records and hospital linkage) and additional linked data sources. The EU-ADR Alliance databases include over 21 million of active patients, enabling us to access a broad range of participants including pediatric populations. All databases comply with European Union guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiologic research. Since 2013, eight observational studies have been conducted in the respiratory, musculoskeletal and cardiovascular fields, resulting in several publications and conference presentations. The methodological challenges encountered during the course of these studies were recently analyzed during a bespoke workshop organized by the EU-ADR Alliance network.

Results: The studies follow a standardized structured process which has been validated during more than five years of experience. A number of tools and methods have been developed for data curation and analysis. The EU-ADR Alliance researchers actively explore methodological opportunities and challenges that arise in this distributed pharmacoepidemiology network.

Conclusions: The EU-ADR Alliance provides an unprecedented amalgamation of expertise with a solid governance structure and tested working methods allowing to run centralized powered studies and produce clinically meaningful results, thus generating valid and reliable evidence. The network has a capacity to investigate challenges for methods research in pharmacoepidemiology using distributed data. Given the recent incorporation of new databases and increased request for the research questions, the need for methodological innovations will continue to grow.

233 | Does adding claims to Emr data improve comorbidity burden capture: Concerto health AI definitive oncology dataset and symphony linkage study

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Background: Current commercially available oncology electronic medical record (EMR) databases typically have limited data on patient comorbidities which may limit the ability to accurately include/exclude these patients or adjust for these factors in health outcomes research.

Objectives: The objective of this study was to investigate the impact of identifying comorbidities using both EMR and claims data.

Methods: The Concerto Health AI Definitive Oncology Dataset is a deeply curated cohort of patients (pts) derived from a wide range of oncology practices throughout the United States. Concerto Health AI has a co-exclusive partnership with ASCO CancerLinQ and collects data from multiple other sources. These data were deterministically linked to US Symphony Health's (SH) Integrated Dataverse, an anonymized, HIPAA-compliant data set. Advanced (stage IIIb/IV) non-small cell lung cancer (aNSCLC) pts with data curated via manual review by nurse practitioners and diagnosed after 2011 were included. Comorbidities within 1 year prior to advanced diagnosis were categorized using the Charlson Comorbidity Index (CCI). The impact of the claims linkage on inclusion/exclusion (I/E) criteria

was assessed by applying criteria from the IMpower150 clinical study and exploring changes to survival estimates, as calculated using Kaplan–Meier method.

Results: A total of 11,373 aNSCLC pts were identified, of which 7,887 pts were linked to SH. Using only Concerto, 278 pts (3.5%) had a CCI score $\geq$ 1, whereas 3,033 pts (38.4%) had a CCI score-1 using linked Concerto and SH. After applying I/E criteria from IMpower150 using available data elements from Concerto only, 88 pts were identified matching the trial criteria, with a median survival of 15.8 mths (95% CI: 14.4, 21.0). When leveraging Concerto and SH, 8 (9.1%) more patients were excluded (n = 80) based on comorbidities (6 pts) and oral medications (2 pts), with a median survival of 16.6 mths (95% CI: 14.6, 23.4).

Conclusions: The addition of claims to EMR enhanced the ability to identify patient comorbidities given the longer history and broader physician specialty of claims data. Future real-world studies should explore linkages across datasets to better capture comorbidities for patient selection and adjustment.

234 | Data enhancement through linkage: Health plan linkage with PCORnet clinical data research network

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Background: Electronic medical record data (EMR) contains prescriptions written and administrative claims data contains prescriptions dispensed. Linked data across these common pharmacoepidemiology data sources can close gaps in evidence. We linked data from a Health Plan Research Network (HealthCore) and a Clinical Research Network (PEDSnet) within PCORnet.

Objectives: The objective of the health plan linkage was to utilize privacy preserving record linkage (PPRL) methods to link health plan claims data to EMR data in the PCORnet Common Data Model and to explore data on medication dispensings compared to prescriptions to measure the impact on missing data from the PCORnet Antibiotics and Childhood Growth Study (ABX).

Methods: We utilized PPRL methods which included the generation of anonymous hashed linkages to determine the population that overlapped between the two organizations. We linked populations of patients aged 0–2 years using the PPRL anonymous hashes with the Colorado University Record Linkage (CURL) method. We used descriptive analysis to summarize the number of patients from PEDSnet by sex and race and compared characteristics of patients who had a HealthCore health plan linkage to all patients included in the main ABX study. We then described antibiotics use among patients with a health plan linkage by counting the total number of patients who had 1) both prescribing and dispensing records (yPyD); 2) no prescribing or dispensing records (nPnD; 3) prescribing but no dispensing records (yPnD); and 4) dispensing but no prescribing records (nPyD). We then compared 10-day prescribing and dispensing episodes by performing bi-directional matching and presented the proportion of episodes with and without corresponding matching.

Results: The PEDSnet-HealthCore linkage found a total of 4,792 patients with linked records. The linked population was similar with regard to sex to the original ABX cohort with a greater proportion of whites in the linked population. 42.6% and 20.6% of the linked population were true positive (yPyD) and true negative (nPnD) in terms of their antibiotic exposure status, respectively. 23.5% of the linked population had dispensing records not captured by prescription records. There were 13.3% had prescribing records but no dispensing records.

Conclusions: Data linkage can close gaps in data to improve the ability for real world data to generate real world evidence. Prescriptions from EMRs may not be filled and prescriptions may be written from outside organizations leading to additional exposure data capture.

235 | Data enhancement through linkage: Health plan linkage with Pcornet patient powered research networks

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Background: Linking digital patient data to health plan claims can pinpoint opportunities for patient participation in patient-centered outcomes research (PCOR) such as drug safety and comparative effectiveness research. Compared to administrative claims data, patient-generated disease data as reported by patients joining a PCOR-net Patient-Powered Research Networks (PPRNs) can serve as a "silver standard" to validate claims based computable phenotypes. We developed a privacy-preserving record linkage (PPRL) process method to conduct data linkage between PPRNs and health plans.

Objectives: The aims were 1) to implement PPRL, 2) to validate claims based computable phenotypes, and 3) to quantify the selection bias on which patients join a PPRN and then participate in patient-centered research.

Methods: We used PPRL to link members from 4 PPRN registries to enrollees of 14 commercial health plans. Non-linked health plan enrollee cohort who met computable phenotypes of interest were compared to linked PPRN members using bivariate analysis.

Self-reported diagnoses by PPRN members were compared with claims-based computable phenotypes to calculate confirmation rates (study outcome) across varying durations of health plan coverage.

Results: Data for 21,616 PPRN members were hashed. Of these, 4,487 (21%) members were linked, regardless of any expected overlap with the fourteen health plans. A total of 3,546 (16%) PPRN members were commercially insured, and had available data permissions for analysis. Compared to non-linked health plan cohort (*N* = 1,825,115), those who joined PPRNs (*N* = 3,546) were younger (48 vs 56 years), more likely to be female (92% vs 76%) and had fewer all cause hospitalizations (26% vs 35%) or ED visits (36% vs 43%). Members who joined PPRNs and participated in research also showed similar differences compared to the non-linked health plan cohort. For members with ≥5 years of continuous health plan enrollment, the confirmation rates were 93% (95% confidence interval [CI], 87% - 97%) for multiple sclerosis; 91% (95% CI, 82% - 96%) for breast or ovarian cancer; 80% (95% CI, 67%- 90%) for vasculitis; and 67% (95% CI, 60% - 73%) for rheumatoid arthritis, psoriatic arthritis or psoriasis.

Conclusions: This study demonstrated that PPRN membership and health plan data can be successfully linked using PPRL methodology, and used to confirm claims based phenotypes. The selection bias on who joins a PPRN as a member is similar to the bias on who ultimately joins a PPRN research opportunity. Linkage is important for future work related to collection of patient reported outcomes in pharmacoepidemiology research.

236 | CIDACS-RL: A novel search engine-based record linkage system for huge datasets with high accuracy and scalability

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Background: Several open source and commercial record linkage tools, used for identifying and combining records of the same individual from two or more different data sources, are available. However, the volume and complexity of data sets being linked pose a challenge. Hence, designing an efficient linkage tool with reasonably high accuracy and scalability was required.

Objectives: To describe the design and performance of CIDACS-RL (Centre for Data and Knowledge Integration for Health - Record Linkage).

Methods: We developed CIDACS-RL: an iterative deterministic record linkage algorithm based on search engine indexing for scoring and comparing potential matches. A gold standard dataset was created using two Brazilian administrative data sources: the Mortality Information System (SIM) and the Live Birth Information System (SINASC) using exact matching. The case study comprises data from two governmental databases: the Unified Registry for Social Programmes of the Federal Government (CadUnico) and tuberculosis data (SINAN-TB) from the Information System for Notifiable Diseases (SINAN). All data sets contain individual-level. The following attributes were used for linkage: name, mother's name, date of birth, municipality and sex. A simulated cohort was used to evaluate scalability and execution time both in single core and 8-core settings. We assessed the accuracy of the linkage with standard metrics: sensitivity, specificity, positive predictive value (PPV), and area under the ROC curve (AUC).

Results: 3,013,228 from SINASC and 1,293,219 from SIM related to 2015 were used to construct the gold standard dataset, by exact match, adding up to 3,028 records. In this dataset, the sensitivity, specificity, and positive predictive value for the CIDACS-RL algorithm were 99.87%, 99.94%, and 99.93%, respectively. In the case study, the CadUnico had 114,008,179 individual records and SINAN included 1,182,777 reported tuberculosis cases from 2001–2013, after data cleaning for linkage. After a manual review, 17,355 pairs of records were identified as true matches and 12,461 as false matches. Applying an optimal cut-off point (0.896), the sensitivity, specificity, and AUC were 92.5 [95% confidence interval; 92.07, 92.99], 93.5% [93.08, 93.8], 97.2% [96.97, 97.35], respectively. In the simulated cohort, the distributed execution was about four times faster than the serial setting when using a database with 20 million records.

Conclusions: CIDACS-RL algorithm is an innovative linkage tool for huge data sets, with high accuracy, improved scalability, and substantially shorter execution time.

237 | Use of ICD codes and physician notes from electronic medical records to identify cases of a rare disease

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Background: Use of electronic medical records (EMR) is increasingly important in the field of pharmacoepidemiology. A component of EMR, physician notes, can provide additional value as a source of information.

Objectives: To determine whether physician notes would identify additional cases of a rare disease, trigeminal neuralgia (TN), that were not identified solely using ICD codes.

Methods: This study was performed using a general population cohort from the Optum© deidentified electronic health records

dataset including data from 2007-March 2018. Individuals enrolled in integrated delivery networks for at least 6 continuous months were included. Indications of a TN diagnosis were identified using two methods: 1) ICD-9 and ICD-10 codes for TN (350.1 and G50.0, respectively) and 2) keywords from physician notes. To be considered as TN using the physician notes, the keyword "trigeminal neuralgia" or "tic douloureux" needed to be present. Subjects were not counted as having a TN diagnosis based on physician notes if additional information in the notes was unsupportive of the diagnosis. The number of individuals captured using ICD codes and/or physician notes was determined and basic descriptive statistics were examined.

Results: Approximately 27 million individuals in this cohort had at least 6 months of continuous enrollment. Of these individuals, 109,192 had at least one indication of TN (ICD code and/or keyword). It is standard practice in database studies to require two codes with a specific length of time in-between. When we applied this standard definition of two codes at least 27 days apart to the TN-related ICD codes, 34,726 individuals were identified. When employing this same standard definition using keywords from the physician notes, 31,948 individuals were identified. Of these, 17,952 were already captured using the standard definition for ICD codes but an additional 13,996 individuals were retrieved that had not met the standard definition using ICD codes or had no TN-related ICD codes at all, resulting in a total of 48,722 identified cases.

Conclusions: While the majority of individuals with TN were identified using the traditional approach of ICD diagnosis codes recorded in the EMR (71%), in this example the addition of keywords from physician notes adds a meaningful number of individuals. Although the effort required to search physician notes is substantially greater than that for searching ICD codes, in rare diseases where increasing the number of patients available for a study is particularly important, this effort may prove to be worthwhile.

238 | Enhancing SEER data through public health reporting of pharmacy claims for precision cancer surveillance

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Background: The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program is a coordinated system of population-based cancer registries representing 34% of the US population. SEER registries currently collect the first course of treatment, with a gap in longitudinal, detailed treatment data needed to conduct clinically relevant cancer surveillance. SEER is establishing collaborations to expand treatment data collection, including an initial study establishing reporting of oral oncologic treatment through retail pharmacy claims to the Georgia State Cancer Registry (GCR).

Objectives: This initial collaboration seeks to a) facilitate automated capture of oral oncologic agents to fulfill legally mandated public health reporting and b) evaluate enhanced treatment data (e.g. representativeness and coverage) and expand ability to provide relevant cancer health statistics (e.g. patterns of care, health outcomes).

Methods: Oncology Pharmacy Claims (OPC) were securely matched to GCR data as part of legally mandated reporting requirements for cancer. OPC were identified using strict rules to ensure each drug had a specific indication for cancer treatment or treatment-related symptom management. A retrospective analysis was conducted among female patients identified in GCR with Hormone Receptor (HR+) Invasive Breast Cancer (BC), as a single primary neoplasm, between 2013–2016 and matched with OPC (2013–2017) to evaluate representativeness of the data and hormonal therapy treatment patterns among patients with OPC. Aromatase Inhibitor and SERM drug utilization was assessed. Demographic, socioeconomic, and clinical characteristics of patients were evaluated using descriptive statistics. Treatment outcomes evaluated include time to treatment initiation, treatment duration, and adherence using proportion of days covered.

Results: Among the HR+ BC cohort analyzed, 5,364 cases (30%) had an OPC for hormonal therapy; 68% white, 29% black, and 3% identified as another race. The mean age at diagnosis for patients with hormonal OPC was 58 years. Among the hormonal therapy OPC, patients received anastrozole (51%), exemestane (14%), letrozole (27%), and tamoxifen (34%). Additional utilization patterns, treatment characteristics, and adherence measures will be provided.

Conclusions: The addition of pharmacy claims data within cancer registries represents a novel first step towards obtaining more comprehensive treatment data to enhance cancer surveillance (eg. case ascertainment, additional courses of therapy) and evaluate longitudinal patient treatment patterns.

239 | The comorbid burden of gout on health outcomes: Results from linking electronic health records to patient-reported outcomes

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Background: The comorbid burden among gout patients is associated with higher serum uric acid (sUA) and recurring attacks, which may result in greater costs and poorer health-related quality of life (HRQoL). Linked self-reported survey and clinical data from electronic health records provide valuable insights into this relationship.

Objectives: To examine the prevalence of gout and related comorbidities using two nationally-representative surveys, and further characterize patient subgroups according to sUA levels through the linkage of survey data to electronic health records (EHR).

Methods: Data from two cross-sectional, nationally-representative US surveys were used: Patient-Centered-Research (PaCeR) (2015–2018; annual sample ~75,000) and National Health and Nutrition Examination Survey (NHANES) (2015–2016; annual sample 9,971). PaCeR data was linked in a HIPAA-compliant methodology to a large US ambulatory EHR database. Respondents with gout and gout-related comorbidities were identified through self-reported diagnosis, and NHANES estimates were weighted to the general population. Linked PaCeR-EHR respondents were identified as those with 1+ sUA tests in the EHR within 18 months of survey completion (n = 231). Outcomes included patient-reported HRQoL and health status using the SF-36v2. Descriptive and bivariate analyses used ANOVAs and Pearson's correlation coefficients.

Results: Among adults (≥18 years), the annual prevalence of gout was 4.8% in PaCeR-EHR and 4.0% in NHANES. The average age and percent male patients were similar in both data sources (PaCeR-EHR: 64.7 ± 10.8 years, 64.4% male; NHANES: 62.0 ± 12.7 years, 63.7% male). Highly prevalent comorbidities among gout patients included hypertension (PaCeR-EHR = 75.6%; NHANES = 74.0%), coronary heart disease (CHD) (PaCeR-EHR = 19.0%; NHANES = 13.0%), and obesity (PaCeR-EHR = 55.3%; NHANES = 54.8%). Average sUA in gout patients was 5.6 (±1.4) mg/dL, and sUA was positively correlated with number of comorbidities (r = 0.20, p < 0.005). HRQoL also decreased as number of comorbidities increased. For example, the SF-36v2 physical component score was lower for gout patients with one (46.7 ± 10.2), two (42.5 ± 10.0), or three (36.7 ± 15.9) comorbidities compared with patients with no hypertension, CHD, or obesity (52.2 ± 6.6) (p's < 0.001).

Conclusions: Large-scale population-based survey data provide valuable prevalence information. Further, linking survey data with EHR allows for a more comprehensive view of disease burden by delineating the relationship between clinical characteristics and patient-reported burden.

240 | Linking genomic and longitudinal real-world data: Applications to drug development and Pharmacoepidemiology research

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Background: The increasing use of linked genomic and real-world data (RWD) can provide insights for targeted therapies or predicting treatment response. Since 2013 Genomics England has been working in partnership with the NHS in England, Scotland, Wales and Northern Ireland to complete the 100,000 Genomes Project; an initiative that has sequenced 100,000 whole genomes from individuals with rare diseases and cancers. We investigated an infrastructure that allow the linkage between genomic and Hospital Episode Statistics (HES) data.

Objectives: To generate initial insights into the patient cohorts included in the 100,000 Genomes Project and to describe how the linkage can support analytic processes and evidence generation.

Methods: This was an exploratory assessment to describe the linked genomic and RWD. Privacy-protected and de-identified HES data were linked to genomic data from patients with a diagnosis of at least one condition from the 100,000 Genomes Project. Summary descriptive statistics on patient counts were calculated in each cohort. We described the type of studies that the linked genomic and HES data could support.

Results: An exploratory analysis showed that the 100,000 Genomes Project included genomic data from several types of solid tumors (like colorectal, n = 2,880; lung, n = 2,009 and sarcoma, n = 1,030), hematological cancers (n = 454), childhood tumors (n = 143) and many different rare diseases (like cystic kidney disease, n = 1,516 and familial hypercholesterolaemia, n = 501). Using the linkage, comorbid phenotypes and clinical outcomes of patients with cancer or rare disease were defined in the HES data.

Conclusions: Our investigation shows that the systematic application of large scale genomics to RWD is now feasible. Technological infrastructure of the NHS allows to generate linked clinical-genomic datasets for research under rigorous governance processes and privacy protection. Further scientific work is needed to investigate applications of linked genomic-RWD to provide genomic-based evidence for predicting efficacy or safety of drugs, biomarker testing or stratifying patients.

241 | Burden and concordance of information on CYP2D6, CYP2C19, AND CYP2C9 related substrate and inhibitor co-prescriptions from the lifelines cohort: the Pharmlines initiative

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Background: Drug–drug interactions (DDI) are one of the major contributors to adverse drug reactions.

Objectives: We aimed to estimate the burden of substrate and inhibitor of CYP2D6-, CYP2C19-, and CYP2C9-mediated co-prescriptions that may lead to potentially clinically relevant DDIs in the LifeLines cohort. Further, the concordance of questionnaire and prescription database was assessed.

Methods: Data on the prevalence of substrate and inhibitor of CYP2D6, CYP2C19, and CYP2C9 co-prescriptions were collected from the LifeLines participants and linked by Statistics Netherlands to the pharmacy database IADB.nl, as a part of the PharmLines Initiative project. Data analysis were performed at fifth level of ATC codes for all potentially clinically relevant CYP2D6-, CYP2C19-, and CYP2C9-mediated DDIs. The co-prescriptions were divided based on the duration of use of prescribed medications i.e. regularly used medication (RM) and RM combination, RM-non regularly used medication (NRM) combination and NRM-NRM combination. To measure the level of agreement, Cohen's kappa statistics was used and the results were stratified by time windows, sex, and age.

Results: At entry, of all 80,837 medicine users, about two per hundred LifeLines participants were exposed to a CYP2D6/2C19/2C9-mediated potentially clinically relevant DDI. Most of the potential DDIs were mediated by CYP2C19 (1,120 patients), followed by CYP2D6 (590 patients) and CYP2C9 (255 patients). Using an overlapping time window of three months, kappa values were moderate at 0.53, 0.56, and 0.43 for CYP2D6, CYP2C19, and CYP2C9-mediated DDIs, respectively. Subgroup analysis by the type of medication indicated that the potential DDIs between RM-RM and RM-NM combination mostly had better kappa values than NRM-NRM. The influence of gender on the concordance values was different for different CYPs. Among older persons agreement levels were higher for all CYPs-mediated potentially clinically relevant DDIs than among the younger population.

Conclusions: CYP2D6/2C19/2C9-mediated potentially clinically relevant DDIs were frequently observed in the LifeLines cohort. The agreement between the LifeLines cohort data and the prescription data is moderate. Future pharmaco-epidemiological studies should preferably combine the two data sources to achieve the highest accuracy of drug exposure rates.

242 | Do Oral antineoplastic treatment data differ between EMR & Claims: Concerto Health AI Definitive Oncology Dataset & Symphony Linkage Study

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Background: Electronic Medical Records (EMRs) are increasingly being used for health outcomes research because they contain a rich array of clinical data. Oral medications are captured via structured medication order fields or abstracted from the clinical notes; however, it's unknown how these correspond with dispensations.

Objectives: The objective of this study was to better understand how oral antineoplastic orders captured from an EMR database compare to dispensations from pharmacy claims.

Methods: The Concerto Health AI Definitive Oncology Dataset is a deeply curated cohort of patients (pts) derived from a wide range of oncology practices throughout the United States. Concerto Health AI has a co-exclusive partnership with ASCO CancerLinQ & collects data from multiple other sources. These data were deterministically linked to US Symphony Health's (SH) Integrated Dataverse, an anonymized, HIPAA-compliant data set. Only advanced (stage IIIb/IV) non-small cell lung cancer (aNSCLC) pts with curated data via manual review by nurse practitioners & oral antineoplastics prescribed for lung cancer were included in this analysis. Among a subset of pts that had a dispensation within 90 days of their 1st EMR order, treatment duration was calculated as time from 1st to last order/claim (before a 30-day gap) plus 30 days supply, for EMR & claims, respectively.

Results: Of 19,175 aNSCLC pts from Concerto, 8,864 pts were linked to SH. Among linked pts, there were 2,057 pt-drug instances; 750 (36.5%) were in both Concerto and SH, 1,160 (56.4%) in Concerto but not SH, and 147 (7.1%) in SH but not Concerto. Median time from 1st order in Concerto to 1st dispensation in SH was 16 days (interquartile range (IQR): 6, 78), with 76% of pt-drug instances having a dispensation within 90 days of 1st Concerto order. Median treatment duration was 44 (IQR: 30, 125) and 93 (IQR: 41, 241) days based on Concerto and SH, respectively.

Conclusions: Concerto EMR orders identified more pts treated with oral antineoplastics, though treatment durations were longer using SH claims. Limitations of this analysis include use of orders from EMR instead of abstracted start and end dates and use of open

claims with limited specialty pharmacy data. Linked datasets may provide more robust capture of orals data and warrant further research.

243 | Combining a prospective registry with a retrospective medical chart review

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Background: The OPsumit® USers Registry (OPUS) provides real-world data on the use and safety profile of Opsumit, an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH), a rare and severe condition. The OPUS registry was an FDA post-marketing requirement focusing on the class-effect of hepatotoxicity. The OPsumit® Historical USers (OrPHeUS) medical chart review study complemented OPUS, to achieve the requested sample size of 5000 patients newly treated with Opsumit within 5 years in the combined analysis.

Objectives: To evaluate the appropriateness of combining OPUS and OrPHeUS data.

Methods: The studies were designed to be as similar as possible. Exploratory heterogeneity assessment on key variables was performed, with bootstrap 95%CI, using PAH patients who represented the majority of patients.

Results: The combined OPUS (n = 2086) and OrPHeUS (n = 2984) dataset included 4072 (80.3%) PAH patients; 96 (61.9%) of 155 participating sites contributed to both studies. The median (range) Opsumit initiation year was 2016 (2014–2018) in OPUS and 2015 (2013–2016) in OrPHeUS; median (95%CI) age was 62 (61, 63) and 61 (60, 62) years, respectively. For patients with a WHO functional class (FC) assessment $\leq$3 months from Opsumit initiation (OPUS 71.7% and OrPHeUS 21.9%), the proportion (95%CI) in WHO FC I/II was similar: 39.2% (36.5, 41.9) and 36.1% (32.0, 40.1). The median (95%CI) Opsumit exposure time in OPUS was 11.9 (11.1, 12.7) and in OrPHeUS was 15.6 (14.7, 16.4) months, and annual visit rate (95%CI) was 3.6 (3.5, 3.7) and 3.3 (3.2, 3.4) visits/year, respectively. The annual liver test (LT) rate (95%CI) was lower in OPUS (1.8 [1.7, 1.9]) than in OrPHeUS (2.2 [2.1, 2.4]), as was the proportion of patients with a liver test. This might have been related to the hepatotoxicity concern in the first years after Opsumit launch in Oct 2013, which may have lessened after daily care experience.

Conclusions: The similarities between OPUS and OrPHeUS studies enabled combined analyses. The higher rate of liver tests in OrPHeUS may have induced a detection bias, potentially leading to more liver test abnormalities being detected. However, this did not change the overall conclusion about the (hepatic) safety of Opsumit.

244 | Abstract Withdrawn

245 | Building an integrated real-time data ecosystem to enhance care delivery for asthma patients in Singapore

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Background: Asthma affects an estimated 273 million people worldwide, with Singapore having one of the highest asthma prevalence rates. The real-time capture, aggregation and analysis of real-world electronic clinical data provides important information for improving the care of asthma patients in Singapore.

Objectives: To develop an asthma real-world data ecosystem (RWDE) for a large academic medical centre in Singapore through a public-private partnership with Singapore Health Services (SingHealth), Duke-NUS Medical School and GlaxoSmithKline. This abstract describes the data linkages, source data verification and validation steps in the creation of the RWDE.

Methods: Multiple clinical data sources such as the electronic medical records and clinical measurement result system, were linked using the SingHealth enterprise data warehouse (EDW). To ensure accurate data transfers, back-end data retrieved from the EDW was matched with the front-end data captured at the point of care. The data quality assurance includes a gated stepwise process to ensure the correct integration of data from various sources. As part of the data validation process, demographics and clinical information were retrospectively extracted for asthma patients visiting the Singapore General Hospital (SGH) from October 2012 to October 2017, and exploratory descriptive analyses (EDA) performed.

Results: Testing of the RWDE yielded satisfactory results. Descriptive statistics of key variables were checked to ensure that the extracted data were of high veracity. In our EDA, a total of 621 asthma patients from SGH were included. Mean age of the cohort was 55.1 years and 43.0% were males. 21.3% were smokers or ex-smokers. Common comorbidities include allergic rhinitis and gastro-esophageal reflux disease. 58.6%, 19.3%, 16.1% and 6.0% were of Chinese, Indian, Malay and other ethnicities, respectively. The majority had their Asthma Control Test scores (83.9%) and spirometry results (62.6%) documented. 58.0% and 60.4% of the patients were provided with a

Written Asthma Action Plan and had their inhaler technique assessed, respectively. Overall, results from the EDA are concordant with other studies on asthmatics conducted at SGH.

Conclusions: The development and application of an asthma RWDE in SGH enables real-time access and analysis of large-volume tertiary level data to facilitate clinical research, and to support the future design of clinical decision support systems to improve patient outcomes. The next step will be to incorporate public primary care data from the network of SingHealth polyclinics. FUNDING: GlaxoSmithKline.

246 | Initiation of an innovative study combining digital patient generated data with health records to evolve understanding of Back pain

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Background: Back pain affects up to 80% of the population and is one of the most common reasons for long term sickness. Therefore it is important to understand more about sufferers and to quantify the economic and social burden of the condition and pain management from a patient centric view.

Objectives: To utilize electronic health records (EHR) combined with digital health data from patients to i) assess quality of life (QoL) over time for patients with back pain, and the variation in pain, ii) investigate the epidemiology of back pain, and iii) quantify the economic burden of back pain.

Methods: A collaboration was established between IQVIA, uMotif, EMIS Health, and NIHR and a study was initiated to recruit patients with a diagnosis of acute or chronic low back pain from UK Primary Care. The study utilized a novel, efficient recruitment application called AppScript embedded into the General Practitioner's EMIS practice management software. Patients used a mobile app, uMotif, to provide informed consent and collect information on QoL, work productivity, physical, and mental impacts of the back pain. The patient reported data was combined with retrospective EHR data to provide broader insights from both the health team and the patient.

Results: A study kick-off meeting ensured that the sponsor, chief investigators, facilitators and app providers were aligned on study goals, roles and methods. Study materials, including the patient eSurvey, were developed and Ethics Committee approval was obtained. General Practitioners were recruited and trained. Patient recruitment has begun with the aim of recruiting 150–200 patients with at least 3 months' chronic or acute back pain who will be in the study for 3 months providing data via the mobile app.

Conclusions: This novel use of digital technology reduces the burden of recruitment and data collection from clinicians. Collecting direct patient generated data has the promise of shortening the time needed to complete a study, reducing costs, improving quality of research data and reducing recall bias, while still being acceptable to patients. Having the ability to collect timely patient generated insights and link this to routine healthcare data represents a new approach to driving insights and understanding of common and impactful conditions such as back pain.

247 | Does NA-NSAID use reduce the mortality among endometrial cancer patient?

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Background: An anti-neoplastic effect of non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs) has been suggested, mainly through suppression of cyclooxygenase, isoform 2 (COX-2). Elevated levels of COX-2 in malignant endometrial cells have led to the hypothesis that NA-NSAID can improve the prognostic outcome among endometrial cancer patients.

Objectives: To examine whether post-diagnostic use of NA-NSAIDs is associated with reduced cancer mortality in a large nationwide registry-based cohort of endometrial cancer patients.

Methods: From the Danish Cancer Registry we retrieved all women with a diagnosis of endometrial cancer. Women who were diagnosed between 2000 and 2012, aged 30–84 years, who had no history of cancer (except non-melanoma skin cancer) and were alive one year after cancer diagnosis were eligible for the study. NA-NSAID use was defined as one or more prescriptions after date of diagnosis and was further characterized by cumulative amount, intensity and duration of use, and COX-2 selectivity. Follow-up started one year after diagnosis and continued until death, emigration, or end of study, whichever came first. Primary outcome was endometrial cancer specific mortality. Using Cox regression models, adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the association between post-diagnosis NA-NSAID use and endometrial cancer mortality with NA-NSAID use included as time-varying variable. In pre-defined sensitivity analyses to test the robustness of the results and to account for the influence of time-varying confounders, drug use was treated as a time-fixed variable with follow-up starting at 1 year and 5 years after diagnosis, respectively. The potential impact of competing events was tested by Fine and Gray's proportional subdistribution hazard model.

Results: The study population comprised 6,694 endometrial cancer patients and during follow-up 753 died from endometrial cancer. NA-NSAID use was associated with a HR of 1.07 (95% CI 0.91–1.26) for endometrial cancer mortality. Neither the selective COX-2 inhibitors (HR 1.05, 95% 0.84–1.32) nor nonselective NA-NSAIDs (HR 1.10, 95% CI 0.90–1.35) were associated with a reduced

endometrial cancer mortality. The analyses on the time-fixed exposures and subdistribution hazards yielded similar results.

Conclusions: In conclusion, NA-NSAID use was not associated with endometrial cancer mortality among Danish patients.

248 | Inhibition of the renin-angiotensin system and survival in patients with pancreatic cancer

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Background: The renin-angiotensin system may mediate tumor growth in pancreatic cancer. Drugs inhibiting this system may therefore be associated with survival in patients with pancreatic cancer.

Objectives: To examine the association between prediagnostic use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and survival in pancreatic cancer patients.

Methods: A population-based cohort study of all patients aged over 18 years diagnosed with pancreatic ductal adenocarcinoma in Denmark during 1997–2016. Patients were followed for a maximum of three years from date of diagnosis until death or end of follow-up (23 May 2018). Patients were classified as ACEi-users or ARB-users if they had filled a prescription for one of these drug types in the year before pancreatic cancer diagnosis. Patients with no prescriptions of either drug type were classified as non-users. We computed median survival with associated interquartile range (IQR) according to exposure status and crude and adjusted hazard ratios (HRs) and associated 95% confidence intervals (95% CI) using Cox proportional hazards regression model, adjusting for age, sex, year of diagnosis, Gagne comorbidity score, and cardiovascular disease. We conducted sensitivity analyses comparing ACEi users with ARB users and excluding patients exposed to both drugs (n = 116); and second, extending the exposure period to two years before pancreatic cancer diagnosis. In the latter analyses, we restricted to patients with prescription drug data available for the period of interest.

Results: Of 11,662 pancreatic cancer patients, 1,289 (11.2%) were ACEi-users, 983 (8.5%) were ARB-users, and 116 (1.0%) were exposed to both drug types. Median age was lower in non-users (67 years) compared with ACEi (70 years) and ARB (71 years) users. There were no differences in tumor stage at diagnosis according to drug exposure. ACEi-users had more comorbidity than ARB-users and non-users. Median survival was 4.3 (IQR: 1.6–10.4) months in ACEi-users, 5.0 (IQR: 1.7–11.2) months in ARB-users, and 4.6 (IQR: 1.8–10.8) months in non-users. Compared with non-users, neither ACEi (adjusted HR: 1.00; 95% CI: 0.94–1.07) nor ARB use (adjusted HR: 0.97; 95% CI: 0.91–1.05) was associated with survival. The sensitivity analyses had only little effect on the HRs.

Conclusions: Exposure to antihypertensive drugs acting on the renin-angiotensin system before pancreatic cancer diagnosis was not associated with survival in patients with pancreatic cancer.

249 | Real-world assessment of clinical outcomes among first-line (1 L) Sunitinib patients with metastatic renal cell carcinoma (MRCC) by the international Mrcc database consortium (IMDC) risk group

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Background: Sunitinib is a standard treatment for 1 L mRCC. Findings from several clinical trials suggest that clinical outcomes of mRCC patients treated with 1 L sunitinib may vary across prognostic risk groups (i.e., favorable, intermediate, poor risk), defined by IMDC criteria. A gap in the literature on the effectiveness of 1 L sunitinib by IMDC prognostic risk group in the real-world setting exists.

Objectives: This study assesses clinical outcomes and provide benchmarks for mRCC patients treated with 1 L sunitinib in the real-world to provide contemporary benchmarks for outcomes and survival.

Methods: Clear cell mRCC patients ≥18 years of age who initiated sunitinib as 1 L therapy between 2010–2018 at select IMDC clinical sites were included in this real-world retrospective database study. Kaplan Meier analysis was used to estimate median time to treatment discontinuation (TTD) and overall survival (OS) by IMDC risk groups based on Karnofsky Performance Status <80%, diagnosis to treatment interval < 1 year, anemia, neutrophilia, hypercalcemia and thrombocytosis.

Results: Among 1,769 1 L sunitinib patients with clear cell in this real-world clinical dataset, 318 (18%) had favorable, 1,031 (58%) had intermediate and 420 (24%) had poor IMDC risk. Across the favorable, intermediate, and poor risk groups, patients had similar mean age in years, gender distribution, and year of sunitinib initiation (age: 63.8, 62.9 and 62.6; male: 74%, 75%, and 72%; sunitinib initiation year of 2010–2013: all 71%). In the favorable risk group, 99% received nephrectomy vs 88% in intermediate and 66% in poor risk group. Median TTD was 15.0, 8.5, and 4.2 months (mos) in the favorable, intermediate, and poor risk groups, respectively, and was 7.1 mos in the combined intermediate/poor risk groups. Median OS was 52.1, 31.5, and 9.8 mos in the favorable, intermediate, and poor risk groups, respectively, and was 23.2 mos in the combined intermediate/poor risk groups.

Conclusions: This real-world study based on a contemporary cohort of 1 L sunitinib mRCC patients found a median OS of 52 mos which sets a new benchmark for clear cell mRCC in the favorable risk group. OS

in the intermediate and poor risk groups are similar to previous reports. This affects patient counseling and clinical trial design.

250 | Antihistamines and survival from ovarian cancer: A population-based cohort study and in vitro cell viability study

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Background: Epithelial ovarian cancer is associated with poor prognosis, since it is often diagnosed in a late stage and often becomes resistant to chemotherapy. A subclass of antihistamines with cationic amphiphilic drug (CAD) characteristics have been associated with improved cancer outcomes, in pre-clinical and observational studies. In this study, we evaluate the potential of these antihistamines to improve survival after ovarian cancer.

Objectives: To assess whether CAD antihistamines improves the survival in ovarian cancer patients.

Methods: We performed a cohort study including all 1-year survivors of epithelial ovarian cancer between 2000 and 2015 aged 30–84 years. Information on filled prescriptions of antihistamine, use of other drugs, comorbid conditions and socioeconomic parameters was retrieved from nationwide prescription, medical and demographic registries. By means of Cox proportional hazards models, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) for use of CAD antihistamines and ovarian cancer mortality. The underlying timescale was time since 1 year after diagnosis. Use of antihistamines was defined as filling at least one prescription between 6 months before and 12 months after diagnosis. We used an active comparator approach comparing CAD-antihistamine users with users of non-CAD antihistamines. In secondary analysis we moved the baseline to three years after diagnosis and defined use of antihistamines as use within three years after diagnosis. Finally, we tested the effect of clinically relevant CAD and non-CAD antihistamines on cell viability in three serous ovarian cancer cell lines, including OVCAR-3, UWB1.289, and ovc316. Separate one-way ANOVA was used to evaluate cell death according to dose for each antihistamine in each of the three cell lines.

Results: We identified 5075 1-year survivors after ovarian cancer and of these 484 patients used antihistamines between 6 months before and 1 year after diagnosis. Of the 484 users of antihistamines 148 were classified as CAD users. Use of CAD antihistamines was associated with a HR of 0.74 (95% CI: 0.51–1.06) compared to use of non-CAD in 1-year survivors, whereas the HR was 0.63 (95% CI: 0.40–0.99) for 3-year survivors among 145 CAD antihistamine users and 292 non-CAD users. Similar results were seen when comparing to patients not using antihistamine. Cell viability experiments showed consistent dose–response relationships with cell death for all CAD antihistamines, but not for non-CAD antihistamines.

Conclusions: Use of CAD antihistamines may improve survival after ovarian cancer.

251 | Response and adherence to Nilotinib in daily practice (RAND-study): An in-depth observational study of patients with chronic myeloid leukemia treated with Nilotinib

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Background: In chronic myeloid leukemia (CML), oral treatment needs to be taken indefinitely in the majority of patients and specifically for nilotinib, the necessity of a twice daily, fasted schedule is an extra burden. Non-adherence to CML treatment may influence plasma levels and has been recognized as a determinant of treatment failure in CML.

Objectives: To gain insight into adherence with the use of nilotinib in daily clinical practice and its influence on exposures and treatment outcome.

Methods: A multicentre prospective observational study conducted between August 2013–April 2017. CML patients treated with nilotinib were followed for twelve months. Achievement of a major molecular response (MMR) within the first twelve months of nilotinib treatment was assessed. Adherence was measured by three methods: medication event monitoring system (MEMS) (proportion of days covered [PDC]), pill count (adherence rate [AR]), and self-reported Medication Adherence Report Scale (MARS-5). Nilotinib trough plasma concentrations were measured at baseline, three, six, and twelve months.

Results: Sixty-eight patients (57.0 ± 15.0 years;48% female) participated. At baseline, 29 patients were newly starting nilotinib (subpopulation-A) and 39 were already on treatment with nilotinib (subpopulation-B) with a median treatment duration of 39 months (range 3–92). The overall 1-year MMR rate ranged from 44–75%. Median PDC and AR were 99.6 and 100.2 in subpopulation-A and 97.6 and 98.1 in subpopulation-B, respectively. Three and five patients, respectively, had PDC and AR <90%. The percentage of patients reporting any non-adherence behaviour (MARS-5) increased in subpopulation-A from 8% at three months to 26% at twelve months, and remained steady in subpopulation-B at 23–30%. Average trough plasma concentration was 1084 ± 556 ug/L (range 196–2540). Six patients (9.8%) had a plasma concentration below the therapeutic target level (<490 ug/L) at any time. There was no association between nilotinib trough level or nilotinib adherence and MMR at twelve months.

Conclusions: Substantial non-adherence (<90%) to nilotinib was rare and nilotinib blood levels were above the therapeutic target in 90% of patients. Achievement of MMR on nilotinib was not related to nilotinib non-adherence or inadequate blood levels. However, incidental non-adherence increases over time to a quarter of patients, emphasizing the importance of continuous support of medication adherence in CML care.

252 | Comparative efficacy and safety of immune checkpoint inhibitors for untreated and treated advanced non-small cell lung cancer: Meta-analysis and meta-regression analysis

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Background: In recent years, more and more randomized clinical trials and observational studies have been conducted and demonstrated that many Immune checkpoint inhibitors (ICIs) can significantly improve the survival rate of advanced non-small cell lung cancer (NSCLC). Many meta-analyses studies have been conducted to address possible inconsistencies in clinical trial results, and to achieve comprehensive conclusions. However, only a few studies have explored the efficacy and safety of ICIs for advanced NSCLC in detail by subgroup analyses.

Objectives: This meta-analysis systematically and quantitatively evaluated the efficacy and safety of ICIs compared with chemotherapy treatment for untreated advanced NSCLC.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) and the Cochrane Collaboration guidelines, electronic databases (PubMed, Embase, Web of Science and Cochrane Library) were searched for all clinical trials and observational studies in NSCLC using ICIs. Data about overall survival (OS), progression free survival (PFS), all-grade adverse events (AEs) and high-grade (3–5) AEs were pooled. Meta-regression was performed for further subgroup analyses.

Results: A total of 10 trails with 5,277 patients (3 with nivolumab; 3 with pembrolizumab; 3 with atezolizumab; and 1 with durvalumab) were included in this meta-analysis. We demonstrated that ICIs therapies significantly improved OS (HR = 0.67, 95% CI 0.62–0.72, $P < 0.05$) and PFS (0.74, 0.64–0.86, $P < 0.05$) in treated advanced NSCLC, while the results were not always significant in untreated advanced NSCLC: OS (0.84, 0.63–1.14, $P = 0.265$) and PFS (0.66, 0.47–0.91, $P = 0.012$). In terms of safety, ICIs had a significantly lower risk of any all-grade AEs (OR = 0.48, 95% CI 0.33–0.71, $P < 0.05$) and high-grade AEs (0.27, 0.14–0.51, $P < 0.05$) in treated advanced NSCLC; while the results were not always significant in untreated advanced NSCLC: any all-grade AEs (0.54, 0.21–1.38, $P = 0.198$) and high-grade AEs (0.57, 0.17–1.84, $P = 0.341$). The results of meta-regression also showed that OS, PFS, all-grade and high-grade AEs were better for patients with squamous histology and higher PD-L1 expression.

Conclusions: In conclusion, compared with chemotherapy, ICIs improve OS and PFS in advanced NSCLC with fewer all and higher-grade adverse effects in treated patients, but not always in untreated patients. Especially, ICIs as a prefer treatment option for patients with squamous histology and higher PD-L1 expression.

253 | Lifestyle factors and systemic breast cancer treatment- a cross-sectional UK study

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Background: Differences exist in how patients are allocated systemic breast cancer treatment based on their body mass index (BMI). However, there is limited evidence regarding whether other lifestyle factors (e.g. smoking status and alcohol consumption) also play a role in treatment allocation for such patients.

Objectives: To assess whether a patient's lifestyle factors (BMI, smoking status and alcohol intake) are associated with the treatment administered.

Methods: This was a cross-sectional study using linked UK data from CPRD (CPRD GOLD primary care, Hospital Episode Statistics Admitted Patient Care, NCRAS Cancer Registration Data and the newly available NCRAS Systemic Anti-Cancer Therapy dataset). Cases included women with incident breast cancer registered between 2013–2015 based on the London Breast Cancer Alliance (LCA) definitions. The latest BMI, smoking status and alcohol status recorded in the patient's primary care record prior to diagnosis were extracted. The primary outcome was whether a patient was treated with a systemic treatment (epirubicin, doxetaxcel, flourouacil, paclitaxel or trastuzumab). Descriptive analysis of the outcomes of interest stratified by exposure and other covariates was undertaken. Logistic regression was used to generate odds ratios (OR) with 95% confidence intervals (95% CI).

Results: 3,791 female patients with incident breast cancer were included with a mean age of 60.6 (standard deviation 13.8). Of those, 26% were obese, 12% were current smokers and 72% were current drinkers. In total, 906 (24%) had systemic treatment recorded. Due to relatively small numbers, confidence intervals were wide, and some results were not statistically significant. However, obese patients had similar odds of receiving systemic treatment compared to underweight/healthy weight cases (unadjusted OR 0.98; 95%CI 0.76–1.26) while current smokers had higher odds of receiving treatment (unadjusted OR 1.37; 95%CI 1.02–1.84) compared to never smokers. Current drinkers had slightly higher odds of receiving treatment (unadjusted OR 1.12; 95%CIs 0.86–1.46) compared to never drinkers. Adjusted analyses will be presented at the conference.

Conclusions: These results suggest that there may be differences in treatment allocation for breast cancer patients based on lifestyle factors. Given that prognosis has been shown to vary by treatment, further research in larger patient populations and/or a longer study period is warranted.

254 | Can we modulate response to preoperative therapy in rectal cancer patients by ACE inhibitors?

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Background: Only 50% of the rectal cancer patients respond to preoperative treatment and some patients even show progression during treatment. Therefore, it is important to identify factors that could influence tumor response to preoperative chemoradiation in rectal cancer.

Objectives: The aim of this study was to assess the effect of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on tumor response to preoperative chemoradiation for rectal cancer.

Methods: Data on patients who received chemoradiation prior to surgery for rectal cancer between 2010–2015 were retrieved from linkage between the PHARMO Database Network, Dutch Pathology Registry and Netherlands Cancer Registry. Pathological complete response rates (pCR) were compared between patients who did or did not use ACEIs/ARBs during treatment. Multivariable analysis was performed using logistic regression.

Results: Out of 345 patients, 92 patients (26.7%) used ACEIs/ARBs during treatment. Median age was 65 years (range 30–85). Older and male patients were more likely to use ACEIs/ARBs. pCR (ypT0N0) was observed in 17.4% of patients using ACEIs/ARBs compared to 14.6% of patients who did not use ACEIs/ARBs (p = 0.595). A good response (ypT0–1 N0) was observed in 21.7% of ACEIs/ARBs patients versus 19.4% of patients who did not use ACEIs/ARBs (p = 0.724). Multivariable analysis, taking into account background variables and co-medication, showed increased pCR in patients using beta-blockers (odds ratio 2.34, 95% confidence interval 1.01–5.41).

Conclusions: In this retrospective cohort, the use of ACEIs/ARBs was not associated with tumor response to preoperative chemoradiation in rectal cancer patients. Thereby, the suggested potentiating effect of ACEIS/ARBs could not be confirmed in our study. Further research could be directed to investigate a possible benefit of beta-blockers or other anti-hypertensive drugs.

255 | Effectiveness of Bevacizumabin metastatic colorectal cancer: The observational cohort study in Indonesia

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Background: Bevacizumab is a well-established first-line treatment for metastatic colorectal cancer. However, there is scarce evidence in the literature about its effectiveness in clinical practice in Indonesia.

Objectives: The objective of the this cohort study was to compare the overall survival (OS), Progression free survival (PFS) and cost of treatment in patients with mCRC treated with bevacizumab + chemotherapy (B + CT) compared to chemotherapy only (CT) in an Indonesian clinical practice setting.

Methods: Design: Cohort retrospective **Setting**: Hospital-based medical records 2009–2017 **Exposures or interventions:** Bevacizumab + chemotherapy (B + CT) compared to chemotherapy only (CT) **Main outcome measures**: Overall survival (OS), Progression free survival (PFS), Percentage of each combination therapy, cost of combination therapy Incident patients with mCRC were identified during the period 2009–2017 from four hospital-based medical record in Indonesia. Cases were linked to health care utilization databases to obtain the entire spectrum of health services provided to each patient. Patients starting a first-line treatment with B + CT or CT alone from the diagnosis were included in the study cohort.

Results: Of 139 patients with mCRC included in the study cohort, 69.1% received first-line B + CT, and 30.9% received CT. Patients receiving B + CT were underwent surgery more frequently. The median OS was 12.5 and 8.8 months for B + CT and CT, respectively (p = .011). The median PFS was 10.0 and 5.7 months for B + CT and CT, respectively (p = .011). Patients with B + CT received combination therapy in the following: bevacizumab + oxaliplatin + capecitabine (45.8%, cost 201,610,508 IDR), bevacizumab + oxaliplatin + leucovorin +5FU (40.6%, cost 276,481,952 IDR), bevacizumab + irinotecan + leucovorin +5FU (13.5%, cost 280,273,593 IDR). Patients with CT received combination therapy in the following: oxaliplatin + leucovorin +5FU (46.5%, cost 176,051,373 IDR), oxaliplatin + capecitabine (39.5%, cost 104,336,179 IDR), irinotecan + leucovorin +5FU (14.0%, cost 252,833,552 IDR).

Conclusions: In this Indonesian real-world setting of unselected mCRC, the OS of patients treated with B + CT was similar compared

with CT. Definitive evidence of an improvement in OS cannot be drawn. The cost of combination therapy in patients with B + CT higher than with C + T.

256 | Performance of Abiraterone and enzalutamide in metastatic castration-resistant prostate cancer men: A head to head comparison based on a 2014–2017 French population study

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Background: Considering clinical data published since 2011 as regard the metastatic castration resistant prostate cancer (mCRPC) treatment, in patients where chemotherapy is not yet needed, clinicians should consider two per os therapeutic options, abiratérone (ABI) or enzalutamide (ENZ), two next-generation androgen receptor-targeted agents (AR).

Objectives: Using the French national health insurance database (SNDS), the aim of this study was to compare effectiveness of ABI and ENZ as first line treatment in mCRPC men with a direct comparison.

Methods: Thanks to the SNDS (Système National des Données de Santé), new users of ABI and ENZ were included between January 2014 and Decemeber 2015, and followed by December 2017. Main outcome was overall survival (OS). With an "intent-to-treat" principle, a survival analysis was performed, estimating hazard ratio with Cox proportional hazard model and using a propensity score (SIPTW method). ABI was the reference group.

Results: Between 2014 and 2015, among 4783 patients without history of chemotherapy, 83% and 17% were new users of ABI and ENZ, respectively. The mean age was similar in groups, around 78 years. Crude incidence rate of death was 26.0 for 100 PA [95%CI: 24.9–27.1]) for ABI and 23.8 for 100 PA [95%CI: 21.5–26.4] for ENZ. Survival analysis showed a significant benefice of ENZ compared to ENZ: adjusted HA 0.86 [95%CI: 0,77–0.96].

Conclusions: In a direct comparison, our population-based study in almost 5000 French mCPRC patients showed a significant OS increase with ENZ compared to ABI.

257 | Comparative effectiveness of Efavirenz and protease inhibitors in patients with human immunodeficiency virus - a meta-analysis

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Background: In many parts of the world, non-nucleoside reverse transcriptase inhibitor- and protease inhibitor-based regimens (NNRTIs and PIs) continue to be used in the management of patients with HIV. The World Health Organization recommends efavirenz as the NNRTI of choice for initiating HIV treatment.

Objectives: To determine the relative effectiveness of efavirenz and PIs using a meta-analytic approach.

Methods: Data was obtained through a systematic review of randomized controlled trials (RCTs) conducted between 1987 and 2018 comparing efavirenz with PIs. The review was conducted by searching Embase, PubMed, Cochrane, and clinicaltrials.gov databases using the PICO (Population-Intervention-Comparator-Outcome) search strategy and following a sequence from title screen to abstract screen and then full-text screen. The publications assembled for the study consisted of RCTs of treatment naïve HIV patients aged 13 and older initiating treatment with an efavirenz-based vs a PI-based highly active antiretroviral therapy (HAART) regimen. RCTs including patients with hepatitis or tuberculosis co-infection were excluded. Included publications were assessed for potential bias using the Cochrane risk of bias tool. The main outcome of interest was the proportion of patients who were virologically suppressed. Random-effects meta-analysis was conducted using the robust variance estimation approach.

Results: Fifteen studies met the inclusion and exclusion criteria. The trials totaled 7,186 patients of which 1,700 (23.7%) were females. Follow-up ranged from 24 weeks to 144 weeks. Average age ranged from 33 years to 44 years. Average baseline CD4 count ranged from 32 cells/mL to 557 cells/mL while average baseline viral load ranged from log10 4.5 copies/mL to log10 5.5 copies/mL. Virological suppression (<50 copies/mL) at 48 weeks was 56%–100% vs 51–100% for EFV vs PI, respectively (Odds ratio (OR) range = 0.76–2.10). Meta-analysis showed that patients receiving efavirenz-based regimens had 37% higher odds of virological suppression compared to PI-based regimens OR = 1.37, 95% CI = 1.06–1.77, p = 0.02). The Egger test suggested the presence of publication bias (B = 0.927, t = 2.214, p = 0.033). The main threat to the quality of evidence was attrition bias.

Conclusions: Regarding virological suppression, efavirenz was more effective than protease inhibitors and, therefore, might be ideal for the management of treatment naïve patients with HIV in settings

where NNRTIs and PIs are used. Publication bias, however, suggests caution in interpretation of results.

258 | Comparative effect of four antimalarial treatments on hematocrit in children in Southwest Nigeria

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Background: Anemia in malaria has both central (dyserythropoiesis) and peripheral causes (phagocytosis of both infected and uninfected erythrocytes and haemolysis). However, it is often difficult to disentangle the anemia effect of malaria from its treatments.
Objectives: To compare the change in hematocrit following four antimalarial treatments among children of microscopically-confirmed *Plasmodium falciparum* infection.
Methods: Data were extracted from 313 case record forms of children that met the eligibility criteria aged 3–119 months enrolled in antimalarial clinical trials in Southwest Nigeria between 1998 and 2014. Study participants were followed up over a 28 day period according to the World Health Organization recommendation for treatment of malaria research participants. Enrollment criteria included symptoms compatible with acute uncomplicated malaria, including parasite density of at least 1000/μL and absence of chronic illness or danger signs of severe malaria. Change in hematocrit level from baseline through the treatment period and 28 days post treatment were compared among children treated with artemether-lumefantrine (82), artovaquone-proguanil (41), artesunate-amodiaquine (156) and chloroquine (34). Repeated measures analysis was done by fitting a general linear model (GLM).
Results: The median age of the study population was 25 months and 54% were males. The mean differences (95% CI) in hematocrit from baseline were 4.7 (95% CI = 3.6, 5.8), 4.4 (95% CI = 2.7, 6.0), 3.8 (95% CI = 3.0, 4.7) and 2.4 (95% CI = 0.5, 4.4), for artemether-lumefantrine, artovaquone-proguanil and artesunate-amodiaquine and chloroquine, respectively. Using the general lineal model, repeated measure analysis showed that there were significant differences in the mean hematocrit level over the 28-day follow-up among the four treatment groups ($p < 0.05$).
Conclusions: All children experienced increases in hematocrit after treatment, with artesunate-amodiaquine appearing to result in a greater increase in hematocrit than other antimalarial drugs.

259 | Continuous cefazolin infusion versus cefazolin plus probenecid for the ambulatory treatment of uncomplicated cellulitis: A retrospective cohort study

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Background: The preferred ambulatory IV therapy for cellulitis is often once-daily cefazolin combined with once-daily oral probenecid (C + P). However, due to a national probenecid drug shortage in 2011, our centre developed a replacement protocol for the administration of cefazolin continuous infusion (CCI) using elastomeric infusers.
Objectives: Our goal was to compare treatment efficacy, duration of IV therapy, and recurrence rates associated with CCI and C + P using data from a hospital centre.
Methods: We conducted a non-inferiority single-centre retrospective cohort study using the emergency department medical records. Patients received either C + P (cefazolin 2 g IV once daily + probenecid 1 g PO once-daily) or CCI (cefazolin 2 g IV loading dose, followed by cefazolin 6 g IV via continuous infusion over 24 hours, via an elastomeric infuser). Treatment efficacy, duration of IV therapy, and recurrence rates were compared.
Results: A total of 203 patients were analyzed, with 107 included in the CCI arm and 96 in the C + P arm. Overall, CCI users and C + P users were comparable in their sociodemographic and clinical variables measured at admission. Increased odds of achieving successful treatment was observed among the CCI group, however it did not reach statistical significance (OR, 95% CI: 2.25, 0.84–6.07). Recurrence rates were similar between both groups (1.91, 0.32–11.31). The average duration of IV therapy was similar between groups ($p = 0.6$).
Conclusions: With results suggesting that CCI was non-inferior to C + P, and that both approaches required similar treatment durations, CCI could represent an acceptable alternative to C + P for the ambulatory IV treatment of cellulitis.

260 | Factors associated with viral suppression among HIV-positive Kenyan gay and bisexual men who have sex with men

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Background: The UNAIDS 90–90-90 target has prioritized achieving high rates of viral suppression.
Objectives: We identified factors associated with viral suppression among HIV-positive gay, bisexual, and other men who have sex with men (GBMSM) in Kisumu, Kenya.
Methods: HIV-positive participants in the Anza Mapema study were offered antiretroviral therapy (ART) regardless of CD4 count. HIV viral load was assessed at baseline and after 6 and 12 months of follow-up. Viral suppression was defined as <1,000 copies/mL. Sociodemographic, sexual behaviors, and psychosocial characteristics were assessed via audio computer-assisted self interview. We used generalized estimating equations to estimate the associations

between baseline and time-dependent predictors and viral suppression at 6 and 12 months.

Results: Seventy-five HIV-positive men were enrolled in the Anza Mapema study, of which 63 had at least one viral load measured during follow-up. Among 52 men with a viral load measure at month 6, 37 (71%) were on ART and virally suppressed. Among 59 men with a viral load measure at month 12, 37 (63%) were on ART and virally suppressed. In the final multivariable model, men who reported receptive or versatile sexual position during anal intercourse with a male partner had reduced odds of viral suppression (aOR = 0.20; 95% CI: 0.08–0.50). Greater levels of coping self-efficacy were associated with increased odds of viral suppression (aOR = 1.10; 95% CI: 1.03–1.16).

Conclusions: Despite extensive initiation, retention, and adherence support, the rate of viral suppression in this population did not meet the UNAIDS 90–90-90 target (81% for individuals aware of their HIV status). Pervasive stigma against male-malesex, especially men who practice receptive anal sex, may underlie our findings, which highlight the need for advocacy and stigma reduction efforts. Because coping self-efficacy was a protective factor, efforts to promote resilience in addition to healthy sexual identity development may lead to improved care outcomes among GBMSM in this area.

261 | Predicting relapse episodes in patients with multiple sclerosis treated with disease modifying therapies in a large representative real-world cohort in the United States

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Background: A relapse of multiple sclerosis (MS) interferes with a patient's ability to function at home and at work. Early and accurate identification of patients at risk of relapses improves quality of life and reduces cost of care.

Objectives: To use advanced analytics to predict relapses among MS patients treated with disease modifying therapies (DMTs) identified from a large, representative database of linked EMR and claims data.

Methods: The OM1 Data cloud collects, and links structured and unstructured data, including extensive clinical and claims data on patients from a variety of provider practice types across the US. The study includes data from January 2015–June 2018. MS patients treated with a DMT prior to Dec 31, 2017 (index date) and had no evidence of relapse in the 30 days prior to the index were included in this analysis. Relapse was defined as an MS-related inpatient stay, emergency room visit, or outpatient visit with documented MS and a corticosteroid prescription within 7 days. The outcome of interest was whether the patient experienced a relapse within 6 months post index. Random forests, classification and regression trees were used to identify pre-index predictors. Models were built in a training set with randomly selected 80% of patients and validated in the remaining 20% of patients. The cutoff value for high-risk patients was determined based on optimal model performance.

Results: This study included 18,137 patients, 7.8% of whom had relapses; median age was 54 (IQR: 45–62) years. In the validation set, the model correctly identified relapse outcomes in 84% of patients. Among the most significant predictors were the number of relapses in the previous 12 months, antiemetic medication use, skeletal muscle relaxants, and MS-related fatigue symptoms. The area under the curve for both the training and validation sets were above 0.70. Among patients identified as high-risk (14% of patients), 20.3% experienced a relapse, and among patients identified as low-risk by the model, 5.8% experienced a relapse.

Conclusions: We developed a predictive model for relapse using data elements routinely collected in electronic medical records and insurance claims among DMT-treated MS patients. The patients identified at high risk had nearly a 4-fold relapse rate than patients identified at low risk.

262 | Edaravone utilization and outcomes within a nationally integrated health system

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Background: The Veterans Health Administration (VA) provides care for over 4,000 Veterans with amyotrophic lateral sclerosis (ALS). Edaravone was approved for ALS in 2017, and the VA has implemented a national prior authorization process for edaravone, approved for approximately 10% ALS Veterans. Given limited real-world data, the VA initiated a surveillance effort to monitor the safe and appropriate use of edaravone in Veteran patients.

Objectives: This pharmacovigilance initiative evaluated the patient characteristics, utilization, safety and effectiveness of edaravone use.

Methods: A descriptive cohort analysis was conducted. Diagnoses, procedure, demographics, prescription and death data were obtained from prescription databases, corporate data warehouse and the vital statistics files. Patients with ALS receiving at least one cycle of edaravone from 8/1/2017 to 12/31/18 were included. Veteran characteristics included demographics, service connection, and comorbidities. Utilization measures included, edaravone use/discontinuation and concomitant riluzole use. Outcomes included mortality, emergency department (ED)/hospitalization visits and functional status as identified by surrogate markers such as mechanical ventilation, gastric function, and durable medical equipment (DME) use. Safety and effectiveness outcomes were compared at baseline and at 6-month follow-up. Descriptive statistics summarized characteristics, utilization, and outcomes. Outcomes were compared at baseline and follow-up using McNemar's tests with p less than 0.05 as statistically significant for ED/hospitalization and descriptive statistics for functional status outcomes.

Results: Out of 272 Veterans who received edaravone, mean age was 65 years, 93% were male, 67% white, 75% service connected, and 5.5% had a listed comorbidity. Veterans received a mean 6.5 cycles of edaravone, with 40% discontinuation, and 61% received riluzole in combination with edaravone. Overall mortality was 10%. Outcomes at follow-up were not significantly different from baseline for any ED/hospitalization (38% vs. 36%, p = 0.36). Functional status markers were increased from baseline for tracheostomy (0% vs. 3.0%), mechanical ventilation (0.6% vs. 2.4%), and PEG placement (2.4% vs. 4.2%), and decreased for DME use (5.4% vs. 2.4%).
Conclusions: Evaluations to date suggest that the effectiveness of edaravone may be associated with surrogate markers of functional status. Future outcome evaluations will also utilize chart reviews. Utilization and outcome monitoring will be continued to evaluate access, safety and effectiveness of edaravone.

263 | Using artificial intelligence and real-world data to identify drugs to repurpose for Parkinson's disease

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Background: About 7–10 million people worldwide are living with Parkinson's Disease (PD). Currently there is no cure or treatment to slow disease progression. As electronic medical data continues to expand, opportunities for novel analyses for long standing problems become feasible. We have used machine learning to identify drugs that may have a disease modifying effect in PD and analyzed real-world data to investigate the effect of exposure on PD risk modification.
Objectives: To test antihypertensives for potential influence on the risk of PD diagnosis.
Methods: Using IBM Watson for Drug Discovery we identified antihypertensives as a class of drugs that may have a disease modifying effect in PD. Using the IBM MarketScan Research Databases, we constructed a cohort of individuals with incident hypertension (HTN). Exposure to HTN medications was classified as single agent, double agent or 3+ agents. Drugs were collapsed into major drug categories, including alpha-blockers (AB), beta-blockers (BB), ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), Renin Inhibitors (RI), dihydropyridine calcium channel blockers (DHP-CCB), non-dihydropyridine CCB (CCB) and diuretics. We conducted univariate and multivariate Cox Proportional Hazards Ratios with exposure assessment as a time-dependent covariate. Exposure categories were individual drug categories, paired drug categories, 3 or more drug categories, and no drug exposure. Diuretics were used as the referent group in all analyses. We consider 3 or more and no drug exposures to be of limited value due to difficulty in interpretation and so do not report their results. Age at HTN diagnosis, sex, and several comorbidities were included in multivariate analyses.
Results: In univariate analyses we found that compared to diuretics alone, ACEi with diuretics, ARBs with DHP-CCB, ARBs with diuretics, DHP-CCBs alone, and DHP-CCBs with diuretics were significantly associated with decreased risk of diagnosis of PD. In multivariate analyses, ACEi with diuretics remained significant (hazard ratio = 0.60, p-value <0.01) as did ARBs plus DHP-CCBs (hazard ratio = 0.55, p-value <0.01).
Conclusions: We show that DHP-CCB with ARBs, as well as ACEi with diuretics, show the most promise for a potential decrease in risk of PD diagnosis. Our analysis was unique in that we were able to analyze single and combination therapies, which to our knowledge has not been done before. As more clinical data becomes available and larger datasets emerge, there is promise for the application of data mining to tackle questions that could not previously have been addressed.

264 | Efficacy and safety of interventions used for Management of Diabetic Neuropathy Pain: A frequentist network meta-analysis

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Background: Diabetic neuropathy (DNeP) is associated with a wide range of clinical manifestations, accounting for a massive amount of economic burden to healthcare system.
Objectives: The purpose of this study was to assess efficacy and safety of pharmacological interventions used in managing DNeP.
Methods: A comprehensive search strategy in PubMed, Embase and Cochrane Library was built to identify randomized controlled trials involving the treatment of DNeP. The studies satisfying pre-defined eligibility criteria was included in network meta-analysis, direct and indirect comparison evidence for the estimation of the mean difference and odd ratios. The efficacy end point include 30% pain reduction from baseline.
Results: A total of 45 trials consist of 10511subjects were included in the Random effect mixed treatment comparison. 16 and 44 trials reported 30% pain reduction and withdrawal outcomes respectively. NMA of 30% pain reduction reported least efficacy of placebo compared to all other treatments (Lamotrigine, duloxetine Carbamazepine, duloxetine 120 mg, duloxetine 60 mg). For safety outcome, Pregabalin 300 mg, pregabalin 150 mg, pregabalin/duloxetine, gabapentin were at greater risk for withdrawal from study compared to sodium valproate, OR, CI: 1.17 (0.15; 8.96), 1.18 (0.15; 9.60), 1.28 (0.16; 9.99), 1.26 (0.15; 10.59) respectively. After considering both efficacy and safety outcomes, pregabalin/duloxetine and carbamazepine exhibited highest probability compared to others.
Conclusions: This NMA suggests Pregabalin 600 mg, Gabapentin 3000 mg, arbamazepine, venlafaxine, Lamotrigine were most efficacious in pain relief and Oxcarbazapine and pregabaline 600 mg were safer drugs in adult patients with DNeP.

265 | A systematic review of ketamine for treatment-resistant depression

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Background: Healthcare professionals often prescribe ketamine as a treatment for immediate relief of depression and in some cases, treatment of suicide ideation. Ketamine may be beneficial for patients who did not respond positively to other treatments for depressive symptoms in major depressive disorder (MDD).

Objectives: To compare the effectiveness of ketamine on treatment-resistant depression based on the dosages.

Methods: This is a systematic review comparing the effectiveness of ketamine given for treatment-resistant depression for 3 different dosages (0.25 mg/kg, 0.50 mg/kg, and 0.75 mg/kg). We searched Pubmed and EBSCOhost for trials completed in 2010–2018 from any country, using the search words "ketamine" and "depression." Inclusion criteria includes adult population (age 18+), diagnosis of depression (MDD) and use of ketamine. Studies were appraised for quality using the Mixed Methods Appraisal Tool. This literature included randomized clinical trials, systematic reviews, case series, and case reports, focusing primarily on clinical trials and case reports.

Results: This systematic review identified eight eligible studies which evaluated the beneficial effect of ketamine on depression in terms of dosage and comparison with anti-depressant medications. Researchers found that the higher dose of 0.75 mg/kg was more effective; however a bolus dose of 0.5 mg/kg was more effective than infusion and no differences were found in the effectiveness when 0.75 mg/kg was administered using a different method of administration.

Conclusions: Ketamine is very effective in patients who have not responded well to other medications for treatment of depression. Ketamine has a rapid-onset compared to other antidepressant medications -- even when given in small doses for treatment-resistant depression and has minimal severe side effects. Most patients tend to experience dizziness, nausea, or anxiety, which can be relieved with bed rest.

266 | Investigating the potential role of BDNF and PRL genotypes on antidepressant response in depression patients: A prospective inception cohort study

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Background: Two-thirds of patients with major depressive disorder (MDD) do not respond optimally to antidepressant medication. Brain-derived neurotrophic factor (*BDNF*) has been associated with the response to antidepressant drugs in mood and anxiety disorders and prolactin (*PRL*) is a pituitary hormone with behavioral effects which may be involved in the antidepressant pharmacological response acting as a neurotrophic factor within the brain.

Objectives: To investigate the relationship between *BDNF* and *PRL* genotypes with short-term antidepressant drug response in drug-naïve patients with a major depressive disorder.

Methods: In a prospective inception cohort design, we included 186 Russian participants (28 men and 158 women) of 18–70 years clinically diagnosed with depressive disorder who initiated antidepressant medication, including SSRIs and TCAs. These patients had not been treated with antidepressant drugs in the preceding three months with 54.5% never been treated with antidepressant drugs. DNA polymorphisms were genotyped for rs1341239 within *PRL* and for rs6265 and rs7124442 within *BDNF*. We measured the primary clinical outcome by differences in scores using the Hamilton Depression Rating Scale (ΔHAMD) between baseline and week two, and week two and week four. Higher ΔHAMD score denotes better clinical outcome. Paired-sample t-tests determined the statistical significance between ΔHAMD between the two time-points. Independent T-Test determined the statistical significance between polymorphisms and ΔHAMD in baseline and week two, and week two and week four.

Results: Comparisons between genotypes did not reveal any significant differences in scores during the first two weeks of treatment (all p-values >0.05). For the latter two weeks, homozygous C *BDNF* rs7124442 responded significantly worse (5.60 ± 3.64) in comparison to homozygous T during this period (8.51 ± 4.26). Further analysis of homozygous C *BDNF* rs7124442 revealed significance in all women (5.60 ± 3.64) and post-menopausal (≥ 50 years) women (4.90 ± 4.06) but not in pre-menopausal (< 50 years of age) women (7.00 ± 2.34) in comparison to homozygous T.

Conclusions: *PRL* rs1341239 genotype did not affect HAMD score differences in patients. Difference in HAMD scores for *BDNF* rs6265 genotypes were not found to be significant in most patients. Homozygous C *BDNF* rs712442 patients were found to respond significantly worse in the last two weeks of treatment, with the exception of pre-menopausal women. This work was in part supported by the Russian Foundation for Basic Research, grant #17–29-02205.

267 | Identification of weekly or every-other-week administration schedules for Cetuximab in the treatment of metastatic colorectal cancer in US claims data

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Background: After an initial dose of 400 mg/m^2, cetuximab (CET) at a dose of 250 mg/m^2 in combination with chemotherapy (CT) is approved for once-weekly (q1w) use in the treatment of metastatic colorectal cancer (mCRC). In clinical practice, off-label use of CET 500 mg/m^2 administered every other week (q2w) has been reported. To study the comparative effectiveness and safety of q1w and q2w CET using US claims data, we first aimed to assess a method of classifying q1w and q2w schedules where administration schedules of anticancer therapy infusions are not available.

Objectives: To describe the accuracy of the method used to identify CET administration schedules.

Methods: Using IBM MarketScan, we identified a cohort of patients with mCRC treated with CET + CT between 2010 and 2016. Patients were required to have ≥1 CRC diagnosis, no other cancer diagnoses, and ≥ 2 consecutive CET infusions in combination with a CT claim within ±28 days. Administration schedules were derived from the median observed days between each subsequent CET infusion during follow-up. Patients with a median duration of 4 to 10 days between CET claims were classified as q1w; patients with a median duration of 11 to 18 days were classified as q2w. The root mean squared error (RMSE) and mean absolute difference (MAD) of observed durations between claims were assessed by comparing them with theoretical values: 7 days for q1w and 14 days for q2w.

Results: A total of 2,869 patients with mCRC exposed to CET were identified; 1,865 were classified in the q1w group (65.0%) and 1,004 in the q2w group (35.0%). Mean age of patients was 60.1 ± 11.7 years for q1w and 58.1 ± 11.1 years for q2w. Most patients were male: 57.5% and 60.8% in q1w and q2w, respectively. There were 28,478 and 8,248 total claims in the q1w and q2w groups, respectively, with mean durations between claims of 8.1 ± 3.8 days (first and third quartile [Q1-Q3]: 7–7) and 15.0 ± 4.8 days (Q1-Q3: 14–14). In the q1w group, 75.6% of durations between 2 consecutive claims were exactly 7 d, and in the q2w group, 65.5% of durations were exactly 14 d. Comparison of observed data points with theoretical values suggests small differences for both schedules: the RMSE was 1.86 days in the q1w group and 2.01 days in the q2w group; the MAD was 1.17 days in the q1w group and 1.33 days in the q2w group.

Conclusions: In this large US claims database, the method defined to derive different administration schedules for CET based on observed durations between claims was shown to be accurate as the observed durations between consecutive claims were close to the expected durations for each considered schedule.

268 | Treatment patterns and outcomes of 159 Ibrutinib-treated MCL patients in the US: A retrospective electronic medical record database and chart review study

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Background: Ibrutinib, a Bruton tyrosine kinase inhibitor, was approved in the US for the treatment of relapsed/refractory mantle cell lymphoma (MCL) in 2013. However, real-world data on ibrutinib use is limited.

Objectives: To examine ibrutinib use, dosages, and reasons for treatment discontinuation among MCL patients treated in a community oncology practice setting.

Methods: The study population consisted of adult MCL patients treated with ibrutinib between November 1, 2013 and October 31, 2016, who were not enrolled in a clinical trial and had ≥2 visits to a US Oncology Network (USON) clinic. Patients with other primary cancers were excluded. Patient data were sourced from USON's electronic health records system, iKnowMed (iKM)™, which provided demographics and clinical and treatment characteristics. Manual chart review confirmed ibrutinib treatment patterns. Duration of ibrutinib therapy (DOT), overall survival (OS), and progression-free survival (PFS) from treatment initiation were estimated using Kaplan–Meier methods. Patients were censored if their treatment was ongoing for DOT. Censors for OS and PFS were patients lost to follow up or those who did not experience a failure event.

Results: Overall, 159 eligible MCL patients were identified through iKM: 88.7% were Caucasian (*n* = 141), 76.1% were male (*n* = 121), and 73.6% were diagnosed with Stage IV disease (*n* = 117). Median follow-up was 16.1 months. Approximately 7.5% (n = 12) of patients received ibrutinib as first-line therapy (1 L), compared with 54.1% (*n* = 86) in 2 L and 38.4% (*n* = 61) in 3 L+. Median ibrutinib dose at initiation was 560 mg (range: 140–700). During ibrutinib treatment, 16.4% (*n* = 26) of patients experienced a dose reduction. Dose holds occurred in 30.2% (*n* = 48), 66.7% (*n* = 32) due to toxicities. The overall discontinuation rate was 83.6%. The primary reasons for discontinuation were disease progression (*n* = 46, 34.6%) and toxicities (*n* = 34, 25.6%). Median DOT was higher for patients initiating treatment in 3 L+ (14.9: 95% CI 8.8–17.1) vs other lines. Median PFS was 19.6 months (95% CI: 16.5–24.3) for the overall population and median OS was 25.8 months (95% CI: 19.9-not reached).

Conclusions: Our real-world findings on survival are consistent with clinical trials on ibrutinib in relapsed/refractory MCL, although our discontinuation rate (~84%) was higher vs the trials (~58%), which had a similar median follow-up (16.1 vs 15.3 months, respectively). Our

findings provide additional data on MCL treatment patterns and patient outcomes in clinical practice.

269 | Factors associated with receipt and overall survival of concurrent Chemoradiotherapy versus single modality therapy in Unresectable stage III NSCLC

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Background: While concurrent chemoradiotherapy (cCRT) is standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC), some patients receive single modality therapy, i.e., systemic therapy or radiotherapy.

Objectives: This study aimed to identify predictors of type of therapy received, and differences in overall survival (OS) by therapy type in a Medicare population.

Methods: This retrospective study used Surveillance, Epidemiology and End Results - Medicare data (2009–2014). Stage III NSCLC patients aged ≥65 yrs, with ≥1 claim for systemic therapy (chemotherapy or targeted therapy) or radiotherapy within 90 days of diagnosis were included. cCRT patients had overlapping claims for chemotherapy and radiotherapy ≤90 days from start of therapy; remaining patients were grouped by first therapy received. Sequential CRT patients and those with surgical resection of tumor were excluded from this analysis. Logistic regression was used to analyze predictors of cCRT. Multivariable Cox proportional hazards models were used to compare OS between therapies.

Results: Of 4,544 patients identified, 51% received cCRT, 21% systemic therapy, and 27% radiotherapy. Across groups, cCRT patients were likely younger (p < 0.001), White (p < 0.001), male (p = 0.015), and with a good predicted performance status (PS) (p < 0.001). After adjustment, patients with a higher Charlson Comorbidity Index (CCI) were less likely to receive cCRT vs. single modality therapy (odds ratio [OR]: 0.93, 95% CI: 0.90–0.97, p < 0.001), as were patients with stage IIIB vs. IIIA NSCLC (OR: 0.84, 95% CI: 0.73–0.96, p = 0.008). Good predicted PS was associated with increased odds of receiving cCRT (OR: 1.75, 95% CI: 1.52–2.01, p < 0.001). Older age and Black race were significantly predictive of not receiving cCRT, while sex was not predictive of therapy type. Median OS was 14.7 months (mo) for cCRT vs. 10.9 mo for systemic therapy (adjusted hazard ratio [HR]: 1.36, 95% CI: 1.24–1.49, p < 0.001) vs. 7.8 mo for radiotherapy (adjusted HR: 1.55, 95% CI: 1.42–1.69, p < 0.001).

Conclusions: Only 51% of patients received cCRT. Younger age, White race, having stage IIIA NSCLC, a favorable PS, and lower CCI were predictive of receiving cCRT. Given the survival benefit, physicians should be encouraged to pursue cCRT in patients with unresectable stage III NSCLC. Further efforts to develop less morbid therapies are critical in this population.

270 | Comparison of real-world treatment patterns, persistence, healthcare resource utilization (HRU) and costs between octreotide and Lanreotide for the treatment of neuroendocrine tumors (NET)

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Background: There has been limited research assessing differences between somatostatin analogues (SSAs) as treatments for NET.

Objectives: This study aims to assess treatment pattern, persistence, HRUs and costs among patients (pts) with NET receiving long-acting octreotide vs lanreotide.

Methods: Retrospective claims data from Symphony Health Solutions were analyzed for NET pts who initiated octreotide or lanreotide (index date) between 01/2015–11/2017 for ≥90 days. Pts with continuous clinical activity (≥180 pre and ≥ 90 days post index date) and no prior non-surgical NET treatment were included. A 1:1 propensity score matched sample was used to compare the two SSA groups with respect to treatment persistence (time to treatment discontinuation [TTD] using Kaplan–Meier) and to all cause and NET related HRUs and costs (provider charges for medical services and insurance payments for prescription drugs) using adjusted rate ratio (RR) and adjusted mean cost difference (CD) with 95% bootstrap confidence interval (CI), respectively.

Results: Among 2,043 NET pts identified, a balanced matched cohort of octreotide and lanreotide pts (N = 543 each) was achieved. In both cohorts, mean age was 65 years and baseline Charlson Comorbidity Index was 5.7. Approximately 80% of matched pts initiated monotherapy; others used SSAs in combination with chemo-, targeted or liver-directed therapy as first line therapy. Median TTD was directionally longer but did not reach statistical significance among octreotide vs lanreotide (19.2 vs 17.5 months, p = 0.6). Numerically lower and non-statistically significant hospitalization rates were observed among octreotide than lanreotide pts (RR [CI]: all cause = 0.87 [0.73, 1.05]; NET related = 0.85 [0.63, 1.15]). Statistically significantly fewer NET related outpatient visits (1.05 vs 1.10 per pts per month [PPPM]; RR [CI]: 0.95 [0.92, 0.99]) and lower total mean healthcare costs PPPM were observed for octreotide than lanreotide (CD [CI]: all cause = −$3,701 [−$5,205, −$2,355]; NET related = −$3,752 [−$4,948, −$2,455]).

Conclusions: This study shows similar treatment patterns and persistence between SSA cohorts. Octreotide appeared to be associated with less HRU and total healthcare costs compared with lanreotide.

271 | Predictors of granulocyte Colony stimulating factor administration among metastatic colorectal cancer patients

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Background: Despite the widespread success of chemotherapy in treating various forms of cancer, it's use is limited by certain toxicities such as neutropenia. When used for prophylaxis, colony stimulating factors (CSF) are useful in preventing neutropenia, as well as reducing its duration and severity. Current American Society of Clinical Oncology (ASCO) guidelines recommend chemotherapy dose reduction as a viable alternative to CSF administration. Understanding the factors associated with CSF use may help decrease excessive utilization of CSF, which may result in cost savings and enhanced clinical practice.

Objectives: To determine patient characteristics that predict CSF administration in a cohort of metastatic colorectal cancer patients who received chemotherapy.

Methods: In this retrospective observational study, we utilized data from the electronic health records of metastatic colorectal cancer patients who received care at a multi-center oncology practice network between July 2013 to December 2014. Logistic regression models were employed to explore the demographic (age, gender), clinical (disease, year of diagnosis) and therapeutic (febrile neutropenia [FN] risk, line of therapy, duration of treatment) factors associated with CSF administration. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated. All statistical analyses were performed using SAS 9.4 and alpha was set at 0.05.

Results: There were 2541 chemotherapy regimens corresponding to 2131 patients. 344 (13.5%) of the regimens had at least one CSF administration. The CSF administered was pegfilgrastim. In the multivariate analysis, age, gender, FN risk, duration of treatment, and line of therapy were significantly associated with CSF administration. Patients who received CSF administration were significantly more likely to be younger (ORs range: 0.24–0.85), be female (OR = 1.39; 95% CI = 1.08–1.39), have higher FN risk (OR = 1.86; 95% CI = 1.34–2.52), have a duration of treatment between 13–23 months (OR = 1.57; 95% CI = 1.09–2.10), and be on their 2nd line of therapy (OR = 1.51; 95% CI =1.09–2.10).

Conclusions: CSFs were moderately utilized in this population. Our results demonstrate significant demographic and therapeutic variation in CSF administration. Most of the associations are consistent with recommendations for dose reduction. Targeting the factors associated with CSF use can help with education regarding appropriate use of dose reduction in lieu of CSF for this population.

272 | Contemporary chemotherapy treatment patterns in non-small cell lung cancer patients: An analysis of an Optum claims data

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Background: The NSCLC treatment landscape has changed significantly with the addition of new targeted drugs and combination therapies.

Objectives: The aim of this study was to assess the most recent treatment patterns in a health care claims data base stratified by lines of therapy (LoT).

Methods: This was a retrospective cohort study based on Optum claims database. Patients who met the following criteria were included: At least two diagnosis claims at different dates for lung cancer during 2015 to 2017; Age $\geq$ 18 years at the lung cancer diagnosis; No other cancer diagnosis or chemotherapy within six months prior to the earliest diagnosis; Secondary malignancy after the primary diagnosis; At least one systemic treatment after the primary diagnosis; Continuous health plan enrollment for at least 6 months prior to the primary diagnosis until at least 28 days after the chemotherapy initiation; No SCLC-related treatments. Patients were followed from the chemotherapy initiation date until discontinuous enrollment, death, or end of database. First LoT was defined as all chemotherapy drugs a patient filled during 28 days after the earliest chemotherapy date. If a patient initiated a different drug after 1st LoT, the initiation date of that new drug was defined as the initiation date of 2nd LoT. All chemotherapy drugs the patient filled during 28 days after the initiation date of 2nd LoT were defined as 2nd LoT. The same definition was for 3rd LoT and so on.

Results: The study cohort consisted of a total number of 5,082 patients (52% males). Approximately 61% of patients were over 70 years of age, with the mean age of 70.9 years (SD = 8.7). In 1st LoT, nearly 40% of patients received platinum plus taxane combination (39.3%) with similar proportion of patients receiving platinum-based mono- or combination therapy (39.1%). The most frequent 1st LoT regimen was carboplatin plus paclitaxel (31.9%), followed by carboplatin plus pemetrexed (17.7%), pembrolizumab (5.8%) and erlotinib (4.5%). 33% of patients received 2nd LoT. The most frequently used treatment in 2nd LoT was nivolumab (42% of patients who received the 2nd line), followed by pembrolizumab (7.6%) and carboplatin plus pemetrexed (5.1%). 8% of patients received 3rd LoT. The most frequent treatment used in 3rd LoT was nivolumab (33.5%), followed by docetaxel monotherapy (15.6%) and gemcitabine (6.2%). The median duration of 1st LoT, 2nd LoT, and 3rd LoT was 92, 83, and 78 days, respectively.

Conclusions: The IO drugs were most frequently used treatment regimens in 2nd and 3rd LoTs documenting significant role of targeted treatment regimens in NSCLC.

273 | Trends in the promotion and utilization of programmed death Receptor-1 blocking antibodies

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Background: Immune checkpoint inhibitors have experienced rapid uptake across patients with cancer, especially in older adults - a population underrepresented in immunotherapy clinical trials. Receipt of pharmaceutical manufacturer payments has been associated with higher rates of prescribing; however, the role of such payments on the adoption of immunotherapies among older Americans with cancer remains unknown.

Objectives: To identify trends in pharmaceutical manufacturer promotion and Medicare Part D utilization of programmed death receptor-1 (PD-1) blocking antibodies: pembrolizumab (Keytruda®) and nivolumab (Opdivo®).

Methods: We used General Payments files (2014–2016) from the Centers for Medicare and Medicaid (CMS) Open Payments Database and Part D Prescriber files (2014–2016) from the CMS Medicare Providers Utilization and Payment Data. We identified healthcare providers who received a promotional payment or wrote prescriptions (≥11) for anti-PD-1 immunotherapies. Descriptive statistics were used to assess payment patterns and utilization trends.

Results: Healthcare providers received 89,876 general payments totaling more than $22 million for anti-PD-1 agents. Pembrolizumab represented 58% ($12,878,426) of promotional spending, while nivolumab comprised 68% (61,480) of all payments. A total of 3,147 Medicare Part D claims were filed, with 14% (435) of prescriptions filled for pembrolizumab and 86% (2,712) of prescriptions filled for nivolumab. Despite higher promotional spending on pembrolizumab in both 2014 (94% or $1,499,586) and 2016 (60% or $7,504,985), Part D utilization of pembrolizumab lagged behind nivolumab, only comprising 22% (155) and 11% (267) of prescriptions in 2015 and 2016, respectively.

Conclusions: Despite being outspent by pembrolizumab's manufacturer, annual growth of nivolumab's market share outpaced that of its competitor. Use of pembrolizumab may have been limited due to minimal Part D health plan coverage; physician preference for and experience with nivolumab (resulting from earlier Food and Drug Administration approval of expanded indications); or observed trends not being reflective of a provider's patient population or overall prescribing habits.

274 | Patterns and predictors of first-line targeted therapy utilization among older adults diagnosed with metastatic renal cell carcinoma

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Background: The management of patients with metastatic renal cell carcinoma has changed dramatically with the approval of targeted therapies. While these therapies demonstrate benefit in the setting of clinical trials, their utilization among older adults, aged 66+ years, in real world settings is largely unknown.

Objectives: This study aimed to examine patterns and predictors of first-line targeted therapy utilization among older adults diagnosed with metastatic renal cell carcinoma.

Methods: We conducted a cohort study using the SEER-Medicare database. Patients aged 66+ years old with a primary diagnosis of metastatic renal cell carcinoma were identified from 2007 through 2013. The primary outcome was initiation of first-line targeted therapy within four months of diagnosis. Descriptive statistics summarized targeted therapy utilization, the prevalence of specific agents, and temporal trends. Multivariable logistic regression yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of targeted therapy versus no targeted therapy initiation.

Results: Of the 1,643 patients diagnosed with metastatic renal cell carcinoma, 28.9% received first-line targeted therapy, 4.6% received non-targeted therapies, and 66.5% received no treatment within four months of diagnosis. Among those initiating target therapy, the most commonly agents included sunitinib (57.6%), temsirolimus (17.9%) and pazopanib (13.5%). Overall, use of first-line targeted therapy among older patients with metastatic kidney cancer increased over time, from 25.9% in 2007 to 36.3% by 2013. Patients with clear cell histology and distant metastases were more likely to receive first-line targeted therapy, while those aged 85+ (OR = 0.33 95%CI 0.20, 0.55) or with a high frailty score (>50% OR = 0.22 95%CI 0.10, 0.49) were less likely to receive first-line targeted therapies.

Conclusions: Overall, use of first-line targeted therapy among older metastatic renal cell carcinoma patients has increased over time. Age, frailty, and tumor characteristics appeared to be key drivers for therapy initiation.

275 | Demographics, clinical characteristics and treatment sequencing in stage 3 Unresectable non-small cell lung cancer patients: A Cancerlinq cohort

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Background:

Objectives: To describe the demographics, clinical characteristics and treatment sequencing among a real-world cohort of stage III unresectable non-small cell lung cancer (NSCLC) treated with chemo-radiation therapy (CRT) in the US.

Methods: Cancerlinq Discovery Database (CLQ), launched by the American Society of Clinical Oncology (ASCO) in 2016. CLQ consists of longitudinal, demographically and geographically diverse data aggregated from oncology practice Electronic Health Record (EHR) databases in the US. This retrospective cohort comprises 324 stage III unresectable NSCLC patients who received concurrent, platinum-based chemoradiation between January 1, 2007 and December 31, 2017 (study period). A patient was considered unresectable if s/he did not have surgery within 6 months of the stage III diagnosis date (study index date). A patient's follow up period was defined as the study index date until the end of the study period, patient death, or loss to follow up, whichever event occurs first.

Results: The cohort was mostly male, white, with a mean age of 66.86 years at index. Nearly all of the cohort (93.57%) had an initial diagnosis of stage III (75.31% IIIA, 2.78% IIIB); 2.47% had an initial stage I diagnosis and 4.00% had an initial diagnosis of stage II. The most common histology was squamous cell carcinoma (46.61%), followed by adenocarcinoma (41.05%). Curation related to clinical characteristics (eg ECOG status, smoking status and other comorbidities) are ongoing, so they are largely missing at this time. During the mean 26.64 months of follow up time, the cohort received 1.60 lines of therapy. The most common treatment sequence during the follow up period consisted of platinum therapy +CRT (82.72%); almost 10% of patients received platinum+CRT, followed by immuno-oncology (IO) therapy. Approximately 38.30% of patients progressed to line of therapy 2 (LOT2) and 29.84% progressed to line of therapy3 (LOT3), with nearly 18% of patients receiving immuno-oncology (IO) therapy during LOT2 or LOT3.

Conclusions: This exploratory analysis of a stage III unresectable NSCLC cohort is descriptive in nature and suggests that the CLQ Discovery Database can be used to construct generalizable cancer cohorts. Future analyses will focus on validation of CLQ as a real-world data source, using findings from other retrospective, observational studies conducted by AstraZeneca as a benchmark.

276 | Chemotherapy patterns, survival and healthcare resource utilization among patients with advanced small cell lung cancer in Indiana state

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Background: Small Cell Lung Cancer (SCLC) is often diagnosed at an advanced stage.

Objectives: To investigate real-world chemotherapy patterns, overall survival, and HealthCare Research Utilization (HCRU) for patients diagnosed with advanced SCLC.

Methods: We linked an Indiana electronic health record (EMR) database and Indiana State Cancer Registry to identify adult SCLC patients. Eligible patients were either initially diagnosed with stage III/IV SCLC or progressed to metastasis during 2005–2015. Patients were followed from their advanced SCLC index date until the earliest date of last visit, death or end of the study period. A line of therapy (LOT) started from the first date of receiving a SCLC chemotherapy agent and ended upon receipt of a new treatment, a treatment gap ≥90 days or end of follow-up, whichever occurred first. Time-to-event analyses were performed using the Kaplan–Meier method for duration of treatment (DOT), time-to-next-treatment (TTNT), and overall survival (OS).

Results: A cohort of 498 advanced SCLC patients were identified, including 429 initially diagnosed with advanced disease and 69 with chart-confirmed metastasis. Median overall survival was 10.1 months from first-line chemotherapy, and 7.7 months from second-line chemotherapy. First-line chemotherapy was received by 464 (93.2%) patients, including 127 (27.4%) cisplatin-based regimens and 240 (51.7%) carboplatin-based regimens. Carboplatin plus etoposide was the most commonly observed, received by 217 (46.8%) patients, followed by cisplatin plus etoposide (27.4%). Median DOT was 2.2 months. Median TTNT was 8.9 months. The mean number of healthcare visits during first-line treatment was 3.0 per patient per month, including 2.8 outpatient visits, 0.2 inpatient visits and 0.1 emergency visits. Ninety-five (19.1%) patients continued with second-line chemotherapy, including 25 (26.3%) carboplatin-based regimens, 20 (21.0%) topotecan based regimens, and 15 (15.8%) paclitaxel-based regimen. Topotecan monotherapy (20%) was the most commonly used regimen, followed by carboplatin plus etoposide (15%). Median DOT was 2.6 months and median TTNT was 6.3 months. During second-line treatment, the mean number of healthcare visits was 3.5 per months, including 3.2 outpatient visits, 0.1 inpatient visits and 0.1 emergency visits.

Conclusions: Patients with advanced SCLC had short life expectancy. Most patients received chemotherapy with short DOT and TTNT. The study highlighted high unmet medical need among advanced SCLC patients.

277 | Use of electronic healthcare data to study the real-world utilization of target therapy and immunotherapy for the treatment of lung cancer: A systematic review

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Background: During the last decade, pharmacotherapy of lung cancer has evolved rapidly due to the authorization of novel anticancer drugs as target- and immunotherapies for patients with advanced stage non small cell lung cancer (NSCLC). In this contest, the re-use of routinely collected electronic healthcare data (EHD) can complement evidence

from clinical trial providing information on the real-world use of drugs in large and unselected populations.

Objectives: To retrieve and describe published studies that, through the analysis of routinely collected EHD, provided information on the real-world utilization of target- and immunotherapies for lung cancer.

Methods: A systematic review of PubMed database was performed to identify all retrospective, observational studies published from 2016 to March 2018. Only studies based on routinely collected EHD providing information on the real world use of novel anticancer drugs used for lung cancer were included.

Results: A total of 131 publications were found of which 19 met the inclusion criteria. Only 1 study was performed in Europe while 11 were performed in the United States. Ten studies used data from record linkage of administrative, medical records and cancer registry data. In 4 cases, an hospital-based cohort, ranging from 85 to 16,413 subjects, was analyzed. The remaining studies were population-based with a study population from 164 to 77,756 patients). Six studies only, provided information on the molecular characterization of lung cancer. Performance status was reported in 4 studies. Eight out of 19 studies, described the pharmacotherapy for locally advanced/metastatic NSCLC: the study period ranged between 2006 and 2016 and the percentage of patients treated with platinum regimens and tyrosine kinase inhibitors (TKI) ranged from 52 to 85 and from 6 to 32, respectively. Only 1 study concerned immunotherapy with 17% of patients receiving nivolumab.

Conclusions: This systematic review highlighted the paucity of published studies on the topic. Notably, only 1 study was performed in Europe. Record linkage of administrative data, medical records and cancer registries was the most used approach. Information on molecular characterization of tumors and performance status of patients, which are often fundamental for the appropriate use of target- and immunotherapies, were reported in few studies only. Only a minority of advanced stage NSCLC patients currently receive novel antineoplastic drugs, particularly immunotherapy.

278 | Relapsed/refractory primary mediastinal large B-cell lymphoma: A structured review of epidemiology, treatment guidelines, and real-world treatment practices

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Background: Relapsed or refractory primary mediastinal large B-cell lymphoma (rrPMBCL) after first-line therapy confers a challenging clinical situation and poor prognosis. Trial data and treatment guidelines for rrPMBCL are scarce, and management is largely based on clinical experience.

Objectives: To determine the incidence, prevalence, and mortality rates associated with rrPMBCL, and identify clinical practice guidelines and real-world patterns of care.

Methods: Electronic literature databases (time frame: 1997–2017) and specialist conferences (time frame: 2015–2017) were searched for literature reviews or studies unpublished as full-text, respectively. Inclusion criteria were adults (≥ 18 years) with rrPMBCL from studies in Australia, Canada, European nations, Japan, Korea, and the United States, published in English, with no restrictions on interventions/comparators used. Screening and data extraction steps were performed by separate reviewers.

Results: Ten epidemiology studies reported on PMBCL as the primary patient group or as a subgroup. Of these, one study reported on rrPMBCL. PMBCL had higher prevalence among females than males (61% versus 39%) and in Caucasians (79%). Between 10–30% of patients with PMBCL still experience progression or relapse. Despite availability of high-dose therapy followed by autologous stem cell transplantation for rrPMBCL, progression-free survival (PFS) is 27% at 5 years. Twelve published treatment guidelines on PMBCL were identified, of which 4 provided recommendations for rrPMBCL. Sixteen studies provided data on real-world treatment, most were retrospective, single-center studies with small patient numbers. Chemotherapy/immunochemotherapy (with or without radiotherapy), followed by high-dose treatment and stem cell transplantation, was the mainstay of salvage therapy. In most cases, real-world care followed published treatment guidelines, with deviations in the specific chemotherapy agents used.

Conclusions: To our knowledge, this is the first structured review to assess real-world treatment patterns in rrPMBCL, attempt to define its epidemiologic characteristics, and determine the management recommendations in treatment guidelines. The results highlight the paucity of epidemiologic data and evidence-based recommendations available. Large prospective and retrospective studies are needed to improve the available evidence.

279 | Association between regular use of aspirin and prevalence of melanoma in males: Findings from the 2015 US National Health Interview Survey

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Background: Melanoma is more common in men (29.8 new cases per 100,000 persons) than in women (17.7 new cases per 100,000 persons). Focus of the melanoma research has shifted from therapy to prevention, especially for the males, due to the poor prognosis and health burden. Studies had suggested that regular use of aspirin might decrease the risk of developing some types of cancer, but protective effect of aspirin for melanoma in males was contradictory and inconsistent.

Objectives: We examined whether self-reported regular use of aspirin was associated with the prevalence of melanoma in a national sample of the United States (US) male adults.

Methods: This cross-sectional study included a nationally representative of US male adults from the 2015 National Health Interview Survey. Regular aspirin users were those who self-reported regularly taking aspirin at least 3 times per week in the survey year. Melanoma was measured by participants' self-report. We used a weighted multivariable logistic regression model to examine the association between regular use of aspirin and melanoma adjusting for sociodemographic and health status factors (e.g., smoking). Adjusted odds ratios (aORs) with 95% confidence interval (95%CI) were reported.

Results: Among eligible 108,884,206 participants in 2015, 21.0% were regular aspirin users, and they were more likely to be older, Whites, lower educated, insured, having smoke and alcohol, and receiving skin check than non-regular aspirin users. The prevalence of melanoma was higher for regular aspirin users (1.8%) than that for non-regular aspirin users (0.5%, $p < 0.001$). However, in a multivariable analysis, regular aspirin users (aOR = 1.7, 95% CI = 0.67–4.46) were not associated with a decreased prevalence of melanoma.

Conclusions: Regular aspirin use was not associated with a lower self-reported prevalence of melanoma among US male adults in 2015. Healthcare providers should have a more conservative attitude toward the protective effect of aspirin for melanoma in males before further clinical trials and longitudinal studies.

280 | Comparison of availability and accessibility of Immuno-oncology (IO) drugs for cancer treatment among Japan, Korea, China and Taiwan

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Background: Cancer immunotherapies are prosperously developed and brought to markets. Up to present, five drugs of cancer immuno-oncology therapy categorized as immune checkpoint have been approved and marketed in many Asian countries, which are ipilimumab, nivolumab, pembrolizumab, atezolizumab and durvalumab. Availability and accessibility of immuno-oncology therapies are two of the crucial elements for drug utilizations in cancer treatments.

Objectives: This study aims to compare 5 immune-oncology therapies' availability and accessibility between 4 Asian countries, Japan, South Korea, China and Taiwan, by their approval time and indications, health insurance coverage and reimbursement limitation.

Methods: The approval time and indications (availability) of the 5 cancer immunotherapies across the 4 Asian markets will be acquired by from the database of PMDA, KFDA, CFDA and TFDA. The accessibility of those along with price settings will be obtained from the authorities' health insurance system database primarily. Taiwan will be taken as the reference country to which, the availability and accessibility of the five cancer immunotherapies among three other countries will be compared.

Results: Only 2 of the 5 immuno-oncology drugs, nivolumab and pembrolizumab, are approved and launched in all the 4 target markets. Compared to Taiwan, the approval time of nivolumab and pembrolizumab appear to be in a lag in China by 25 months and 26 months respectively, while those are in a more advanced manner in Korea by 15 months for both. The indications for different cancer types approved by TFDA in Taiwan are of the most extensive among the 4 countries for pembrolizumab, nivolumab and atezolizumab while those are only selectively approved for certain cancer types by PMDA, KFDA and CFDA. In terms of accessibility of the 5 immune-oncology drugs, Korea and Taiwan are the only 2 countries listing nivolumab and pembrolizumab, and ipilimuamb in the national health insurance system respectively.

Conclusions: From availability perspective, the indications approved for various cancer types are the most extensive in Taiwan while the accessibility of nivolumab and pembrolizumab are so far only present in Korea. The 2 drugs are being covered by the health insurance under Risk Sharing Agreement (RSA) with different scope and occasions of the applications. Ipilimumab is currently the only immuno-oncology drug listed in the national health insurance system in Taiwan at a NHI price similar to the market price in Japan.

281 | Treatment trends for localized prostate cancer: A comparison of androgen deprivation therapy and curative treatments in the linked SEER-Medicare database, 2004–2013

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Background: Initial management of localized prostate cancer (PCa) includes therapies with curative intent (prostatectomy, radiation) or expectant management (active surveillance, watchful waiting). Immediate androgen deprivation therapy (ADT) alone using gonadotropin-releasing hormone (GnRH) analogs has sometimes been administered as initial therapy, particularly in older patients who may be poor candidates for radiation or surgery, but there is little evidence supporting this approach.

Objectives: We characterized initial treatment trends among U.S. Medicare beneficiaries diagnosed with localized PCa from 2004 to 2013 and investigated changes in ADT treatment trends by PCa risk over time.

Methods: Men ≥65 years old, enrolled in Medicare Fee-for-Service, with incident non-metastatic PCa between 2004 and 2013 in the SEER (Surveillance, Epidemiology, and End Results) registry were identified. SEER cancer cases were linked with Medicare records, with patients' cancer risk (low, intermediate, high) characterized based on the National Comprehensive Cancer Network guidelines. Patients were followed up to 21 months after diagnosis to identify initial treatments, categorized into four mutually exclusive groups: 'prostatectomy', 'radiation', 'ADT alone', or 'expectant management'.

Results: There were 103,242 men ≥65 years old with localized PCa including: 29,331 with low-risk; 40,720 with intermediate-risk; and 33,191 with high-risk disease. During the 10-year study period, most high-risk patients received curative-intent therapy with radiation (49%) or prostatectomy (15%). In 2004, initial treatment with ADT alone was common (29%) among high-risk patients, but declined steadily to 14% in 2013. The small proportion of low- and intermediate-risk patients who received ADT alone also declined, from 6% and 10%, respectively, in 2004, to 2% and 3%, in 2013. The proportion of low-risk patients receiving expectant management increased sharply during this time, from 22% to 50%.

Conclusions: Although most patients with localized PCa were treated with expectant management or curative-intent therapies, some received initial treatment with ADT alone using GnRH-analog drugs, despite unclear benefit and known risks. Our data show that treatment of localized PCa with ADT alone declined steadily in all risk groups during the 10-year period of study.

282 | Potential inappropriate Underdosing in patients initiating non-vitamin K Oral anticoagulants: Findings from the French National Healthcare Database

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Background: Post-marketing data have raised concerns about potential inappropriate underdosing associated with non-vitamin K oral anticoagulants (NOAC) in atrial fibrillation (AF) patients but mostly based on field and registry studies with small sample sizes.

Objectives: To describe potential inappropriate underdosing in NOAC at treatment initiation in patients with AF using the large national French National Healthcare databases (50 million beneficiaries).

Methods: A population-based cohort study included patients with AF initiating NOAC therapy in 2015–2016. Potential inappropriate underdosing with NOACs was defined as initiation of NOAC therapy in patients at risk of stroke in whom reduced doses of NOAC were prescribed with no identified clinical justification. The proportion of AF patients initiating reduced-dose NOAC (dabigatran 75 or 110 mg; rivaroxaban 10 mg or 15 mg and apixaban 2,5 mg) with an HAS-BLED score < 3 among all NOAC new users with a CHA_2DS_2-VASc score ≥ 2 was used as proxy to quantify potential inappropriate underdosing in NOAC new users. Due to the nature of data used with no access to medical data such as patient's weight, glomerular filtration rate and exact alcohol consumption and, to better identify patients at risk of stroke, analyses were replicated in patients i) with CHA_2DS_2-VASc score ≥ 4 and ii) aged 75 and over with a history of arterial thromboembolic events (ATE).

Results: A total of 127,841 new users of NOAC therapy with AF were identified in 2015–2016 (mean age: 74.1 ± 11.6; 50.1% women). Reduced doses were prescribed in 40.0% of NOAC new users. Among the 116,391 NOAC new users with AF with a CHA_2DS_2-VASc score ≥ 2, 29.1% (*N* = 33,845) were prescribed a reduced dose although they had an HAS-BLED score < 3 (dabigatran: 46.3%; rivaroxaban: 27.2%; apixaban: 28.3%). This proportion was 33.4% (*N* = 24,281) and 14.5% (*N* = 1,379) when considering patients with a CHA_2DS_2-VASc score ≥ 4 (*N* = 72,608) and aged 75 and over with a history of ATE (*N* = 9,503), respectively. Among patients with a CHA_2DS_2-VASc score ≥ 2 and HAS-BLED<3, differences in baseline characteristics were observed according to the type of NOAC dose prescribed, e.g. patients with reduced-dose NOAC were older and frailer than those with standard-dose NOAC.

Conclusions: Taken together with results of US, Japanese and European registries, these data suggest that inappropriate underdosing might be a common issue in NOAC new users with AF. Regulators and physicians should carefully consider this emerging NOAC pattern of use for which increased risk for adverse outcomes has been shown.

283 | Trends in Oral anticoagulants prescribing in patients with type 2 diabetes mellitus: A population-based study in the United Kingdom

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Background: Diabetes and cardiovascular diseases are often coexistent, with many diabetes patients suffering from cardiovascular complications. Oral anticoagulant medications (OACs) are widely prescribed for the prevention and treatment of cardiovascular diseases.
Objectives: To explore the prescribing pattern of OACs in Type 2 Diabetes Mellitus (T2DM) in the United Kingdom between 2001 and 2015.
Methods: An observational drug utilization study was conducted using electronic health records in The Health Improvement Network (THIN) primary care database. Patients with T2DM aged >18 and registered within the THIN database between 2001 and 2015 were identified using the Read Codes. Oral anticoagulant medications were categorized into three groups: warfarin, DOACs and other anticoagulant medications including acenocoumarol, pentosan polysulfate and phenindione. The prevalence rate of OACs presented per 100 patients with 95% confidence interval (CI) was calculated and stratified by age, gender, and therapeutic classifications annually between 2001 and 2015. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).
Results: A total of 361,635 individuals with T2DM were identified, of which 36,570 were prescribed OACs from 2001 to 2015. The prevalence of OAC prescribing increased by 50.8% [from 4.4 (95% CI 4.2–4.6) in 2001 to 6.6 (95% CI 6.5–6.7) in 2015 per 100 patients]. The prevalence of warfarin prescribing decreased by 13.9% [from 98.9 (95% CI 98.4–99.4) in 2001 to 85.1 (95% CI 84.6–85.7) in 2015 per 100 patients]. This corresponded with an increased prescribing of direct oral anticoagulants (DOACs) [from 0.1 (95% CI 0.08–0.23) in 2010 to 17.6 (95% CI 17.1–18.2) in 2015 per 100 patients] during the same period.
Conclusions: Prescribing of OACs in patients with T2DM increased from 2001 to 2015. Since the introduction of DOACs there has been a clear shift in prescribing toward these agents. Future studies are needed to assess the safety of the co-administration of oral anticoagulant medications and antidiabetic therapy among patients with T2DM.

284 | Trends in utilization and predictors for initiation of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications

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Background: Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for pain, fever, and inflammation. Clinical guidelines advice against NSAID use in patients with cardiovascular disease. It is unknown to what extent the increased awareness of cardiovascular risks of NSAIDs have translated into decreased use in patients with cardiovascular disease.
Objectives: To study temporal trends in use of NSAIDs among patients with cardiovascular disease and to determine predictors for initiation.
Methods: From the Danish National Patient Registry, we identified patients with a first ever inpatient diagnosis between 1996 and 2016 for the following cardiovascular diseases: myocardial infarction (overall and according to ST-segment elevations in the ECG), stable angina pectoris, atrial fibrillation or flutter, heart failure, ischemic stroke, venous thromboembolism, valvular heart disease, and infective endocarditis. The cohorts were identified separately (i.e., a patient may be included in more than one cohort). Using the Danish National Prescription Registry, we mapped 1- and 5-year prevalence of NSAID use after cohort entry over time, standardizing to the year 2000 age composition. Predictors of NSAID initiation was estimated using logistic regression.
Results: Overall, the use of NSAIDs showed a slight decline throughout the study period. The 1-year prevalence initially increased from 1996 (19%) to 2002 (23%) after which it declined until 2016 (14%). The 5-year prevalence followed a similar trajectory, from 39% in 1996, over 43% in 2002 to 29% in 2012. Identical patterns were seen across cardiovascular contraindications, except for an even stronger relative decline among patients with ischemic heart disease (1-year prevalence among patients with myocardial infarction declined from 18% in 2002 to 10% in 2016). The majority of NSAID use was ibuprofen (57% of all NSAID users during the study period) followed by diclofenac (25%). However, over time, the use of ibuprofen increased alongside a decline in the use of diclofenac and etodolac, and a marked drop in use for coxibs. Users of individual NSAIDs were generally comparable in terms of baseline comorbidity. The strongest predictors of NSAID use was osteoarthritis, rheumatoid arthritis, obesity and sleep apnoea. Further, younger age predicted use of ibuprofen, naproxen and diclofenac, while older age predicted use of etodolac and coxibs.
Conclusions: Although declining, NSAID use remains considerable in patients with cardiovascular contraindications.

285 | Oral anticoagulant (OAC) prescribing for stroke prevention in older people (aged 75+) with atrial fibrillation (AF) in the UK

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Background: Although international guidelines recommend OACs be considered for individuals ≥75 years with AF, they are underused in

this patient population. Direct OACs (DOACs) (dabigatran, rivaroxaban, apixaban, edoxaban) were introduced as alternatives to warfarin (WAR) in 2011; utilization patterns comparing OACs in older patients have not been described. We hypothesized that there would be differences in the characteristics of older patients prescribed DOACs compared to warfarin.

Objectives: To describe OAC utilization in UK primary care for older people with AF (OPwAF) from 2011–2017. To examine time on index OAC and switching between OACs during the study period. To compare baseline characteristics of new OAC users.

Methods: A cohort of OAC users aged ≥75 years, newly started on WAR or DOAC between 2011 and 2017 were extracted from the Clinical Practice Research Datalink (a UK database containing data from primary care). Users required a Read code for AF before index date or within 1 month (1/12) and ≥ 1 year free of OAC. Exclusion criteria were valvular AF, other indication for OAC, or ≥ 2 OACs prescribed on index date. Follow-up continued until date of last OAC script. We abstracted demographic, prescription and co-morbidity data and calculated stroke risk score (CHA_2DS_2-VASc, ↑ score = ↑ stroke risk). Time on OAC was defined as time from index to last script for the index OAC. Switching was defined as having a script for a different OAC ≤ 3/12 from last index OAC script.

Results: Our final cohort included 24409 patients (15393 WAR, 9016 DOAC). DOACs comprised 3.2% of new OAC users in 2012 but increased to 84.7% in 2017. Rivaroxaban and apixaban were the most frequently prescribed DOACs (47% and 43% of all DOAC users, respectively). The median time on index OAC was shorter for DOACs than WAR (307 vs 624 days). Risk of failure on DOAC was 23% higher than WAR (HR 1.23, 95% CI 1.18–1.29). Ten percent of patients switched OAC during the study period (76% from WAR to DOAC, 5% DOAC to WAR, 19% DOAC to DOAC). There were no significant differences in demographics between patients prescribed WAR or DOAC. Mean CHA_2DS_2-VASc scores suggest similar stroke risk per group (WAR 4.28, DOAC 4.31); more DOAC patients had history of stroke/TIA/thromboembolism (50% vs. 45%).

Conclusions: DOACs are now prescribed in preference to WAR for OPwAF in UK general practice. Demographics and stroke risk for OPwAF commenced on DOACs are broadly similar to those started on WAR; investigation of other factors that influence OAC choice is warranted. OPwAF switch predominantly from WAR to DOAC: reasons for switching require further investigation.

286 | Sex differences in Cardiometabolic treatment among patients with type 2 diabetes

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Background: Treatment recommendations for patients with type 2 diabetes are similar for males and females. Sex differences in adverse drug reactions of cardiometabolic treatment have been observed, which may lead to differences in prescribing.

Objectives: To assess sex differences in prescribing of cardiometabolic treatment among patients with type 2 diabetes.

Methods: Cohort study using the Groningen Initiative to Analyze Type 2 diabetes Treatment (GIANTT) database, which includes general practice data from almost all adult patients with type 2 diabetes in the province of Groningen, the Netherlands. We assessed (1) level, (2) type, and (3) dose of glucose-lowering, blood pressure-lowering and lipid-lowering treatment in 2013, after an update of the treatment guidelines. Level was defined according to the step-wise treatment recommendations; type was defined by ATC codes; dose was assessed for 9 commonly prescribed drugs and categorized in classes. Sex differences were assessed using logistic regression analyses, adjusting for age, diabetes duration, body mass index, comorbidity, and baseline level of the related risk factor.

Results: Of the 27,172 included patients, 50% were females and the population was on average 67 years old. Females were less likely to receive glucose-lowering (0.85, 95%CI 0.76–0.94) and lipid-lowering (0.89; 95%CI 0.82–0.98) drug treatment than males. They were less likely to receive metformin (0.77; 95%CI 0.71–0.84), sulfonylureum derivatives (0.90; 95%CI 0.83–0.97), but more likely to receive insulin (1.16; 95%CI 1.04–1.29). They were less likely to receive ACE-inhibitors (0.67; 95%CI 0.62–0.72), calciumblockers (0.84; 95%CI 0.77–0.91) but more likely to receive ARBs (1.27; 95%CI 1.17–1.38) and diuretics (1.32; 95%CI 1.22–1.43). Furthermore, they were less likely to receive high doses of metformin, glimepiride, enalapril, rosuvastatin but no significant differences were seen for dosing of gliclazide, pioglitazone, losartan, metoprolol, simvastatin.

Conclusions: Adjusting for potential confounders, such as age and comorbidity, we showed several sex differences in the treatment of patients with type 2 diabetes. Females received lower levels of glucose-lowering and lipid-lowering treatment and different types of blood pressure-lowering drugs. Further studies are needed to assess the reasons for these differences and whether treatment guidelines should include more sex-specific recommendations.

287 | Beta-blocker choice and exchangeability in patients with heart failure and chronic obstructive pulmonary disease: An Italian register-based cohort study

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Background: Current clinical guidelines suggest that for patients with heart failure (HF) and concurrent chronic obstructive pulmonary disease (COPD), metoprolol/bisoprolol/nebivolol should be preferred. Nevertheless, studies suggest a high proportion of carvedilol usage that is in opposition to above-mentioned recommendations.

Objectives: This study aims to investigate beta-blocker exchangeability and the predictors of carvedilol choice in patients with HF and COPD that were naïve to carvedilol, metoprolol, bisoprolol, and nebivolol.

Methods: Caserta Local Health Unit databases (Italy) were used as data sources. The study outcome was the odds ratio (OR) of receiving carvedilol versus other beta-blockers. Age, sex, year of inclusion in the study population, chronic comorbidities according to the Elixhauser Comorbidity Index and the 500 most prevalent potential predictors for carvedilol choice were included in a logistic regression model to assess predictors of carvedilol choice. Kernel density estimations (KDE) were used to assess the overlap in propensity scores (PS) and preference scores (PFS) distributions for receiving carvedilol. Beta-blocker exchangeability is assumed if half of the distributions of the PFS is between 0.3 and 0.7.

Results: The study population included 10091 patients of which 2011 exposed to carvedilol. The mean age was 77.7 years. The estimated overlapping area of two KDE of PS among beta-blockers was 57%. Accordingly, the exchangeability according to the PFS criteria was not reached. Atrioventricular block (AB) (OR 8.20; 95% Confidence Interval, *95%CI* 1.30–51.80), cerebrovascular thrombosis (CT) (OR 7.06; 95%CI 1.14–43.68), chronic kidney disease (CKD) (OR 4.32; 95%CI 1.16–16.02), and acute HF (OR 1.97; 95%CI 1.28–3.03) hospitalizations within two years prior to the first beta-blocker prescription were statistically significantly associated with carvedilol choice. Analogously, the redemption of human insulin (OR 3.00; 95%CI 1.24–7.24), fondaparinux (OR 2.47; 95%CI 1.17–5.21) or strontium ranelate (OR 2.03; 95%CI 1.06–3.90) within one year prior to the beta-blocker prescription was significantly associated with a higher odd of receiving carvedilol.

Conclusions: This study suggests absence of exchangeability between carvedilol and metoprolol/bisoprolol/nebivolol users and a preferential choice of carvedilol in patients with HF, COPD and concurrent CKD, AB, CT, acute HF or redeeming human insulin, fondaparinux or strontium ranelate.

288 | Patterns of use of $P2Y_{12}$ inhibitors in patients with acute coronary syndrome in routine clinical practice

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Background: Acute coronary syndrome (unstable angina, elevated ST-segment myocardial infarction (STEMI), and non-STEMI) is associated with significant morbidity and mortality. Antiplatelet therapy remains a mainstay for managing ACS patients, particularly those undergoing percutaneous coronary intervention (PCI). Few studies have evaluated how ACS patients are managed in clinical practice, particularly after the introduction of several new $P2Y_{12}$ inhibitors ($P2Y_{12}$i).

Objectives: To evaluate the patterns of $P2Y_{12}$i use in patients with ACS who underwent PCI in various clinical settings.

Methods: Patients aged ≥18 who had an emergency room visit and/or were hospitalized with newly diagnosed ACS (index date), had continuous observation from at least one-year before to 30 days after the index date, and did not receive coronary artery bypass surgery 30 days after the index date were eligible for the study. Proportions of $P2Y_{12}$i use (clopidogrel, prasugrel, ticagrelor) with first dispense within 30 days of the index diagnosis were evaluated for 3-time periods: 01/01/2007 to 12/31/2011 (P1), 01/01/2012 to 12/31/2016 (P2); and on or after 01/01/2017 (P3), using 4 healthcare databases in the US: IBM MarketScan® (Commercial (CCAE), Multi-State Medicaid (MDCD), and Medicare Supplemental (MDCR)) and Optum© De-Identified Clinformatics® Data Mart Database - Socio-Economic Status (Optum).

Results: During the study period from 1-1-2007 to 12-31-2017, about 235,000 ACS patients undergoing PCI were identified. The proportions of $P2Y_{12}$i use varied across study periods and databases. For CCAE, MDCR, and Optum, the proportions of $P2Y_{12}$i use were 88%, 81%, and 81% for P1; 82%, 76%, and 69% for P2; and 86%, 77%, and 68% for P3, respectively. It was observed that since the approval of prasugrel (2009) and ticagrelor (2011), the use of clopidogrel has declined: from 74% (Optum) to 78% (CCAE) in P1 down to 34% (CCAE) to 49% (MDCR) in P3, in part due to the uptake of other $P2Y_{12}$ therapies, mainly ticagrelor: from 8% (Optum) to 14% (CCAE) in P2 to 20% (Optum) to 40% (CCAE) in P3. For MDCD, the proportion of $P2Y_{12}$ use was notably lower regardless of the study period: 48% in P1 and 37% in P2 (no data available for P3).

Conclusions: Despite evidence from clinical trials that prasugrel and ticagrelor are associated with a greater reduction in major cardiovascular events compared to clopidogrel, adoption of these newer $P2Y_{12}$ inhibitors appears moderate, with greater uptake in younger, commercially insured patients. Studies may be needed to further evaluate why $P2Y_{12}$ therapies are generally underutilized in Medicaid patients with ACS undergoing PCI.

289 | Exposure to N-nitrosodimethylamine and N-nitrosodiethylamine-contaminated angiotensin-II receptor blockers products in the United States

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Background: In 2018, probable human carcinogens - N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) were discovered in valsartan-containing products. The US Food and Drug Administration coordinated a voluntary recall of these products that subsequently expanded to include irbesartan and losartan-containing products. Current data suggest contaminated products were introduced as early as 2010. Ongoing characterization of use of these products is crucial for future pharmacoepidemiologic safety assessments.

Objectives: To assess the utilization of NDMA/NDEA-contaminated angiotensin II-receptor blocker (ARBs) in the Sentinel Distributed Database.

Methods: Between 01/01/2010 and 06/30/2018, we identified patients at least 18 years old, newly treated (365-days washout period) with an ARB. Using NDCs, valsartan products were categorized as NDMA-positive, NDMA/NDEA-positive, NDMA/NDEA-negative based on FDA's testing of finished drug products (FDPs) and manufactured recalled products lots. Exposure episode lengths were defined using days supplied, allowing a gap of 15 days or less to create continuous treatment. Follow-up began on the dispensing date until the first occurrence of: disenrollment, end of data, end of the exposure episode, switching to any of the comparator exposure groups, or death. Only the first valid exposure episode that occurred during the study period was included.

Results: A total of 3,909,866 new ARB initiators, except valsartan were identified. Among the valsartan users, 102,083 patients were exposed to an affected product (28,838 NDMA- or NDMA/NDEA-positive and 73,245 recalled products). Prevalence of new initiators was highest in 2016 and 2015, respectively. There were 141,261, and 860,275 patients in the NDMA-negative and other valsartan product categories, respectively. The majority of exposure episodes were censored at the end of continuous treatment. The median follow-up time from index dispensing to end of follow-up ranged from 0.7 years (for NDMA -positive) to 2.4 years (for NDMA-negative products).

Conclusions: Exposure to NDMA/NDEA-contaminated products appears to be low with follow-up time that is notably right-censored for cancer outcomes. An updated analysis expanded to other ARBs is planned when more data become available and the testing of the FDPs is completed.

290 | Pharmacological treatment patterns in heart failure: A real world cohort study

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Background: Although the efficacy and safety of existing therapies of heart failure (HF) have been demonstrated in clinical trials in the last 35 years, little is known about the treatment patterns of HF in clinical practice, especially in France.

Objectives: To describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalization for HF, in a French real-world setting.

Methods: A cohort of patients aged 40 years old and older, with an incident hospitalization for HF between January 1, 2008 and December 31, 2013, was identified in the EGB, a 1/97 permanent random sample of the French nationwide claims database. All patients who died during the index hospitalization or with a period of at least 3 consecutive months with no healthcare dispensing recorded were excluded. All included patients were followed one year. HF drugs of interest were: beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), aldosterone antagonists (AA), diuretics, digoxin or ivabradine. Drug exposure was assessed quarterly using a Proportion of Days Covered >66% (> 60 days out of the 90 days of the quarter covered by the treatment of interest), by considering HF drugs individually or in combination. Drug changes were assessed between each quarter over the first year of follow-up.

Results: Between 2008 and 2013, 7,387 patients from the EGB were included in the cohort study. The mean age at baseline was 77.7 years (±12.0 years) and 51.6% were women. During the follow-up, 24.4% of patients died and 20% did not receive any HF treatment. During the first quarter following initial hospitalization, 42.7% of patients had diuretics, 26.0% had BB, 25.7% had or ACEI, 7.4% had ARB, 7.6% had AA, 4.7% had digoxin and 1.3% had ivabradine. The most frequent combination was BB/ACE/ARB (23.4%). These proportion remained globally constant over the follow-up. The main change occurred between the first and the second quarter and concerned 53.1% of the initially untreated patients; by the second quarter, 22.2% of them initiated a BB/ACEI/ARB combination, 13% a diuretic alone, 7.4% a BB and 4.9% a BB/ACEI/ARB/AA combination.

Conclusions: This study provides precious information on treatment patterns after an initial hospital admission for heart failure at a time when new treatments for heart failure are emerging.

291 | Non-aspirin non-steroidal anti-inflammatory drug use in the Nordic countries 2000–2016 from a cardiovascular risk perspective: A drug-utilization study

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Background: Evidence on the cardiotoxicity of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) - particularly diclofenac and the newer selective COX-2 inhibitors - has accumulated during the last decade.
Objectives: To examine whether the use of NSAIDs in the Nordic countries changed as evidence on the cardiotoxicity of specific NSAIDs accumulated.
Methods: We conducted a drug-utilization study using nationwide wholesale statistics and prescription registries in Denmark, Finland, Iceland, Norway, and Sweden 2000–2016. Our main outcome measures were yearly total sales expressed as defined daily doses (DDD) sold per 1,000 inhabitants per day and yearly prevalence of prescription use as prescription users per 1,000 inhabitants.
Results: Total sales of NSAIDs increased in all countries and were highest in Iceland with 74.3 DDDs/1,000 inhabitants/day sold in 2016, followed by Finland (73.9), Sweden (54.4), Norway (43.8), and Denmark (33.1 in 2015). Diclofenac use declined after 2008 in all countries, but remained the most widely prescribed NSAID in Norway with 63 prescription users/1000 inhabitants in 2016. Diclofenac sales also remained high in Iceland (12.7 DDD/1,000 inhabitants/day), Norway (8.1), and Sweden (7.8). Since its introduction in 2003, the use of etoricoxib, a newer selective COX-2 inhibitor, increased in all countries except Denmark, with highest sales in Finland (6.7 DDD/1,000 inhabitants/day in 2016).
Conclusions: Given existing evidence on the cardiovascular risks associated with use of diclofenac and etoricoxib, the persistent high use of diclofenac in Iceland, Norway, and Sweden and increasing use of etoricoxib in most of the Nordic countries pose a cardiovascular health concern.

292 | Trends in prescription of thiazide and thiazide-like diuretics in the UK

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Background: Hypertension is an important public health problem, and effective treatment reduces the cardiovascular complications such as stroke, myocardial infarction, heart failure and early death. National Institute for Health and Clinical Excellence (NICE) guidelines for the management of hypertension 2011 suggested using indapamide in preference to bendroflumethiazide in cases when a diuretic is to be initiated or changed. A recent systematic review highlighted a lack of studies on comparative efficacy of monotherapy with bendroflumethiazide versus indapamide.
Objectives: The aim of the study was to describe trends in the prescriptions of thiazide and thiazide-like diuretics overall and as first-line monotherapy after a diagnosis of hypertension in the UK and to investigate the impact of the publication of NICE guideline (CG127) in 2011 on prescribing patterns.
Methods: Information on prescriptions was obtained from Information Services Division (ISD) Scotland, OpenPrescribing.net and the Clinical Practice Research Datalink (CPRD). Choice of anti-hypertensive therapy was described by age and time period (before and after the guidelines). Thiazide and thiazide-like diuretic prescriptions were described by year, age of patient and geographical area. Logistic regression and interrupted time series regression modeling were used in data analysis.
Results: Prescribing of thiazide and thiazide-like drugs as first-line monotherapy for hypertension decreased throughout the UK between the period 1990 and 2017. The thiazide diuretic, bendroflumethiazide remained the most prescribed drug of this class despite an increase in prescription of the thiazide-like drug, indapamide, since 2011. There was variation within the UK in the prescribing of thiazide and thiazide-like diuretics. Patients with a history of diabetes prior to their first prescription for hypertension were more likely ($P < 0.001$) to be prescribed indapamide in 1990–2010 compared to 2011–2016. Patients were more likely to be prescribed indapamide if they had established cardiovascular disease or a high ratio of indapamide versus bendroflumethiazide use within their medical practice, for both time periods, thus confirming the influence overall practice policy in addition to patient characteristics.
Conclusions: The NICE 2011 Hypertension Guidelines were associated with an increase in the use of indapamide and a reduction in the use of bendroflumethiazide. However, the proportion of indapamide used remains much lower than bendroflumethiazide, particularly in some regions. This suggests that adoption of the advice in the guideline has been limited.

293 | Temporal changes in the prevalence of cardiovascular drugs use in persons with and without Alzheimer's disease, a retrospective cohort study

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Background: Both cardiovascular diseases and Alzheimer's disease (AD) are common in aging populations. There is little information about the use of cardiovascular (CV) drugs in relation to AD diagnosis.
Objectives: To investigate the changes in prevalence of CV drug use in relation to AD diagnosis, and compare the prevalence to a matched cohort without AD.
Methods: Our study is based on the retrospective register-based Medication Use and Alzheimer's disease (MEDALZ) cohort which includes all community dwellers who received a clinically verified AD diagnosis during 2005–2011 in Finland. Point prevalence of CV drug use during a two-week observation period was counted every six months, from five years before to five years after AD diagnosis. Each person in the AD

cohort was matched with one comparison person without AD by age, sex, and region of residence on the date of AD diagnosis (index date). Use of CV drugs was extracted from the Prescription Register by Anatomical Therapeutic Chemical-classification system codes C* (excluding C04 and C05) and modeled with PRE2DUP method. Longitudinal associations between AD and CV drug use were studied with generalized estimating equations (logistic regression).

Results: On the index date, the use of CV drugs was equally common among persons with and without AD (approximately 70% in both cohorts). The differences in CV drug categories were also relatively small. Beta blockers were the most commonly used in both AD (44.2%) and non-AD cohort (43.9%), followed by statins, with approximately one third of both groups (AD 33.6% and non-AD 31.5%). Calcium channel blockers were used more commonly in the non-AD cohort (20.2% and 22.9% in AD and non-AD cohorts, respectively). Angiotensin converting enzyme inhibitors (AD 22.2%; non-AD 20.9%) were more commonly used than angiotensin II receptor blockers drugs (AD 13.9%; non-AD 16.9%). Loop diuretics were somewhat more common among persons with AD (17.9% in the AD cohort; 17.1% in the non-AD). Overall, the trajectories of use were divergent for different CV drugs, but the common trend was that the prevalence of the use increased before the AD diagnosis among both groups (for example, for any CV drug RR:1.05 95% CI 1.03–1.08). After AD diagnosis the prevalence began to decline among persons with AD (for any CV drug RR:0.60 95% CI 0.59–0.62).

Conclusions: The prevalence of CV drug use was similar in persons with and without AD until the AD diagnosis. After that, the prevalence of CV drug began to decline among persons with AD compared to non-AD. Further studies are needed to determine the difference in CV treatment practices.

294 | Characteristics of NOAC users aged less than 65 years in the sentinel system

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Background: A number of studies comparing non-vitamin K antagonist oral anticoagulants (NOACs) have reported differential benefits and harms among those over age 65 years with atrial fibrillation (AF). However, little information is available on the benefit-harm profiles in those under age 65.

Objectives: To inform the feasibility of a similar safety study in those under age 65 we examined characteristics of and utilization among NOAC initiators for all indications in that age group in the Sentinel Distributed database (SDD).

Methods: New users of NOACS (rivaroxaban, apixaban, dabigatran) aged between 18 and 64 years from October 2010 to September 2015 were identified in SDD. New use was indicated by no use of any NOAC or warfarin in the 183 days prior to the index dispensing. Patients were categorized according to NOAC type and strength. Characteristics of each NOAC exposure group were assessed including: age, sex, health service utilization and potential indications for use.

Results: There were 128,954 NOAC initiators under age 65 during the study period. The mean age was 55 years and 72.0% of users were aged between 51–64 years. Males accounted for 61.0% of new users; however, rivaroxaban 10 mg and apixaban 2.5 mg users tended to have slightly more female initiators. The most frequently initiated NOAC was rivaroxaban 10 mg (40,197 new users) followed by rivaroxaban 20 mg (36,874 new users), and dabigatran 150 mg (21,260 new users). Atrial fibrillation (40.9%) appeared to be the most common potential indication for use followed by joint replacement (19.5%) and knee surgery (11.6%). Around 39% of all NOAC users had no history of AF, pulmonary embolism (PE) or deep vein thrombosis (DVT) as did 70.7% of apixaban 2.5 mg and 94.7% of rivaroxaban 10 mg users. History of surgery was most common in new users of rivaroxaban 10 mg (56.3% joint replacement, 35% knee surgery and 19% hip surgery) and apixaban 2.5 mg users (38.6% joint replacement, 23.1% knee surgery 13.2% hip surgery). Initiators of dabigatran 150 mg (88.4%), dabigatran 75 mg (78.6%), rivaroxaban 20 mg (59.8%), and apixaban 5 mg (78.2%) commonly had a history of AF and no history of PE or DVT.

Conclusions: Rivaroxaban was the most commonly prescribed NOAC in those under age 65 in the Sentinel System. Safety assessments, similar to those conducted in patients over 65 years old, are therefore warranted. Since many NOAC initiators had AF, future safety studies in those under age 65 could exclude rivaroxaban 10 mg and apixaban 2.5 mg users as they appear to be used for indications other than AF.

295 | Impact of serious infection on continuation of chronic disease medications

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Background: There have been over 50 studies in the past 15 years evaluating the protective effects of statins among patients with infections, but the collective results of these studies have been inconclusive. The definition of statin exposure varies greatly between studies, including periods of initiation and continuation in relation to the onset of infection, which is likely responsible for the unexplained heterogeneity.

Objectives: The objective of this study was to assess the effects of serious infections on statin utilization patterns in Veterans Affairs (VA) patients hospitalized between 2002 and 2015 with *Staphylococcus aureus* bacteremia.

Methods: Our national retrospective cohort study assessed statin exposures, focusing on statin drug, dose, and duration of use, among patients who were cultured and admitted to a VA hospital on the same day. The collection date of the blood culture served as the index date and exposure mapping was used to identify statin exposures in the 30 days before and after culture (total 61 days).

Results: We included 6,109 patients with *S. aureus* bacteremia exposed to statins. About one third of patients received the same statin drug and dose for the duration of the observation period (30.9%). Change in statin dose, but not drug, was observed in 5.2% of patients, and 1.9% changed their statin drug and dose at least once during the observation period. Statin medication was initiated during the observation period in 10.5% of patients, and 28.9% of the initiations occurred within the 5 days before or 5 days after the admission/culture. Statin discontinuation, without later reinitiating, occurred in 10.3% of patients, with 11.8% of discontinuations occurring within the 5 days before or 5 days after the admission/culture. Statins were discontinued on hospital admission day, creating a gap in therapy, in 1.2% of included patients. Prior to admission, 51.4% of patients took a statin every day for the 30 day period, and 7.9% of patient did not take a statin until after admission. Simvastatin was the most common statin (75.7%) and the most common doses were 20 mg (17.8%), 40 mg (17.5%), and 80 mg (9.6%).
Conclusions: Two-thirds of patients experienced a change in statin therapy, either as a discontinuation, gap in therapy, or change in drug/dose. This study identified more accurate definitions of statin utilization among those with precipitating events, and provides an example of how to use exposure mapping for improving operational definitions of exposure.

296 | Variation in patient characteristics in atrial fibrillation treatment: A real-world assessment of contact force and Cryoballoon technology

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Background: Catheter ablation is an effective treatment for patients with atrial fibrillation (AF) who are drug refractory or intolerant to drugs.
Objectives: To compare characteristics among AF patients undergoing ablation using a contact force (CF) radiofrequency catheter (THERMOCOOL SMARTTOUCH® Catheter) versus a cryoballoon (CB) catheter (Arctic Front™/Arctic Front Advance™ Catheter).
Methods: Patients aged 18 years and above with AF who had an elective ablation procedure between January 1, 2014 and June 30, 2017 were identified. Patients who underwent catheter ablation, surgical ablation, valvular procedures, or left atrial appendage occlusion during the 12-month pre-index admission were excluded. Patients with AF who underwent catheter ablation using either the CF THERMOCOOL SMARTTOUCH® Catheter or the Arctic Front™/Arctic Front Advance™ CB Catheter without any additional point-to-point catheter use during an inpatient or outpatient hospital admission were identified. Characteristics of patients in the two catheter groups were compared using student t-test or chi-square test.
Results: A total of 3,715 patients were in the final sample, with 1,409 in the CF THERMOCOOL SMARTTOUCH® Catheter group and 2,306 in the Arctic Front™/Arctic Front Advance™ CB Catheter group. The average age of patients in the CF group was lower than patients in the CB group (63.21 ± 10.21 vs 64.52 ± 10.76, $p = 0.0002$). When examining clinical characteristics, a significantly higher proportion of patients in the CF group had sleep apnea (26.90% vs 20.69%, $p < 0.0001$), obesity (16.96% vs 9.24%, $p < 0.0001$), chronic pulmonary disease (16.18% vs 13.57%, $p = 0.0287$), renal disease (6.10% vs 4.55%, $p = 0.0379$), congestive heart failure (19.87% vs 15.57%, $p = 0.0007$), atrial flutter (32.65% vs 18.86%, $p < 0.0001$), valvular disease (18.45% vs 14.44%, $p = 0.0012$), and cardiomyopathy (7.38% vs 4.90%, $p = 0.0018$) as compared to patients in the CB group. The average Charlson Comorbidity Index (CCI) score was significantly higher ($p = 0.0002$) in the CF group (0.90 ± 1.18) as compared to the CB group (0.75 ± 1.12).
Conclusions: In this real-world study, patients undergoing ablation using the CF THERMOCOOL SMARTTOUCH® Catheter had higher comorbidity burden as compared to those who had ablation using the Arctic Front™/Arctic Front Advance™ CB Catheter. Further research is needed to better understand differential in outcomes among patients with high comorbidity status undergoing ablation using a CF Catheter versus the CB Catheter.

297 | Real-world DOAC and VKA use: The PHARMO-anticoagulation cohort

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Background: Anticoagulation with vitamin K antagonists (VKAs), including acenocoumarol, phenprocoumon and warfarin, has been the standard of care for more than 60 years, but has been associated with drug use-related hospital admissions due to bleeding events. Dosing requires close monitoring of therapeutic levels. Direct oral anticoagulants (DOACs), which have been on the market since 10 years, do not require close monitoring. DOACs include factor II inhibitors (dabigatran) and factor Xa inhibitors apixaban, rivaroxaban and edoxaban).
Objectives: To create a real-world dynamic cohort of patients using DOACs or VKAs with the aim to set a basis for safety and efficacy outcome monitoring.
Methods: Patients with recorded dispensings of DOAC or VKA between 2008 and 2017 were selected from the Out-patient Pharmacy Database of the PHARMO Database Network, resulting in the PHARMO- anticoagulation cohort. Outcome data are available from hospital admission records and for a subset of the patients, detailed patient information from the GP Database is available.
Results: During 2008–2017 a total of 77,189 patients using DOACs and 249,210 patients using VKAs were identified; 22,512 were in both groups. DOAC users were 69.9 ± 12.1 years at the time of first use; 44% used rivaroxaban, 30% dabigatran, 17% apixaban, 3% edoxaban and 7% had used multiple DOACs over time. VKA users (74% used

acenocoumarol, 21% phenprocoumon and 5% used both over time) were 70.6 ± 14.1 years at the time of first dispensing in the study period; this is a mix of new and prevalent users. For about 25% of the population detailed medical information from GP records is available.

Conclusions: The PHARMO-anticoagulation cohort provides real-world information on DOAC and VKA use in the Netherlands and delivers comprehensive insights in anticoagulation-related safety, efficacy and resource utilization.

298 | Trends in cardiovascular drug use and cardiovascular disease mortality in Serbia

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Background: CVD drugs are biggest drivers of pharmaceutical expenditure in Serbia, but there is limited data about the impact this high utilization has had on the mortality of CVD.

Objectives: The aim of this study was to determine the trends in cardiovascular drug use and mortality in Serbia.

Methods: The data on utilization of cardiovascular drugs expressed in in defined daily doses per 1000 inhabitants per day (DID) (from 2006–2016) was retrieved from the Medicines and Medical Devices Agency of Serbia. The WHO database was searched for the mortality data (ASDR per 100 000 inhabitants, from 2006 to 2015).

Results: Utilization of CVD drugs in Serbia showed a steady increasing trend (from 399.79 DID in 2006 to 632.80 DID in 2016, 58.3% relative increase). There was an increase in the beta-blocking agents (by 56%) and calcium channel blockers (by 81%), while use of nitrates showed a decreasing trend overtime. ACE inhibitors were the most commonly used drugs in all years analyzed (≈39% of group C), but patterns of use of changed. Biggest changes were obsreved in the use of angiotensin receptor blockers (ARB, 0.06 to 11.3 DID) and fixed combinations. Fixed combinations of ACE inhibitors and thiazide diuretics were used almost 7 times more in 2016 (73 DID), than 2006 (11.9 DID), while steady increasing trend was also observed for ARB and thiazide combinations (0.1 in 2006, 1.7 in 2012 and 16.7 DID in 2016). Fixed combinations accounted for 14% of total utilization in 2016, compared for just 3% in 2006. The use of lipid modifying agents (ATC group C10) doubled during the observed period (from 12.74 to 25.8 DID, relative increase 102.5%), mostly on the account of increase in use of atorvastatin, whose utilization increased 5 times over the study period. Overall mortality from diseases of the circulatory system was significantly lower in 2016 (329) than in 2006 (424). Significant decrease in mortality from ischemic heart diseases (100.7 to 60.9) and cerebrovascular diseases (121.3 to 75.3) was noted. However, mortality from hypertensive diseases increased (23.4 in 2006 to 35.9 in 2016). A.

Conclusions: The increasing trends in use of CVD and a decrease in mortality from ischemic heart diseases and cerebrovascular diseases was observed in this study. Biggest increase was noted in the use of antihypertensive fixed combinations and statins.

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299 | Prescribers' compliance with SmPC recommendations for dabigatran, rivaroxaban, and Apixaban - a European comparative drug utilization study

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Background: Despite a tremendous increase in prescribing of direct oral anticoagulants (DOACs) in recent years limited data is available on prescribers' adherence to registered indications (ICs), contraindications (CIs), special warnings/precautions (SW/PCs), and potential drug–drug interactions (pDDIs).

Objectives: The aim of this study was to assess in six European databases prescribers' adherence to the Summary of Product Characteristics (SmPC) of three DOAC compounds (dabigatran, rivaroxaban, and apixaban) with a special focus on IC, CI, SW/PC, and pDDI.

Methods: This retrospective cohort study was conducted in databases covering regionally/nationally representative populations in five European countries (Denmark, Germany, Spain, the Netherlands, and United Kingdom). The study cohort consisted of adult patients (≥18 years) initiating dabigatran, rivaroxaban or apixaban between

2008 and 2015. ICs, CIs, SW/Ps and pDDIs as registered in the SmPC of the DOACs were mapped to respective coding systems.

Results: 407,576 patients initiated DOACs during the study period (rivaroxaban: 240,985 [59.1%], dabigatran: 95,303 [23.4%], apixaban: 71,288 [17.5%]). In 2015, non-valvular atrial fibrillation was the most common IC registered, representing more than 60% of incident DOAC users in most databases. For the whole study period, a substantial variety between the databases was found regarding the proportion of patients with at least one CI (inter-database range [IDR]: 8.2% to 55.7%), with at least one SW/PC (IDR: 35.8% - 75.2%), and with at least one pDDI (22.4% to 54.1%). In 2015, the most frequent CI was 'malignant neoplasm' (IDR: 0.7% - 21.3%) whereas the most frequent SW/Pc were 'prescribing to the elderly (75 years or older)' with an IDR from 25.0% to 66.4%. The most common single compound class pDDI was 'concomitant use of nonsteroidal antinflammatory drugs' with an IDR between 3.0% to 25.3%.

Conclusions: CIs, SW/Ps, and pDDIs were present in a significant number of new DOAC users. Differences between all databases might be related to 'true' differences in prescription behaviour, but could also be partially due to differences in database characteristics.

300 | Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease - a cross-sectional study

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Background: Adherence to clinical practice guidelines in coronary heart disease (CHD) patients has been shown to reduce morbidity, mortality and overall treatment costs.

Objectives: To describe adherence to prescription guidelines for medical treatment of CHD and explore factors associated with treatment goal achievement for blood pressure, cholesterol and glycated hemoglobin (HbA1c).

Methods: We have analyzed data from the seventh wave of the Tromsø Study, a population-based prospective health study conducted in 2015–16, inviting all inhabitants in the municipality of Tromsø, Norway, aged ≥40 years. We included all participants reporting myocardial infarction, angina, percutaneous coronary intervention and/or coronary artery bypass surgery (n = 1481). Self-reported medication use and treatment goal measures (blood pressure, low-density lipoprotein (LDL)-cholesterol and HbA1c) were compared to the European Guidelines on cardiovascular disease prevention in clinical practice (version 2012), which were prevailing in Norway in 2015–16.

Results: The prevalence of medical CHD treatment was 66.1% for acetylsalicylic acid, 70.9% for blood pressure lowering medicines and 76.4% for lipid lowering drugs (LLDs), while 48.5% used all three medication groups. The blood pressure target (<140/90 mmHg, <140/80 mmHg if diabetic) was achieved by 58.0%, LDL-cholesterol target (<1.8 mmol/l) by 9.3%, and HbA1c target in diabetics (HbA1c of <7%, n = 199) by 41.2% of the participants. Among participants using blood pressure lowering medicines, 54.7% reached the blood pressure target, compared with 66.1% among the non blood pressure medicine users. Equivalent proportions for cholesterol was 12.1% among participants using LLDs and 1.0% for non-users. We are investigating potential associations between low treatment goal achievement and factors like time since diagnosis, specific medication use, demography, health (co-morbidity/co-medication), and lifestyle.

Conclusions: Our preliminary results show that treatment goal achievement among CHD-patients is low, especially for lipid management. The connection between treatment guidelines and reaching the recommended treatment goals is unsatisfactory, but this can be due to underlying factors that we will present at the conference.

301 | Antihypertensive drug combinations to optimize blood pressure control in black patients

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Background: Guidelines on the treatment and management of hypertension stipulate the use of combination therapy containing either a calcium channel blocker (CCB) or diuretic for the treatment of hypertension in blacks.

Objectives: We compared the effectiveness of combination drug therapy containing diuretics and/or CCBs in controlling blood pressure (BP).

Methods: This cross-sectional research was carried out at the outpatient clinics in a tertiary institution in south-west Nigeria. Prescription of hypertensive patients that i). were above 18 years old ii). contained more than one antihypertensive medication iii). had been on a combination for>1 month iv). had recorded BP reading was evaluated. The treatment group was classified as prescriptions containing i.) CCB + diuretics ii.) CCB + angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) iii.) CCB + diuretics + ACEI or ARB iv.) Diuretics + ACEI or ARB. The effectiveness of drug combinations to lower BP to acceptable thresholds (<140/90 mmHg) was studied. Presence of diabetes mellitus (DM), cardiovascular disease (CVD) and chronic kidney disease (CKD) and antihypertensive medication prescribed in these conditions were evaluated. Effect of age, sex, number/combination of antihypertensive medication prescribed and concomitant disease on BP control was assessed. Chi-square and Pearson's correlation in SPSS Version 23 was used to test for associations.

Results: Nine hundred and eighty-six prescriptions were included in the final analysis. The mean age of patients was 61 ± 11 (30–85) years, Females = 55%. The most prescribed drug combination was diuretics + CCB + ACEI or ARB (331 (33.6%)). Diuretics + ACEI or

ARB, CCB + diuretics and CCB + ACEI or ARB was prescribed to 225 (22.8%), 222 (22.5), 209 (21.2%) of the patients respectively. Diuretics + ACEI or ARB was prescribed to 45.9% of hypertensive patients with CVD. CCB + diuretics was prescribed to 65.6% and 38.5% of patients with DM and CKD respectively. BP control was observed in 431 (43.7%) of the patients. BP control was significantly higher in patients on either Diuretics + ACEI or ARB (57.5%) or CCB + Diuretic (51.6%) (χ^2, $p < 0.01$). The number of drugs prescribed correlated with BP control ($r = 0.084$, $p < 0.01$). Patients receiving 3 drugs had the worst BP control. The number of health problems did not correlate with BP control. Patients having cardiovascular disease had significantly worse BP control than patients with other complications ($r = -0.084$, $p < 0.01$).

Conclusions: BP control was less than average. Patients receiving a fewer number of drugs and on diuretics had better blood pressure control.

302 | Sacubitril/Valsartn (Entresto) utilization and prescribing patterns in Northern Ireland: A repeated, cross-sectional study

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Background: In April 2016, the National Institute of Clinical Excellence (NICE) approved the new chronic heart failure medication (CHF) Entresto (sacubitril/valsartan) for treating symptomatic CHF, giving patients the right for full access. Although, Entresto has been accepted for use by the Northern Ireland (NI) Manged Entry Process, it is not listed on the NI formulary not it is first line for CHF therapy. The utilization pattern of Entresto is unclear.

Objectives: To evaluate the utilization pattern and uptake of Entresto in the primary care setting in NI and identify any regional variations.

Methods: Repeated, cross-sectional study using the Prescription Cost Analysis (PCA) data from November 2016 to October 2017. PCA provides information on number of items, quantity, strength and cost of all the prescriptions dispensed in the community setting in NI. Monthly utilization pattern was measured using number of items dispensed, number of defined daily doses (DDD)/1000 inhabitant/day, and net ingredient costs. Number of DDD/1000/day was stratified regions to identify any regional variation. The cost of Entresto as a percentage of all heart failure medications was also calculated. Data were analyzed used descriptive statistics and liner regression to test any trend change over time.

Results: Overall, there was insignificant increase in the prescribing of Entresto over the study period. The number of dispensed items fluctuated during the study period, with insignificant increase of 21.7% from 143 items in November-2016 to 174 items in October-2017 ($p > 0.05$). Similar pattern was observed with number of DDD/1000/day, with insignificant increase of 31% from 0.0008 DDD/1000/day to 0.0011. Likewise, the monthly cost increased by 36.9% from £11,438 to £51,660 in October-2017. By the end of the study period, Entresto accounted for only about 4.4% of the total cost of all heart failure medications. Significant regional variations were observed among the 5 Irish regions, with Belfast as the only region which showed steady increase in number of DDD/1000/day.

Conclusions: The utilization and uptake of Entresto was low and slow in NI which reflects the current NI formulary. This might highlights the issue of securing enough resources to fund this expensive medications given the financial pressure on the Irish healthcare system. However, the observed regional variations highlights the need for further research to explore the factors associated with this variations.

303 | Pain relief and function restoration after primary Total knee arthroplasty: An evaluation using knee injury and osteoarthritis outcome score in real world data

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Background: Knee Injury and Osteoarthritis Outcome Score (KOOS) is currently used by Centers for Medicare and Medicaid Service to instruct value-based payment programs. However, so far, few studies attempted to use KOOS score in real world data to evaluate pain relief and function restoration after TKA.

Objectives: This study aims to evaluate changes in KOOS score (scale 0–100) after TKA surgery, including all five subscales: pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL).

Methods: Through data partnership with Mercy-Technology-Service, patients who underwent primary TKA surgery and with available KOOS score were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. Baseline KOOS was determined by the most recent measurement three-months before surgery. Due to the sparse distribution of follow-up KOOS measurement, we analyzed the follow-up KOOS scores 30–180 days after surgery. The higher increase in KOOS scores indicates greater function restoration or pain relief. Mean difference and 95% CI were estimated using paired-t-test. Total KOOS score was calculated by averaging the five subscales. Factors associated with total KOOS score change 30-days after surgery were investigated using multiple linear regression.

Results: In total, 230 (0.9%) out of 24,830 TKA patients were identified with both baseline and follow-up KOOS scores 30–180 days after surgery (Age median 65y (IQR: 60.0–72.8); 64% female; 59%

commercial insured; median day of follow-up measurement after surgery: 58d (IQR: 43–101)). The mean score difference of follow-up to baseline for pain, other symptoms, ADL, Sport/Rec and QOL were 23.4 (95% CI: 20.6–26.3), 20.9 (95% CI: 18.0–23.9), 24.6 (95% CI: 21.6–27.7), 9.8 (95% CI: 6.7–13.0), and 26.7(95% CI: 23.6–29.8), respectively. Higher baseline KOOS score (β = −0.65, $p < 0.001$), longer OR time (β = −0.18, $p = 0.009$), and elder age (β = −0.36, $p = 0.004$) were significantly associated with lower KOOS increase 30–180 days after surgery.

Conclusions: TKA patients in this study reported significant improvement in pain, other symptoms, ADL, function in sport and recreation and QOL 30–180 days after surgery. Further studies with larger sample size and longer follow-up measurement are warranted.

304 | Knee injury and osteoarthritis outcome score availability evaluation in real world data

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Background: Knee Injury and Osteoarthritis Outcome Score (KOOS) is currently used by Centers for Medicare and Medicaid Service to instruct value-based payment programs. However, little is known about its availability in real world databases.

Objectives: To evaluate the availability of KOOS score after TKA surgery in real world data and investigate factors associated with KOOS measurement availability.

Methods: Through data partnership with Mercy Technology Services (the IT arm of St. Louis-based Mercy health system), patients who underwent primary TKA surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. Patients with at least one KOOS measurement were identified. A descriptive analysis was performed to compare patients who ever had KOOS reported and those who were without any KOOS measurement. Preoperative and intraoperative variables associated with KOOS availability ($p < 0.2$) in the crude analysis were included in the multivariable logistic regression development. Manual backward selection was used to obtain the final model.

Results: In this study TKA population, 1,615 out of 24,830 (6.5%) patients were with reported KOOS measurement. Patients who were older (10-year increment: aOR: 1.09, 95% CI: 1.01, 1.16, mean (SD): 66.7(9.8) vs 65.5 (9.8)), being current smoker (aOR: 1.42, 95% CI: 1.15, 1.77), having higher BMI (aOR: 1.04, 95% CI: 1.03, 1.05) and higher number of hypertension prescription prior to surgery (10- increment: aOR: 1.46, 95% CI: 1.07, 2.01) were statistically significantly associated with increased odds of unavailable KOOS measurement. Baseline pain level (scale 0–10) (aOR: 0.97, 95% CI:0.94, 0.99), number of opiate prescription prior to surgery (10-increment aOR: 0.71, 95% CI:0.57, 0.88), number of anticoagulation prescription prior to surgery (10- increment aOR: 0.2, 95% CI:0.12, 0.34), and recovery room time (10-minutes increment: aOR: 0.94, 95% CI:0.93, 0.95) were factors that statistically significantly associated with decreased odds of unavailable KOOS measurement.

Conclusions: KOOS availability in real world database was poor (6.5%). More efforts are needed to increase KOOS measurement in TKA population, especially among patients who are with lower baseline pain level. When making conclusions using KOOS score, researchers should consider potential bias brought by non-random KOOS missing. Future studies using other real-world data sources are warranted.

305 | Evaluation of three database-derived comorbidity measures to predict infections, extended length of stay and readmissions after Total knee replacement

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Background: The three database-derived comorbidity measures, Charlson, Elixhauser and Functional comorbidity measures have been used as risk-adjustment tools in quality and safety data. However, there is no data on their performance in patients that undergo total knee replacement (TKR).

Objectives: To evaluate the discriminative ability of the Charlson, Elixhauser and Functional comorbidity measures for predicting infections, extended length of stay (LOS) and readmissions after TKR.

Methods: Patients who underwent total knee replacement between January 1, 2010 and December 31, 2017 in IBM Commercial database were identified. The outcomes of interest were (1) infection within three months post-TKR, (2) extended LOS defined as ≥3 days of stay for TKR (3) all-cause readmissions within three months post-TKR. For each outcome, four multivariable logistic regression models were constructed. One base model that included age, gender and year of surgery and three models with the variables in the base model and a comorbidity measure, Charlson, Elixhauser or Functional. The predictive performance of the Charlson, Elixhauser and Functional comorbidity measures was assessed using the area under the receiver operating characteristic curve (AUC) derived from these regression models.

Results: A total of 200,396 patients with TKR were identified. The mean (SD) age of the cohort was 56.7 (5.4) years and most were females (59.7%). For infection, AUC of base, Charlson, Elixhauser and Functional comorbidity measure models were 0.570 (95% CI, 0.566–0.575), 0.599 (95% CI, 0.594–0.603), 0.608 (95% CI, 0.604–0.612) and 0.608 (95% CI, 0.604–0.613), respectively. For extended LOS, AUC of base, Charlson, Elixhauser and Functional comorbidity measure models were 0.6044 (95% CI, 0.601–0.608), 0.622 (95% CI, 0.618–0.625), 0.626 (95% CI, 0.623–0.630) and 0.621 (95% CI, 0.617–0.624), respectively. Finally, for readmissions, AUC of base,

Charlson, Elixhauser and Functional comorbidity measure models were 0.528 (95% CI, 0.523–0.532), 0.551 (95% CI, 0.547–0.556), 0.570 (95% CI, 0.566–0.575) and 0.565 (95% CI, 0.560–0.569), respectively.

Conclusions: The discriminative ability of the Charlson, Elixhauser and Functional comorbidity measure was poor (all AUC <0.7) in predicting infections, extended LOS and readmissions after TKR. Of the three comorbidity measures, Elixhauser models had better discriminative ability. Future research developing comorbidity measures with improved discriminative ability for outcomes after TKR would be of value.

306 | Association between early diagnosis of post-surgical infection and reoperation following Total knee arthroplasty

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Background: Post-surgical infection (PSI) is significantly associated with increased risk for reoperation after total knee arthroplasty (TKA). However, little is known about the timing of diagnosis of PSI and rate of reoperations. Early diagnosis of PSI may help surgeons select appropriate strategy mostly with an antibiotic therapy and minimal surgical intervention.

Objectives: To evaluate the association between early diagnosis of any and deep PSI and reoperations after TKA.

Methods: This was a retrospective cohort study of patients undergoing TKA between 2014 and 2017 using IBM® MarketScan® Commercial, Multi-State Medicaid and Medicare Supplemental databases. Patients were included if they had a diagnosis of PSI within six months after TKA and continuous enrollment six months prior to and two years after TKA. Early diagnosis of any PSI and deep PSI were defined as any claim for PSI and deep PSI, respectively within 11 days of TKA. Two separate multivariable logistic regressions controlling for patient demographic and clinical characteristics were developed to examine the association between an early diagnosis of any PSI and deep PSI and reoperation within two years after TKA.

Results: A total 3,398 patients with any PSI were identified, of which 1401 (41.2%) patients had deep PSI. The mean (standard deviation, SD) age of the cohort was 63.0 (10.7) years with 62.4% females and the mean (SD) Elixhauser score was 2.0 (1.9). The top three comorbidities were hypertension (64.1%), diabetes (24.9%) and obesity (21.0%). The rates of reoperations within two years of TKA were 6.4% for any PSI and 12.4% for deep PSI. The adjusted models showed that there were 43.0% lower odds of reoperation [odds ratio (OR), 0.57, 95% confidence interval (95% CI), 0.39–0.84] with an early diagnosis of any PSI and 41.0% lower odds of reoperation (OR, 0.59, 95% CI, 0.38–0.90) with an early diagnosis of deep PSI compared to the delayed diagnosis of any PSI or deep PSI, respectively (both $p < 0.01$).

Conclusions: This study found that the early diagnosis of any PSI and deep PSI was significantly associated with a lower risk of reoperation as compared to delayed diagnosis of PSI following TKA. Patients with delayed diagnosis of PSI may have a biofilm developed on the implant surface by the infecting organisms that may reduce the effectiveness of antibiotic treatment thereby requiring aggressive surgical strategy involving reoperation.

307 | Early diagnosis of post-surgical infection and reoperation following Total hip arthroplasty

Abhishek S. Chitnis[1]; Piyush Nandwani[2]; Chantal E. Holy[1]

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Background: Post-surgical infection (PSI) is significantly associated with morbidity and increased risk for reoperation after total hip arthroplasty (THA). The timing of diagnosis of PSI is crucial in determining the subsequent medical and surgical management. Early diagnosis of PSI especially deep infection may have a lower risk of reoperations as compared to PSI diagnosed late as with the latter there may be formation of the biofilm on the implant surface by the infecting organisms that reduce susceptibility to antibiotic treatment thus requiring aggressive surgical strategy including reoperation.

Objectives: To evaluate the association between early diagnosis of any and deep PSI and reoperation after THA.

Methods: This was a retrospective cohort study of patients undergoing THA between 2014 and 2017 using IBM® MarketScan® Commercial, Multi-State Medicaid and Medicare Supplemental databases. Patients were included if they had a diagnosis of PSI within six months after THA and continuous enrollment six months prior to and two years after THA. Early diagnosis of any and deep PSI were defined as any claim for PSI and deep PSI, respectively within 11 days of THA. Two separate multivariable logistic regressions controlling for patient demographic and clinical characteristics were developed to examine the association between an early diagnosis of any PSI and deep PSI and reoperation within two years after THA.

Results: A total 1,883 patients with any PSI were identified, of which 882 (46.8%) were deep PSI. The mean (standard deviation, SD) age of the cohort was 65.0 (13.7) years with 57.5% females and the mean (SD) Elixhauser score was 2.0 (2.1). The top three comorbidities were hypertension (60.1%), diabetes (20.1%) and chronic pulmonary disease (19.0%). The rate of reoperation within two years of THA was 21.5% for any PSI and 25.1% for deep PSI. The adjusted models showed that there were 34.0% lower odds of reoperation [odds ratio (OR), 0.66, 95% confidence interval (95% CI), 0.49–0.90] with an early diagnosis of any PSI and 42.0% lower odds of reoperations (OR, 0.58, 95% CI, 0.38–0.88) with an early diagnosis of deep PSI compared to a delayed diagnosis of any PSI or deep PSI, respectively (both $p < 0.01$).

Conclusions: This study found that the early diagnosis of PSI and more so deep PSI was significantly associated with a lower risk of reoperation as compared to delayed PSI diagnoses following THA. Early diagnosis of PSI may help surgeons select appropriate strategy to possibly retain the implant without reoperations.

308 | Similar epidemiologic trends on arthroplasty-related adverse outcomes suggest common modifying role of sex/race-related patient factors in various arthroplasties

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Background: As part of translational research for predictive evaluation of real-world performance, we are developing new evidentiary approaches incorporating putative patient-related risk predictors and outcome modifiers. Our previous research (as reported at ICPE 2015–2017) revealed sex/race-related modifying effects on adverse outcomes in hip arthroplasty.
Objectives: This project is focused on overall sex/race-associated trends in implant-related adverse outcomes in various arthroplasties.
Methods: Data from the Nationwide Inpatient Sample of the Agency for Healthcare Research & Quality (2010–2014) were used for a retrospective analysis of arthroplasty related discharges with or without adverse outcomes, as identified by ICD9 codes. The main outcomes of interest were Mechanical Loosening, Dislocation, Periprosthetic Fracture, Periprosthetic Osteolysis, and Articular Bearing Surface Wear. The arthroplasties were grouped as Hip, Knee, and Other (i.e., prosthetic procedures for shoulder, finger/wrist, elbow, and ankle). Using SAS v.9.3 (Proc Logistic: unadjusted and adjusted for interactions among age, race, and arthroplasty status), the occurrence of adverse outcomes was compared in the sex/race-stratified subpopulations with various arthroplasties.
Results: Per our analysis of inpatient population, arthroplasty procedures in general were found to be more frequent among females. As shown by overall analyses on the sex/race-stratified discharges associated with various arthroplasties, Dislocation and Periprosthetic Fracture were more prevalent among females, while Periprosthetic Osteolysis and Wear were more prevalent among males. Race/ethnicity had additional, mostly independent, modifying effects, *e.g.*, risk increases for Periprosthetic Osteolysis and Articular Bearing Surface Wear among White males with different arthroplasties, or for Mechanical Loosening among Black Males with Knee arthroplasty.
Conclusions: Epidemiologic evidence on various arthroplasties strongly suggests that arthroplasty-related adverse outcomes share similar sex/race-related modifying effects, suggesting possible role of genetic background and other patient-related factors, regardless of device type. Further studies on the sex/race-stratified subpopulations are expected to elucidate the underlying genetic and non-genetic causes and thereby benefit development of health care measures addressing the outcome heterogeneity and health disparities in the growing population of patients with arthroplasties.

309 | Surgical stapler malfunctions: A systematic review of the literature

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Background: Surgical staplers are complex medical devices that have been on the market for decades. They are used in surgery for resection or transection of organs, and for anastomoses.
Objectives: This systematic review was conducted to describe the occurrence of surgical stapler malfunctions, describe the types of malfunctions, and identify the consequences associated with surgical stapler malfunctions reported in the literature.
Methods: The PubMed and EMBASE electronic databases were searched from the dates of surgical stapler inception to 30 May 2018 using terms related to surgical stapler malfunction. The search was limited to English language, and human only papers, and we excluded conference abstracts. Eligible studies included clinical trials, observational studies, systematic reviews and case reports. The search yielded 378 unique records after removing duplicates. Of these, 49 articles were retained after screening titles and abstracts, and underwent full-text review. 40 articles were retained for data extraction.
Results: Surgical procedures performed were open, laparoscopic or robotic surgeries involving the kidneys, lungs, liver, or gastrointestinal system. Surgical stapler malfunctions were reported in 0% to 19.2% (median, 1.8%) of surgeries involving surgical staplers and 0.1% to 5.2% of stapler deployments. In surveys of surgeons conducting surgeries with surgical staplers, up to 73% reported personal experience of, and 86% reported knowing of, someone experiencing stapler misfire or malfunction during surgery. The most common device malfunctions were malformed staples or staple line, and missing staples. Most of the studies did not report the consequences of malfunction, or only reported that the intraoperative complications produced by stapler malfunction were managed by repeated stapling or with suturing (uneventful outcomes). In studies reporting complications arising from stapler malfunction, bleeding and conversion to open surgery/altering of surgical plan were the most reported consequences. Laparoscopic surgeries sustaining stapler technical failures had higher likelihood of conversion to open surgery, higher odds of transfusion and higher odds of death and morbidity, compared to surgeries with no stapler failure. Variability in reported frequencies of malfunctions may be due to the difficulty of determining if this is due to surgeon experience or error, or due to technical failure.

Conclusions: The results of the systematic review indicate that surgical stapler malfunction may not be uncommon and may produce adverse outcomes such as conversion to open surgery, bleeding, and morbidity.

310 | Safety and effectiveness of intrauterine devices: Gynecological history and sexual behaviour of study participants from the European active surveillance study on LCS12

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Background: Intrauterine contraceptive methods, such as Mirena and CU-IUDs, have a high contraceptive efficacy. LCS12 (Jaydess) is a new IUS containing Levonorgestrel, with lower initital release rates per day compared to Mirena (14 µg vs. 20 µg). LCS12 is indicated for contraception for up to 3 years use. Data from routine clinical practice comparing the contraceptive effectiveness of LCS12, Mirena and CU-IUDs is not available so far.

Objectives: The primary outcome of the "European Active Surveillance Study on LCS12" (EURAS-LCS12) study is contraceptive failure in users of LCS12, Mirena or any CU-IUD. Secondary outcomes are risk of ectopic pregnancies, pelvic inflammatory disease (PID), and uterine perforation.

Methods: Large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of approximately 48,000 study participants in ten European countries (Austria, Czech Republic, Finland, France, Germany, UK, Poland, Spain, Italy, and Sweden). Women are enrolled by health care providers and complete a questionnaire including questions on their socio-economic status and individual sexual behavior. Patients receive 5 follow-up quest'res within 3 years. All patient-reported outcomes of interest are validated with the treating physician.

Results: Until end of August 2018, 46,242 women were enrolled by the prescribing HCPs, thereof 5,239 (11%) LCS12 users, 23,461 (51%) Mirena users and 15,097 (33%) CU-IUD users. LCS12 users were considerably younger than users of other IUDs (mean age 26.9 years vs. 36.2 years in Mirena and 30.8 years in CU-IUD users). 65% of LCS12 users were nulliparous compared to 11% of Mirena and 25% of CU-IUD users. Overall, 10% of study participants were breastfeeding at time of insertion: 10% of Jaydess users, 9% of Mirena and 13% of CU-IUD users. Participants were asked for the number of sexual partners in the 12 months preceding the IUD insertion: 74% of LCS12 users had one partner, compared with 87% of Mirena and 80% of CU-IUD users; and 20% of LCS12 users had 2–5 partners, compared with 7% and 15% in Mirena and CU-IUD users, respectively. Of those participants with a new partner in the 12 months before the IUD insertion, 60% of LCS12, 37% of Mirena and 56% of CU-IUD users used a condom.

Conclusions: In the EURAS-LCS12 study, the three user cohorts show substantial differences regarding age and gynecological history, as well as showing large differences between the countries. Further sensitivity analysis, including the influence of associated factors, will be done after recruitment is completed.

311 | Accuracy of molecular diagnostic tests for drug-resistant tuberculosis detection in China: A systematic review

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Background: To face the major challenge in the management of drug-resistant tuberculosis (TB) across the world, molecular diagnostic tests have been recommended as a rapid and effective way to detect patterns of drug resistance, which is critical to promote proper treatments, improve patient outcomes, and reduce further spread.

Objectives: This systematic review evaluated the accuracy of molecular diagnostics for the detection of drug-resistant TB in Chinese patients.

Methods: Three English databases (EMBASE, PUBMED, and the Cochrane Library) and four Chinese databases (CNKI, SinoMed, WanFang, and VIP) were searched for eligible studies that evaluated the accuracy of molecular diagnostics against drug susceptibility testing (DST) for detecting drug resistance in Chinese TB patients. Two researchers independently screened the literature according to the inclusion and exclusion criteria, extracted data and assessed the quality of each study with QUADAS-2. A bivariate random-effects meta-analysis was conducted to pool sensitivity and specificity by index test and drug-resistance type.

Results: A total of 159 studies were included, focusing on four molecular tests: Xpert assay, Line Probe assay (LPA), Genechip assay, and MeltPro assay. Comparing with DST reference standard, Xpert can diagnose rifampicin-resistant TB accurately, with a pooled sensitivity and specificity of 92% (90%, 94%) and 98% (97%, 98%), respectively. LPA also performed well for rifampicin resistance, with a pooled sensitivity of 91% (88%, 93%) and specificity of 98% (96%, 99%), but not for isoniazid and second-line drugs due to lower sensitivity (under 80%). The pooled sensitivities of Genechip for rifampicin, isoniazid, and multidrug resistance were 89% (86%, 91%), 79% (75%, 82%), and 79% (73%, 84%), respectively, and the specificities were all above 97%. Similarly, MeltPro had better sensitivity and specificity for first-line drugs, varying from 87% to 89% and 97% to 98%, respectively, than for second-line drugs.

Conclusions: The Xpert assay, LPA, Genechip assay, and MeltPro assay are credible methods with high accuracy for rifampicin

resistance detection, but they may not be appropriate for other anti-TB drugs due to low sensitivity. Since discordance still exists between phenotypic DST and molecular diagnostics, we recommend molecular assays as an early guide for TB treatment until DST results can be administered.

312 | Comparing detection of medical device recalls using quality control and disproportionality analyses methods of spontaneous complaint reports

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Background: Device spontaneous report data sources include FDA's adverse event database (MAUDE), complaints, and recently, the International Medical Device Database (IMDD). Evidence from higher quality data sources can take months or yea rs and are often costly, therefore structured contemporaneous assessment of spontaneous reports is a necessary component of proactive surveillance. However, current literature on signal detection in spontaneous reports for devices is sparse.

Objectives: We compared statistical trending methods from pharmacovigilance and manufacturing quality control on recalled devices across two groups by indicated use (per IMDD) by examining corresponding spontaneous reports (per MAUDE). We measured time to detection of a signal and false positive/negative rates.

Methods: We searched the IMDD device roster (Dec 19 2018) for classifications and cross-referenced against MAUDE (2009-'18) using fuzzy keyword matching. Two IMDD classifications, "Dental" and "Neurological", were selected with 380 reports across two devices and 29,682 reports across 4 devices, respectively. Known signal periods were identified using IMDD recall dates and compared against prior time periods. Non-signal periods were also assessed as negative controls. Analysis assumes continuous monthly review. Statistical algorithms assessed include 3 quality control (QC) algorithms, x-bar chart, CUSUM, SPRT, and 3 disproportionality (DPA) algorithms, PRR, GPS, and BCPNN. Two counting methods were considered. Analysis was in R 3.5.2 using the mds and mdsstat packages.

Results: A total of 6 and 16 analyses (combination of signal periods and counting methods) were assessed for each algorithm for dental and neurological, respectively. In dental, where the data are low volume (0 to 10 events per month) and just one comparable device exists, DPA algorithms had lower sensitivity but higher specificity. QC algorithms had higher sensitivity but lower specificity. In neurological, where the data are higher volume (20 to hundreds per month) with 3 comparable devices, the opposite was true where DPA algorithms had high sensitivity/low specificity while QC had low sensitivity/high specificity.

Conclusions: This study reviews tradeoffs of trending algorithms used in medical device surveillance in spontaneous reports. Algorithm performance is highly dependent on available comparable devices, time under surveillance, parameters, data quantity and quality. Due to these complexities, care is needed when selecting appropriate trending methodologies for a given context.

313 | Physician adjudication of angioedema in patients with heart failure on angiotensin-converting enzyme inhibitor therapy

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Background: Angioedema, a potentially fatal adverse event of angiotensin-converting enzyme inhibitor (ACEI) therapy, occurs more often in patients with heart failure. Cohort studies conducted with healthcare databases can identify possible angioedema events during ACEI therapy using International Classification of Diseases (ICD) diagnosis codes. Few studies have undertaken physician adjudication of events to confirm angioedema and estimate the positive predictive value (PPV) of diagnosis codes.

Objectives: Our objective was to calculate the PPV of ICD-9 and 10 diagnosis codes for angioedema according to physicians' confirmation of events after reviewing the text of health records.

Methods: We included patients from five health plans in the United States (US) that contribute to the Cardiovascular Research Network (CVRN): Kaiser Permanente (KP) Northern California, KP Southern California, KP Northwest, KP Mid-Atlantic States and the Henry Ford Health System. We assembled a cohort of patients with heart failure based on diagnostic criteria. We identified incident users of ACEIs between July 2006 and December 2017. We followed patients until the first diagnosis of angioedema or censoring: (1) discontinuation of ACEI therapy; (2) initiation of a different renin-angiotensin-aldosterone system (RAAS) blocking therapy; (3) completion of 365 days of ACEI therapy; (4) disenrollment from the health plan; (5) death; or, (6) end of the study on December 31, 2017. We identified angioedema using ICD-9 code 995.1 (Angioneurotic edema not elsewhere classified) or ICD-10 codes in the T78.3 series (Angioneurotic edema). Physicians reviewed coded angioedema events against the text of the electronic health record. To confirm a diagnosis, we required the documentation of signs or symptoms consistent with angioedema (e.g., facial swelling). We calculated the PPV as the number of confirmed events divided by all events with a diagnosis code. When an event could not be confirmed because of incomplete documentation, we classed the event as unconfirmed.

Results: We observed 141 possible angioedema events in 45,483 patients (26,039 patient-years). Physicians confirmed 119 events. Twenty-two events were not confirmed, including 13 events with incomplete documentation. The PPV was 0.84 (95% confidence interval, 0.78 to 0.90).

Conclusions: The PPV of an ICD-9 or 10 code for angioedema was high. Our cohort's PPV is consistent with a previous US cohort study--conducted 20 years earlier--of patients on ACEI therapy, which adjudicated events with similar clinical criteria.

314 | Validity of low birth weight and small for gestational age in the Medicaid analytic extract database

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Background: The accuracy of low birth weight (LBW) and small for gestational age (SGA) in administrative healthcare records is critical for perinatal pharmacoepidemiology studies, however, data on the validity of these diagnoses is scarce.

Objectives: To assess the validity of LBW and SGA diagnoses in the Medicaid Analytic eXtract (MAX) database.

Methods: Using 1999–2010 MAX linked to birth certificates (BC) in Florida (FL), Texas (TX), and New Jersey (NJ), we identified live births where mothers and infants were enrolled ≥30 days from birth in Medicaid. We included linked deliveries with both valid gestational age (GA) and birth weight (BW) on the BC. We identified deliveries with LBW based on presence of an in- or outpatient encounter for mother or infant in the first 30 days after delivery and grouped them based on ICD-9-CM into: < 500 grams, 500–999, 1000–1499, 1500–1999, 2000–2500 grams. The same approach was used to obtain SGA (ICD-9-CM codes 656.5, 656.51, 656.53, 764.0x, 764.1x, 764.9x). We considered GA and BW on BC as the gold standard and flagged infants with BW below the 10th percentile of the U.S. reference for a given GA week as SGA. We calculated the sensitivity (SE), specificity (SP), and positive/negative predictive value (PPV/NPV) of MAX-based LBW groups and SGA and stratified by gender for evaluating the performance of SGA diagnosis code.

Results: We identified 1,533,881 live births, including 548,741 in FL, 972,027 in TX, and 13,113 in NJ. All five LBW groups had low SEs (<60%), high SPs (>99.0%) and NPVs (>99.0%), whereas PPVs varied. Infants with BW 2000–2500 grams had the highest PPV (92.1%, 95% CI 91.9%–92.4%), followed by 1500–1999 grams (87.5%, 87.0%–88.0%), 500–999 grams (38.7%, 37.7%–39.80%), 1000–1499 (34.6%, 33.9%–35.4%), and < 500 grams (5.5%, 4.8%–6.3%). Among 53,216 deliveries with SGA diagnoses determined based GA/BW from the BC, SE of the SGA ICD-9-CM codes was 16.3%; SP was 99.1%; PPV was 77.3% (76.9%, 77.6%); NPV was 86.3% (86.2%, 86.3%). PPV of the SGA diagnosis code was 82.5% (82.1%, 83.0%) for male infants, and was 69.6% (69.0%, 70.2%) for females.

Conclusions: Identification of LBW and SGA infants using ICD-9-CM code from administrative healthcare records had low SE but high SP and NPV. PPVs may be acceptable for LBW infants greater than 1500 grams and SGA.

315 | Validity of diagnosis-based case definitions for chronic kidney disease in a Japanese database

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Background: Chronic Kidney Disease (CKD) is a silent condition with no specific treatment. The CKD stage can be determined by estimated Glomerular Filtration Rate (eGFR), derived from serum creatinine (SCr) values, but the laboratory test results are usually limited in administrative databases. Therefore, it is challenging to identify CKD patients in administrative databases.

Objectives: To assess the validity of diagnosis-based case definitions for CKD in a Japanese claims database.

Methods: An insurance claims database linked to annual health checkup data were used. All subjects aged 18–74 years old with >1 valid SCr values in 2015–2016 were extracted. CKD stage was determined based on the eGFR value derived from two consecutive SCr values at least 3 months apart. Patients on dialysis or post-kidney transplantation were excluded. The usage pattern of pre-specified, CKD-related Japan-specific standardized diagnosis codes during 1 year of follow-up period were reviewed and some were combined. Then, the diagnosis codes (individual or combined) that were used for >5% of patients in at least one of the CKD stages were selected. Sensitivity and positive predictive value (PPV) to identify CKD stage G3a or above, G3b or above, G4 or G5 and G5 were estimated against eGFR-defined CKD.

Results: In total, 452,818 subjects in CKD stage 1 or 2 and 16,779 patients in stage G3a or above were identified. Median age was 45 years and 71.1% were male. 95% (14,992/15,776) of stage G3a patients did not have any of the pre-specified CKD-related diagnosis codes while 73.3% (110/150) and 95.9% (47/49) of stage G4 and G5, respectively, had one or more of the pre-specified diagnosis codes. The most frequently used diagnosis codes were "chronic renal failure", "CKD", and "diabetic nephropathy". In stage G4 and G5, "CKD stage 4", "CKD stage 5" and "End Stage Renal Failure" were also used. Case definition using any of the pre-specified CKD-related diagnosis codes resulted in sensitivity of 7.1%, 41.0%, and 78.9% and PPV of 26.5%, 9.1%, and 3.5% to distinguish CKD stage G3a or above, G3b or above and G4 or G5 from all the other subjects, respectively. For stage G5, "End Stage Renal Failure" gave 42.9% sensitivity and 72.4% PPV while combination of "End

Stage Renal Failure" or "CKD Stage 5" gave 51.0% sensitivity and 69.4% PPV.

Conclusions: Identification of CKD patients using diagnosis-based case definitions did not result in high sensitivity and PPV in this setting. Subjects aged >75 years and females were under-represented and the results may not be generalizable. eGFR-based definition would be preferable to investigate CKD patients in this database.

316 | Development of computable phenotypes to identify heart failure patients with preserved ejection fraction

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Background: Patients with heart failure (HF) with preserved ejection fraction (HFpEF) currently have limited therapy options. A better understanding of the HFpEF population is needed to develop targeted treatments. Research using claims databases is often conducted to characterize demographics and prevalence of conditions as well as to assess market need and uptake of treatments, but careful identification of the condition of interest is needed and is often limited by data availability in claims databases.

Objectives: To develop and validate computable phenotypes for HFpEF using data elements available in claims databases in a cohort of Framingham criteria-validated HF patients as the gold standard.

Methods: Using resources from the Rochester Epidemiology Project (REP), this retrospective study utilized an existing cohort of Olmsted County, Minnesota residents meeting the Framingham criteria for HF. Adults aged ≥20 years diagnosed with HF between January 2007 and December 2015 with an available measure of left ventricular ejection fraction (LVEF) were included. The gold standard definition of HFpEF included meeting the validated Framingham criteria for HF and having a LVEF ≥50%. Computable phenotypes of claims-type data elements in the REP (including ICD9 and ICD10 diagnostic codes and lab test codes) both individually and in combinations were assessed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with respect to the gold standard.

Results: 2,035 Olmsted County residents had Framingham-validated HF with 1,172 (58%) meeting the gold standard definition for HFpEF (LVEF ≥50%). One in-patient or two out-patient diagnosis codes of ICD9 428.3X or ICD10 I50.3X had 46% sensitivity, 88% specificity, 84% PPV, and 54% NPV. The addition of 1 BNP/NT-proBNP lab test code reduced sensitivity to 32% while increasing specificity to 91% (PPV = 84%, NPV = 50%). Broadening the diagnostic codes to ICD9 428.0, 428.3X and 428.9 or ICD10 I50.3X and I50.9 increased the sensitivity at the expense of decreasing specificity (diagnostic code-only model: 87% sensitivity, 8% specificity, 56% PPV, 30% NPV; diagnostic code and BNP model: 54% sensitivity, 51% specificity, 60% PPV, 45% NPV).

Conclusions: Measures widely available in claims databases have potential for identifying the subset of HF patients with preserved ejection fraction. Although prone to some misclassification, we identified computable phenotypes that may be used in commercially available claims databases to gain a deeper understanding of the characteristics of the HFpEF population.

317 | Validity of claims-based algorithms to identify acute kidney injury, acute liver injury, severe complications of urinary tract infections, breast cancer, and bladder cancer among patients with type 2 diabetes: A pilot study

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Background: The validity of coding algorithms using diagnostic and/or procedural codes to identify acute kidney injury (AKI), acute liver injury (ALI), severe complications of urinary tract infections (UTI), breast cancer or bladder cancer is not well studied.

Objectives: To estimate the positive predictive value (PPV) of the coding algorithm for each outcome in a pilot validation study among patients with type 2 diabetes newly initiating anti-diabetic drugs during 2014–2017.

Methods: We identified provisional cases for each outcome using predefined coding algorithms in the HealthCore Integrated Research Database (HIRD). Among provisional cases, we randomly sampled 250 patients hospitalized for AKI, 96 hospitalized for ALI, and 250 who visited the emergency department or had an inpatient hospitalization for severe complications of UTI (i.e., pyelonephritis or urosepsis). We also sampled patients with at least two diagnoses within 60 days apart during outpatient, inpatient, or physician office visits for invasive female breast cancer (n = 100) or invasive/*in situ* bladder cancer (n = 20). Two clinicians blinded to information on study drugs, independently reviewed available medical records and adjudicated the case status according to pre-defined clinical criteria. When there was disagreement, final case status was decided by a committee with a third reviewer. PPVs and 95% confidence intervals (CI) of the coding algorithms were estimated.

Results: Among 125 AKI, 45 ALI, and 125 UTI provisional cases reviewed, 48 AKI, 19 ALI, 71 UTI cases were confirmed. After review, 39 AKI, 10 ALI, and 28 UTI cases remained provisional due to

insufficient information in selected medical records. Restricting to confirmed cases and non-cases yielded corresponding PPVs of 56% (95%CI, 45%, 66%) for AKI, 54% (95%CI, 38%, 71%) for ALI, and 73% (95%CI, 64%, 82%) for UTI. Among 50 breast and 12 bladder cancer provisional cases reviewed, 41 breast and 9 bladder cancers were confirmed. Restricting to confirmed cases and non-cases yielded corresponding PPVs of 84% (95%CI, 73%, 94%) for breast and 90% (95%CI, 71%, 100%) for bladder cancer after respectively excluding one breast and two bladder cancer provisional cases without sufficient information for adjudication.

Conclusions: This pilot study suggests that our coding algorithms have high PPVs to capture breast and bladder cancer cases, but lower PPVs for AKI, ALI and severe complications of UTI. Further evaluation of the algorithms for acute outcomes is needed.

318 | Standardizing EMR lab data for improved safety surveillance

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Background: The clinical details in electronic medical record (EMR) data are increasingly critical for active safety surveillance of marketed drugs. Many of FDA's Sentinel queries were unsuccessful because claims data were 'insufficient' due to lack of laboratory results.

Objectives: Our objective was to standardize laboratory data from US and non-US EMR databases into a common structure to enable active safety surveillance analyses to be conducted and compared across data sources that do not use a standardized coding system, such as Logical Observation Identifiers Names and Codes (LOINC).

Methods: UBC developed an approach to transform source data into a cohesive and accurate database of lab results based on standardized units and test names, while minimizing loss of data. Steps included 1) performing an algorithmic search using keywords from the FDA's Sentinel test definitions to select appropriate lab names; 2) review and acceptance by UBC European and US clinicians of test names, test specimen type, and units; and 3) verification of unit matching or conversion of units to a single valid unit for each test type. The initial effort focused on 3 liver function tests (LFTs) that are important for safety assessment: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and Total Bilirubin. Three EMR databases were included: 2 US and 1 EU.

Results: Across the three databases, the algorithmic search discovered 107 unique test names that represented LFTs (Step 1). However, slightly more than half of these initial matches (62 test names, 58%) were *excluded* from the final LFT group based on clinician review (Step 2). Reasons for exclusion included: incorrect initial classification by the algorithm (26%); test name indicated a different clinical measurement such as 'direct bilirubin' rather than 'total bilirubin' (14%); non-acceptable specimen type, such as urine vs. blood (13%); or other reasons (0.9%). The 45 clinically approved LFT names were associated with 149 unique units in the lab results (e.g., Total Bilirubin measured in mmol/L or mg/dL). After removing test results with units that could not be matched or converted to the standard (Step 3), our transformed LFT database contained 260 million records. Importantly, only 1.1% of the original LFT records could not be included as a valid LFT result.

Conclusions: Diverse and 'messy' lab data found in real-world EMR databases can be successfully converted into a standardized data model. However, close clinical scrutiny and unit conversions are critical to enable efficient and meaningful safety evaluations involving lab results from multiple databases.

319 | Suitability of administrative claims databases for bariatric surgery research

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Background: Claims databases are often considered a suboptimal data source for obesity research due to the lack of information on body mass index (BMI). Due to insurance reimbursement requirement, the validity of BMI-related diagnoses in claims databases may be sufficient to permit comparative effectiveness and safety research of bariatric procedures.

Objectives: To assess the validity of BMI-related diagnosis codes in claims data for patients who underwent bariatric surgery.

Methods: We identified a retrospective cohort of patients aged 18+ who had bariatric surgeries using the OptumLabs® Data Warehouse (2007–2018), which contains linked de-identified claims and electronic health record (EHR) data. Eligible patients had at least 1 BMI (kg/m^2) recorded in the EHR in the 6-month baseline period preceding the index procedure. We evaluated the performance of the BMI-related ICD-9-CM and ICD-10-CM diagnosis codes for two major measures: (1) the presence of a baseline BMI $\geq$ 35 (an important cohort selection criterion; classified as a binary variable); (2) the last baseline BMI prior to surgery (an important baseline confounder; classified as a categorical variable). We used patients' BMI in the EHR as the gold standard to estimate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the BMI-related diagnosis codes in the claims database.

Results: Among 4842 eligible patients, 218 (4%) had adjusted gastric banding, 2314 (48%) Roux-en-Y gastric bypass, and 2310 (48%) sleeve gastrectomy. The population was largely female (74%) with a mean age of 50 years. BMI-related codes were present for 4431 (92%) patients and slightly more prevalent in the ICD-10-CM than ICD-9-CM coding era (93% vs 91%). Compared to patients with codes, those without codes were more likely to be male, older and had a lower BMI. In the subcohort of 4431 patients with codes, the diagnosis codes for the presence of a baseline BMI $\geq$ 35 had a sensitivity 99.5%, specificity 62.0%, PPV 98.2% and NPV 84.9%.

When classifying the last baseline BMI into broad categories, the sensitivity of BMI-related diagnoses codes for underweight (BMI ≤ 19), normal weight (BMI 20- < 25), overweight (BMI 25- < 30) and obesity (BMI ≥30) was 100%, 48.9%, 40.4% and 99.8%; the PPV was 71.8%, 79.3%, 74.2% and 99.1%, respectively. Categorizing using finer BMI categories increased sensitivity to above 60% for most BMI categories for morbid obesity (e.g. BMI 35- < 40, 62.6%; 40- < 45, 63.8%).

Conclusions: It is feasible to use claims databases for obesity-related research, especially among patients where BMI-related coding is required for insurance reimbursement.

320 | Description of bariatric surgery coding in the UK clinical practice research datalink and hospital episodes statistics

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Background: Bariatric surgical procedures (BS, weight loss surgeries) are performed in hospital and recorded ambiguously with codes not separable from surgeries treating gastric cancer/ulcer and pyloric valve malfunctioning. To date, consistency between BS codes in the UK Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES) has not been assessed.

Objectives: To assess consistency of BS entries in CPRD and HES.

Methods: We conducted a descriptive study in all patients in UK-based CPRD linked to HES (April 1998–March 2017). We estimated sensitivity, specificity, positive and negative predictive values (PPV/NPV) of BS codes in the CPRD compared to HES overall and separately in patients eligible only from a first obesity entry until occurrence of a differential indication for BS (gastric cancer/ulcer, pyloric valve malfunctioning) or the patient record end (referred to as valid patients). We considered primary BS codes (potential first-time surgeries) only for sensitivity and PPV estimations and primary and secondary BS codes (e.g. maintenance) for specificity and NPV estimations. Furthermore, we described primary BS counts in CPRD and HES yearly from April to March overall and in valid patients only.

Results: Among 7,357,007 patients in CPRD-linked HES, we identified 14,874 BS entries in either CPRD and/or HES. BS entries yielded a sensitivity and specificity of 33.2% and 99.9%, respectively, and a PPV and NPV of 52.2% and 99.8%, respectively. Among 1,191,219 valid patients, we identified 5662 BS entries in either CPRD and/or HES. BS codes yielded a sensitivity and specificity of 71.0% and 99.8%, respectively, and a PPV and NPV of 52.2% and 99.9%, respectively. Yearly primary BS counts plateaued between 1998/99 and 2003/04 at around 180 HES and 250 CPRD entries overall, and at around 25 entries in both HES and CPRD in valid patients, before increasing to a peak of 953 HES and 709 CPRD entries overall, and to 415 HES and 531 CPRD entries in valid patients between 2010 and 2012. Subsequently until 2016/17, BS counts in HES decreased slightly and in CPRD strongly to 883 and 234 entries overall, and in valid patients, to 140 HES and 180 CPRD entries.

Conclusions: Restricting the study population to obese patients free of BS differential indications, compared to the overall population, BS became less frequently recorded in HES than in the CPRD, sensitivity of BS doubled to 71% (i.e. 29% of BS entries in HES not referred back to CPRD), PPV of BS remained at 52% (i.e. 48% of BS entries in the CPRD not supported by HES) and due to general low BS prevalence, specificity and NPV remained at almost 100%.

321 | Development and validation of a predictive model for incident heart failure in subjects under 65 years old with newly diagnosed atrial fibrillation

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Background: The incidence of both atrial fibrillation (AF) and heart failure (HF) have been increasing in the US. Negative outcomes including stroke, myocardial infarction, and death are experienced at a higher rate in those with both conditions compared to those with only one of the conditions. It is important to understand the factors that make patients with one of the disorders prone to the development of the other disease.

Objectives: The objective of this study was to use machine learning to develop a model for predicting the probability of developing any HF, HF with Reduced (HFrEF) and Preserved (HFpEF) Ejection Fraction in patients under 65 years old with newly diagnosed AF.

Methods: We used administrative claims data from the Optum© De-Identified Clinformatics® Data Mart Database (Optum) and IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) datasets from 2000–17. The target populations were subjects under 65 years old with newly diagnosed AF and the outcome populations were subjects who developed HF at 3–12 months (M) and 12–36 M after AF. Using regularized logistic regression, we included covariates for condition occurrence, drug exposure, and clinical observations and measurements within 365 days of the index date (AF). Internal validation of the models was performed by applying the model developed on 75% of the CCAE data to the remaining 25%. External validation of the models was performed by applying the model developed on CCAE to Optum.

Results: At 3–12 M after AF, for internal validation the areas under the Receiver Operating Curves (AUCs) (95% CI) were 0.732 (0.727, 0.737), 0.719 (0.714, 0.724), and 0.760 (0.755, 0.765) for developing

any HF, HFrEF, HFpEF, respectively, indicating good discrimination. For external validation, the AUCs (95% CI) were 0.746 (0.742, 0.750), 0.717 (0.713, 0.721), and 0.757 (0.753, 0.761) for developing any HF, HFrEF, HFpEF, respectively, indicating good external generalizability. We found similar model performance at 12–36 M. The models predicted associations with HFrEF development for factors such as cardiomyopathy, ischemic heart disease, and high-ceiling diuretics. The model predicted associations with HFpEF development for factors such as diabetes, edema, and polyneuropathy.

Conclusions: These models provide a tool to help clinicians develop a more effective treatment plan for their patients. Patients may be more likely to adhere to treatment after understanding their personal risk of HF.

322 | Validity of chemotherapy procedure codes in the Danish National Patient Registry: A validation study

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Background: The chemotherapy procedure codes in the Danish National Patient Registry is used for administrative purposes and is a potentially valuable resource for pharmacoepidemiological research. The validity of chemotherapy procedure codes has, however, only been evaluated in one smaller study.

Objectives: To assess the validity of chemotherapy procedure codes in the Danish National Patient Registry for patients with colorectal cancer by estimating the positive predictive value (PPV) and sensitivity.

Methods: We identified 440 random patients in the Region of Southern Denmark with a diagnose of colorectal cancer. All chemotherapy procedure codes and medical records between May 2016 and May 2018 were obtained. Duplicates on the same calendar day in the Danish National Patient Registry were excluded. We systematically examined all patient records and recorded all chemotherapies the patient received. Using the medical record as the gold standard, we computed the positive predictive value and sensitivity of chemotherapy procedure codes in the Danish National Patient Registry.

Results: We identified 2830 treatments. The overall PPV was 0.94 (95% CI, 0.93–0.95), and the overall sensitivity was 0.91 (95% CI, 0.90–0.92). Considering single chemotherapy regimens, the PPV of FOLFOX-regimen (5-FU/folinic acid and oxaliplatin) was 0.95, (95% CI, 0.92–0.97), although oxiplatin was only given in 76.7% of the treatments, while the sensitivity was 0.93 (95% CI, 0.89–0.95). The PPV for FOLFIRI-regimen (5-fluorouracil, leucovorin, and irinotecan) was 0.97, (95% CI, 0.92–0.99) and the sensitivity was 0.80 (95% CI, 0.73–0.86). The PPV for bevacizumab was 0.93, (95% CI, 0.86–0.96) and the sensitivity was 0.97 (95% CI, 0.94–0.99). The PPV for cetuximab was 0.98, (95% CI, 0.95–1.00) and the sensitivity was 0.87 (95% CI, 0.82–0.91).

Conclusions: The validity of the chemotherapy procedure codes recorded in the Danish National Patient Registry is very high, supporting their use in pharmacoepidemiological studies.

323 | Validation of an algorithm to predict treatment discontinuation status in electronic health records

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Background: Treatment duration (TD) may serve as a proxy measure for treatment tolerability and effectiveness, which can inform the clinical management of patients. Cohorts derived from EHRs provide an opportunity to understand TD from a broad group of patients and understand how a treatment is administered in routine clinical practice. To estimate TD, it is essential to be able to accurately identify patients that have discontinued therapy at a particular time point. A patient's treatment end date of a systemic anti-cancer therapy regimen is not readily collected in a structured format in EHRs. To address this limitation a stepwise algorithmic approach based on data readily available in the EHR was developed to predict if a patient had discontinued intravenous treatment.

Objectives: To evaluate the accuracy of predicting treatment discontinuation status in an EHR cohort based on a last treatment administration (LTA) algorithm.

Methods: A cohort of 1,000 advanced non-small cell lung cancer patients with exposure to at least 1 cycle of a cancer immunotherapy (CIT) agent (atezolizumab, nivolumab, or pembrolizumab) were selected for abstraction. A patient's discontinuation status was both abstracted from medical notes (gold standard) and predicted from the LTA algorithm. Briefly, the LTA algorithm defined a discontinuation or censor on treatment according to the observed absence of the exposure of interest (without visit interruption) or the presence of death recorded, within a pre-defined observation period (OP) following LTA. The sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) of a patient's discontinuation status based on the LTA algorithm against the gold standard abstracted data were estimated. Sensitivity analyses were conducted that varied the OP within the LTA algorithm.

Results: 877 patients had confirmed treatment exposure and 68% were considered to have discontinued treatment based on abstraction. Validation metrics varied by CIT and OP ranging from 74% to 94%, 42% to 98%, 82% to 99%, 41% to 91% for SE, SP, PPV and NPV.

Conclusions: The LTA algorithm adequately identified patients that have discontinued intravenous treatment based on data readily available in the EHR. OP assumption, follow-up time and

discontinuation rate impacts accuracy estimates. Clinical and pharmacological relevance of the OP should be considered when applying such an algorithm and should be considered in sensitivity analyses.

324 | The predictive value of acute cerebrovascular codes in the BIFAP primary care database

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Background: In primary care (PC) databases, operational definitions to identify cerebrovascular accidents (CVA) are required for observational research.

Objectives: To estimate the positive predictive value of the CVA type recorded among initiators of oral anticoagulant drugs (OAC) in The Primary Care Database For Pharmacoepidemiological Research (BIFAP) in Spain.

Methods: In this cohort study, patients in BIFAP aged 18 years were included when initiating OAC during 2008–2016. Individuals were then followed up until a first International Classification of Primary Care (ICPC) or Diseases (ICD-9) code for ischaemic stroke (IS), haemorrhagic stroke (HS), unspecified CVA (uCVA without mention to stroke or transient) or transient ischaemic attack (TIA), the end of available data, death, or the study ended. The gold-standard was the recorded evidence of confirmed CVA in the clinical profiles. Anonymized profiles were manually reviewed to retrieve recorded evidence for diagnosis confirmation: including a CVA mentioned as final diagnosis in a discharge letter from hospital, specialist (neurologist, internal, etc.) or CAT/MRI unit, or as a PC physician's free text comment (including CVA diagnosed in hospital, as cause of death, or "stroke code" activation). 'Possible CVA' status was assigned when there were only signs or symptoms recorded, a diagnosis written as doubtful, not clear differential diagnosis or no additional information available. 'Discarded CVA' were past episodes or an alternative diagnosis.

Results: Out of 51023 OAC initiators, 1930 had a recorded CVA, including 592 IS, 254 HS, 485 UCVA, and 605 TIA [6 patients had >1 CVA records]. The confirmation was 60.6% of IS, 71.7% of HS, 50.3% of uCVA and 31.4% of TIA, while 34.1%, 24.8%, 40.8% and 67.3% were the respective figures for possible CVA, and 5.2%, 3.5%, 8.9% and 1.3% for discarded CVA, respectively. A quarter of the IS, HS and uCVA while 39% of TIA did not include additional information or included only signs or symptoms. The recorded type of CVA was misclassified in 0.4% of HS, 3.4% of IS and 3.4% of TIA. A final specified CVA type was mentioned in 34.4% of uCVA. mentioned in 34.4% of uCVA.

Conclusions: In BIFAP, the HS recording had the highest confirmatory evidence and the lowest misclassification of the CVA type versus other CVA. Contrarily, TIA had the lowest confirmation proportion since only signs or symptoms without any stronger evidence to fill the confirming criteria were available in most of them. This might be explained by the severity of the event. A third of uCVA records had further evidence of the ischemic, hemorrhagic or transient nature of the episode.

325 | Identifying active hepatitis C and tuberculosis infection cases using United States medical claims data

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Background: New and reactivated hepatitis C (HepC) and tuberculosis (TB) infections are important outcomes in studies of DMARDs and biologic drugs to treat psoriasis and psoriatic arthritis (PsA). Active HepC and TB infections are contraindications for many DMARD and biologic treatments; thus, patients are screened for these infections at the time of treatment initiation or change. In US claims data, HepC and TB diagnostic codes are recorded as the indication for screening tests without knowledge of active infection status. Furthermore, following an active infection event, diagnostic codes are typically recorded repeatedly thereafter, regardless of current infection status. Therefore, it is difficult to distinguish between routine care, an incident infection, and a new reactivation event in patients with a history of HepC or TB. Thus, to avoid case misclassification, it is important to understand claims data recording practices to accurately identify incident or reactivated HepC and TB infections.

Objectives: To identify new or reactivated HepC and TB infections among patients with treated psoriasis or PsA using MarketScan claims data.

Methods: We identified patients with treated psoriasis or PsA between March 2014 and December 2016. We identified all patients with at least one HepC or TB diagnosis during follow-up and then evaluated the presence, duration, and timing of HepC or TB treatment. Our final HepC and TB case definitions included patients who received a diagnostic code and at least 60 days of HepC or TB treatment within 15 days of a diagnosis code. We stratified the results by HepC and TB history status to evaluate differences in identifying new versus reactivated infections.

Results: We identified 124,714 patients with treated psoriasis or PsA. There were 688 patients who received at least 1 HepC diagnostic code, of which 177 (26.5%) also received a HepC treatment during follow-up. The final case series consisted of only 141 patients, or 20.5% of the 688 identified based on the presence of HepC diagnoses alone. We identified 369 patients who received at least 1 TB diagnostic code, of which 88 (23.8%) also received a treatment for TB during follow-up. The final TB cases series consisted of only 56 patients, or 15.2% of the 369 patients identified based on having a TB diagnosis

alone. The proportion of cases retained in the final case series differed by prior HepC or TB history status.

Conclusions: This study suggests that when using claims data careful consideration of timing of HepC and TB diagnoses, receipt of and duration of treatment, and a patient's infection history is necessary to minimize case misclassification.

326 | Identification of patients with suicidal ideation or attempt in electronic health record data

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Background: Although International Classification of Diseases, 9th Revision (ICD-9) codes for suicidal ideation (SI) and suicide attempt (SA) exist, these are likely to under-capture the true number of events. Natural language processing (NLP) of full text clinical notes may provide an opportunity to identify missed SI and SA events.

Objectives: To develop and validate SI and SA algorithms using a combination of ICD-9 codes and NLP data within an electronic health record (EHR) database.

Methods: In the context of a study of binge-eating disorder, patients with SI and SA were identified using NLP of clinical notes within Optum's EHR database. The NLP created unique fields, including concept (e.g., suicide precautions), note section (e.g., plan), fact type (e.g., positive), modifiers (e.g., active), and sentiment (e.g., deny). An algorithm was created using combinations of NLP fields (e.g., active suicidal ideation) to identify SI and SA patients between January 2009 and September 2015. Chronologic sequences of NLP concepts and modifiers extracted from the clinical notes were reviewed for a sample of patients at each iteration of the SI and SA algorithms. After the algorithms had been refined, a sample of de-identified clinical notes was sought from 50 patients with SA, many of whom also had SI (total of 568 clinical notes) and manually reviewed to assess algorithm performance. An emergency medicine physician reviewed the clinical notes and adjudicated the presence of SI and SA. Adjudication results led to a final iteration of the algorithms. Adjudication results were also used to assess performance characteristics: the positive predictive value (PPV) for each algorithm was calculated as the number of confirmed SI/SA patients divided by the total number of algorithm-identified SI/SA patients.

Results: A total of 545 (96%) clinical notes were received with at least one note for each of the 50 patients. The PPVs were 75% (95% CI 43 to 95%) for suicidal ideation and 27% (95% CI 6 to 61%) for suicide attempt.

Conclusions: Using combinations of SI- and SA-related NLP terms in an EHR database led to an algorithm for SI identification that was reasonable in terms of predictive value. However, the SA algorithm did not perform as well and overestimated the number of SA events.

327 | The recording and incidence of inflammatory bowel disease in Girls' primary care medical Records in Spain

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Background: An implication of the human papillomavirus vaccination on the development of Inflammatory Bowel Disease (IBD) in girls has been suggested.

Objectives: To validate the IBD recording in the Spanish Primary Care Database For Pharmacoepidemiological Research (BIFAP), for evaluation of that association, and estimate the IBD incidence.

Methods: The cohort study was made of girls aged 9–19 years registered in BIFAP in 2002–2016 with at least one year of primary care (PC) records. The date when those inclusion criteria were met was the start date to follow-up to a recorded IBD, 19 years of age or died, end of information, or 31/12/2016. IBD was recorded through International Classification of Primary Care (ICPC) or Diseases (ICD-9) codes or free-text in specialist referrals fields. Anonymized PC records were reviewed to retrieve diagnosis confirmation (a positive colonoscopy or biopsy, a specialist letter or PC physician's free-text comments mentioning it) or discarding (negative procedure results, alternative diagnosis or reference to family history) information. Prescriptions of intestinal anti-inflammatory agents (aminosalicylic acid, local corticosteroids, azatioprine and mercaptopurine) and systemic glucocorticoids within 2 years were collected. The IR of IBD per 10^5 girls-years was estimated.

Results: Out of 480,634 girls in the study cohort, 323 had a first ever recorded IBD. Among them, 38.7% (N = 125) 'confirmed incident' IBD cases, 1.5% (N = 5) 'confirmed at a prevalent date' and 21.4% (N = 64) discarded IBD were identified. Information about IBD was missing in 129 patients (39.9%) that we categorized as 'possible IBD'. Sixty out of 64 discarded were referrals to specialist either related only to family history (N = 44) or confirming an alternative diagnosis (N = 9) or negative IBD results (N = 7). The median age at IBD was 15.2 years. Anti-inflammatory agents were prescribed in 89.60% of confirmed incident, 80.0% of prevalent, 3.1% of discarded, and 58.1% of possible IBD, as was azatioprine in 48.8%, 20.0%, 0.0%, and 27.1% respectively, and mercaptopurine in 1.6% of discarded and 2.3% of possible IBD. The IR was 6.74 'confirmed incident' IBD diagnosis increasing up to 13.69 per 105 girls-years when including 'possible' IBD.

Conclusions: A third of the girls with a recording IBD included specialist evidence confirming the diagnosis while most of those with missing evidence, had treatment indicated for IBD. Both recording patterns may be useful for IBD research in BIFAP. The IR of IBD was higher than previously published although methodological differences should be considered.

328 | Validity of atrial fibrillation in electronic medical records: A Single University hospital experience in Japan

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Background: Large healthcare databases offer unique research opportunities in cardiovascular medicine, despite concern regarding the accuracy of data. The validity of diagnosis of atrial fibrillation (AF) in healthcare databases was examined in several studies decades earlier, without reporting the modern risk score for thromboembolism (ie, $CHADS_2$/CHA_2DS_2-VASc scores).

Objectives: To assess the accuracy of diagnosing AF, AF-related comorbidity, and $CHADS_2$/CHA_2DS_2-VASc scores in an electronic medical record (EMR) in a single university hospital in Japan.

Methods: Eligible patients were those who received medical services at Kyoto University Hospital in 2014 at inpatient and/or outpatient settings. Up to 300 patients were enrolled to create each of the following cohorts: inpatients with AF, those without AF, outpatients with AF, and those without AF. The accuracy of these diagnoses and scores in the EMR was calculated using medical chart records as the reference standard. Metrics were reported as sensitivity, specificity, the positive predictive value (PPV), and the negative predictive value (NPV) for diagnosis of AF and its comorbidity, and as correlation coefficient for $CHADS_2$/CHA_2DS_2-VASc scores.

Results: The sensitivity, specificity, PPV, and NPV were 97%–99%, 92%–99%, 92%–99%, and 97%–99% for diagnosis of AF, and 73%, 95%, 77%, and 94% for bleeding episodes, respectively. Correlation statistics were 0.46–0.59 for the $CHADS_2$ score and 0.64–0.73 for the CHA_2DS_2-VASc score.

Conclusions: The diagnosis of AF and AF-related comorbidity in an EMR were highly accurate, but correlation for the $CHADS_2$/CHA_2DS_2-VASc score was modest in our setting. Despite a single-center experience, our findings will be helpful to interpret the reliability of diagnosing AF and related conditions in research using EMRs.

329 | Identification of transfused individuals in electronic health records and claims databases utilizing different coding systems

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Background: The FDA Center for Biologics Evaluation and Research started the Biologics Effectiveness and Safety Initiative (BEST) in 2017 to enhance its hemovigilance (HV) capability, in collaboration with IQVIA, and the Observational Health Data Sciences and Informatics Consortium. Identification of transfused individuals (TI) with blood components can inform HV activities and transfusion guidelines. Health insurance billing (administrative claims), and electronic health records may provide rich data sources to support safety monitoring of blood transfusions. In the United States, billing systems for blood components include the ICD9/ICD10-PCS, HCPCS Level I and II, and revenue codes. Currently all US blood banks and hospitals use the Information Standard for Blood and Transplant (ISBT128), a standardized global coding system for identification and labeling of human origin medical products.

Objectives: Assess and compare the capability of billing and ISBT128 coding systems to identify recipients of blood components.

Methods: A TI is defined as a person receiving at least one blood component (RBC, platelet, plasma) regardless of the unit number, in a specified year using billing codes or ISBT128 codes. TI were identified using billing and ISBT128 codes categorized to identify red blood cells (RBC), platelets, and plasma. We used billing and ISBT128 data from three data sites of the BEST: Columbia University, Stanford University, and Regenstrief Institute. The Observational Medical Outcomes Partnership Common Data Model standardized vocabulary version 5.0.1 was used to identify TI during the period January 1, 2010 to December 31, 2017.

Results: We were able to identify TI with specific blood components using both billing and ISBT128 codes. The number of TI identified using the ISBT128 codes remained relatively stable over time after AABB standardization to ISBT128 in 2012–2013, irrespective of the component or site. For platelet and plasma exposures, TI reflected in billing codes matched those from ISBT 128 codes for limited periods of time at a single data site, but for most observation years at each site, billing codes greatly under-estimated TI (compared to ISBT128) by a varying range. The variation in number of identified TI across the sites is more prominent using the billing codes compared to ISBT codes.

Conclusions: Overall, billing codes underestimated the number of TI compared to ISBT128 codes regardless of component type although the estimates varied across sites. The ISBT128 coding system is a better means for HV activities and captures a larger proportion of transfusions.

330 | Systematic review of algorithms used for identifying acute myocardial infarction, ischemic heart disease and stroke in Italian administrative healthcare databases

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Background: Acute myocardial infarction (AMI), ischemic heart diseases (IHD) and stroke are serious and potentially fatal cardiovascular diseases (CVDs) which may lead to hospitalizations, require periodical medical monitoring and life-long drugs use, thus having an high impact on both public health and Healthcare Service expenditure. In this contest, Italian administrative databases (IAD), which routinely collect patient-level information on healthcare services reimbursed by the National Healthcare Service, are increasingly used for identifying and monitoring the occurrence of these CVDs.

Objectives: To identify and describe case-finding algorithms used in the past 10 years for the identification of AMI, IHD and stroke in IAD.

Methods: A systematic literature review was performed. PubMed database was searched to retrieve all articles published between 2007 and 2017 describing algorithms used for the identification of AMI, IHD and stroke in IAD. The 1st part of the search string was disease-specific, while the 2nd concerned the use of IAD. Among all pertinent papers, data were extracted only from papers describing algorithms used to identify: i)disease occurrence, ii)disease-based cohorts,iii)outcomes.

Results: A total of 17 original algorithms for AMI, 5 for IHD and 27 for stroke were found. Moreover, we identified 3 algorithms for ST elevation myocardial infarction, 3 for Non-ST elevation myocardial infarction, 8 for ischemic stroke and 3 for hemorrhagic stroke. Hospital discharge diagnoses (HDD) were used in all algorithms. For each of the three CVDs, a difference of ≥1 ICD9CM code was always observed across different algorithms. In few cases, diagnoses from co-payment exemption registry, drug prescriptions (DP) and death certificates (DC) were used as additional algorithm components. External validation was performed only in one case: primary HDD of AMI (ICD9CM code 410) was reported to have a positive predictive value between 86% and 52.7%, according to diagnostic criteria used as the gold standard.

Conclusions: HDD represent the main source of data for the identification of AMI, IHD and stroke in IAD. However, a remarkable heterogeneity, in terms of both data sources and codes used, was observed across algorithms aimed to identify the same event and for the same objective. This was likely due to the lack of evidence on algorithms' validity. Finally, although DC,emergency room records, DP and exemption from co-payment can be leveraged to refine AMI,IHD and stroke identification,these data sources are still underutilized.

331 | Validation of major cardiovascular events in a multi-database post-authorization safety study of Prucalopride

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Background: A post-authorization safety study (PASS) was conducted to assess the cardiovascular safety of prucalopride, comparing the occurrence of major adverse cardiovascular events (MACE, a composite of hospitalization for acute myocardial infarction [AMI], hospitalization for stroke, and in-hospital cardiovascular death) among initiators of prucalopride and among a matched comparator cohort. The study was conducted in five data sources from three European member states: the United Kingdom (UK), Germany and Sweden.

Objectives: To report the validation process of MACE endpoints conducted for the prucalopride multi-database PASS in the UK data sources: Clinical Practice Research Datalink (CPRD), the Health Improvement Network (THIN), and the Information Services Division (ISD) Scotland.

Methods: Potential MACE events were identified using an automated algorithm based on previous studies. Validation was conducted per the common validation plan, which included (1) direct confirmation via linkage to hospital records (CPRD only); (2) requests for additional clinical information through questionnaires (CPRD), free text (THIN), or original hospital case records (ISD); (3) patient profile review by study investigators (CPRD/THIN) to rule out non-cases; and (4) event adjudication by three clinicians, all blinded to exposure, for all potential endpoints not previously confirmed or determined as non-case. Cases were assigned final status of definite, probable, possible, or non-cases.

Results: The electronic algorithms identified 260 potential MACE events, of which 38 cases were considered confirmed via linkage to hospital records (CPRD only), 91 were considered non-cases after profile review (CPRD and THIN), and 13 were not available for adjudication (THIN and ISD). Of the remaining 118 potential cases, 62 were adjudicated as definite, 10 adjudicated as probable, 13 as possible, and 33 as non-cases. The general practitioner questionnaire response rate in CPRD was 79%, free text was available for all potential cases from THIN, and all but three requested hospital case records from ISD were retrieved. This was the first observational study in Scotland in which access to hospital case records was granted.

Conclusions: A common validation protocol, with local adaptations based on the types of clinical information available in each data source, allowed for the validation of MACE endpoints in the prucalopride multi-database PASS in three UK data sources.

332 | How accurate are ICD-10 codes in identifying cases of syphilis?

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Background: International Classification of Diseases (ICD) codes are used to identify cases of syphilis in administrative claims. To date, no study has validated the use ICD codes for syphilis identification.
Objectives: To examine the validity of ICD-10 codes for identifying cases of syphilis.
Methods: We constructed a retrospective cohort of patients between 10/1/2015 and 12/31/2016 using the Indiana Network for Patient Care (INPC), the nation's oldest and most comprehensive community health information exchange. Included patients were between 13 and 44 years old and received either ICD-10 diagnosis for syphilis (A51.x, A52.x and A53.x) or laboratory testing for syphilis. For validation, the INPC was queried to obtain a list of all medical record numbers and dates of ICD diagnosis and laboratory test results for all potential cases. If a case had multiple syphilis ICD diagnoses, only the first was assessed. ICD results were evaluated by comparing to syphilis laboratory tests within 60 days of the ICD diagnosis date. Each case was categorized as one of the following: true positive (TP), ICD diagnosis of syphilis and positive syphilis test; false positive (FP), syphilis ICD code and no positive syphilis test; false negative (FN), no syphilis ICD code and a positive syphilis test; and true negative (TN), no syphilis ICD code and a negative syphilis test. Validity of ICD diagnoses were measured by calculating sensitivity and positive predictive value.
Results: A total of 31,787 patients received either an ICD diagnosis or were tested for syphilis. Of the 31,787 patients, 87 were TP, 56 FP, 616 FN, and 31,028 were TN. Among the cases with an ICD diagnosis, 31.5% had no testing, 60.8% tested positive for syphilis, and 7.8% tested negative for syphilis. Positive predictive value (PPV) was found to be 60.8% (95% CI: 60.7%–61.0%) and sensitivity was 12.4% (95% CI: 12.3%–12.4%).
Conclusions: ICD codes are not recommended to identify cases of syphilis in administrative claims. This study, using a population-based cohort, demonstrated low PPV and utilization of syphilis ICD codes. Possible reasons for the low PPV and sensitivity could be clinicians diagnosing patients solely on symptoms or delaying diagnosing patients until laboratory test results are available without updating the electronic health record.

333 | Validation of a complex algorithm for the diagnosis of metastatic castration-resistant prostate cancer within a claims database

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Background: An algorithm was developed in the French nationwide claims database (SNDS) to identify cases of metastatic castration-resistant prostate cancer (mCRPC). The usual way to validate such an algorithm is reviewing patients' medical charts. An alternative within a irreversible pseudonymised database is to use all healthcare use information to identify diagnosis and/or treatment of prostate cancer, then resistant and metastatic stage.
Objectives: To assess and validate mCRPC algorithm using the wealth of data available in SNDS.
Methods: 100 of 14 050 mCRPC patients identified by the algorithm and 100 of 372 273 non-mCRPC patients were randomly selected within SNDS. The 6-year medical history of each of these 200 patients was reconstituted (Long term disease registration [LTD], drug dispensings, procedure codes, hospitalizations, lab tests). These 200 cases were randomly divided into 2 groups of 100 cases. Two groups of independent experts including an urologist and an oncologist each adjudicated blindly the mCRPC status of 100 cases. In case of disagreement within a pair of experts, the 4 experts collegially assessed the case. Positive (PPV) and negative (NPV) predictive values of the algorithm were calculated.
Results: 92 out of 100 mCRPC cases and 93 out of 100 non-mCRPC cases were concordant between the experts and the algorithm, resulting in an algorithm PPV of 0.92 and a NPV of 0.93.
Conclusions: The wealth of data available in the SNDS makes it possible to implement algorithms to detect complex diseases, and to validate them *via* the reconstitution of medical history. The present results show good performance of the algorithm for the identification of mCRPC in the SNDS. In addition, the validation study detected some parameters that could be used to optimize the algorithm's performance.

334 | A validation exercise: Identifying hospitalizations for heart failure among patients with COPD in the CPRD

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Background: The validity of algorithms to identify hospitalizations for heart failure (HF) among patients with chronic obstructive pulmonary disease (COPD) in the Clinical Practice Research Datalink (CPRD) in the United Kingdom has not been described.
Objectives: To validate potential cases (including deaths) of hospitalization for HF in patients with COPD in the CPRD.

Methods: Hospitalizations for HF in a cohort of new users of selected COPD medications (September 2012–June 2017) were identified electronically through: (1) primary and secondary discharge diagnosis for HF in the Hospital Episode Statistics (HES), (2) HF recorded as cause of death in the Office for National Statistics (ONS) and a code for hospitalization within 30 days before in the CPRD General Practitioner Online Database (GOLD), and (3) HF diagnosis and a record for hospitalization within 30 days in the CPRD-GOLD when linkage to HES/ONS was not available. A questionnaire (Qx) was sent to the general practitioners (GPs) to confirm diagnosis. For cases with conflicting information from Qx, adjudication was performed through manual clinical review of the patient profiles. The positive predictive value (PPV) was calculated as an indicator of the validity of HF diagnosis.

Results: There were 2,283 potential HF cases identified in 51,319 individuals with COPD aged ≥40 years. A Qx was sent to the GPs for 1,176 potential HF cases identified from active practices. The response rate was 69.7%. Among the Qx received, 656 Qx (55.8%) included evaluable information. Of these 656 potential cases, 434 were confirmed (PPV = 66.2%). The cases confirmed were 97 of 102 cases (PPV = 95.1%) identified through HES primary discharge diagnosis, 168 of 350 cases (PPV = 48.0%) identified through HES secondary discharge diagnoses, and 169 of 204 cases (PPV = 82.8%) identified through CPRD GOLD diagnosis code and a hospitalization code. PPVs were similar among patients with or without prior history of hospitalization for HF.

Conclusions: Among patients with COPD, the algorithms used to identify hospitalizations for HF through HES primary discharge diagnosis and through GOLD HF diagnosis and hospitalization codes had a high PPV. The algorithm that identified cases through secondary discharge diagnosis had a lower PPV but contributed to a high proportion of the total cases confirmed.

335 | Psychotropic co-medication in Dutch children and adolescents using psycho-stimulants; a prescription sequence symmetry analysis

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Background: Psychiatric side effects like anxiety, depression, psychotic symptoms and hallucinations are frequently reported after the initiation of psycho-stimulant treatment. However, co-morbidities present in ADHD children include behavioral disorders, anxiety, autism, bipolar, depression and sleeping problems, making it difficult to disentangle possible side-effects from these co-morbidities.

Objectives: Assess a possible association between the initiation of psycho-stimulants and psychiatric side-effects in children and adolescents.

Methods: We performed a symmetry analysis, with a study period from January 1, 2008 to December 31, 2017, using the IADB.nl prescription database. We included all children and adolescents (<20 years) who received a first prescription of both a psycho-stimulant and another psychotropic drug within 12 months (not on same date). A sequence ratio, adjusted for prescribing time trends, was calculated.

Results: In total, 3462 patients (mean age 14.0 years; 69% male) were incident users of both psycho-stimulants and other psychotropic medications with 12 months: 2451 received first a prescription for a psycho-stimulant whereas 1011 were first prescribed another psychotropic drug. The adjusted sequence ratio (ASR) was 1.45 (95%CI: 1.05–1.84) for all psycho-stimulants and all groups of psychotropic medications together. When stratifying the data, no increased ratios were obtained between initiating methylphenidate and psychotropic medications whereas significant increased ratios were found between the initiation of atomoxetine and antidepressants (ASR = 1,62 CI95% (1.20–2,04)), hypnotic and sedative drugs (ASR = 1,42, CI95% (1,03-1,81)) and antipsychotic drugs (ASR = 1,81, CI95% (1.37–2.26)).

Conclusions: We found an association between the initiation of psycho-stimulant treatment and the risk of being prescribed other psychotropic medications. Stratified analyses suggest that this association may especially exist between initiation of atomoxetine treatment and antidepressants and antipsychotics, whereas the risk of psychiatric side effects in patients initiating methylphenidate treatment seems not to be increased.

336 | Utilization of neuromuscular blocking agents and their reversal agents among children: A Cerner database study

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Background: Sugammadex (BRIDION) was approved by the US FDA in December 2015 for the reversal of neuromuscular block (NMB) induced by rocuronium and vecuronium in adults undergoing surgery and approved for use in both adults and children in the EU in 2008. Sugammadex use in children has been reported in the US, but to what extent is not clear.

Objectives: Describe the utilization pattern of NMB agents (rocuronium and vecuronium) and factors associated with the use of reversal agents (neostigmine and sugammadex) in US hospitalized children.

Methods: Cross-sectional study of pediatric hospital stays including exposure to rocuronium/vecuronium between 2015 and 2017 within the Cerner database, a hospital-based EMR database across 600 facilities in US. Logistic regression estimated factors associated with the use of sugammadex vs neostigmine.

Results: A total of 21,845 pediatric hospital stays were exposed to rocuronium (76%), vecuronium (18%), or both (6%). Among them, 43% were girls; 48% white; 33% 0–1 year and 38% 12–17 years. In this population, 32% received neostigmine for reversal in 2015 (before sugammadex approval); in 2017 28% received neostigmine and 8% received sugammadex. A total of 642 children received sugammadex

in 2016–2017. Compared to neostigmine users (*n* = 3862), sugammadex users tend to be older (mean age: 13 vs 11 years), more likely to be in teaching hospitals (80% vs 70%), with longer stays (2017, IQR was (1, 4) vs (1, 3) days). Appendicitis was the most common primary diagnosis for both sugammadex (11%) and neostigmine (14%) users, though primary diagnoses were largely missing (23% and 43% among sugammadex and neostigmine, respectively). Multivariable logistic regression (including calendar year, patient demographics, hospital status, admission source, and the use of vecuronium vs rocuronium) suggested that children who were older (age 12–17 years vs 0–1 year: OR 1.96, 95% CI 1.36–2.83), Hispanic or Latino (OR 2.03, 95% CI 1.55–2.67), in teaching hospitals (OR 1.26, 95% CI 1.00–1.59), or admitted through emergency departments (OR 1.65, 95% CI 1.06–2.58) were more likely to receive sugammadex than neostigmine.

Conclusions: In Cerner 2015–2017, among children rocuronium was more commonly used than vecuronium, and sugammadex use was observed since 2016. Sugammadex and neostigmine users varied by demographic, clinical, and site level characteristics. Limitations of the database should be noted, specifically limited participating hospitals, a substantial amount of missing data, and observations may not be generalizable to pediatric populations not included in Cerner.

337 | Temporal trends in opioid prescription dispensing among commercially insured children and adolescents undergoing outpatient surgery in the United States, 2000–2015

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Background: Children who undergo invasive surgical procedures in the outpatient setting are often prescribed post-operative opioids for pain management to be administered by a caregiver. As these patients are not monitored post-operatively in a clinical setting, they are at an increased risk of opioid-related adverse events that are not readily caught and addressed by healthcare professionals.

Objectives: We sought to describe temporal patterns of opioid prescription dispensing among children and adolescents undergoing outpatient surgeries in the United States (US) using a large, national sample of privately insured individuals and their dependents with fee-for-service plans.

Methods: Using IBM's MarketScan Commercial Claims and Encounters Database (2000–2015), we estimated annual proportions and 95% confidence intervals (CIs) of pediatric outpatient surgeries that had an associated short-acting opioid prescription claim. Results were stratified by age, sex, geographic region, body system, and whether the opioid was codeine. Changes in annual proportions of each opioid type (e.g., codeine, dihydrocodeine, hydrocodone, fentanyl, hydromorphone, meperidine, morphine, oxycodone, oxymorphone, pentacozine, propoxyphene, tapentadol, and tramadol) were examined. Using weight from the CDC growth chart, we explored changes in dosing (based on weight-adjusted morphine equivalents).

Results: We identified 16,366,646 unique outpatient pediatric surgeries from 2000–2015, of which 7.6% (*n* = 1,241,956) had an associated short-acting opioid prescription claim. Compared to surgeries without an associated opioid claim, those with an associated opioid claim were more common among individuals who were 12–17 years old, male, and resided in the US South. There was an overall decline in the annual proportion of outpatient pediatric surgeries with an associated opioid prescription claim (from 0.095 (95% CI: 0.093, 0.097) in 2000 to 0.057 (95% CI: 0.057, 0.058) in 2015). Over the study period, we observed that non-codeine opioid dispensing stayed fairly stable, while codeine dispensing declined. As the relative proportion of codeine declined, those of hydrocodone, oxycodone, and tramadol increased.

Conclusions: Given the known risks associated with opioid use in children, the decline in surgery-associated opioid claims is reassuring; however, continued monitoring of opioid trends is needed. Our results suggest that safe opioid use education targeted at healthcare professionals treating certain subpopulations could have greater impact.

338 | Psychotropic prevalence among a US commercially-insured youth: 2007–2015

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Background: The prevalence of psychotropic use among youth in the US started to rise in the early 2000s. This led to concerns about overuse of certain therapeutic classes (i.e., antipsychotics) and use in some patient subgroups (i.e., very young). Research on psychotropic prevalence among commercially insured youth is limited and warrants investigation to better understand the distribution of psychotropic use in this population.

Objectives: The goal of this study was to establish the prevalence of psychotropic use among commercially insured youth in the US.

Methods: The IQVIA™ PharMetrics Plus adjudicated claims database was used to estimate the annual (2007–2015) cross-sectional population prevalence of six psychotropic classes. The psychotropic classes were: stimulants, antidepressants, antipsychotics, anxiolytics, mood stabilizers, and sedatives. We identified all individuals ≤18 years with at least one month of prescription coverage in each study year. Psychotropic class use was defined as at least one dispensing of the six psychotropic classes during the year. We estimated the overall and class-specific population prevalence for the entire sample and stratified by gender and age group (<5; 5–9; 10–14; 15–18). Generalized estimating equations (GEE) were used to assess significant changes in prevalence, comparing 2015 to 2007.

Results: Overall psychotropic prevalence significantly increased by 0.06% per year from 5% in 2007 to 7% in 2015. Compared with 2007, the odds of psychotropic class use increased: 45% (95%CI = 1.42–1.48) for stimulants, 94% (95%CI = 1.90–1.99) for antidepressants, 23% (95%CI = 1.19–1.28) for antipsychotics, 29% (95%CI = 1.26–1.32) for anxiolytics, and 14% (95%CI = 1.09–1.19) for mood stabilizers in 2015. Overall psychotropic prevalence increased in 2015 compared to 2007 in both genders (female: OR = 1.43; 95%CI = 1.40–1.45 and male: OR = 1.72; 95%CI = 1.69–1.75). Relative to 2007, the odds of overall psychotropic use in 2015 decreased by 15% (OR = 0.85; 95% CI = 0.80–0.90) among those aged <5 years. Significant increases were observed in all other age groups; 5–9 (OR = 1.39; 95%CI = 1.34–1.44), 10–14 (OR = 1.36; 95%CI = 1.34–1.39), and 15–18 (OR = 1.58; 95%CI = 1.54–1.60). The observed increases were largely due to significant increases in stimulants and antidepressants use among those aged 5–9 and stimulants, antidepressants, antipsychotics, and anxiolytics use among those aged 10–14 and 15–18.

Conclusions: Psychotropic use in commercially-insured youth demonstrated growth in most therapeutic classes, with the exception of youth aged <5.

339 | Cough and cold medicine recommendations for children in the United States, 2002–2015

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Background: In 2008 the Food and Drug Administration (FDA) recommended that children under age 2 not use over-the-counter (OTC) cough and cold medicines (CCM) given concerns about efficacy and safety. Manufacturers also voluntarily re-labeled CCM for children ≥4, and the American Academy of Pediatrics recommended avoiding CCM in children <6. Subsequent studies through 2010 showed equivocal impact on CCM use.

Objectives: To study trends in physicians' recommendations for traditional CCM and, for comparison, antihistamines in the US pediatric population.

Methods: We used the National Ambulatory Medical Care Surveys (2002–2015) and National Hospital Ambulatory Medical Care Surveys (2002–2015, outpatient/emergency department), US-representative surveys of office- and hospital-based ambulatory settings, respectively. The study sample consisted of all visits for children <18. We measured all visits with recommendations for traditional CCM (drugs containing antitussives, decongestants, or expectorants), sub-classified by the presence of opioid ingredients (codeine or hydrocodone). We included codeine monotherapy for visits for respiratory diagnoses. Separately, we studied single-agent antihistamines for acute respiratory infections. To compare age-specific trends before and after the advisory, we conducted logistic regression with a 3-way interaction between elapsed time ([survey year-2002]/14), era (2002–2008 vs. 2009–2015), and age group. Analyses were adjusted for sex, insurance, race/ethnicity, clinical setting, and region, incorporating visit weights, clustering, and strata for the complex survey design.

Results: In a sample representing 3.1 billion pediatric visits over 14 years, US physicians ordered approximately 95.7 million CCM, of which 12.0% (95% CI 10.0%, 14.3%) contained opioids. During the study period, recommendations for opioid-containing and non-opioid CCM declined substantially, while recommendations for antihistamines rose. After 2008, compared to older children (adjusted odds ratio [aOR] 0.7–1.3), the trend in recommendations for non-opioid CCM appeared to decline more strongly among children <2 (aOR 0.3, 95% CI 0.1, 1.01), and among children <6 for opioid-containing CCM (aOR 0.1). In contrast, the trend in recommendations for antihistamines increased in all age groups after 2008.

Conclusions: Physicians' recommendations for traditional CCM have steadily declined in the US since 2002. These declines seemed to accelerate in young children after the FDA's 2008 public health advisory, with possible replacement by increasing recommendations for off-label antihistamines.

340 | Pediatric antibiotic use: A Nationwide observational study

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Background: Antimicrobial resistance (AMR) is a major public health concern worldwide. One of the key strategies to contain AMR is the prudent use of antimicrobials. The burden of infectious diseases in childhood is substantial with consequent frequent antibiotic prescribing. The scale and pattern of pediatric antibiotic use has been found suboptimal previously. To plan targeted interventions, a more in-depth analysis is needed.

Objectives: To describe antibiotic use among children in relation to prescribers' age and seasonality.

Methods: Systemic antibiotics (ATC: J01) prescribed at ambulatory visits in 2017 were retrieved from the database of the National Health Insurance Fund. Data were stratified by age-groups (patient and prescriber) and gender (patients). Analysis was focused on children aged 0–19 years. Prescribers were categorized into 3 age groups (<40 yrs, 40–65 yrs, >65 yrs). Antibiotic use was expressed as number of prescriptions and standardized as number of prescriptions per 100 children inhabitant per year and per month. Population data were derived from Eurostat. For quality assessment, the proportion of narrow-spectrum (N) beta-lactams and macrolides, as defined by the European Centre for Disease Prevention and Control, was calculated.

Results: In total, approximately 6.8 million antibiotic prescriptions were redeemed at pharmacies in 2017. Almost one-third of these prescriptions were issued for children, in majority (66%) by doctors aged 40–64 yrs. 108.3 antibiotic prescriptions per 100 children per year was issued. Co-amoxiclav (J01CR02) was the most frequently prescribed antibiotic for children, however its relative proportion differed greatly by age-group of prescribers (<40 yrs: 41.3%, 40–65 yrs: 31.0%, >65 yrs: 27.5%). Younger doctors tended to prescribe less narrow-spectrum antibiotics than older doctors (N% <40 yrs: 2.6%, N% 40–65 yrs: 3.5%, N% >65 yrs: 5.8%). Antibiotic prescribing peaked in January with 16.6 prescriptions per 100 children per month, while lowest use was detected in July (4 prescriptions per 100 children per month). No patient gender differences were observed in the seasonality pattern.

Conclusions: Antibiotic prescription patterns differ by prescribers' age group. Our results may suggest that interventions should primarily focus on middle-aged and young prescribers as they issue most prescriptions and tend to prescribe less narrow-spectrum agents.

341 | Drug-induced hearing disorders in children

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Background: Around 34 million children worldwide have disabling hearing loss. Damage to the auditory system limits quality of life of patients, leading to serious consequences especially for psychosocial development of children. It can have a negative impact on communication, with significant vocational, educational and social consequences. Drugs is one of the causes of a hearing disorders.

Objectives: The objective of our study was to characterize drug-induced hearing disorders in a pediatric population.

Methods: Reports of Adverse Drug Reactions (ADR) registered under the MedDRA term "hearing disorders" until December 2018 in pediatric population (< 18 years).were extracted from the French PharmacoVigilance Database (FPVD). We performed a retrospective and descriptive analysis of ADR reports. Characteristics of patients (age, gender, medical history), characteristics of ADRs (Lowest Level Term = LLT MedDRA term of ototoxic adverse reactions, seriousness) and "suspected drugs" (ATC classification system 2nd and 5th levels) were analyzed.

Results: A total of 68 ADR reports were identified, involving adolescents (*n* = 34, 5%), children (*n* = 29, 42.6%) and infant (*n* = 5, 7.3%). Overall, 38 notifications (55.9%) involved girls. A total of 51 reports (75%) were "serious" (*n* = 51). The most frequent hearing disorders (LLT MedDRA term) were: deafness (*n* = 31, 45.6%), hypoacusis (*n* = 20, 29.4%), bilateral deafness (*n* = 6, 8.8%), auditory disorders (*n* = 4, 5.9%), and vertigo (n = 4, 5.9%). The most involved ATC 2nd level were antibacterials for systemic use (*n* = 30, 29.4%), antineoplastic agents (*n* = 25, 20.6%), vaccines (*n* = 12, 16.2%), analgesics (n = 3, 4.4%), antiepileptics (n = 3, 4.4%), corticosteroids for systemic use (n = 3, 4.4%) and immunosuppressants (n = 3, 4.4%). Suspected drugs (ATC 5th level) were: amikacin (*n* = 10, 14.7%), cisplatin (*n* = 8, 11.8%), doxorubicin (n = 4, 5.9%), vincristine (n = 4, 5.9%), ceftriaxone (n = 3, 4.4%), clarithromycin (n = 3, 4.4%), isotretinoin (n = 3, 4.4%), MMR vaccine (n = 3, 4.4%), and vancomycin (n = 3, 4.4%).

Conclusions: This study shows that 75% of drug-induced hearing disorders in pediatric population were "serious", deafness being the most frequent ADR reported. As expected, the most frequently suspected drugs were antibacterials for systemic use (amikacin, clarithromycin) and antineoplastic agents (cisplatin, vincristine). Moreover, if it is difficult to conclude for doxorubicine, ceftriaxone and MMR vaccine due to an association with an ototoxic drug or known hearing loss risk factors. More interestingly, this review suggests that ototoxicity of vancomycin and isotretinoin needs further research.

342 | Prescribing patterns of antiasthma medication in children and adolescents in primary Care in France

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Background: Little is known about the short and long-term therapeutic management of asthmatic children.

Objectives: The aim of this study was to assess the prescribing patterns of antiasthma drugs in primary care.

Methods: This is a retrospective cohort study performed between January 2011 and December 2017 using the EGB (Echantillon Généraliste de Bénéficiaires) database, a 1/97th sample of the French national healthcare insurance system. Claims data for all individuals aged from 5 to 18 years' old who had received at least one antiasthma drug in the study period without any delivery in the previous 24 months and with 24 months of follow-up after first delivery, were analyzed.

Results: A total of 7,680 children and adolescents (68.6% aged 5–11, 31.4% aged 12–18 years) were delivered at least one antiasthma drug (ATC code R03) during study period. The majority (66%) did not redeem another prescription in the following year (occasional users), when 18.4% redeemed prescriptions twice (low users) and 15.6% ≥3 times (high users). Most users (67%) were delivered only one class of

R03 per dispensing in the first year and short-acting β2-agonists was the most frequently dispensed antiasthma drug class (46% of drugs dispensed). However, 33.4% of users were not prescribed short-acting β2-agonists and 42% were delivered antibiotics concomitantly to R03 drugs. During the second year, only 27% of first-year users redeemed R03 prescriptions: 15.8% among occasional users, 35.5% of low users and 64.7% of high users. Short-acting β2-agonists was still the most frequently dispensed antiasthma drug class (42.3%) among second-year users and only 0.1% of R03 users were prescribed long-acting β2-agonists in monotherapy. However, among low and high first-year users who redeemed R03 drugs during the second year, 39.7% did not use inhaled corticoids alone or in association to long-acting β2-mimetics.

Conclusions: A significant proportion of children and adolescents that used antiasthmatic drugs, even on a regular basis, did not redeem prescriptions of these drugs in the long term. This finding may correspond either to the widespread use of antiasthmatic drugs in indications other than asthma or to an undertreatment of asthmatic children and adolescents.

343 | Application of Phevaluator for assessment of pediatric phenotype algorithms for type 1 diabetes mellitus using diagnostic predictive modeling in observational claims databases

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Background: This study explores the utility of different phenotype algorithms (PAs) for identification of subjects ≤18 years of age with type 1 diabetes mellitus (T1DM) in administrative claims data. All data in a subject's record, including inpatient/outpatient diagnosis codes, clinical observations, and prescriptions, were used to inform the diagnostic predictive model.

Objectives: To use a tool (PheValuator) to assess seven pediatric PAs for T1DM.

Methods: We used three administrative claims datasets: Optum© De-Identified Clinformatics® Data Mart Database- Socio-Economic Status (OPTUM); IBM® MarketScan® Multi-State Medicaid (MDCD) and Commercial Claims and Encounters (CCAE) from 2010–18. Using PheValuator involves 1) creating a diagnostic predictive model for T1DM, 2) applying the model to 2 M randomly selected subjects, and 3) comparing each subject's T1DM predicted probability to inclusion/exclusion in PAs. Predicted probability is used as a measure to classify positive/negative cases. Seven PAs for pediatric T1DM, including ≥1-time diagnosis (dx) in a hospital inpatient setting (≥1X-IP); ≥1-time dx in a hospital outpatient setting (≥1X-OP); ≥2 dx in a hospital outpatient setting (≥2X-OP); ≥1-time dx and insulin (INS) prescription (≥1X + INS); ≥1-time dx and glucagon prescription (≥1X + glucagon); ≥1-time dx and no metformin (MET) prescription (≥1X + no MET); ≥1-time dx and INS and no MET prescriptions (≥1X + INS + no MET) were examined.

Results: The PA ≥1X-OP showed the highest sensitivity (98.2% (OPTUM), 98.0% (CCAE), 94.1% (MDCD) from all PAs. ≥1X + glucagon had the highest PPVs (98.8% (CCAE), 97.8% (OPTUM), 96.3% (MDCD)) with lower sensitivities (80.2%, 80.1%, 79.2%). The lowest sensitivities and PPVs were observed for PA ≥1X + no MET (sensitivity/PPV: 5.8%/77.9% (CCAE), 5.5%/69.6% (OPTUM), 14.9%/77.1% (MDCD)). The PAs with prescriptions for INS, ≥1X + INS and ≥ 1X + INS + no MET had higher sensitivities than the PA ≥1X + glucagon (93.4% (CCAE), 94.6% (OPTUM), 88.4% (MDCD) ≥1X + INS; 88.4% (CCAE), 89.7% (OPTUM), 76.5% (MDCD) (≥1X + INS + no MET) vs. 80.2% (CCAE), 80.1% (OPTUM), 79.2% (MDCD) (≥1X + glucagon). Specificities were high for all PAs (> 99%).

Conclusions: Using PheValuator we evaluated seven pediatric PAs for T1DM and determined the ≥1X-OP PA had the highest sensitivity and the PA ≥1X + INS + no MET had the highest PPV. Understanding the performance characteristics of PAs is critical for improving the accuracy of research using observational data.

344 | Annual number of pediatric inpatient orthopedic and neurological surgeries in the United States using different data sources

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Background: Surgical site infections are associated with significant morbidity. Reliable baseline epidemiology data is needed to estimate the population at risk. This study aimed to estimate the number of pediatric inpatient orthopedic and neurological surgeries in the US from different data sources, and the percentage of surgeries which are elective, a potential target population for interventional strategies.

Objectives: Estimate the annual number of pediatric inpatient orthopedic and neurological surgeries and percentage of elective surgeries in the US using de-identified claims data for commercially insured (Optum® Clinformatics® Data Mart, OCDM) and Medicaid insured (Truven MarketScan Multi-state Medicaid database, MM) children and compare the estimates of select inpatient surgeries to weighted national estimates from the HCUP Kids' Inpatient Database (KID).

Methods: Inpatient orthopedic and neurologic surgeries in 2012 among children ages 0–17 years were identified using ICD-9-CM procedure codes from the OCDM, MM, and KID. The surgery rates from claims data were calculated as the number of surgeries divided by the number of children with medical coverage for at least one month in 2012. To project the number of surgeries in the US, the rate was multiplied by the number of children in the US in 2012. Elective surgeries were identified from the OCDM and defined as

surgeries with elective admission type and where patients were not transferred from another institution or admitted through the emergency room (admission type/channel not available in MM or KID).

Results: The number of pediatric inpatient orthopedic and neurologic surgeries per 100,000 persons in 2012 was 116 in OCDM and 130 in MM corresponding respectively to projected 85,365 and 95,595 surgeries in the US. 46% of these surgeries were elective. The 3 most common sub-categories with high percentage of elective surgery were: ortho bone osteotomy (OCDM: 38 surgeries per 100,000 persons [27,706 surgeries in the US], 65% elective; MM: 23 [16,956]; KID: 79 discharges per 100,000 [57,996 discharges in the US]); plastic/ortho surgery (OCDM:16 [11,603], 54% elective; MM: 15 [11,304]; KID: 35 [26,113]); and fusion (OCDM:13 [9,617], 71% elective; MM: 16 [12,014]; KID: 18 [13,049]).

Conclusions: The OCDM and MM databases tended to have similar surgical rates by sub-category type but the KID was higher, possibly due to the survey of discharge codes rather than surgeries. It may be helpful to use multiple databases to estimate, validate, or verify estimates of pediatric surgeries in order to reliably asses the target population.

345 | Safety and effectiveness of piperacillin/Tazobactam (Zosyn®) for treatment of hospital acquired pneumonia (HAP): Novel approach to assessment of drug safety in children

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Background: US legislation formalized requirements for investigations to produce pediatric-specific data on pharmaceutical agents. However, the reticence to enroll children in prospective studies remains a barrier to completing studies in a timely manner. Novel approaches are needed to efficiently and accurately produce pediatric data.

Objectives: This study aimed to assemble a cohort of children with hospital acquired pneumonia (HAP) to estimate risk of serious adverse events (SAEs) and assess effectiveness of piperacillin/tazobactam (P/T) compared to other HAP antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin).

Methods: This was a multicenter retrospective cohort study of patients treated for the indication of HAP between 2003 and 2016 in 7 US hospitals. Data on medications and diagnosis codes from the Pediatric Health Information System (PHIS) were screened to identify possible HAP patients. Subsequent medical chart review was performed to confirm HAP diagnosis, and to determine HAP therapy, occurrence of SAE, and clinical outcomes. A multivariable Poisson regression model inclusive of propensity score weights was developed to compare SAE rates between groups.

Results: Of 1899 admissions with possible HAP identified in PHIS screening, 407 (21.4%) met study inclusion criteria. 141 patients were in the P/T group and 266 patients were in the comparator group. An adjusted comparison showed similar SAE rates between P/T and comparator group (incidence rate ratio: 0.85, 95% confidence interval [CI]: 0.26, 2.75). A comparable proportion of patients in both groups were categorized as clinically improved within 14 days of HAP therapy initiation: 90.78% in P/T and 91.73% in the comparator group. Mortality rates within 30-days from HAP treatment initiation was 3.6% in P/T and 4.5% in comparator group.

Conclusions: This novel multistep methodology using administrative and medical record data was successful in efficiently completing a safety and effectiveness study of P/T in children. SAE rates and clinical outcomes were similar between P/T and comparator group.

346 | Estimating patient age to support EMA pediatric investigation plans in the UK clinical practice research database (CPRD)

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Background: New drug applications to the European Medicines Agency (EMA) require a Pediatric Investigation Plan (PIP) to describe the potential for drug exposure in children. Although PIPs expect reporting in specific age-classes, including neonates (0–27 days), accurate age classification is often difficult in data sources where the date of birth (DOB) is redacted for anonymisation. The CPRD offers the potential to better assess age, as the data contain month of birth for children aged under 16 years. However, it remains unclear if this level of detail is sufficient to classify accurately age at first registration date (FRD) using the EMA mandated age-classes.

Objectives: To assess the potential of the CPRD to estimate patient age in children to support EMA Pediatric Instigation Plans, with an emphasis on neonates.

Methods: A cohort of patients first registered from 2012 to 2017, and within 1 month of their known month of birth (MOB), was identified. Estimated DOBs (eDOBs) were derived using all available data for children and, where available, their algorithmically linked mothers. Full details of these methods are not provided on the request of CPRD's Information Governance Team. The age (in days) at FRD was

estimated comparing the eDOB with a "default" method calculated using only the mid-point of the CPRD-provided MOB. The number of patients classified as neonates at FRD using eDOB and the default DOB is reported. All analyses were based on estimated age and reported at an aggregate level to protect patient confidentiality. This is a GSK funded study, approved by the Independent Scientific Advisory Committee, and conducted in collaboration with CPRD's internal Observational Research Team.

Results: Of 228,868 patients registered within one month of their known MOB, 88% had information available to generate an eDOB. The mean absolute difference in age at FRD between the eDOB and "default" DOB was 7.7 (SD = 4.39) days. The proportion of the cohort classified as neonates at FRD using eDOB was (73% *n* = 166,243) vs. default (68% *n* = 155,854).

Conclusions: The results suggest important misclassification of neonates when using only the MOB information provided by CPRD. This has implications for PIPs and other studies of neonates where accurate assessment of age is required. Ethical considerations, and strategies to better assess age in collaboration with ISAC and CPRD's research team are discussed.

347 | Prevalence and incidence of antiasthma medication use in children: A Nationwide prescription study in France

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Background: Use of antiasthmatic medications has increased over the years worldwide.

Objectives: The aim of this study was to describe the pediatric use of antiasthma drugs in children in France.

Methods: Data were retrieved from the permanent sample (1/97th) of the French national healthcare database - the *Système National des Données de Santé* (SNDS) for all individuals aged from 5 to 18 years old (*n* = 143,909) from 1 January 2011 to 31 December 2017. Prevalence and incidence rate of antiasthmatic dispensing were calculated. Volume of use was assessed as total number of prescriptions dispensed. All analyses were stratified by calendar year, age (5–11, 12–18 years) and gender. Users were classified as occasional if they were dispensed antiasthmatic drugs only once during the year, low users if they were dispensed twice and high users if they were dispensed three or more times in the calendar year.

Results: The annual prevalence of antiasthmatic drug use varied between 12 (2011) and 11 (2017) per 100 persons and incidence varied between 4.3 (2013) and 3.8 (2017) per 100 PYs. Prevalence and incidence of use were highest in children aged between 5–11 years and in boys. In 2017, the most prescribed antiasthmatics were short-acting β2-agonists (41.8% of drugs dispensed) mainly salbutamol, followed by fixed associations of inhaled corticoids and long-acting β2-agonists (20.9%) mainly salmeterol-fluticasone, inhaled corticoids alone (18.6%) mainly fluticasone, and leukotriene antagonists (17.2%). However, differences were observed in most dispensed drugs with regards to age groups. Most users were occasional (53%) and only one third redeemed deliveries on a regular basis (high users: 28%). No trend was observed in the percentages over time or with regards to gender and age group.

Conclusions: Use of antiasthmatic drugs in France is higher than previously described in other European countries. Prevalence of use is also higher than the prevalence of asthma as assessed in epidemiological national studies indicating that these drugs are overprescribed.

348 | Pediatric codeine prescriptions in outpatient and inpatient settings in Korea

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Background: Codeine has long been used for children as an analgesic and antitussive agent. Using codeine to children under 12 years is increasingly being restricted in many countries owing to safety concerns, though it is still widely used.

Objectives: To examine the patterns of prescribing codeine for children under 12 years and to identify characteristics associated with pediatric codeine prescriptions in outpatient and inpatient setting in Korea.

Methods: A retrospective observational study was conducted to examine codeine prescriptions and patients' characteristics. We used the Korea Health Insurance Review and Assessment Service-National Patient Sample database. The study participants were patients who were prescribed codeine as inpatients or outpatients between 2011 and 2016. The study drugs contained codeine phosphate as the only analgesic and antitussive agent and codeine combination products that contain acetaminophen or ibuprofen as an active ingredient. Pediatric codeine use was defined as codeine prescribed at least once for a child under 12 years old. The frequency and proportion of pediatric codeine users were analyzed by age group (0–2, 3–6, 7–11 years), sex, year, region, diagnosis, type of medical institution, and co-prescribed medication. Logistic regression analyses were performed to identify characteristics associated with pediatric codeine users.

Results: Of all patients younger than 12 years old, 512 816 (55.2%) and 16 541 (1.7%) were treated with codeine in outpatient and

inpatient settings, respectively, ($p < .0001$). The mean age of these users was 5.6 and 6.3 years, respectively. The most frequent diagnoses for pediatric codeine users were acute bronchitis (40.2%) and acute upper respiratory infection (27.1%) in out- and in-patient settings, respectively. Odds of pediatric codeine prescriptions were highest for outpatients at general hospitals (adjusted Odds Ratio, aOR = 7.85; 95% Confidence Interval, CI, 7.20–8.55) and clinics (aOR = 7.44; 95% CI, 6.84–8.11) and for inpatients at tertiary hospitals (aOR = 4.77; 95% CI, 4.29–5.31) and general hospitals (aOR = 4.24; 95% CI, 3.81–4.71). The proportion of pediatric patients treated with codeine showed little change in the temporal trend. There appears to be seasonality for the proportion of outpatient codeine users.

Conclusions: Codeine was frequently prescribed for children in Korea compared to the U.S. and the U.K., especially in general hospitals and clinics. Efforts to limit codeine use in children are required to prevent the occurrence of codeine-related adverse events.

349 | Characteristics of pediatric patients prescribed sertraline: Insights from the sertraline pediatric registry for the evaluation of safety

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Background: Sertraline has been used to treat various psychiatric conditions in children and adolescents in clinical practice. It is unknown whether sertraline users differ from non-users in baseline disease characteristics and if long-term sertraline use impacts pediatric growth and development.

Objectives: To describe the baseline disease characteristics of patients enrolled in the Sertraline Pediatric Registry for the Evaluation of Safety (SPRITES).

Methods: SPRITES is an open-label, post marketing study of outcomes in pediatric patients treated with sertraline compared to psychotherapy (for up to 3 years) in clinical settings in the United States. Patients were prescribed sertraline at baseline (or within 45 days prior) or psychotherapy. Baseline data included demographics, psychiatric history, concomitant psychiatric medications. Primary outcomes were: 1) measures of cognitive and emotional development (Trails B, BRIEF), physical development (height and weight), and pubertal status. Data were also collected on present/lifetime risk of suicide-related events using the Columbia-Suicide Severity Rating Scale.

Results: Study enrollment occurred April 2012 to July 2017. SPRITES enrolled 941 patients between the ages of 6 to 17 years. Patients' baseline mean age was 11.9 years, 57.2% were female, and 81.2% were white. Most patients (78.4%) had an anxiety disorder and 15.6% were diagnosed with OCD. Mean age of onset at first mental illness was 7.91 years, and the most frequently reported family history of mental illness was depressive and anxiety disorders (63.2%, 60.5%, respectively). When compared to the no pharmacologic treatment group, a higher percentage of sertraline-treated patients received prior: psychotherapy (59.0% versus 34.4%), psychotropic medications for a psychiatric disorder (14.1% vs 3.3%), and non-sertraline selective serotonin reuptake inhibitors (SSRIs) (8.6% vs 1.2%). Most patients were moderately ill on Clinical Global Impressions-Severity scale, and a higher percentage of sertraline-treated patients had a moderate to severe mental impairment score (73.0% versus 57.8%, respectively). The sertraline-treated group also reported higher levels of lifetime and baseline suicidal ideation/behavior compared to the no pharmacologic treatment group.

Conclusions: SPRITES is the first study to examine the long-term safety of sertraline or any SSRI in pediatric patients with follow-up consistent with usual practice. Baseline data suggest patients prescribed sertraline are reflective of a more mentally ill study population.

350 | Prevalence of kabuki syndrome in Europe: A literature review and database analysis

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Background: Kabuki syndrome is a rare congenital disorder characterized by distinctive facial features, intellectual disability, abnormal stature, and other physical abnormalities. There is a paucity of data on prevalence of Kabuki syndrome in Europe.

Objectives: To review available data on prevalence of Kabuki syndrome (KS) in Europe,and calculate prevalence of KS in United Kingdom (UK) primary care.

Methods: Key words and text words for KS were combined to search for relevant European studies published to date, using computerized databases. A study to assess prevalence of KS in the UK using the Clinical Practice Research Datalink (CPRD), a large primary care database, was conducted. The numerator for the CPRD analysis included all patients with a clinical code for KS in their medical history who were registered with a general practice and who were alive on 31 December 2017. The denominator included all eligible patients in the CPRD registered and alive on 31 December 2017.

Results: Five published studies reporting European prevalence data for KS were found. The DYSCERNE pilot project, a Europe-wide study, found the prevalence of KS ($n = 3$) in 2010–2012 was estimated to range between 0.1 and 0.9 per 10,000. An Italian study using data from the Tuscany Registry of Congenital Anomalies and the Tuscany Registry of Rare Diseases found the prevalence of KS was 0.195 per 10,000 (95% CI 0.063–0.455) births ($n = 5$ KS cases and 256,256 live births in Tuscany between years 2006 to 2013). A study in the Italian province of Sassari in Sardinia found a prevalence of KS among 9–20 year olds of 0.86 per

10,000 (n = 5 KS patients). A study in the Spanish province of Badajoz reported a prevalence of 0.2 per 10,000 persons between 1988 and 1990 (n = 5 KS cases, catchment area approximately 250,000 persons). The 2018 Orphanet Report Series reported the prevalence of KS in Europe was estimated to be 0.31 per 10,000 persons. The analysis using the UK CPRD indicated a prevalence of KS in the UK of 0.08 per 10,000 persons (95% CI 0.06–0.10; *n* = 48/6,258,143).

Conclusions: Some of the studies reviewed included relatively small samples, and varied in their methodology and patient populations. While there was some heterogeneity in the available data on prevalence of KS in Europe, estimates were consistently below 1 per 10,000. Improvements in the definition of specific diagnostic criteria for KS as well as wider availability of genetic testing, and better awareness about the condition will help enhance the detection rate moving forwards. Hence prevalence estimates should be updated over time.

351 | Does geographic access to providers matter for pediatric ADHD treatment engagement and medication adherence?

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Background: ADHD management requires frequent provider visits that may put a significant travel burden on families of children with ADHD.

Objectives: To examine the impact of geographic access to providers on ADHD treatment engagement and medication adherence in children and adolescents with newly diagnosed ADHD.

Methods: A retrospective cohort study was conducted using the 2013–2016 claims data from a Medicaid Managed Care plan active in the area around Houston. Individuals aged 4–18 years with an incident ADHD diagnosis were identified. Geographic access measures used were: a) Travel distance to the provider who made ADHD diagnosis/initiated the treatment, defined as the shortest route calculated from Google Maps®. b) Primary care providers (PCP) density per 10,000 residents within a 5-mile travel distance radius from the population center of each patient's zip code; and c) mental health specialist density. Density was calculated by geographic information system based floating catchment method using ArcGIS®. Patients were followed for 3 months post-index ADHD diagnosis to assess the treatment engagement defined as receiving ≥2 sessions of psychotherapy for ADHD, ≥2 ADHD prescriptions or both. Among those who were engaged in pharmacotherapy, treatment adherence was assessed using proportion of days covered (PDC) within 300 days post-index prescription. Multivariate logistic regression was conducted to test the association between the geographic access measures and the odds of treatment engagement and medication adherence.

Results: A total of 10,206 cases with an incident ADHD diagnosis were identified, of which 62% had access to 5 PCPs and 82% had access to ≥1 specialist within 5 miles of travel distance. PCPs initiated the treatment in ~70% cases and nearly a half traveled 5 to 15 miles to the providers who initiated their ADHD treatment. The treatment engagement rate was 55% and the mean PDC was 0.54 (±0.24) among those engaged in treatment. None of the geographic access measures were significantly associated with ADHD treatment engagement and treatment adherence (e.g. effect of travel distance on treatment engagement: 5–15 miles vs <5 miles: OR = 1.17, 95% CI [0.93–1.47]; >15 miles vs <5 miles: OR = 1.19, 95% CI [0.93–1.52] and effect of PCP density on treatment engagement: 5–10 PCP vs < 5 PCP: OR = 0.96, 95% CI [0.72–1.27]; >10 PCP vs < 5 PCP: OR = 1.18, 95% CI [0.90–1.54]).

Conclusions: Different from the treatment for pediatric depression, a significant geographic access barrier was not found in the care for pediatric ADHD. This may be due to PCPs' in-depth participation in ADHD diagnosis and treatment.

352 | Proactive risk assessment of intrathecal chemotherapy in pediatric oncology at referral Hospital in Kenya: A cross sectional study

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Background: Chemotherapeutic agents are classified as high alert medications due to their high toxicity, narrow therapeutic range and potential for medication related problems. Intrathecal chemotherapy is associated with potentially fatal but preventable medication errors.

Objectives: To determine the prevalence of intrathecal chemotherapy and the associated hazards in pediatric oncology patients at Kenyatta National Hospital.

Methods: Patient demographics, diagnosis and indication for intrathecal chemotherapy data was obtained retrospectively from medical records of pediatric patients on chemotherapy admitted between January and December 2015. Data was collected between October and December 2016 and analyzed descriptively and by logistic regression. To identify the potential hazards associated with the prescribing, dispensing, preparation and administration of intra-

thecal chemotherapy, a multidisciplinary team of nine members working in pediatric oncology was interviewed. The Healthcare Failure Mode and Effect Analysis was used to identify potential failure modes, which were subjected to hazard and decision tree analyses.

Results: A total of 281 patient records were retrieved and 198 patients were on chemotherapy. Out of the thirty three patients (16.7%) on intrathecal chemotherapy, 23 were males while 10 were females. A total of 151 intrathecal doses were administered. The study identified 54 failure modes. Ten failure modes were deemed to have a sufficient likelihood of occurrence and severity to warrant control measures. These include; inability to determine the date the preceding intrathecal dose was administered and dispensing unlabeled medication for intrathecal administration. Seven failure modes were identified as single point weaknesses whose occurrence would lead to process failure. These include; generation of an incorrect medication order from a prescription, and errors in intrathecal dose determination.

Conclusions: The current practice of intrathecal chemotherapy does not provide adequate safeguards to ensure patient and provider safety. Key recommendations were made in the form of computerized prescribing and ordering, induction training and regular competence assessment and adequate supply and availability of equipment and materials.

353 | Antibiotics utilization in pediatric respiratory tract infections at tertiary care hospitals in an Indian City

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Background: Respiratory tract infections (RTIs) are the most common medical emergencies in children, especially during the first years of life and account for 25% of deaths among children (aged below 5 years) in developing countries possibly owing to poor understanding of antibiotic drug utilization patterns. Appropriate and rational usage of antibiotic is the key to manage RTIs which may lead to decreased mortality. Hence, the present study was undertaken to explore the drug utilization pattern of antibiotics in the treatment of respiratory tract infections in pediatrics (Aged below 15 years).

Objectives: To assess the antibiotic drug utilization in pediatric population suffering with respiratory tract infections which include upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI) and recurrent respiratory tract infection (RRTI).

Methods: The study undertaken was a prospective descriptive cross-sectional study carried out at two tertiary care hospitals for a duration of six months from April, 2018 to September, 2018). Pediatric out patients with respiratory tract infection were enrolled in the study and relevant data were collected and recorded in data collection form which includes various sections of important information like demographics, present complaints, diagnosis, prescribed medications (dose, route, total quantity, duration and cost), and investigations. All the relevant and necessary data were collected from patient's prescriptions; interviewing the patient care takers and diagnostic laboratory reports.

Results: Out of 1082 patients (Mean age-6.8 years) enrolled in the study, majority of patients were males (62%), and in them most of the patients were infants (aged 1 month to 2 years; 58%) and young children (2 years to 6 years; 27%). The study population included a higher proportion of patients from urban area (59%) compared to rural area (41%). The study results indicated a higher incidence (76%) of LRTI followed by URTI (15%) and RRTI (10%). It was found that β- lactams (71%) were highly prescribed in the respiratory tract infections followed by macrolides (19%), fluoroquinolones (4%) and aminoglycosides (3.5%). Among various macrolides, azithromycin was highly prescribed drug (69%) especially in RRTIs.

Conclusions: In conclusion the study indicated that the cephalosporins were highly prescribed in pediatric RTIs. But, in the treatment of recurrent respiratory tract infections, macrolides were preferred over other classes of antibiotics.

354 | Comorbidities and treatments in United States youth with chronic musculoskeletal pain

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Background: Chronic musculoskeletal (MSK) pain has been associated with other chronic illnesses, including mental illness, and with high rates of pain medication use. Few studies have investigated treatment patterns and comorbidities associated with chronic MSK pain in youth across the US.

Objectives: To identify comorbidities and treatments associated with chronic MSK pain in a nationally representative sample of US youth.

Methods: We used the National Ambulatory Medical Care Survey (2002–2015) and outpatient National Hospital Ambulatory Medical Care Survey (2002–2011), which contain national cross-sectional, visit-level data on demographics, reasons for visit (RFV), diagnoses, and drugs ordered in outpatient US clinics. The study included all visits for youth age 8–24, excluding those with MSK pain whose duration could not be determined. We identified visits for chronic (≥3mo) or acute (<3mo) MSK pain based on the main RFV. We

compared comorbidities and drugs ordered in visits for chronic MSK pain with visits for either acute MSK pain or any reason besides chronic MSK pain, using chi-square tests and logistic regression, adjusting for age, sex, race, ethnicity, insurance, and setting of care.

Results: Chronic and acute MSK pain accounted for 1.2% and 4.0% of all visits, respectively. Compared to visits for acute MSK pain, visits for chronic MSK pain were more commonly accompanied by diagnoses of a chronic illness (39.5% vs. 20.3%, adjusted odds ratio [AOR] 1.9, 95% CI 1.4, 2.5). Mental disorders (14.9% vs. 4.4%, AOR 2.7, 95% CI 1.7, 4.5) and prescribed psychotropic drugs (25.3% vs. 10.9%, AOR 1.8, 95% CI 1.1, 3.0) were also more common in visits for chronic MSK pain than in visits for acute MSK pain. In contrast, the prevalence of mental disorders and psychotropic drug orders was lower in visits for chronic MSK pain than in visits for other reasons. Opioids (28.0% vs. 15.9%, AOR 1.5, 95% CI, 1.01, 2.1) and gastrointestinal drugs (9.9% vs. 4.0%, AOR 2.4, 95% CI 1.1, 5.2) were more commonly ordered for chronic MSK pain than for acute MSK pain; nonsteroidal anti-inflammatories (NSAIDs) were less commonly ordered for chronic pain (36.4% vs. 37.7%, AOR 0.70, 95% CI 0.55, 0.89), and muscle relaxants were ordered at similar rates in visits for chronic and acute MSK pain.

Conclusions: Compared to those with acute MSK pain, youth with chronic MSK pain in the US are more likely to have other chronic conditions, including mental illness, and be prescribed psychotropic drugs and opioids, but less likely to receive NSAIDs. Further research in longitudinal settings will help clarify the temporality of these relationships and associated clinical outcomes.

355 | Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs in pediatric patients

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Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe dermatologic adverse reactions. Although these reactions are rare in incidence, they have been associated with antiepileptic drugs (AEDs), along with certain other medication classes. Though AEDs are used in children, studies evaluating SJS/TEN in pediatric populations exposed to AEDs studies are limited.

Objectives: To quantify the reporting odds ratio (ROR) and proportional reporting ratio (PRR) of SJS/TEN in children exposed to AEDs.

Methods: A disproportionality analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) was performed for a 42-month period (July 2014–December 2017). Exclusion criteria consisted of follow up reports, missing age, and patients ≥18 years old. A search was conducted using the medical dictionary for regulatory activities (MedRA) terms "Stevens-Johnson syndrome" and "toxic epidermal necrolysis" and reports were reviewed for inclusion. The ROR, PRR, and 95% confidence intervals (CI) were calculated for each medication compared to non-AEDs, as well as for the entire class, using OpenEpi.

Results: There was a total of 95,221 reactions reported for pediatric patients during the study period with 5,831 (6%) consisting of AEDs. There were 148 reports of SJS/TEN within the study period, with AEDs having the most reports of any medication class (*n* = 42, 28%), followed by nonsteroidal anti-inflammatories (NSAIDS; *n* = 23, 16%). Of the 34 AEDs assessed, 24% (*n* = 8) had at least 1 report of SJS/TEN: carbamazepine (*n* = 1), clonazepam (*n* = 5), diazepam (n = 1), lamotrigine (*n* = 27), levetiracetam (*n* = 3), oxcarbazepine (n = 2), rufinamide (n = 1), and valproic acid (n = 2). AEDs as a class had a ROR of 6.1 (CI 4.3–8.7) and a PRR of 6.1 (CI 4.3–8.7). Only 4 AED medications had statistically significant risk estimates with rufinamide having a ROR of 46.8 (CI 6.2–353.6) and a PRR of 44.4 (CI 6.5–301.8), clonazepam with a ROR 38.3 (CI 15.3–95.7) and a PRR of 36.7 (CI 15.2–88.2), lamotrigine with a ROR of 36.0 (CI 23.4–55.3) and a PRR of 34.6 (CI 22.8–52.4), and oxcarbazepine with a ROR of 11.3 (CI 2.8–46.2) and a PRR of 11.2 (CI 2.8–44.8).

Conclusions: AEDs as a class had approximately a 6-fold increased risk of SJS/TEN compared to all other non-AED medications. A significant disproportionality signal for SJS/TEN was observed with rufinamide, clonazepam, lamotrigine, and oxcarbazepine. Proper consultation should be given to patients when initiating these agents to alert their parents of early warning signs for this potentially fatal adverse reaction.

356 | Efficacy of Pidotimod in children: A systematic review

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Background: As the only marketed drug with oral bioactive immune promoter, pidomide is widely used in children with respiratory tract and urinary tract infections and low immune function. However, the research results are inconsistent, and its effectiveness is controversial and there is still a lack of systematic evaluation to evaluate its effectiveness.

Objectives: To systematically evaluate the efficacy of pidotimod in children, and provide evidence of evidence-based medicine for clinical treatment.

Methods: Databases including Pubmed, The Cochrane Library, EMbase (Ovid), CNKI, CBM, VIP and WanFang Database were searched from inception to January 2018,to collect randomized controlled trials (RCTs) about pidotimod in children. Two reviewers independently screened literature, extracted data, evaluate the quality of included studies,and meta-analysis was performed by RevMan 5.3.

Results: 318 RCTs involving 27500 children were included. The result of meta-analysis showed that compared with the control group, the pidotimod group could significantly reduce the number of respiratory tract infection[MD = −2.79, 95%CI(−3.12, −2.46), $P < 0.05$],the time of respiratory tract infection[MD = −4.15, 95%CI(−4.72, −3.58),P < 0.05], the time of fever[MD = −1.47,95%CI(−1.77,-1.17),P < 0.05] in recurrent respiratory tract infection. And pidotimod could reduce the time of fever [MD = −0.25,95%CI(−0.38,-0.11),P < 0.05] in mycoplasma pneumoniae pneumonia, the time of fever [RR = 1.163,95%CI(1.043,1.297,P < 0.05)] in hand-foot-mouth disease,incidence of anaphylactoid purpura followed up for 6 months[RR = 0.370,95%CI(0.215, 0.636),P < 0.05] in anaphylactoid purpura,but there was no significant difference between the pidotimod group and the control group in the incidence of asthma followed up for 1 year[RR = 0.80,95%CI(0.60, 1.06),$P > 0.05$]in asthma.

Conclusions: Current evidence shows that, Pidotimod may be effective for respiratory tract infection,asthma,hand-foot-mouth disease, could reduce disease relapse and relieve symptoms related to illness. Due to limited quality included studies more strict designed and multicenter clinical researches are needed to verify the above conclusion.

357 | Antibiotics prescribing among children under five at a tertiary healthcare facility south East Nigeria

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Background: Inappropriate use of antibiotics especially in children undermines treatment goals constituting significant danger to the development of the child. Local monitoring of prescribing in relation to diagnosis is essential for enhanced prescription practices.

Objectives: The study aimed to describe use pattern of antibiotics among children under five at a university teaching hospital south east Nigeria.

Methods: A cross-sectional observational study was conducted in a university teaching hospital in south eastern Nigeria, selected based on availability of reliable data and consent to participate in the study. Data were retrospectively collected from patient folders and prescription records over the period of January to June 2016, using a customized form for relevant information. Only cases prescribed antibiotics were included for analysis while incomplete data were excluded. The antibiotics were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system and analyzed to include the Daily Defined Dose (DDD) per patient pay day.

Results: A total of 286 children folders were reviewed out of which 208 were prescribed antibiotics. Only one antibiotic was prescribed in 78% of encounters while up to three were prescribed per patient in 6% of cases. Most (57%) of prescribed antibiotics were through oral route while 47% were prescribed for parenteral administration. Cephalosporins (47%) followed by penicilins (42%) were the most prescribed classes of the antibiotics, with amoxicillin (16%) as the most commonly prescribed agent. Gastrointestinal disorders (32%), followed by malaria (24%) were the most commonly diagnosed conditions.

Conclusions: Findings suggest significant rational prescribing of antibiotics in the study facility. However, there appears to be an overuse of penicilins and cephalosporins mostly among children aged below one year, with limited laboratory investigations. There is scope for enhanced adherence to guidelines to help prevent antibiotic resistance and improved child health outcomes.

358 | Appropriateness of postoperative analgesic doses among pediatric surgical patients in a teaching Hospital in Northwest Nigeria

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Background: Inappropriate uses of analgesics and suboptimal treatment are a global problem and concerning to healthcare management of postoperative pain, particularly in children. Information relating to the management of postoperative pain in children is generally limited, particularly in low and middle income countries. Such information is, however, unavailable from the Northwest Nigeria.

Objectives: To describe the types of analgesic drugs used postoperatively for children and evaluated the appropriateness of their doses to ensure best practices. Factors predicting the risk of underdosed analgesic drugs were also determined.

Methods: We performed a retrospective chart review of patients administered analgesic drugs after surgery between 1 January 2015 and 31 December 2017. Exposures were categories of analgesic drug doses (underdose, normal dose, and overdose). Simple descriptive and comparative statistical analyses were performed. Logistic regression was used to build analgesic underdose risk prediction model.

Results: A total of 194 patients received 281 analgesic drugs. Summarily, 112 (57.67%), 77 (39.7%), and 5 (2.76%) patients received single, double and triple analgesic drugs, respectively. Paracetamol (148; 52.7%) and pentazocine (77; 27.54%) were the most commonly used analgesic drugs. Of the 7 different analgesic drugs, overdosing (64; 22.8%) and underdosing (89; 31.7%) were recorded. There was a statistically significant association between analgesic drug types and categories of dose appropriateness; *p* less than 0.001. None of the patients' demographics or the number of analgesic drugs used predicted the risk of underdosing.

Conclusions: Inappropriate use of analgesic drugs (overdosing or underdosing) is common and cuts across all analgesic drug types and all age groups. A substantial number of children underdosed with the analgesic drugs suggested pain under-treatment.

359 | Observation versus prophylactic antibiotics in late preterm infants with premature rupture of membranes: A pragmatic randomized controlled trial

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Background: This study aimed to compare the effect of expectant observation versus prophylactic antibiotics in the prevention and treatment of infections in late preterm infants born to mothers with premature rupture of membranes (PROM).

Objectives: This study aimed to compare the effect of expectant observation versus prophylactic antibiotics in the prevention and treatment of infections in late preterm infants born to mothers with premature rupture of membranes (PROM).

Methods: Design A pragmatic randomized controlled trial. **Setting** NICU of West China Second University Hospital (WCSUH). **Patients** Infants between 34 and 36 weeks gestation weighting ≥1500 grams born to mothers with PROM. **Interventions** Infants were randomized to either prophylactic antibiotic group (cefuroxime, 30 mg/kg q12h, 48 hours) or expectant observation group. **Main outcome measures** The incidence of sepsis and the incidence of systemic bacterial infection during hospitalization.

Results: A total of 120 infants were enrolled (*n* = 60/group), 113 of whom were followed during follow-up. There was no significant difference in terms of sepsis or systemic bacterial infections between the 2 groups during hospitalization (RR 0.25, 95% CI 0.01 to 5.66, *P* = 0.48; RR 0.80, 95% CI 0.23 to 2.84, *P* = 0.73). Twelve (20.0%) infants in the expectant observation group received antibiotics during hospitalization. No death or fungal infection occurred in the two groups. The risk of readmission due to infection seemed to be higher in expectant group, but without statistically significant difference (8.3% vs 1.7%, RR 5.10, 95%CI 0.58 to 45.12, *P* = 0.14).

Conclusions: Expectant observation strategy could be considered in late preterm infants born to mothers with PROM to reduce unnecessary consumption of antibiotics. Future study with sufficient sample size should compare the long term outcomes following these two approaches.

360 | Drug-related problems in pediatric patients with respiratory disease hospitalized in Rionegro Antioquia, Colombia

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Background: Drug related problems (DRP) are common cause of morbidity and mortality worldwide. The evidence about incidence of DRP in the pediatric population, in developing countries is scarce.

Objectives: The objective of this study was to determine and characterize the frequency of problems related to medications in patients with respiratory pathology.

Methods: Cross-sectional and analytical study. A stratified random sampling of 110 clinical records of patients hospitalized in the pediatric service was analyzed, whose main reason for hospitalization was some diagnosis of respiratory pathology. Nursing records and medication administration were additionally reviewed.

Results: 110 patients were studied, with an age (median) of 30.5 months, mainly of females 79% (*n* = 87). The most frequent diagnoses among the patients studied were bronchiolitis 39% (*n* = 43), pneumonia 34.55% (*n* = 38) and asthmatic crisis 20.91% (*n* = 23). The estimated incidence density of DRP was 10.62 cases per year. The DRP most frequently encountered were prescription-prescription problems (81%), followed by problems of therapeutic duplicity (11%) and adverse drug events (7%). 79% of the indication-prescription problems occurred in patients with bronchiolitis mainly related to the use of bronchodilators or hypertonic solution. 83% of duplicity problems were noted in asthmatic crisis mainly simultaneous use of two inhaled corticosteroids or antimuscarinics. The most frequently reported adverse event was epistaxis due to the use of oxygen or nebulized medication.

Conclusions: This is the first study in the pediatric population focused on respiratory pathology in our country. It is necessary to establish educational and computer tools that prevent and warn this type of medical errors.

361 | Assessment of clinical Care for Infants with neonatal abstinence syndrome in an electronic health record database

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Background: Administrative claims data are increasingly being used in observational studies of medication exposure and safety in pregnancy. However, certain research questions may not be adequately addressed using claims information alone due to limitations in ascertainment or clinical granularity. As an example, studies of treatment and outcomes among infants exhibiting neonatal abstinence syndrome (NAS) following in-utero exposure to opioids may depend on assessment tools and treatments (both pharmacologic and non-pharmacologic) that do not result in specific claims. Other data sources, such as electronic health records (EHR) databases may provide this information either as a standalone resource or through linkage to claims.

Objectives: To present a real-world view of pharmacological and non-pharmacological management and measures among neonates with NAS using an EHR database. Two individual cases of NAS clinical characteristics and management based on the Finnegan scoring system illustrate the findings.

Methods: A random sample of 100 neonates with clinical notes that indicate NAS was identified within the Optum EHR database. We excluded those with missing activity dates to arrive at 74 for whom we generated a chronological listing of clinical notes. Manual review of these listings was conducted to evaluate the presence of Finnegan scores and characterize those available.

Results: From the 74 neonates with NAS mention in clinical notes, 36 (49%) had Finnegan scores, most showing repeat measurements over the course of the hospital stay. Out of the 74, 43 (58%) had pharmacotherapy consisting of morphine (30), methadone (25), phenobarbital (16), clonidine (3) and buprenorphine (11), as either monotherapy or in combination. Non-pharmacological care was observed in the clinical notes for 25 (34%), and included mentions of calming (18), swaddling (1), holding (3) and use of breast pump (10). One newborn female with an initial Finnegan score of 16, received a combination of morphine, methadone, phenobarbital and buprenorphine, and was discharged with a Finnegan score of 4 after 13 days of inpatient treatment. A newborn male without Finnegan mention in the clinical notes was treated with buprenorphine, calming, holding and use of a breast pump. The infant was discharged after 6 days of inpatient stay.

Conclusions: The availability of EHR databases allows for a more complete clinical picture to be developed among neonates with NAS. Certain research questions may benefit from the use of EHR, and this data source should be considered when conducting a pharmacoepidemiology study.

362 | Antimicrobial prescribing in infants in Indonesia

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Background: Antimicrobial resistance has become a global health emergency and is mainly caused by inappropriate antibiotic use in clinical and community setting.

Objectives: to evaluate the antimicrobial prescribing pattern in infant in Indonesia.

Methods: A cohort analysis was conducted in 1621 participants from Rotavirus Vaccine RV3BB Phase IIb trial conducted in Indonesia from January 2013 through July 2016. The concomitant medication recorded all medications, including antibiotics until the 18 months of follow-up. Information's regarding antibiotic prescribing including the frequency, duration of usage, formulation, classes, indications, and their association with the vaccine trial were evaluated, including prophylactic antibiotic and perinatal.

Results: Of 1621 participants, 551 (33.99%) received at least one antibiotic for treatment of infections during the 18 months observation period. The number of illness episodes were significantly associated with the incidence of antibiotic prescribing (p-value<0.05). A total of 951 antibiotic were prescribed during 18 months follow up, with some (7.57%) were antimicrobial combination. The average duration of antibiotic course was 4.77 days, and no significant association with the RV3-BB vaccine was observed. Penicillin and sulphonamides were the most common antibiotic classes prescribed (39.01% and 24.60%, respectively). Among illness that were treated by antibiotic, 84.78% of prescribed for upper respiratory tract infection, non-bloody diarrhea 74.85%. Prophylactic antibiotics were prescribed in 1244 (76.74%) participants and antibiotic prescribed in 235 mothers of participants (14.50%) during perinatal period.

Conclusions: The prescribing rate suggested need an improvement of antimicrobial stewardship implementation in our setting. The overuse of antibiotic in URTIs and non-bloody diarrhea was still a major problem. Different classes of antibiotic were also inappropriately prescribed and may risk development of antimicrobial resistance.

363 | Pharmacist-conducted review prevents potential prescribing errors of neonatal parenteral nutrition: A cross sectional study

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Background: Parenteral nutrition [PN] Preparations are considered as high alert medications per the Institute For Safe Medication Practices [ISMP]. Thus, medication errors involving PN bear heightened risk to patients especially for vulnerable populations as neonates. Previous studies highlighted pharmacists' contribution to PN prescribing, monitoring, prevention of medication errors and education of other health care professionals.

Objectives: The purpose of this study was to assess the impact of pharmacist-conducted PN order review on the prevention of potential prescribing errors.

Methods: A pharmacist reviewed all PN orders of neonatal intensive care unit [NICU] patients of King Faisal military hospital, Khamis Mushait, Saudi Arabia. Pharmacist's recommendations were communicated to the prescribers for appropriate action. A cross sectional study was conducted to detect prescribing errors prevented due to Pharmacist's recommendations since January 2017 till December 2017. Medication errors were categorized by two pharmacists and a neonatologist per the Pharmaceutical Care Network Europe (PCNE) drug related problem classification v 8.02.

Results: During the study period, 2350 PN orders were reviewed by Pharmacist, 214 prescribing errors were detected and prevented in 199 orders (8.47% of orders). Dosing errors and omission errors constituted the highest percentage of errors prevented (69.6% and 22.4% respectively). Sub-therapeutic doses were found in 44.4% of errors while Supra-therapeutic doses were detected in 25.2% of them. The remaining 7.9% of prescribing errors were due to incomplete patients' data. More than 96% of prescribing errors involved eight components of PN orders; Dextrose (17.1%), lipids and fat soluble vitamins (16.6%), Heparin (15.5%), Magnesium Sulphate (10.9%), Sodium Chloride (10.4%), Amino Acids (9.9%), Phosphate (9.3%) and Potassium Chloride (7.3%).

Conclusions: Pharmacist-conducted review of PN orders seems to have significant role in prevention of prescribing errors.

364 | Outpatient and inpatient use of ribavirin among children under 14 years old in Yinzhou District, Ningbo, China

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Background: Ribavirin is a synthetic nucleoside antiviral drug. The number of adverse drug reaction (ADR) reports of ribavirin has increased significantly, and the common types of ADRs at home and abroad are different.

Objectives: To explore the clinical use of ribavirin among children under 14 years of age in Yinzhou district, Ningbo, China.

Methods: Outpatient and inpatient records from 2010 to 2016 in Yinzhou healthcare information database were used. We extracted patient identification number, birth date, gender, International Classification of Diseases code version 10 (ICD-10), medical institution code, prescription date, generic name, dosage form and route of administration from the database to analyze the clinical use of ribavirin. SQL was used to clean original data and R software was used to analyze the data. The main statistical indicator is the number of prescriptions.

Results: (1) Outpatient use: The number of prescriptions for children aged 14 and under accounted for 50.56% of the total prescriptions. For ribavirin injection, the proportion of prescriptions for children aged 14 and under was 50.40% of the total ribavirin injection prescriptions and the main reason for ribavirin injection use was acute upper respiratory tract infection. For ribavirin granules and tablets, the proportion of prescriptions for children aged 14 and under was 77.19% and the main reason for use was acute upper respiratory tract infection. For Ribavirin eye drops, the proportion of prescriptions for children aged 14 and under was 28.97% and the main reason for use was conjunctival disorders. For ribavirin aerosol, the proportion of prescriptions for children aged 14 and under was 99.12% and the main reason for use was viral infection of skin and mucosal lesions. For ribavirin oral solution, the proportion of prescriptions for children aged 14 and under was 52.61% and the main reason for use was acute upper respiratory tract infection. (2) Inpatient use: The number of prescriptions for children aged 14 and under accounted for 9.15% of the total prescriptions. For ribavirin injection, the proportion of prescriptions for children aged 14 and under was 9.84% of the total ribavirin injection prescriptions and the main reason for ribavirin injection use was acute respiratory tract infection. For Ribavirin eye drops, the proportion of prescriptions for children aged 14 and under was 9.37% and the main reason for use was keratitis.

Conclusions: Irrational ribavirin use still existed in China. Medical institutions at all levels should strengthen the monitoring and control of ribavirin use to promote rational use of ribavirin.

365 | The association between antipsychotic polypharmacy and potential ADEs in pediatric psychiatric patients

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Background: A number of studies on antipsychotic polypharmacy (APP) have exhibited increasing trend of APP prevalence among pediatric patients, especially for Western countries. Polypharmacy is closely related with inappropriate drug use and consequently induces potential adverse drug events (ADEs). However, APP in pediatrics is

inadequately understood in Asian countries and the study on association between APP and ADEs has been rare.

Objectives: The aim of this study was to investigate the prevalence of APP and to explore the association between APP and potential ADEs in Korean psychiatric patients aged 2–19 years.

Methods: We used Health Insurance Review and Assessment Service - Pediatric Patients Sample (HIRA-PPS), which consists of nationally representative claim data. We selected psychiatric patients aged 2–19 years with F codes (ICD-10) from 2012 to 2016 (2012, *n* = 38,724; 2013, *n* = 34,836; 2014, *n* = 33,721; 2015, n = 33,195; 2016, n = 33,714). Potential ADEs was defined according to the list of ICD-10 codes by Stausberg J & Hasford J. The incidence of the ADEs was assessed from July to December in patients without the ADEs history from January to June in each year. Antipsychotics were classified according to the drug classifications of the Korea Food and Drug Administration (KFDA). APP was defined as the prescription of an average of two or more antipsychotic active ingredients per day for 6 months from January to June in each year. Descriptive statistics and logistic regressions were conducted to explore prescription patterns and risk factors associated with pediatric polypharmacy.

Results: The prevalence of pediatric APP was increasing in recent 5 years, which were 1.4%, 1.6%, 1.7%, 2.0%, and 2.2% in 2012, 2013, 2014, 2015, and 2016, respectively. When we explore the prevalence of APP according to age groups, the APP prevalence was higher in adolescents (aged 14–19 years: 2.6%) than preschool children (aged 1–7 years: 0.2%) and school aged children (aged 8–13 years: 1.4%). The proportion of potential ADEs was elevated with increasing daily mean of polypharmacy, especially for adolescents (without APP: 2.5% vs. with APP: 7.2). After adjustment for socio-demographics and admission history, the pediatric psychiatric patients with APP was 2.5 times higher risk of potential ADEs with statistical significance in multivariate logistic regression analysis.

Conclusions: Pediatric psychiatric patients with APP experienced a greater risk of potential ADEs. This result suggests that the introduction of a medication review system for pediatric psychiatric patients with APP is needed to reduce the potential ADEs.

366 | Determinants of aminoglycoside trough levels among pediatric patients in a large referral Hospital in Kenya: A prospective cohort study

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Background: Aminoglycosides antibiotics used in pediatrics for the management of severe infections. Routine measurement of aminoglycoside levels is required to monitor efficacy and toxicity; however this is not routinely done in resource limited settings and dosing is largely empiric.

Objectives: To determine aminoglycoside trough levels and factors affecting trough levels in pediatric patients at the Kenyatta National Hospital (KNH).

Methods: A prospective descriptive cohort study was conducted in the pediatric wards of the Kenyatta National Hospital between May and September 2018. All pediatric patients aged 5 < years receiving amikacin or gentamicin treatment were recruited. Patient records were reviewed daily by the principal investigator and aminoglycoside trough levels were determined on day three before the third dose of aminoglycosides. Patients' baseline characteristic and kidney function were also collected. The main outcome variable was aminoglycoside serum trough levels and this was used to stratify participants according to dosing. Linear and logistic regression was used to analyze the data; patients were categorized in the sub therapeutic range or otherwise. Ethical and institutional approval was obtained from KNH/UON Ethics and Research Committee.

Results: Overall, 140 pediatric patients were recruited into the study. The prevalence of aminoglycoside use was 57.12%. The most common indication for use was pneumonia 117 (83.45%). One hundred and ten patients were treated with gentamicin with a median dose of 53 mg [IQR: 21,70]/kg body weight for a duration of 7 days. Thirty patients were on amikacin with a median dose of 105 [IQR: 85,210] for a duration of 7 days. Nearly all the patients on amikacin (90%) had serum levels below the therapeutic range (<3.4 microgram/ml) in contrast to only 30 patients on gentamicin (27%) (>2 microgram/ml). The predictors for sub-therapeutic levels were age < 18 months (adjusted OR 0.36, 95% CI: 0.14–0.92), and weight < 10kgs (adjusted OR 0.2, 95% CI: 0.07–0.53).

Conclusions: There was a high prevalence of under dosing in pediatric patients who received aminoglycosides particularly for amikacin; therefore there is need to review and update the existing aminoglycoside use protocols to include therapeutic drug monitoring.

367 | The effect of antipsychotic polypharmacy on seizure incidence in pediatric psychiatric patients

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Background: Seizure has been reported the one of important side effect due to both typical and atypical antipsychotics. Considering this, antipsychotic polypharmacy (APP) can more elevate the risk of antipsychotic-related seizure (ARS) in psychiatric patients. However, the study on the effect of APP on ARS has been rare in pediatric patients.

Objectives: The main purpose of this study was to explore the association between APP and ARS in Korean psychiatric patients aged 2–19 years.

Methods: We used nationally representative claim data known as Health Insurance Review and Assessment Service - Pediatric Patients Sample (HIRA-PPS). Psychiatric patients was defined using F codes (ICD-10) from 2012 to 2016 (2012, *n* = 38,724; 2013, *n* = 34,836; 2014, *n* = 33,721; 2015, n = 33,195; 2016, n = 33,714). The case of seizure was defined according to the ICD-10 codes of G40 (Epilepsy and recurrent seizures) and R56 (Convulsions, not elsewhere classified). In a merged data of 5 years from 2012 to 2016, the incidence of seizure was identified from July to December in patients without the seizure history from January to June in each year. Antipsychotics were determined based on the drug classifications of the Korea Food and Drug Administration (KFDA). The APP was assessed only in 6 months from January to June in each year and it was defined when two or more antipsychotic active ingredients were prescribed per day, averagely. Multiple logistic regression as statistical analysis was performed.

Results: The proportions of seizure incidence were similar in recent 5 years, which were 1.5%, 1.4%, 1.6%, 1.7%, and 1.7% in 2012, 2013, 2014, 2015, and 2016, respectively. When we explore the incidence case of seizure according to APP exposure level, the incidence rate of seizure was higher in pediatric patients prescribed more than 2 antipsychotic medications (3.9%) than in patients without antipsychotic medication (1.7%). The seizure case was frequently observed in the pediatric patients with younger age (age 1–7 years), medical aid beneficiary, and admission history. After adjustment other related factors, Odds Ratio (OR) of APP in developing seizure was 1.7 (95%CI = 1.40–2.07) .

Conclusions: Pediatric psychiatric patients with APP exhibited the higher risk of seizure incidence. These results suggest that the APP may be a significant risk factor of possible ARS in pediatric patients. The further investigations using long-term follow-up data are needed to confirm the association between APP and ARS.

368 | Data-driven identification of adverse event reporting patterns for Japan in the WHO global database

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Background: Adverse event (AE) reporting patterns vary between countries, given differences in reporting culture, clinical practice and underlying patient populations. Japan collects over 50,000 domestic AE reports yearly and shares serious reports with VigiBase, the WHO global database of individual case safety reports. Understanding these reports in the global context could be helpful for regulators worldwide and aid hypothesis-generation for Japanese-specific vulnerabilities to adverse drug reactions.

Objectives: To explore differences in the reporting of AEs between Japan and other countries contributing to VigiBase.

Methods: vigiPoint is a method for data-driven exploration in pharmacovigilance. It outlines data subsets, pinpoints key features and facilitates expert review, using odds ratios subjected to statistical shrinkage to distinguish one data subset from another. Here, we compared 260,000 Japanese reports in VigiBase to 2.5 million reports from the rest of the world (RoW; of which 51% from US). This included reports in E2B format classified as serious and received between 2013 and 2018. Reporting patterns for which the 99% credibility interval of a shrunk log-odds ratios were above 0.5 or below −0.5 were flagged as key features. The shrinkage was set to the vigiPoint default (1% of the Japanese data subset).

Results: There were higher reporting rates in Japan from physicians (83% vs 39%) and pharmacists (17% vs 10%). It was also more common to see reports with more than five drugs per report (22% vs 14%) and reports with a single adverse event (72% vs 45%). More than half of the Japanese reports had a vigiGrade completeness score above 0.8 compared to about 1 in 5 in RoW. There were more reports than expected for patients aged 70–90 years and fewer reports for adults aged 20–60 years.

AEs reported more often in Japan included interstitial lung disease, hepatic function abnormal, platelet count decreased, neutrophil count decreased and drug eruption. AEs reported less often included death, fatigue, dyspnoea, fatigue and headache. Drugs reported more often in Japan included prednisolone, methotrexate and peginterferon alfa-2b. Drugs reported less often included rosiglitazone, adalimumab as well as blood substitutes and perfusion solutions.

Conclusions: Analysis of Japanese AE reports in global context has revealed key features that may reflect possible pharmaco-ethnic vulnerabilities in the Japanese, as well as differences in AE reporting and clinical practice. This knowledge is essential in the global collaboration of signal detection afforded by the WHO Programme for International Drug Monitoring.

369 | The utilization of a new tool in signal management - who drug standardized drug groupings

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Background: Screening of large databases of spontaneous reports of suspected adverse drug reactions (ADR) is performed by disproportionality analyses at the level of single drug - ADR pairs. Subsequent signal refinement may include exploration of additional clinically relevant concepts within the MedDRA hierarchy and potential drug class effects within the Anatomical Therapeutic Classification (ATC). WHODrug Standardized Drug Groupings (SDG) are specific classifications of drugs of interest, grouped according to properties such as their pharmacological effect or metabolic pathway.

Objectives: To demonstrate the utility of an SDG in the refinement of a signal nintedanib - colitis identified by statistical screening of Vigibase.

Methods: Disproportionality analysis was performed on 13 February 2019 in VigiBase, the global database for individual case safety reports; the combination of nintedanib - colitis (MedDRA PT) was highlighted with an IC_{025} of 0.96. An initial clinical review was undertaken to determine the need and/or direction of signal refinement within VigiBase data. Disproportionality analyses were performed for relevant adjacent terms in the MedDRA dictionary, as well as for drug groupings using both the ATC and SDG.

Results: Clinical review revealed nintedanib to be a small molecule tyrosine kinase (TK) inhibitor blocking vascular epithelial growth factor (VEGF), fibroblast GF and platelet-derived GF receptors. A mouse model reveals VEGF inhibition to be associated with regression of capillaries in intestinal villi, and gastrointestinal perforation is included in the Summary of Product Characteristics. Subsequent exploration of adjacent MedDRA PTs revealed IC_{025} of 0.02 for "colitis ischaemic" and 2.22 for "gastrointestinal perforation". Nintedanib is in ATC code LO1XE "protein kinase inhibitors" and in the SDG "Antiangiogenic drugs with antagonistic effect on the VEGFR, inhibiting actions on VEGF or VEGFR TKs". Respective disproportionality at ATC level was IC_{025} 0.04 for "colitis ischaemic" and IC_{025} 2.34 for "gastrointestinal perforation"; at the SDG level was IC_{025} 1.23 and IC_{025} 5.37.

Conclusions: Standardized drug groupings are a useful tool in the signal management process. Refinement of the signal "nintedanib-colitis" using an SDG provided stronger evidence of a potential causal relationship compared to ATC. Exploration of potential drug class effects in during signal assessment may be improved by use of WHODrug SDG.

370 | Identifying signals of drug–drug interactions involving direct-acting Oral anticoagulants: A translational biomedical informatics approach

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Background: Drug–drug interactions (DDIs) with oral anticoagulants are associated with increased risk of serious bleeding. Few studies have examined DDIs involving direct-acting oral anticoagulants (DOACs).

Objectives: To systematically identify which potentially interacting drugs are most likely to affect the rate of hospital presentation for serious bleeding when taken concomitantly with DOACs, using real world clinical data.

Methods: We identified all oral medications (i.e. precipitants) frequently co-prescribed with dabigatran, rivaroxaban, apixaban, and edoxaban within OptumInsight Clinformatics Data Mart, 2010–2016. First, we performed physiologically based pharmacokinetic (PBPK) modeling based on the inhibition of cytochromes P450s to predict which potential interacting drugs are likely to affect the rate of serious bleeding. Second, we conducted a high-throughput pharmacoepidemiologic screening study using self-controlled case series design and Optum claim data. We included adults with at least one dispensed DOAC prescription and at least one hospital presentation for serious bleeding. Conditional Poisson regression was used to estimate rate ratios and 95% confidence intervals comparing precipitant exposed vs. unexposed time for each DOAC-precipitant pair. To minimize within-person confounding by indication for the precipitant and to distinguish a DDI from an inherent effect of the precipitant on bleeding risk, we used pravastatin as a negative control object drug. Multiple estimation was adjusted using Semi-Bayes shrinkage.

Results: We predicted one moderate DDI (apixaban and clonidine) and one weak DDI (apixaban and fluconazole) based on PBPK modeling. We identified 45, 36 and 28 precipitants associated with increased rate of serious bleeding when used concomitantly with dabigatran, rivaroxaban and apixaban, respectively. Using pravastatin as the negative control, there were 23, 12 and 16 precipitants associated with elevated rate of serious bleeding for dabigatran, rivaroxaban, and apixaban, respectively. Among these DDI signals, 38 (75%) were not documented in DDI knowledge databases Lexicomp and/or Micromedex. The results of PBPK prediction and pharmacoepidemiologic screening were poorly correlated.

Conclusions: The identified potential DDI signals need further examination in future studies. In this example, combining the pharmacokinetic prediction and pharmacoepidemiologic screening did not significantly improve the ability to identify DDI signals.

371 | Knowledge attitudes and perceptions on adverse drug events reporting among patients and healthcare providers in rural Uganda

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Background: Drug regulators promote patient safety by monitoring adverse drug reactions. The reporting rate of suspected adverse drug reactions in Uganda is below the average for a well-performing system.

Objectives: To describe patient and healthcare worker knowledge, attitude and practice about adverse drug events and reporting at the community level.

Methods: A cross-sectional survey among respondents from randomly selected households and healthcare workers in Iganga Mayuge HDSS (IMHDSS) in Eastern Uganda.

Results: Of the 1034 community members, 59% sought treatment from private drug shops, 37% from either private clinics, health centers or hospitals while 4% sought treatment from herbalists, friends

or relatives. Over half of the respondents (56%) were aware that drugs can have negative effects, 57% expressed willingness to report an ADE while 43% did not know what to do in case an ADE occurred. Almost half (46%) could not differentiate between an ADE and the disease, and for those who could, the majority (76%) were willing to report an ADE in case it occurred. However, only 34% had ever reported an ADE when it actually occurred to them. For respondents who reported, 43% had their drugs changed, 31% were counseled while 11.5% continued on the same medication. For healthcare providers, 95% knew about an ADE but only 35% (n = 116) have ever reported. Some reasons for not reporting were fear of being victimized or sued upon reporting (35%), reported lack of adequate knowledge about ADE (26%) while 20% thought it would disappear shortly and 14% did not find it necessary to report the reaction.

Conclusions: Patients would want to report an ADE, but they do not have adequate knowledge about ADEs. Healthcare workers do not report because of fear and subjectivity. Dedicated pharmacovigilance interventions at the community level would improve community members' knowledge and hence ADE reporting.

372 | Identifying patients at risk of adverse outcomes from inappropriate polypharmacy

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Background: Polypharmacy is defined as the use of five or more medicines, which does not help distinguish clinically appropriate from inappropriate polypharmacy. Whilst there are various polypharmacy assessment tools, none of them combine the different aspects of medication rationalization to identify patients at risk of adverse events.

Objectives: To develop a score-based polypharmacy tool to identify patients at risk of adverse events.

Methods: A systematic review of existing polypharmacy tools and their validation against patient outcomes was undertaken. Expert doctors and pharmacists in the Quality Use of Medicines (QUM) were surveyed regarding their use of existing validated tools and important factors during polypharmacy assessment. Important medication-related factors identified from the literature and survey findings were subsequently tested against the outcomes of drug-related hospitalisations (DRH), emergency hospitalisations and mortality within one year of discharge from an outpatient multimorbidity clinic using binary logistic regression, before combining them into a final formula for the polypharmacy tool. Medicines on discharge were used for patients aged 65 years or over, discharged from the clinic between January 2010 to February 2017.

Results: The systematic review identified 42 polypharmacy tools, with 31.0% (n = 13) validated against outcomes. Experts in QUM (n = 22) revealed low use of validated polypharmacy tools and stated that whilst the number of medicines is important, medication-related factors such as drug–drug interactions, taking sedatives and anticholinergics, opioids and systemic corticosteroids are also important in polypharmacy assessment. The median age of the 601 patients included was 80.0 years (interquartile range or IQR 73.0–85.0 years), with patients taking a median of 12.0 medicines (IQR 8.0–16.0). The prevalence of drug–drug interactions was 76.4% (n = 459), sedatives and anticholinergics was 49.1% (n = 295), opioids was 18.0% (n = 108) and systemic corticosteroids was 8.3% (n = 50). Opioids predicted DRH, systemic corticosteroids predicted DRH and emergency hospitalisations and sedatives and anticholinergics predicted mortality. The number of medicines predicted emergency hospitalisations.

Conclusions: The prevalence of drug–drug interactions and sedatives and anticholinergics reflects the complexity of care for older multimorbid patients with polypharmacy. Whilst polypharmacy is defined using the number of medicines, this study shows that specific drug classes need to be additionally considered to identify patients at risk of adverse events.

373 | Integrating hypothesis-free signal detection with real-world data into existing signal management systems: A prospective evaluation of potential impact

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Background: Electronic Health Records are potentially useful data sources for the drug safety signal detection. Novel analysis methods and visualization tools can generate signals of disproportionate recording (SDRs) in longitudinal observational data but there is limited prospective testing.

Objectives: The overarching objective of this work was to develop and test a systematic approach equipped to highlight and review SDRs that was scalable and could be integrated into existing signal management systems.

Methods: Temporal patterns between drug claims and health outcomes were studied in the Truven MarketScan database (Jan 2010 - Jun 2015) by generating chronographs for 3 approved therapies: pregabalin (Lyrica), atorvastatin (Lipitor) and varenicline (Chantix). 271 event-drug pairs were identified for this study. All 271 drug-event pairs were screened via Self-Control Case Series, High-Dimensional Propensity Score methods, and findings from Pfizer Spontaneous Reporting System data. Lower bounds of the 95% CI of the test statistics for any drug-event pair >1 were treated as potential SDRs for further investigation and then visually evaluated via chronograph (graphical display of observed and expected counts). Potential SDRs

were reviewed by 3 subject matter experts. A chronograph was determined "positive" if it showed a clear upward trend after prescription compared to before prescription according to pre-defined criteria. Following the review, output was classified further as true positives, true negatives, false positives and false negative using clinical and label-based information.

Results: Among the 136 drug-event pairs reviewed, about 15% (*n* = 21) were labeled events. Only 26 (19%) chronographs are identified as positive of which 81% (n = 21) were false positives. The positive predictive value (PPV) ranged from 0.16 to 0.33; the negative predictive value (NPV) ranged from 0.65 to 0.98. The sensitivity ranged from 0.08 to 0.50 whereas specificity ranged from 0.66 to 0.96.

Conclusions: Signal detection methods/tools need to permit time-efficient discovery and assessment of underlying drug-event pairs. The triage approach produced 136 chronographs that required review from 271 drug-event pairs. Temporal pattern discovery of these data showed moderate-to-high NPV and specificity but poor PPV and sensitivity. Given the poor PPV, and that visual review of chronographs is time consuming, a need to more effectively filter the number of chronographs for manual review was identified for a subsequent analysis.

374 | Application of natural language processing techniques to extract insights for pharmacovigilance from published literatures

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Background: In pharmacovigilance (PV), scientific literatures are important source not only to identify individual case safety reports of adverse events for specific drugs but also to understand research trends including possible emerging safety issues. Because reviewing literatures manually is a time-consuming process, recently developing natural language processing (NLP) techniques may become help to provide insights. As a case study, we have tried to identify characteristics on literatures of rheumatoid arthritis (RA) where therapeutic breakthroughs including approvals of biologics have occurred in recent years.

Objectives: To understand the characteristic contents of literatures using NLP techniques.

Methods: PubMed was searched (1 January 2013 to 31 December 2017), and we collected literature abstracts regarding RA. Several subsets of abstracts were created based on the tags that enabled us to filter them with PV information; those are comprised of abstracts about adverse drug reactions, safety, autoimmune diseases often related with RA (e.g. systemic lupus erythematosus, Sjogren's syndrome) and pregnancy/pregnancy outcomes. Similarly, this research also used the tags about epidemiology information to filter abstracts with epidemiologic study methods. After pre-processing each set of abstracts' texts (e.g. removing stop words), TF-IDF analysis was performed to identify characteristic words in each set. In addition, Latent Dirichlet Allocation (LDA) was performed to find out 20 specific topics from the texts with epidemiology information. All analysis was carried out using R statistical software for text-mining.

Results: We identified 2064 abstracts regarding RA. Overall, the most frequently appearing words were RA (3021 appearances), patients (2683), arthritis (1627), disease (1450), rheumatoid (1418) and treatment (985). Some characteristic words could be identified by reviewing words that have relatively high TF-IDF scores in PV information; interestingly, certolizumab-pegol was found because it is the first tumor necrosis factor-alpha inhibitor approved in Europe for medication available for women with RA during pregnancy in 2018. Additionally, LDA revealed some research topics such as cancer genetics, cardiovascular outcomes, efficacy of biologics, life styles and disease activities.

Conclusions: Analyzing literatures using NLP techniques can be helpful to efficiently explore insights including what kinds of safety-related events exist and how diseases are investigated by pharmacoepidemiologic studies.

375 | Applying prescription sequence symmetry analysis to detect unknown adverse drug reactions in a Chinese claims database

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Background: Many adverse drug reaction (ADR) warning systems are based on current knowledge. Thus, signal detection methods that can identify unknowns ADRs are needed.

Objectives: To explore ways of detecting unknown ADRs using prescription sequence symmetry analysis (PSSA) in a Chinese national claims database.

Methods: We applied PSSA to determine which drugs might have hepatotoxicity in the database of National Basic Medical Insurance for Urban Employees (NBMIUE). Several liver-protective drugs were chosen as marker drugs of liver injury. All the patients with at least one prescription of these marker drugs between 01/01/2015 and 31/12/2015 were included in the study and all of their records were extracted from the data source. 4-digit and 5-digit codes of the Anatomical Therapeutic Chemical (ATC) Classification System were used respectively to classify all the prescribed drugs in the study population and each drug category identified was used as an index drug for further PSSA analysis. Crude sequence ratios (CSR) were calculated. CSRs with lower limits of confidence interval bigger than 1 were considered positive PSSA results. These positive results were then interpreted as known ADRs, false positive results induced by bias or unknown ADRs, based on drug labels, literature review, knowledge base searching and expert consultation. Descriptive statistics were used to summarize each type of the results.

Results: A total of 57,008 liver protective drug users were included. They used altogether 661 classes of drug identified by 5-digit ATC codes, among which 133 positive signals were found by PSSA (20.1%). After interpretation, 97 positive signals were considered as known ADRs (72.9%), 34 false positive signals (25.6%) and 2 unknown ADRs (1.5%). Positive predictive value based on this interpretation was 74.4% (95%CI, 66.4%–81.1%) in all drugs and was 100% in traditional Chinese medicine drugs.

Conclusions: PSSA proves to be effective in detecting potential unknown ADR signals in the NBMIUE database. The unknown signals detected in this study need further investigation. Future studies are expected to test the method in patients with longer follow-up period, and also to optimize the process of deciding known ADR and potential bias to improve the efficiency of PSSA in detecting unknown ADRs.

376 | Safety-signal detection for liver dysfunction associated with a drug by utilizing MID-NET®: Results from pilot studies

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Background: The Medical Information Database (MID-NET®) was formally launched in April 2018. One of the notable features of MID-NET® is that it makes many laboratory test results available for analysis. The Pharmaceutical and Medical Devices Agency (PMDA) has conducted pilot studies in different scenarios to examine the potential applicability of the MID-NET® to safety-signal detection.

Objectives: To assess advantages and limitations of the MID-NET® as a safety-signal detection tool.

Methods: We have conducted two pilot cohort studies with two couples of target drugs and comparison drugs (amiodarone vs. nifekalant, and alogliptin vs. vildagliptin) to assess the applicability of MID-NET® by examining the recognized risks: the amiodarone-induced liver dysfunction and the alogliptin-induced liver dysfunction. Each of the studies includes subjects who met the following criteria: 1) who initiated their medication with the target drug or the comparison drug between April 2009 and September 2016; 2) whose first data in the MID-NET® was recorded more than 180 days before initiating the target drug or the comparison drug; 3) whose levels of liver function were within the normal range during the 180-day period before the date on their first prescription, and 4) who did not have concomitant medications of the target drug and the comparison drug on the date of their first prescription. The liver dysfunction was defined as more than five-fold increase in ALT, AST, or/and ALP from the baseline. Every 6 months from 1st April 2009, we calculated the non-adjusted incidence rate ratio and the adjusted incidence rate ratio (aRR), in which subjects in each target drug group were 1:1 matched to subjects in its comparison group, based on sex, age, and the date of the first prescription.

Results: In the study of the first pair (amiodarone vs. nifekalant), the number of subjects was 613 for the amiodarone and 160 for the nifelakant. The aRR indicated a higher risk in the amiodarone compared to the nifekalant (aRR:20.60, 95%CI: 4.92–86.20) after the 6th observational point (March 2012). In the other study, the number of subjects was 4,155 for the alogliptin and 7,472 for the vildagliptin. The aRR indicated a lower risk in the alogliptin compared to the vildagliptin (aRR: 0.76, 95%CI: 0.59–0.98) at the final observational point (September 2016).

Conclusions: Although more careful analysis would be necessary, the MID-NET® has huge potential to detect a safety signal of the liver dysfunction. To properly use MID-NET® in pharmacovigilance, it is essential to extend a range of investigations in other drugs with similar protocols.

377 | Adverse reaction signal detection for statins in a Chinese regional healthcare database using tree based scan statistic method

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Background: With increasing availability, the use of healthcare databases as complementary data source for drug safety signal detection has been explored to cover the limitations of spontaneous reporting. The tree-based scan statistic (TreeScan) is a statistical data mining tool that has been used for drug safety signal detection.

Objectives: To apply TreeScan method for detecting adverse effect signals of statins and evaluate the performance of TreeScan in Chinese Regional Healthcare Database.

Methods: Our study used the Yinzhou healthcare database, a linked primary and secondary care database, in Ningbo city, China, from 2010 to 2016. Patients older than 18 years with diagnosis of hypertension were included. We identified statin users according to the prescription information of out/in-patient. The Adverse Events (AEs) were defined using ICD-10 codes of out/in-patient diagnosis. We first detect the safety signals of statins by using the TreeScan method. In order to better evaluate the performance of the method, we established a set of reference signals by referring to a set of ICD-10 codes to identify AEs. Gold standard for these signals was constructed

by searching published Meta-analysis and systematic reviews and package inserts of statins. By comparing the signals to reference signals, we could compute measures of diagnostic test, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, youden index and area under the curve (AUC). **Results:** A total of 224,187 patients were finally enrolled and divided into two groups (85,758 statin users and 138,429 nonusers). We built a reference set of 126 AEs (ICD-10) including 13 positive signals and 113 negative signals. TreeScan generated 30 positive signals ($P < 0.05$), and 9 of them were known adverse effects. The sensitivity, specificity, PPV, NPV, accuracy, youden index and AUC were 69%, 82%, 31%, 96%, 81%, 52%, 75%, respectively.

Conclusions: TreeScan can be applied as a signal detection method in Chinese Regional healthcare database for drug safety surveillance, simultaneously evaluating small and large number of potential AEs (subsets of diagnosis codes) and adjusting for multiple testing inherent in many overlapping groups evaluated. Comparative evaluation study should be conducted to further evaluate its performance and explore its proper application condition.

378 | High dimensional empirical Bayes screening (ideas) in north American claims and VA electronic medical records

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Background: Suicide is the 10th leading cause of death in the US, and the rate has been rising for 16 years. Most suicide decedents have psychiatric disorders and are actively receiving healthcare, yet the effects of medications on suicidal behavior is intensely debated.

Objectives: To develop a statistical surveillance method based on population claims data and electronic medical records to identify drugs associated with increased or decreased risk of suicide attempts.

Methods: Design: Within-person incident-user cohort to simultaneously assess 923 drugs and suicide attempts. **Setting:** MarketScan (MS) claims for commercially insured patients and medical records of Veterans in the VA Corporate Data Warehouse from 2003–2014. **Participants:** 198,652 subjects with a suicide attempt and days' supply of any medication in either MarketScan (MS) (n = 923) or VA electronic medical records (n = 513). **Exposure:** First filled prescription of each of 923 drugs in MS data, 513 of which were also documented in VA electronic medical records. **Main Outcome:** Suicidal behavior (ICD-9 codes E950-E959). **Statistical analysis:** Mixed-effects logistic regression was used to estimate empirical Bayes (EB) odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for multiple comparisons for the individual drug effects. The EB OR is interpreted as the increased or decreased likelihood that the adverse event will occur following drug exposure.

Results: This new statistical surveillance system found 24 drugs with increased and 36 with reduced risk of suicidal behavior. In both populations (VA and MS), 7 drugs were associated with increased and 20 with decreased risk. The strongest increased risk signals occurred in alprazolam (OR 1.83 (1.57–2.12) (MS), OR 1.70 (1.34–2.16) (VA)), diazepam (OR 1.36 (1.09–1.70)(MS), OR 1.74 (1.42–2.13) (VA)), and hydromorphone (1.72 (1.07–2.79)(MS) and 1.79 (1.21–2.64) (VA)). Among the potentially most protective drugs were folic acid (OR 0.37 (0.25–0.56) (MS), OR 0.56 (0.51–0.62)), mirtazapine (OR 0.37 (0.31–0.45) (MS), OR 0.75 (0.67–0.83) (VA)) and naltrexone (OR 0.43 (0.30–0.60) (MS), OR 0.70 (0.57–0.87)). Of those with decreased risk signals, 22 of 36 (61.1%) are approved psychotropic medications, providing both a degree of validation of the method and reassurance to clinicians about the effectiveness and safety of these drugs in suicidal patients.

Conclusions: High-dimensional empirical Bayes screening for drug safety surveillance is feasible and generates statistically and clinically significant signals of possible risks and benefits of drugs on risk of suicide behavior.

379 | Characterization of drug interaction related signals leading to Eu regulatory action and a methodological review of novel drug interaction signal detection methods in the post-marketing setting

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Background: A growing rise in polypharmacy is often attributed to an aging population and associated co-morbidities. In patients with complex therapeutic regimens, this increases the potential of harmful drug interactions (DI's) which may result in unexpected adverse drug reactions. Current signal detection methods used to identify DI-related signals may not be sufficient. Novel methods utilizing big data sets, machine learning or algorithmic techniques may have a crucial role in DI-related signal detection.

Objectives: The aim of this study is to assess current and novel methods used to identify DI-related safety signals in the post-marketing setting.

Methods: Current methods used to detect DI-related signals will be reviewed using publicly available information from the European Medicines Agency (EMA) on signals leading to post-marketing regulatory action between July 2012 and December 2018. A review of the published literature will also be conducted to identify novel methods used to detect DI-related signals which may have utility in the post-marketing setting. A systematic approach will be used to assess the performance of novel DI signal detection methods based on predefined criteria including, for example, sensitivity, precision and applicability.

Results: Data collection, identification of valid data sources and methodological review are currently in progress. So far, one DI-related

signal which led to post-marketing regulatory action has been identified from the search whereby dehydration was associated with an interaction between tolvaptan (vasopressin antagonist used to treat inappropriate antidiuretic hormone secretion) and diuretic use. This DI-related signal was identified in 2012 based on 16 spontaneous reports. The identification of this signal resulted in an update to product information, regarding a possible interaction between tolvaptan and diuretic use and the risk of renal dysfunction.

Conclusions: The final results of this study will identify whether the majority of DI-related signals in the post-marketing setting are identified from individual case safety and spontaneous reports. Novel methods, utilizing big data sets and advancements in machine learning and computational power, have the potential to identify previously unknown and unexpected DI-related signals.

380 | Using innovative automation to author development safety update reports and enhance cost-effectiveness

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Background: Development Safety Update Reports (DSUR) present a comprehensive review and analysis of pertinent safety information related to investigational drugs collected during specified periods. Producing a quality DSUR is costly, time-consuming, resource-intensive, and requires effective communication across many different stakeholders.

Objectives: Develop an electronic DSUR authoring platform to auto-populate a text-based business template that reduces writing efforts without compromising quality or compliance to save time and money.

Methods: Using data analytics operating model, source documentation was gathered and mapped to 2 relevant text-based templates. The first template included keys which auto-populate via content extraction from various uploaded source documents. The second template served as a framework of text to be submitted in the final draft. Pre-defined fixed product attributes also directed population of optional content. Using expert and text rules as well as natural language processing, data and text were merged without manual intervention. User interfaces were designed on a computerized collaboration platform for answering queries, uploading source documentation, and testing. Multiple feedback cycles mined and scanned relevant source data according to natural language processing logic. Outcomes measured included average hours (h) and costs saved per DSUR.

Results: Twenty-one of the 31 DSUR sections were either fully (n = 9) or partially (n = 12) automated (e.g. marketing approval status, clinical and post-market exposure, executive summary, introduction). In 2017, 5 DSURs were developed with the platform and 2 with manual intervention. Automation saved 26 h/DSUR (182 h total) with cost-savings realized at $7000/report ($35000/year). In 2018, automation saved $49,000. Compliance was maintained at 100% and no decrease in quality was observed.

Conclusions: Automation harmonizes DSUR production and removes human error through consistent use of templates, data sources, and process. Of the 10 sections which could not be currently automated, 5 sections required analysis of safety data. Thus, time saved allowed more time to focus on safety analysis during authoring. Overall, the tool enhanced the potential of the organization to generate large volumes of quality DSURs with limited resources in a timely manner, with improved quality and consistency. It transformed a resource heavy and time-consuming process to a more streamlined and cost effective process.

381 | Impact analyses of European pharmacovigilance interventions on public health burden

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Background: Since implementation of the 2012 pharmacovigilance (PV) legislation in the EU, monitoring the success of PV has become commonplace; however impact of PV regulatory interventions on public health remains mostly unquantified. There is a need for research to identify the best technique for measuring impact of these actions, and guidelines on reporting impact analyses. The overall aim of this study is to quantify the impact of EU marketing authorisation withdrawal, revocation or suspension ("PV regulatory interventions") in terms of morbidity changes.

Objectives: Interim analysis to assess the feasibility of predictive modeling techniques for estimation of public health impact of PV regulatory interventions.

Methods: Prescription products used in primary care whose marketing authorisations were withdrawn, revoked or suspended in France, Germany and the UK between 2012 and 2016 were previously identified. Annual product utilization figures for the year prior to PV action were estimated using IMS France, IMS Germany and the British Health Improvement Network (THIN) electronic health record databases. Systematic searches of PubMed/MEDLINE, and European Medicines Agency and national competent authority websites and documents were conducted to identify quantitative studies for the product and adverse drug reaction (ADR) of interest, allowing risks to be calculated. The public health impact of the intervention was estimated in terms of morbidity reduction due to product withdrawal, revocation or suspension by modeling of usage figures and risk of each ADR. Work continues to obtain background risk data to establish the actual reduction in morbidity attributable to removal of the product from market in this territory.

Results: 18 products were considered for impact analysis; 9 were excluded as no quantitative studies were identified for the respective

ADRs. This interim analysis focused on ketoconazole, metoclopramide and domperidone, and provided a prediction of the number of ADRs avoided per year as a result of marketing authorisation withdrawal, revocation or suspension, and an estimation of the public health impact of each PV action using changes in morbidity as an indicator.

Conclusions: This interim analysis tested a method for predicting public health impact of PV interventions on a subset of products based on drug utilization data and expected changes in morbidity. Results suggest the method could be useful in determining public health impact of future PV actions. The predictive modeling method will be further evaluated prior to completion of this study.

382 | Adverse event report forecasting from custom engagement programs

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Background: New data streams for potential Pharmacovigilance (PV) use are increasing. Pfizer's Customer Engagement Programs (CEPs) annually generate over 150,000 adverse event reports (AERs). Quantitative assessment of AERs from completed CEPs may help predict overall value of individual CEPs in enhancing PV and patient safety.

Objectives: Identify differences in characteristics between completed CEPs that produced AERs and those that did not, and develop a model to predict average monthly AER volume (AMV, calculated as total volume/CEP duration) for a planned CEP.

Methods: We used data on CEP programs and associated AERs between 1/1/2014 to 9/30/2017. Descriptive analysis generated mean (SD), median (range) for continuous variables, frequency and proportion for categorical variables, overall and stratified by CEPs with or without AERs. Multiple linear regression was performed with AMV as dependent variable and CEP characteristics (e.g., country, size, communication channel, etc.) as explanatory variables. Models were fit on original data scale and log transformed scale. Stepwise selection based on F-statistics defined the final model.

Results: Among the 8533 CEPs, AMV of AER ranged 0–5311 (mean 5.52, median 0, SD 68.33). 77.1% CEPs had no AERs. Limited differences were seen between CEPs with and without AERs: CEPs without AER had lower baseline program complexity scores (21.2% vs 4.8% with high scores), tended to be the ones that closed receipt of further AERs upon program end (85.6% vs 92.0%) and had more missing information on PV Levels of the products under the program (23.1% vs 38.7%). The final model ($F(35, 6760) = 11.78$, $p < 0.0001$) explained 6% of the variance ($R^2 = 0.06$) with 10 predictors: country, whether it is a nurse program, type of program (e.g., PSP, MRP), subject type (e.g., patient/consumer, HCP, etc.), size, focus of program(e.g., specific drug versus unbranded disease area), type of communication, number of contacts per subject, type of medical condition, and 'special risk circumstances'. Confidence intervals of the predicted AMV values were very wide due to the heterogeneous nature and other limitations of the data such as the need to combine some variable categories to facilitate model fitting, the clear existence of outlier CEP programs, lack of precise subject numbers, and lack of normality in the data.

Conclusions: While some insights can be drawn from the analysis, the vast heterogeneity across the CEPs and the limited number of AERs in the majority of CEPs prevented very accurate AMV forecasting. A more systematic standardization of design and collection of CEP data may make more accurate prediction of AER in the future.

383 | Evaluating the process of standardizing investigational drug substance names reported to the United States Food and Drug Administration adverse event reporting system

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Background: The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) Product Dictionary (FPD) indexes pre- and post-market suspect drug products to facilitate retrieval of Individual Case Safety Reports (ICSRs) for internal review. Investigational drug (IND) substances are initially identified in ICSRs and FPD by proprietary codes from the sponsor, which may evolve into standardized substance names established by the US Adopted Names (USAN) Council and WHO-International Nonproprietary Names (WHO-INN) Expert Group. The FDA Global Substance Registration System (G-SRS) incorporates the USAN/INN into its database as preferred names, which FPD utilizes to update IND substance codes. IND substance codes that have yet to establish a USAN/INN are grouped under an "Investigational Product" category within FPD to be manually reappointed to their respective USAN/INN once established.

Objectives: To evaluate the process for standardizing IND substances in the FAERS Product Dictionary.

Methods: Synonyms grouped under the "Investigational Product" category in FPD were retrieved up to October 2018. IND substance codes were referenced against G-SRS to determine the existence of their preferred names. Substances with preferred names that did not pre-exist in FPD were added. All substance preferred names had their respective codes reclassified as synonyms so that cases reporting the codes are redirected to the preferred names. IND substances identified only by a code remained in the "Investigational Product" category.

Results: The "Investigational Product" category of FPD retrieved 359 IND substance codes of which 257 remained unchanged as IND codes and 102 corresponded to existing G-SRS preferred substance names. Of these, 41 IND substance codes were reclassified to 36 unique G-SRS preferred names that were already incorporated in FPD, and 61 IND codes were reclassified to 54 unique preferred names that required the creation of new FPD entries. All 102 IND substance codes were reclassified as synonyms to their respective preferred substance names. These updates affected 611 ICSRs in FAERS.

Conclusions: The current process of manually updating IND substances in FPD is insufficient, leading to inconsistencies with coding safety reports as sponsors utilize different synonyms to report the same IND substance, and as an IND code matures to a preferred substance name. An automated process is necessary to track IND substances during development to streamline FPD updates as substance standardization occurs.

384 | Monitoring of medicinal products authorized based on a single-arm trial: The case of a CAR-T cell therapy

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Background: For several reasons, scientific progress is now translating into new therapies that are less likely to have been investigated in traditional randomized clinical trials (RCT). Hence, alternative approaches to evidence generation are evolving thereby also impacting post-authorisation monitoring strategies.

Objectives: With a recently authorized chimeric antigen receptor T (CAR-T) cell therapy as an example (axicabtagene ciloleucel), the aim of the present study is to estimate the power over calendar time of detecting significant deviations in terms of effectiveness and safety when data accrue in health care databases and a single-arm study is used as a reference.

Methods: We performed simulations of different scenarios to explore the temporal patterns of power (1-β) when different assumptions were made with regard to source population and the clinically relevant effects (Δ). As a reference, we used a published pivotal single-arm trial of axicabtagene ciloleucel in patients with diffuse large B-cell lymphoma (DLBCL). We assumed a yearly enrolment rate of 2 patients per million source population. As an effectiveness end-point we chose overall survival at 6 months (reference: 21%) and as a safety end-point we chose aphasia grade 3 occurring after the CAR-T cell infusion (reference: 7%). The type I error rate (α) was set at 5% (one-sided) and a chi-square test was assumed to be used for significance testing.

Results: Assuming a market introduction in 2019, with a source population of 5 million, the time to reach a power of 80% to detect a clinically relevant 10%-point increase of mortality at 6 months was 2025. By increasing the source population to 15 or 25 million, this time as reduced to 2023 and 2022, respectively. The corresponding estimates for a 5%-point increase with source populations of 5, 15 and 25 million were 2038, 2036 and 2035, respectively. With a source population of 5 million, the time to reach a power of 80% to detect a clinically relevant 10%-point increase of aphasia grade 3 was 2022. By increasing the source population to 15 or 25 million, this time as reduced to 2020 and 2020. The corresponding estimates for a 5%-point increase with source populations of 5, 15 and 25 million were 2028, 2026 and 2026, respectively.

Conclusions: When historical controls on ethical grounds are used for a monitoring program, simulations of various monitoring scenarios can provide insights into when important deviations in terms of effectiveness and safety may be detected.

385 | Evaluation of reported adverse drug reactions: A study from a regional spontaneous database in Saudi Arabia

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Background: A spontaneous regional database of adverse drug reactions (ADRs) is considered an essential source for post-market authorization safety information that may lead to the early detection of ADRs.

Objectives: To assess the type, severity, seriousness, causality, completeness of ADRs among a spontaneous regional database.

Methods: A cross-sectional study was conducted to assess all ADRs reports that were submitted to a cluster of hospitals in Saudi Arabia in the period between 2014 and 2018. The database was structured based on the fields of Saudi ADRs form which is similar to the Medwatch® ADRs from. The data included were patient demographics, drug information, event information, relatedness information, laboratory and outcome information, and reporter information. The Naranjo algorithm was used to assess the causality of the ADRs. Furthermore, the completeness was assessed by reviewing the components of the ADRs fields, and how many fields were completed. All data were analyzed by using the Statistical Analysis Software (SAS), version 9.4.

Results: A total number of 209 ADRs reports were reported during the study period. Around 29% of these ADRs reports were received from consumers/patients, while, the rest were submitted by healthcare professionals (HCPs), (71%). As for an ADRs reports completion, it was found that the completion of the information in these reports was 87% for patients and 67% for HCPs ($P < 0.05$). All age groups were represented in these ADRs reports with the most age group that been affected by ADRs were between age of 25–34 years. Female gender was slightly more than male gender as gender distribution (54% vs 46%). A spontaneity reported (209) cases with (249) suspected drugs and (516) reactions. The most reported medication group as suspected drugs had ADRs was Antimicrobial (38.5%), followed by cardiovascular medications (15.8%) ($p < 0.05$). The most severe events were associated with ciprofloxacin, oxytocin, and imipenem-cilastatin. As results from Naranjo assessment for causality, it was found that neurologic events (7%) has high score (≥ 9) of been causal relationship with the suspected drugs followed by cardiovascular and respiratory events (5%). Peginterferon was associated with serious ADR and Lehexol lead to life threating cases.

Conclusions: Consumer reports are considered of a very essential source for ADR reporting. In addition, regional spontaneous reports database is a valuable source for signaling. Commonly used medication groups are associated with a higher risk of developing severe and serious events.

386 | Patterns of adverse drug reactions reported to a hospital- based pharmacovigilance Centre in Bhutan. - a case series study

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Background: Adverse Drug Reactions (ADRs) are leading causes of morbidity and mortality in the hospitalized patients. Approximately 15–20% of hospital budgets are spent on treating ADRs and drug related problems in Europe. Identifying a suspected drugs and type of reactions will help clinicians in signal detection.

Objectives: To identify the common drugs and types of reactions reported to a hospital-based pharmacovigilance centre (JDWNRH) in Bhutan and generate hypotheses to inform further studies on ADR signals detection.

Methods: We conducted a descriptive case series study of individual case safety reports (ICSR) reported to the JDWNRH pharmacovigilance centre from 2010–2018. Data extracted were analyzed to evaluate the pattern of ADRs characterized by patient's socio-demographic information; suspected anatomical therapeutic chemical (ATC) drug classification, council for international organizations of medical science (CIOMS) classification of ADR, and outcome. A causal relation between suspected drug and reaction was assessed using Naranjo's Algorithm. Data management and statistical analyses were conducted using SPSS (v.21).

Results: We identified 109 ICSR reports among which 56 (51.4%) were in females and 24 (22.0%) were in persons 21–30 years of age. The youngest affected patient was a 15-day-old infant. There were 12 (11.0%) reports in children age < 1 year old. Forty-nine (44.9%) were due to anti-infective drugs with 25 (51.0%) of the reactions being urticaria/angioedema rashes. Ten (20.4%) of the hypersensitivity reports were due to Amoxicillin. Twenty (18.3%) reactions were continuing and 67 (61.5%) of the reactions were reported to be serious, of which 45 (67.0%) of reactions were considered to be life threatening and 16(24.0%) reaction resulted in a prolonged hospitalization. Naranjo's causality assessment identified 77(70.6%) reports as probable and 6 (5.5%) as definite.

Conclusions: ADRs have occurred in wide range of age groups starting from neonate to a geriatric population. Urticarial rashes attributed to anti-infective drugs were the most common ADRs reported along with other category of drugs.

387 | Increased risk of allergic reactions associated with Xiyanping injection: A prescription sequence symmetry analysis

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Background: Prescription sequence symmetry analysis (PSSA) is an effective signal detection method for adverse drug events based on electronic medical databases. Due to its easy application and effective control of time-invariant confounders, it can be used to identify unintentional drug effects of traditional Chinese medicine injections, such as estimating the association between xiyanping use and allergic reactions.

Objectives: To investigate the risk of allergic reactions associated with the use of xiyanping in a real-world setting. And to evaluate the feasibility of using PSSA to detect drug safety signal in a nationwide medical database in China.

Methods: A retrospective PSSA study was conducted by using data from the Chinese Basic Medical Insurance Database in 2015. The patients newly initiating both xiyanping (index drug) and antiallergic drugs (marker drug) were identified and selected as study subjects. Antihistamines, glucocorticoids, calcium gluconate and adrenaline were selected as the proxy of allergic reactions. The washout period was set as one mouth and the interval period was set as 3 days. Adjusted sequence ratios (ASR) were calculated as the ratio of patients initiating xiyanping first (causal group) over those initiating an antiallergic first (non-causal group) adjusted for time trends in prescribing, which to investigate the potential association between xiyanping use and allergic reactions.

Results: There were 6 629 patients who newly initiated both xiyanping and an antiallergic drug in our study period. The ASR was 2.45 (95%CI: 2.33–2.59), which indicated an increased risk of allergic infections associated with the use of xiyanping. Signals were detected by each of the four kinds of antiallergic drugs.

Conclusions: The results of PSSA showed that there was a potential association between xiyanping use and allergic reactions. This signal detection method may be a fast and effective method in drug safety evaluation and can be used in the Chinese Basic Medical Insurance Database.

388 | Adverse drug reactions monitoring at the Brazil's pharmacovigilance system from 2008 to 2013

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Background: The Adverse Event Reporting System (Notivisa-drug) is the primary national surveillance database of the Brazilian Health Regulatory Agency (Anvisa) for identifying postmarketing drug safety problems. Notivisa-drug has been replaced since December 2018 by VigiMed - an adapted version of the VigiFlow system of the World Health Organization. VigiMed will allow, for example, the creation of more accurate reports on the reporting of adverse drug reactions.

Objectives: The aim of this study was to analyze suspected adverse drug reactions (ADR) reported in the Brazil's pharmacovigilance system (Notivisa-drug) between 2008 and 2013.

Methods: A descriptive study whose database analysis units were reports of ADR and reports of pairs of drug-adverse reaction. We analyzed all reports of suspected ADR submitted to the Anvisa from the inception of the Notivisa-drug database from 2008 to 2013 with respect to reporting rate (RR), patient characteristics, type and severity of the ADR.

Results: 26,554 reporting were identified in the study period, resulting in a RR of 22.8 per million inhabitants/year. The female sex prevailed (60.5%), as well as the white race (58.1%). Age ranged between 0 to 112 years old (median = 46 years). Almost 1/3 (32.5%) of the suspected ADR reported affected the most vulnerable populations (i.e. elderly and children). 54,288 pairs of drug-adverse reaction were assessed, 59.2% being characterized as severe, especially those that resulted in a clinically important effect (83.1%). The most frequently drug group in severe ADR were L-Antineoplastic and Immunomodulating Agents (32,1%) and J-Anti-infectives for Systemic Use (27.0%), while the most affected System-organ-class was skin diseases and similar conditions (23.7%).

Conclusions: This is a pioneer study assessing Brazil's pharmacovigilance reporting system that resulted in a RR of 22.8 per million inhabitants/year. This RR is far below reported rates of middle- and high-income countries such as New Zealand, Swiss, Sweden and Australia, that reported more than 300 reports per million inhabitants/year or South Africa, with 77 reports per million inhabitants/year.

389 | Mapping Meddra to ICD 9 for signal detection with longitudinal electronic data

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Background: Longitudinal Observational Databases (LOD), such as those from health insurance claims, may provide a source of data for drug safety signal detection. However disease terminologies used in LOD were not designed for this purpose and may be insufficient to accurately describe safety concepts. Mapping between the Medical Dictionary for Regulatory Activities (MedDRA), which was designed for drug safety, and LOD terminologies could facilitate signal detection with LOD by appropriately describing drug safety concepts for signal detection.

Objectives: Develop a method for mapping MedDRA terms to the International Classification of Disease, Version 9 (ICD-9) system and assess the utility of the conversion for signal detection with an Information Component Temporal Pattern Discovery (ICTPD) analysis.

Methods: *Design*: Four conversion tables for the MedDRA to ICD mapping were used in sequence to map Designated Medical Events (DME) for a calcium channel blocker (CCB) to ICD-9 codes. The four conversion tables were from the: (1) Observational Health Data Sciences and Informatics (OHDSI), (2) Internal Auto Encoding Tool, (3) MedDRA v.12 dictionary, and (4) UBC Inc. conversion algorithm from Safety Works® V.6.5.0.

Setting: Patients who were analyzed with the ICTPD were identified among CCB users in the Truven MarketScan® Insurance Claims database which includes US patients with commercial insurance.

Interventions: The conversions produced groups of ICD-9 codes that represented specific MedDRA concepts which, in turn, were assessed with the ICTPD method.

Main outcome measures: Outcome measures included the proportion of MedDRA terms that could be converted to ICD-9 and the number of signals of disproportional recording (SDRs) generated with the ICTPD.

Statistical analysis: Proportions of converted terms and SDRs from the ICTPD analysis were calculated.

Results: Of the 2848 MedDRA DMEs recorded for the CCB, 52% (n = 1461) could be matched with all 4 of the available conversion tables. In the ICTPD analysis, 12.7% (n = 186) of the 1461 MedDRA concepts that were mapped to ICD-9 produced SDRs.

Conclusions: We were able successfully map 52% of the DMEs for a CCB from MedDRA to ICD-9 with 4 separate conversion tables, which allowed an analysis of the DMEs in LOD. Conversion between MedDRA and ICD-9 facilitated the integration of signal detection in LOD and may improve the performance of signal detection systems; however, further research is needed to improve conversion between ICD-9 and ICD-10 to MedDRA as well comparative studies that assess the impact of coding system on signal detection in LOD performance.

390 | Prevalence of colorectal neoplasms and mortality among new users of low-dose aspirin with lower gastrointestinal bleeding

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Background: Aspirin use is associated with reduced risk of colorectal cancer (CRC), though the clinical pathway is incompletely understood. Aspirin inhibits platelet function and may therefore accelerate early bleeding from premalignant colorectal polyps. The bleeding may increase detection and removal of polyps before cancer development.
Objectives: To investigate polyp and CRC detection rates and mortality among new aspirin users with lower gastrointestinal bleeding (LGIB) compared with non-users with LGIB.
Methods: We used Danish nationwide population-based health registries to conduct this prevalence study during 2006–2013. We identified all new aspirin users with a diagnosis of LGIB during the study period. We matched each new user to five non-users with LGIB. Matching was based on gender and age on the LGIB diagnosis date. We computed prevalence and crude and adjusted prevalence ratios (PRs) for colorectal polyps and CRC, and crude and adjusted mortality ratios within six months following LGIB, comparing new aspirin users with non-users.
Results: We identified 1,038 new users of low-dose aspirin with LGIB and 5,190 matched non-users with LGIB. Among new users and non-users, 220 and 950 had endoscopically detected polyps, respectively [PR = 1.16 (95% CI: 1.01–1.32)]. After restricting the analysis to histologically examined polyps, new aspirin users had a higher prevalence of conventional polyps [PR = 1.28 (95% CI: 1.06–1.55)] and serrated polyps [PR = 1.31 (95% CI: 0.95–1.80)]. Stratification by polyp location showed an increased prevalence of proximal colonic polyps among new aspirin users compared with non-users [PR = 1.72 (95% CI: 1.06–2.80)]. New users and non-users had a similar prevalence of overall CRC [PR = 1.04 (95% CI: 0.77–1.39)]. However, after stratifying by CRC location, we observed a lower prevalence of proximal colonic [PR = 0.71 (95% CI: 0.35–1.43)] and rectal tumors [PR = 0.85 (95% CI: 0.53–1.38)] and a higher prevalence of distal colonic tumors [PR = 1.47 (95% CI: 0.89–2.44)] among new users compared with non-users. No difference in mortality was observed [mortality ratio = 1.05 (95% CI: 0.89–1.23)].
Conclusions: The observation that low-dose aspirin is associated with increased polyp detection might indicate that bleeding from proximal polyps leads to earlier detection and removal of polyps before cancer development.

391 | Testosterone replacement therapy and the risk of prostate cancer in men with late-onset hypogonadism

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Background: The association between the use of testosterone replacement therapy (TRT) and prostate cancer remains uncertain, with studies assessing this safety concern having important methodological limitations.
Objectives: The objective of this population-based study was to determine whether TRT is associated with an increased risk of prostate cancer in men with late-onset hypogonadism.
Methods: We used the United Kingdom Clinical Practice Research Datalink to assemble a cohort of 12,779 men, at least 45 years of age, newly-diagnosed with hypogonadism between 1 January 1995 and 31 August 2016, with follow-up until 31 August 2017. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of prostate cancer associated with use of TRT, compared with non-use. Exposure to TRT was lagged by 1 year to account for cancer latency. Secondary analyses assessed the association by TRT formulation, number of prescriptions received, and time since initiation. We also conducted a propensity score-matched cohort analysis to further assess the impact of residual confounding.
Results: A total of 215 patients were newly-diagnosed with prostate cancer during 58,224 person-years of follow-up, generating an incidence rate of 3.7 per 1,000 person-years. Compared with non-use, use of TRT was not associated with an overall increased risk of prostate cancer (3.8 v 3.4 per 1,000 person-years, respectively; adjusted HR, 0.97; 95% CI, 0.71 to 1.32). Results remained consistent in secondary and sensitivity analyses, as well as in the propensity score-matched cohort analysis (HR, 0.87; 95% CI, 0.56 to 1.36).
Conclusions: The use of TRT was not associated with an increased risk of prostate cancer in men with late-onset hypogonadism. These findings should provide some reassurance on the long-term safety of TRT among men with late-onset hypogonadism.

392 | Angiotensin converting enzyme inhibitors and risk of lung cancer: A nested case–control study

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Background: Use of ACE inhibitors (ACEIs) has recently been associated with an increased risk of lung cancer.
Objectives: To examine whether ACEIs are associated with lung cancer compared to use of angiotensin receptor blockers (ARBs) overall, and to examine whether the association varies with duration of use and lung cancer histology.
Methods: We conducted a nested case–control study with a new user, active comparator approach. Cases included all persons with incident, histologically-confirmed lung cancer in Denmark from 2005 to 2015, selected from a cohort of patients who had initiated antihypertensive treatments between 1996 and 2015. Each case was matched to 20 controls on age, sex, and year of initiation of antihypertensive therapy. We used conditional logistic regression to estimate odds ratios (ORs) for lung cancer associated with ever-use of ACEIs compared to ever-use of ARBs. We examined additional categories of

duration of use (< 5, 5–10, and > 10 years of use) and tested for a linear trend with duration of use as a continuous variable. As covariates, we included selected comorbid conditions (e.g. diabetes and COPD), use of NSAIDs, use of statins, number of different drug classes used the year before study start, and highest achieved education. Since ARBs have been suggested to decrease lung cancer risk, we repeated the analyses with use of ever-use of thiazides as reference.

Results: A total of 19,298 cases (median age of 70 years; 53% men) were matched to 385,804 controls. Of the cases, 43% were diagnosed with adenocarcinoma, 23% squamous cell carcinoma, 17% small cell carcinoma, and 17% other types. Compared with ever-use of ARBs, ever-use of ACEIs was associated with an increased risk of lung cancer in the unadjusted model (crude OR 1.08, 95%CI 1.01–1.14), which weakened after adjustment (OR 1.05, 95%CI 0.98–1.11). However, the OR increased with increasing cumulative duration (p_{trend} < 0.001), generating ORs for 5–10 years of use of 1.06 (95% CI 0.96–1.18) and for ≥10 years of 1.16 (95% CI 1.05–1.29). The positive association with ≥10 years of use was strongest for squamous cell carcinomas (OR 1.24, 95%CI 0.99–1.55) and small-cell carcinomas (OR 1.22, 95%CI 0.93–1.59) and weaker for adenocarcinomas (OR 1.12, 95% CI 0.96–1.31). When using thiazides as an alternate reference group, we observed ORs of similar magnitude and direction.

Conclusions: Long-term use of ACEIs was associated with an increased risk of lung cancer, most notably for squamous cell and small-cell carcinomas, with evidence of a duration-response pattern. However, the magnitude of the association was small and only significant for 10 or more years of use.

393 | Low dose aspirin use and colorectal cancer risk

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Background: Large scale epidemiology studies and post-hoc analysis of randomized trials among non-Asian populations showed that long term low dose aspirin (ASA) use was associated with lower risk of colorectal cancer (CRC).

Objectives: To evaluate the association between low dose ASA use and CRC risk in a predominantly ethnic Chinese population.

Methods: We carried out a nationwide nested case control analysis within a study cohort of low dose (most common daily dosage was 100 mg, 150 mg at max) ASA initiators aged 40 or older and age-sex frequency matched nonusers from 2002 until 2010. They were identified from the Taiwan National Health Insurance data and followed through the end of 2015. CRC cases were ascertained from Taiwan Cancer Registry. Controls were randomly selected through risk-set sampling, matched on age and gender at 1:4 ratio to the cases. We defined long term current use (at least 3 years, ≥70% drug-day coverage over 3 years, within 1 year of recency), episodic (less than 3 years, <70% coverage over 3 years, or past use, beyond 1 year of recency), and non-use according to low dose ASA prescriptions prior to CRC diagnosis. After the study protocol was written and upon review of recently published reports, we repeated the analysis in a sub-cohort of subjects who initiated low dose ASA between age 40 to 59 years. Odds ratio (OR) and 95% confidence interval (CI) were estimated by conditional logistic regression to evaluate the association between low dose ASA use and CRC risk. Clinical attributes and healthcare utilization were adjusted as potential confounders.

Results: In a cohort of 4,710,504, mostly ethnic Chinese aged 40 or older, we identified 79,095 CRC cases and 316,380 controls. Median age was 71 years at the time of CRC diagnosis and 59% were men. For long term low dose ASA use, crude OR was 1.08 (95%CI 1.04–1.13) and adjusted OR was 0.89 (95%CI 0.85–0.93). Similar level of risk reduction was observed among episodic low dose ASA users (adjusted OR 0.88; 95%CI, 0.86–0.89). In the sub-cohort of 1,496,073 subjects who initiated low dose ASA between age 40 and 59 and were frequency matched, 18,349 CRC cases and 73,396 controls were identified (median age was 60 at time of CRC diagnosis and 61% were men). Crude OR was 0.93 (95%CI 0.86–1.02) and a 30% risk reduction was observed among long term low dose ASA users (adjusted OR 0.69 [95% 0.63–0.76]). Similar magnitude of risk reduction was observed for those with episodic low dose ASA use (adjusted OR 0.64 [95% 0.61–0.67]).

Conclusions: Long term and episodic low dose ASA use were associated with lower CRC risks in Taiwan. A stronger CRC risk reduction effect was observed among those who initiated ASA between age 40 and 59.

394 | Low-dose aspirin use and endometrial cancer mortality -a Nationwide cohort study

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Background: Accumulating evidence suggests that aspirin use may improve survival in cancer patients. This is of high interest as aspirin is typically inexpensive and has a favorable safety profile. For endometrial cancer however, only few observational studies exist and results are inconsistent.

Objectives: To examine whether post-diagnostic use of low-dose aspirin is associated with reduced mortality among endometrial cancer patients.

Methods: From the Danish Cancer Registry, we identified all women in Denmark aged 30–84 years with a histologically verified diagnosis of primary endometrial cancer during 2000–2012. Data on drug use, mortality and potential confounding factors were retrieved from nationwide registries. Low-dose aspirin use was defined as a minimum of one filled prescription after cancer diagnosis. Follow-up started one

year after cancer diagnosis and the patients were followed until endometrial cancer mortality, other cause mortality, emigration, or end of study, whichever came first. Endometrial cancer mortality was the primary outcome of interest. Using time-dependent Cox regression models, adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the association between post-diagnosis low-dose aspirin use and endometrial cancer mortality. We examined associations according to patterns of use (intensity of use and cumulative amount), and evaluated effect measure modification by tumor characteristics (tumor histology and clinical stage). The exposure was also modeled as a time-fixed variable in exposure windows of one year and five years to account for potential time-dependent confounding. We evaluated the potential impact of competing events by Fine and Gray's proportional subdistribution hazards model.

Results: The study population comprised 6,694 endometrial cancer patients who were followed for a median of 4.5 years (interquartile range: 1.9–8.1). Low-dose aspirin use was associated with a HR of 1.10 (95% CI: 0.90–1.33) for endometrial cancer mortality. Estimates did not vary substantially according to either pattern of use or tumor characteristics. The analyses on the time-fixed exposures and subdistribution hazards yielded similar results.

Conclusions: In conclusion, we found no indication that low-dose aspirin use was associated with reduced mortality of endometrial cancer. Rather, the majority of risk estimates were above one, which may raise a concern for increased mortality with post-diagnostic low-dose aspirin use.

395 | Low-dose aspirin use and risk of head and neck cancer - a population-based case–control study

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Background: Long-term regular use of aspirin has been associated with reduced risk of several types of cancer. However, the epidemiological evidence on low-dose aspirin use and risk of head and neck cancer (HNC) is limited and equivocal.

Objectives: To assess the association between low-dose aspirin use and risk of HNC, and to evaluate the association according to patient characteristics and anticipated association with human papillomavirus (HPV).

Methods: We performed a case–control study nested in the Danish population. All cases with a histologically verified first diagnosis of HNC between 2000 and 2015 and aged 30–84 years were included. Based on prior evidence, cases were categorized into four groups of anticipated HPV-association: strong (oropharynx), moderate (oral cavity), no/weak (ear, sinus, other pharynx), and uncertain (larynx). Population-based controls matched on age and sex were selected by risk-set-sampling in a 1:15 ratio. Information on filled prescriptions of low-dose aspirin (75–150 mg), use of other drugs, comorbid conditions and socioeconomic parameters was retrieved from nationwide prescription, medical and demographic registries. By means of conditional logistic regression, we computed odds ratios (ORs) and 95% confidence intervals (CIs) for HNC associated with low-dose aspirin use (2 or more prescriptions). The association was evaluated according to patterns of use (i.e. recency, duration, intensity and continuity of use), age, sex, and anticipated HPV-association.

Results: Among 12,389 HNC cases and 185,835 controls, there was no association between overall use of low-dose aspirin and HNC (OR: 1.03, 95% CI: 0.97–1.10). Similar neutral results were found when analyzing patterns of use. In stratified analyses based on anticipated HPV-association, overall low-dose aspirin use appeared to slightly increase the risk of HNC with moderate HPV-association (OR: 1.16, 95% CI: 1.04–1.30), while there remained no association with risk of HNC with strong, no/weak or uncertain HPV-association. The risk of HNC was increased in the young age group (30–60 years of age, OR: 1.18, 95% CI: 1.05–1.31), primarily due to increased risk of HNC with moderate HPV-association.

Conclusions: We did not observe an association between overall low-dose aspirin use and risk of HNC overall, regardless of patterns of use. However, low-dose aspirin use appeared to be associated with a slightly increased risk of HNC with moderate HPV-association (oral cavity). This finding has not previously been reported and should be interpreted with caution. Further investigation is thus warranted.

396 | Does use of nonaspirin non-steroidal anti-inflammatory drugs reduce the risk of head and neck cancer in a population-based case–control study?

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Background: Head and neck cancer (HNC) is a common malignancy with great mortality and morbidity and hence there is a need for identification of preventive factors. Preclinical and observational studies report antineoplastic effects of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), but previous observational studies assessing non-aspirin NSAID use and risk of HNC are sparse and with inconsistent results.

Objectives: To estimate the association between use of non-aspirin NSAIDs and risk of HNC, and examine whether this association differs with patient characteristics or anticipated association with human papillomavirus (HPV).

Methods: We conducted a register-based case–control study nested in the Danish population. Cases comprised all patients aged 30–84 years with a histologically verified first diagnosis of HNC during 2000–2015. Based on the literature, cases were categorized into four groups of anticipated HPV-association: strong (oropharynx), moderate (oral cavity), no/weak (ear, sinus, other pharynx), and uncertain (larynx). For each case, 15 age- and sex-matched population-based controls were selected by risk-set-sampling. We obtained information on filled prescriptions of non-aspirin NSAIDs, other drug use, comorbid conditions and socioeconomic parameters from nationwide registries. Conditional logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for risk of HNC associated with use of non-aspirin NSAIDs (2 or more prescriptions). We evaluated the associations according to patterns of use (i.e. recency, cumulative amount and consistent use), age, sex, and anticipated HPV-association.

Results: A total of 12,389 HNC cases and 185,835 controls were included in the study. Overall use of non-aspirin NSAIDs was not associated with risk of HNC after adjustment for potential confounders (OR: 0.99, 95% CI: 0.95–1.03). However, long-term consistent use for 5 years or longer was associated with a 25% reduction in HNC risk (OR: 0.75, 95% CI: 0.62–0.90). We found an inverse association between non-aspirin NSAID use and HNC in the oldest age group (71–84 year old). The stratified analyses by sex or anticipated HPV-association showed no material differences in estimates.

Conclusions: Overall use of non-aspirin NSAIDs was not associated with the risk of HNC with no apparent influence on the estimates by the anticipated HPV-association. However, long-term consistent use may be associated with a reduced risk of HNC and merits further investigation.

397 | Statin use and risk of liver cancer: Evidence from two population-based studies

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Background: Epidemiological studies of statin use and liver cancer risk have produced conflicting results. Results from recent systematic reviews and meta-analyses show that individuals using statins have 40%–50% lower risk of liver cancer compared with non-users of statins. However, another study indicated that the decreased association of statins and liver cancer attenuated after adjusting for indication and contraindication of statins that have not been well adjusted in previous studies.

Objectives: We therefore examined the association between statin use and risk of primary liver cancer in two large independent study populations taking account of important covariates and main indications of statins such as high cholesterol and chronic liver disease.

Methods: We performed a nested case–control study within the Scottish Primary Care Clinical Informatics Unit (PCCIU) database. Five controls were matched to cases with primary liver cancer and we used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations with statin use. We also conducted a prospective cohort study within the UK Biobank using self-reported statin use and cancer-registry recorded primary liver cancer outcomes. Cox regression was used to calculate hazard ratios (HRs) and 95% CIs.

Results: In the PCCIU case–control analysis, 434 liver cancer cases were matched to 2,103 controls. In the UK Biobank cohort, 182 out of 475,768 participants developed incident liver cancer. Statin use was associated with 39% lower risk of liver cancer in the PCCIU (adjusted OR 0.61, 95% CI 0.43–0.87). When we examined specific subtypes of liver cancer in the UK Biobank, statin use was associated with lower risk of hepatocellular carcinoma (HCC) (adjusted HR, 0.48; 95% CI, 0.24–0.94) but not intrahepatic bile duct carcinoma (IBDC) (adjusted HR, 1.09; 95% CI, 0.45–2.64).

Conclusions: We found a consistent inverse relationship between statin use and risk of primary liver cancer which was only seen for HCC but not IBDC.

398 | Safety of menopausal hormone therapy in older breast cancer survivors: A systematic review and meta-analysis

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Background: Due to the higher incidence of hormone responsive tumors in women >50, the safety of hormone replacement therapy (HRT) in older breast cancer survivors may differ from younger age groups.

Objectives: The primary outcome in this review was the risk of tumor recurrence and secondary outcome the relationship with breast cancer-related mortality.

Methods: Medline, CINAHL, Cochrane, Google Scholar and EMBASE databases were searched through August 2018 for studies reporting exposure to HRT in survivors ≥50 at primary diagnosis. Random effects models were used to estimate the combined relative risk (RR) of tumor recurrence and breast cancer-related mortality using the Mantel–Haenszel method and the GRADE quality of evidence determined for the primary outcome.

Results: Overall, nine studies (four cohort, one case–control, four RCTs; n = 16,002) were included. Very low quality evidence from observational studies demonstrated no adverse effect on tumor recurrence with HRT use (RR 0.80, 95% CI 0.53 to 1.19; I^2 = 66%; n = 11,984), while moderate quality evidence from RCTS demonstrated an adverse effect (RR 1.46, 95% CI 1.20 to 1.77; I^2 = 17%; n = 4,108). Similarly, observational studies demonstrated no adverse effect on breast cancer-related mortality (RR 0.32, 95% CI 0.21 to

1.49; I^2 = 0%, *n* = 2,182), while RCTs demonstrated a non-significant higher risk (RR 1.07, 95% CI 0.77 to 1.49; I^2 = 0%; *n* = 3,918).

Conclusions: Ultimately, despite conflicting findings, evidence of sufficient quality suggests that HRT may increase the risk of tumor recurrence in older survivors. However, adverse effect on mortality is unlikely. Caution with HRT use in survivors is further advised.

399 | Clinical outcomes associated with drug–drug interactions of Oral chemotherapeutic agents: A comprehensive evidence-based literature review

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Background: Oral chemotherapy use is increasing due to new drug approvals as well as the convenience of administration of oral drugs. This increased oral chemotherapy use raises the concern of drug–drug interactions (DDIs) with concomitantly administered drugs, which may result in loss of therapeutic effect, decreased tolerability, and/or increased toxicity.

Objectives: The objective of this study was to review existing evidence of clinical impact of DDIs with oral chemotherapeutic agents.

Methods: A comprehensive search of literature using PubMed was conducted in April 2018 and updated in October 2018 for studies of DDIs associated with oral chemotherapy. Included studies were in English. The types of studies that were included were randomized clinical trials, observational studies, and case reports evaluating a DDI between any oral chemotherapy drug and any other drug. Included studies needed to have at least one outcome of clinical relevance potentially attributed to the DDI, for example, effects on survival or toxicity. The quality of the articles was assessed using published metrics appropriate for the study design.

Results: There were 2,626 studies identified in the initial search, of which 35 met all the eligibility criteria. These included 15 retrospective cohort studies, 16 case reports or case series and 4 post hoc analyses of clinical trials. Among these, DDIs contributed to a statistically significant change in a clinical outcome in 12 studies. Eight of these studies evaluated either overall or progression free survival and found that the presence of the DDI was associated with reduced survival. The most frequently evaluated DDIs in the included studies were (a) concomitant use of acid suppressing agents with tyrosine kinase inhibitors (*n* = 10) and (b) warfarin with oral anticancer agents (*n* = 7).

Conclusions: Our findings suggest that more real-world studies evaluating the association between oral chemotherapy DDIs and clinical outcomes are needed. The adverse clinical outcomes due to DDIs may be a reason for treatment failures and therapy discontinuation.

400 | Nonsteroidal anti-inflammatory drug use and breast cancer risk in a prospective cohort study of postmenopausal women

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs), a class of drugs commonly used to treat pain, fever, and inflammation, have been suggested to reduce breast cancer risk through the inhibition of the cyclooxygenase-2 (COX-2) enzymes. However, prospective studies of the association between NSAIDs and breast cancer risk have yielded inconsistent results.

Objectives: We investigated the association between NSAID use and breast cancer incidence in the French E3N prospective cohort.

Methods: E3N includes 98,995 French women born between 1925 and 1950 and insured by a health insurance plan that covers mostly teachers. Self-reported information on lifestyle, anthropometric, reproductive factors and medical history were collected biannually by questionnaires and matched with data from a drug reimbursement database pertaining to years 2004–2014. Women with self-reported NSAID current use in the questionnaires (2000 or 2002) or at least two reimbursements in a 3-month period since 2004 were defined as exposed to NSAIDs. Considering exposure as time-varying, multivariable Cox regression models were used to estimate hazard ratios (HRs) for the association of NSAID exposure with breast cancer risk, overall and by breast cancer subtypes. Effect modification by breast cancer risk factors and comorbidities that might be associated with NSAID use was assessed.

Results: In the current analysis, 62,390 postmenopausal women were followed between 2004 and 2014 (9 years on average, starting at a mean age of 63 years; 2,887 breast cancers). Of them, 6% had been exposed to aspirin, 13% to ibuprofen and diclofenac, 10% to ketoprofen and piroxicam, 8% to selective COX-2 inhibitors and 19% to other non-selective NSAIDs during follow-up. In multivariable models, there was no statistically significant association between NSAIDs overall and breast cancer risk [HR = 1.00 (0.94–1.09)]. The results were the same by types of NSAIDs [$HR_{aspirin}$ = 1.00 (0.82–1.22), $HR_{ibuprofen}$ = 0.93 (0.80–1.07), $HR_{ketoprofen}$ = 1.01 (0.87–1.19), $HR_{diclofenac}$ = 1.02 (0.88–1.18), $HR_{piroxicam}$ = 1.04 (0.90–1.21), $HR_{cox\text{-}2\ inhibitors}$ = 0.98 (0.84–1.15), $HR_{other\text{-}NSAIDs}$ = 1.01 (0.91–1.11)]. The NSAID-breast cancer associations did not differ by breast cancer subtypes, risk factors and comorbidities, nor by duration, dose, intensity of use, or time since first or last use.

Conclusions: NSAID use was not associated with breast cancer risk in this large, prospective cohort of postmenopausal women with up to 10 years of follow-up.

401 | Bile acid Sequestrants and the risk of cancer: A cohort study in the clinical practice research datalink

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Background: Bile acid sequestrants (BAS), a group of lipid-modifying treatments (LMTs), bind to bile acids in the gut and lower their blood level. Evidence from animal models suggested that bile acids may play a role in carcinogenesis.

Objectives: To calculate the risk of overall and site-specific cancer associated with the use of BAS compared with other LMT (including fibrates, nicotinic acid derivatives, bis-phenol antioxidant and ezetimibe), in a large cohort of new users of either medication.

Methods: We used the UK Clinical Practice Research Datalink to identify individuals 18 years or older without prior cancer history and who were newly prescribed BAS (*n* = 10,658) or other LMT (*n* = 34,058) between 1997 and 2017. All individuals were required to have at least 12 months of continuous registration prior to index date. For each BAS users, we selected up to 5 LMT users matched on gender, year of birth and clinic registration, year of first use, and practice region. Follow-up started at the age at first BAS or LMT prescription, and ended at age of first cancer diagnosis, death, last registration or clinic transfer out. We used Cox proportional hazards models to calculate the hazardratio (HR) and 95% confidence interval (CI) of cancer overal and by anatomic site, in BAS users *versus* users of other LMT.

Results: During a median follow-up of 5.2 years (range = less than 1–23.4 years), 3254 incident cancers (*n* = 612 in BAS users; *n* = 2642 in LMT users) were reported. Most frequently reported cancers were cancers of the breast (*n* = 102 for BAS; *n* = 382 for LMT), prostate (*n* = 59 for BAS; *n* = 293 for LMT) and lung (*n* = 50 for BAS and *n* = 291 for LMT). In analyses adjusted for smoking, gender, prior use of aspirin, metformin or statins, the risk of any cancer in BAS users was significantly higher than LMT users (adjusted HR = 1.22, 95%CI = 1.07–1.40); however, differences by cancer anatomic site was noted. Specifically, the data suggested a possible risk reduction in colorectal cancer (HR = 0.75, 95%CI = 0.48–1.19), but higher risk in female breast (HR = 1.25, 95%CI = 0.87–1.78) and pancreatic cancer (HR = 2.85, 95%CI = 1.18–6.84) in BAS users compared with users of other LMT.

Conclusions: Our results suggest that BAS use may modulate risk of certain cancers. Further studies are warranted to elucidate underlying biological mechanisms.

402 | Intensive safety surveillance of anti-cancer medicines subject to additional monitoring: A pilot study

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Background: Chemotherapy-related adverse drug reactions (ADRs) are frequent and often serious. Although spontaneous reporting allow identifying unknown and serious ADRs, underreporting is a limitation. The European legislation foresees the conduction of structured post-authorization safety studies (PASS) and the implementation of a public list of medicines under additional monitoring in order to improve drug safety surveillance.

Objectives: The aim of this study was to test the feasibility and the usefulness of an intensive safety surveillance program to identify adverse drug reactions (ADRs) for medicines under additional monitoring that are used to treat cancer patients within a Portuguese oncology hospital.

Methods: This pilot intensive safety surveillance program was a 3-month prospective, observational study. Patients undergoing treatment with one of the following medicines were included: nivolumab, olaparib, palbociclib, pembrolizumab, pertuzumab, ramucirumab, ribociclib, trastuzumab emtansine, or trifluridine/tipiracil. Potential eligible patients were identified by pharmacists based on prescription data. Clinicians used proper paper-based reporting forms to record ADRs. Clinical secretariats sent those reports through an electronic platform to the pharmacovigilance department for analysis.

Results: Seventy-five patients were on treatment with selected medicines. Of those, 33 (44%) experienced ADRs: 23 (69.7%) cases were serious and 5 (15.2%) unexpected. Considering the number of patients exposed to each medicine and the number of patients experiencing ADRs, trifluridine/tipiracil (72.7%; 8/11) was associated with the highest rate of toxicity, followed by olaparib (66.7%; 2/3), trastuzumab emtansine (50.0%; 3/6), pertuzumab (47.8%; 11/23), pembrolizumab (45.5%; 5/11), palbociclib (25.0%; 1/4), and nivolumab (18.8%; 3/16). A total of 59 ADRs were identified (i.e. 1.8 ADRs/patient), mainly gastrointestinal disorders (*n* = 15; 25.4%), and blood and lymphatic system disorders (*n* = 14; 23.7%).

Conclusions: This intensive safety surveillance program was feasible and allowed identifying serious and unexpected ADRs, adding value to pharmacovigilance and therefore contributing to improve patient safety. Further research is needed to confirm the findings of this pilot study.

404 | Impact of antidiabetic medication use on breast cancer diagnostic characteristics

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Background: Literature suggests that the presence of diabetes increases both the risk and severity of breast cancer. However, knowledge regarding different antidiabetic medication use patterns at baseline and their impact on breast cancer diagnosis remains limited.

Objectives: To identify and compare different antidiabetic medication use patterns among female patients prior to their breast cancer diagnosis and evaluate if different antidiabetic medication use was associated with the breast cancer stage at diagnosis.

Methods:*Design* Longitudinal, retrospective cohort study. ***Settings*** This study used the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database in 2007–2013. Newly diagnosed breast cancer patients were identified in 2008–2013 and were continuously enrolled in Medicare Parts A, B, and D for 12 months before cancer diagnosis (n = 49,255). ***Exposure*** Use of antidiabetic medications, overall and by drug class, during one year prior to breast cancer diagnosis. ***Outcome*** Stage at diagnosis which was further categorized as early (stages 0-II) and advanced (stages III-IV). ***Statistical Analysis*** Chi-square tests were used to compare breast cancer patient characteristics (all were categorical variables: race/ethnicity, geographic region, marital status, and comorbidities) between antidiabetic medication user and non-user groups. For each antidiabetic medication group, logistic regression models were fitted to examine the effects of different antidiabetic medication use on cancer stage at diagnosis while controlling for patient's characteristics.

Results: A total of 1,719 female breast cancer patients used antidiabetic medications during one-year period prior to their breast cancer diagnosis while 6,084 patients were identified as non-antidiabetic users. Although more antidiabetic users (20.36%) had advanced breast cancer compared to the non-user group (14.46%), regression model showed that antidiabetic medication users had similar likelihood (odds ratio [OR] 0.97, 95% CI 0.83–1.14) in getting advanced breast cancer compared to the non-user group. Insulin users were more likely to be in the advanced stage (OR 1.62, 95% CI 1.10–2.40) compared to the metformin-users. Pure metformin users, those who used metformin only during this period, had lower likelihood (OR 0.63, 95% CI 0.43–0.91) compared to non-users.

Conclusions: The relationship between antidiabetic medication use and breast cancer diagnostic characteristics were complex in nature. Considering diabetes severity, exposure to different antidiabetic medications may pose different risks in breast cancer stage at diagnosis.

405 | Inverse association between digoxin and cancers derived from real world data

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Background: Pharmacoepidemiologic studies demonstrated that cardiac glycosides including digoxin may improve survival in cancer patients. Yet, other studies suggest they exacerbate cancer risk. Digoxin can bind estrogen receptors and may increase the risk of estrogen-sensitive breast and uterine cancers. The association between digoxin and cancer remains controversial.

Objectives: We investigated the real world data including claims database and spontaneous reports database and bioinformatics databases to clarify the relationships between digoxin and cancers.

Methods: We performed retrospective data mining study with an integrative approach using real world data and bioinformatics databases. The Japan Medical Data Center (JMDC) claims database (2005–2015) was used to evaluate adjusted sequence ratios (ASRs) by sequence symmetry analysis. Further, the US Food and Drug Administration Adverse Event Reporting System (FAERS, 2004–2016) were used to evaluate reporting odds ratios (ROR) and information component (IC) by disproportionality analysis. For the ASR and ROR, an inverse signal was defined if the upper limit of the 95% two-sided confidence interval was less than 1. For the IC, an inverse signal was defined if the upper limit of the 95% confidence interval was less than 0. Functional relationships between digoxin and cancers were investigated using BaseSpace Correlation Engine (BSCE) to access bioinformatics databases. Microarray gene expression profiles were extracted from the BSCE database and subjected to pathway enrichment analysis.

Results: The number of JMDC claims pertaining to digoxin during the study period was 52,828. Among 3,035 digoxin users, 1,297 incident users who received their first digoxin prescription were identified. In the FAERS database, a total of 300,541 drug-reaction pairs for digoxin were found. Claims and FAERS database analyses suggested a significant inverse association between digoxin and four cancers: gastric, colon, prostate and hematological malignancy. Pathway enrichment analysis based on BSCE suggested digoxin may exert an anticancer effect via peroxisome proliferator-activated receptor alpha and apoptotic caspase cascade pathways.

Conclusions: Database analysis revealed the possibility repositioning digoxin for use in select cancers.

406 | Effect of a clinical pharmacist intervention on the emergency department revisits: A randomized controlled trial

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Background: Revisiting the Emergency Department (ED) for a complication or an unresolved health problem is a lack of quality indicator and a public health problem, affecting patients and healthcare centers. Effect of clinical pharmacist intervention on an ED revisit is still unclear.

Objectives: To determine the effect of a clinical pharmacist intervention on the risk of ED revisit.

Methods: A randomized controlled trial was conducted in patients who received at least one medication before or during an ED visit at a teaching hospital in Santiago, Chile. We randomly assigned patients in a 1:1 ratio to receive standard care in the ED (control =501) and intervention group (n = 500) received clinical pharmacist recommendations to the clinical staff on pharmacological treatments (medication review, drug selection, doses, drug–drug interactions, adverse drug effects and monitoring), and at discharge the intervention also includes patient/caregiver education on drug treatment and therapeutic goals. The primary outcome was the risk of an ED revisit within 30 post-discharge due to a complication or an unresolved health problem related to the previous ED visit. The association between intervention and time to event was examined using multivariable Cox proportional hazards regression models adjusted by sex, age, educational level, reason for ED visit, type of health insurance, polypharmacy (5+ drugs) and customer satisfaction. Statistical significance was determined using two-sided 5% significance level. All statistical analyses were performed using Stata 15.0.

Results: A total of 1001 patients were recruited between April and December 2015, most of them were female (611; 61.5%), the mean age was 50.5 ± 19.5 years. A 19,4% presented polypharmacy and the mean reason of consultation was related to General symptoms and signs (23,4%). There were 47 patients who had an ED revisit within 30 days post-discharge related to the previous ED visit (15 cases in the intervention group versus 32 patients in the control group). The Kaplan–Meier curves show a difference between arms (logrank p = 0.011). The analysis of time to the event shows a decrease of more than a half in the instantaneous hazard of having a re-consultation to the same center (adjusted HR = 0.45; 95%CI 0.24–0.83).

Conclusions: Our study shows that a clinical pharmacist intervention based on recommendations to the healthcare team on drug selection and drug use; patient and caregiver education on drug treatment and therapeutic goals over time, is an effective health strategy to reduce unnecessary ED use within 30 days post-discharge through proactive interventions.

407 | Efficacy gap between phase 2 and subsequent phase 3 trials in oncology

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Background: As the most promising medicines are selected based on phase II trials, the subsequent phase III trials are on average expected to perform worse than phase II trials, due to regression to the mean. There is an increasing trend of new medicines being approved based on phase II trials only. Therefore, it is necessary to investigate the consistency and quantitative impact of this effect.

Objectives: This research aimed to quantify efficacy differences between drug development phases for oncology products. Specifically, the gap between efficacy found in phase II and phase III trials was investigated. Additionally, explanatory variables for efficacy differences were assessed.

Methods: All oncology drugs approved by the European Medicines Agency between 2007 and 2016 were included in this retrospective study. Each indication was included separately. Phase II and phase III trials were retrieved through electronic database searches and matched based on trial and patient characteristics. Effect estimates for objective response rate (ORR), median progression-free survival (PFS) and median overall survival (OS) were included. Analysis was through weighted mixed-effects regression with previous treatment, treatment regimen, blinding, randomization, marketing authorization type and cancer type as fixed effects and the combination of drug and indication as random effect.

Results: 82 phase II-phase III drug-indication groups were identified including 263 individual trials. Mean (SD) ORR, weighted for the size of the trials, was 41.2% (23.0) for phase II and 37.0% (24.8) for phase III. For median PFS and OS, means (SD) were 8.2 (4.2) and 14.7 (6.3) months for phase II and 10.3 (8.6) and 14.3 (6.7) months for phase III, respectively. No significant difference was found between phase II and III results for any of the three efficacy outcomes. However, other trial characteristics that were included in the analyses were associated with outcomes, with significance depending on the outcome assessed.

Conclusions: Overall, effect estimates in this dataset of trials measuring objective response rate and median progression free and/or overall survival did not differ between phase II and phase III trials. These results may encourage decision-makers such as regulators or health technology assessment bodies to look at the overall body of clinical evidence, including patient population characteristics and patient outcomes, instead of differentiating between different phases of clinical development.

408 | Feasibility of using electronic health records to identify patients with chronic obstructive pulmonary disease to enroll into pragmatic trials

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Background: Pragmatic trials may use electronic health records to assess effectiveness of interventions in routine practice. The Clinical Practice Research Datalink (CPRD) conducts such studies in UK primary care practices contributing via different GP software to the CPRD GOLD and, more recently, CPRD Aurum observational databases. Using both databases increases national coverage, but differences in geographical location, data structure and coding raise questions of comparability.

Objectives: To assess the feasibility of using CPRD GOLD and Aurum to identify chronic obstructive pulmonary disease (COPD) patients for a pragmatic trial. Specifically, to estimate the number of COPD patients, establish whether they meet minimum necessary trial criteria, and assess whether patients and data differ between GOLD and Aurum.

Methods: Patients with a GP recorded COPD diagnosis, aged ≥35 years and registered for >1 year on a hypothetical trial enrolment date (31/12/17) were included. Patient characteristics were described overall and in practices active in interventional research.

Results: 56,813 patients in CPRD GOLD and 266,178 in CPRD Aurum met the COPD inclusion criteria; 29,027 (51%) and 174,545 (66%) were from practices active in interventional research. For patients meeting the COPD inclusion criteria, characteristics were comparable across GOLD and Aurum respectively: median age (70, 68 years), proportions male (50, 52%), deprived (50, 49% in top two quintiles), current smokers (38, 40%), and overweight/obese (60, 59%). Proportions of patients with a history of respiratory conditions (e.g. asthma (43, 38%), bronchiectasis (5, 5%), pneumonia (8, 10%)) and disease severity (e.g. MRC grades 3–5 (25, 24%), GOLD grades 3–4 (17, 16%), median FEV1/FVC (63, 67)) were also comparable. However, geographical distribution differed substantially: 39% of patients in GOLD were registered with English practices (28% Scotland, 25% Wales, 9% Northern Ireland), compared to 100% in Aurum. Patients from practices active in interventional research were comparable to the total COPD population.

Conclusions: A substantial number of patients with COPD were potentially eligible for a pragmatic trial using CPRD. CPRD Aurum significantly increased the patient pool, especially among practices active in interventional research, and increased geographical representativeness. Patients and data from the two databases were shown to be comparable across key aspects relevant to a COPD trial. A pragmatic trial using CPRD to recruit patients with COPD is scientifically feasible.

409 | Globalization of clinical trials: Variation in estimated regional costs of pivotal trials, 2015–2016

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Background: Despite the increasing globalization of clinical trials, little is known regarding how the trial site costs vary around the world.

Objectives: We quantified the geographical distribution and regional cost differences for the clinical trials that established the benefits for new therapeutic drugs approved by the U.S. Food and Drug Administration (FDA) in 2015 and 2016.

Methods: We included all pivotal clinical trials for 59 new molecular entities approved by the U.S. FDA in 2015and 2016 that included as least one site in North America. We derived cost estimatesfrom IQVIA's CostPro, a global clinical trial cost estimating tool used by pharmaceutical sponsors. We assessed the patient and site allocation of these trials across eight geographic regions. To quantify the regional cost differences we conducted a within-trial comparison by expressing the estimated regional cost for the sites in each global region as a percent of the cost in North America. We also estimated the percentage breakdown of regional cost components (pass-through, site management, regulatory, and study conduct costs) for each trial, for all endpoints reported the median and interquartile range (IQR).

Results: Overall, 127 pivotal clinical trials enrolled 91,415 patients from 13,264 sites. Most patients (60.3%) and sites (57.3%) were outside North America. A median of 66% (IQR 60–72%) of the total estimated trial costs were regional, with the largest share (53.3%) of regional costs going directly to trial sites with the remainder going to other regional trial management tasks. Differences were greatest in four lower-cost regions: Africa, with an estimated regional cost per site a median of 49% (IQR 44% - 56%) of North America, Central Europe (50%, IQR 41–63%), Middle East (53%, IQR 42–64%)and Latin America (59%, IQR50–70%). Overall, 90 (71%) of the 127 pivotal trials had a total of 3,160 sites in these lower-cost regions. In contrast, savings were more limited in Western Europe, Oceania, and Asia, where estimated regional costs were a median of 78% (IQR 67–89%) of North America. One-quarter of the trials with sites in Asia and Oceana did not achieve cost-savings in those regions relative to North American costs.

Conclusions: Among this sample of pivotal trials for recently approved FDA products, most patients and sites enrolled were outside of North America, with selection of regional sites having a significant impact on total trial costs.

410 | The pragmatic trial: Still a rising star, or old news?

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Background: In the early years of the 21st century, pragmatic trials seemed to be everywhere. The number of trials in Citeline including the term 'pragmatic' in their title or as a design attribution peaked in 2012. Since then, the number of such trials has declined even as the total number of registered trials has increased. We undertook a descriptive summary and overlay of the pragmatic trials presenting in both Citeline's TrialTrove and Clinical Trials. Gov (CT.Gov) in order to look for trends in the employment of this design.

Objectives: To provide a descriptive summary of registered pragmatic trials and to look at trends over time in the terminology used ('pragmatic' vs. 'practical' vs. 'naturalistic' vs. 'large simple', vs. 'cluster randomized' trials or studies.) To compare and contrast the body of work in TrialTrove versus in CT.Gov.

Methods: TrialTrove and CT. Gov were searched separately for trials that included the terms 'pragmatic', 'practical', 'naturalistic', 'large simple', or 'cluster randomized' in either the protocol title or study design field as available. Descriptive data were exported into Excel spreadsheets and using SAS 9.2, listings were sorted, deduplicated and further attributed in order to create two databases of potential pragmatic designs. Data were then summarized and contrasted by source regarding year of study start, trial phase, therapeutic area, indication, sponsor type, and a number of other variables.

Results: There are 2411 unique 'pragmatic' trials registered in Citeline's TrialTrove and 3816 unique such trials in CT. Gov through the end of 2018. Counts of these studies in TrialTrove peak in 2012 then decline, whereas in CT. Gov, the numbers of trials steadily increases through 2018. The term 'pragmatic' (63%) is most often used followed by 'cluster randomized' (30%), with far less frequent use of the terms 'naturalistic' or 'large simple' (7% for both). Therapeutic areas (TA) were similarly emphasized in both registers, with CNS the most common TA followed by metabolic/endocrine, cardiovascular, autoimmune/inflammatory, and infectious disease.

Conclusions: An important difference between TrialTrove and CT. Gov is that whereas Citeline is generally limited to trials involving biopharma or device products, CT. Gov is more general and includes studies that may consist of behavioral interventions (such a counseling or hypnosis) only. We will explore further if pragmatic studies are not necessarily declining in use, but may be shifting to include more non-product interventions and/or if they are giving way to real-world observational study designs.

411 | Data-driven identification of indication for treatment in electronic medical records using cluster analysis in combination with a self-controlled cohort analysis

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Background: When analyzing drug utilization or drug safety in electronic medical records, it is valuable to be able to separate different treatment indications. These may not be explicitly recorded.

Objectives: Develop and evaluate a methodology that identifies patients with similar indication for treatment based on medical events recorded prior to treatment initiation.

Methods: Analyses were performed for a range of drugs in The Health Improvement Network (THIN). We focus here on etoricoxib. THIN contains primary health care data from the UK, and in this study we used data for 10 million patients available in May 2015. Non-administrative Read codes within 30 days before a first-in-patient prescription of etoricoxib were included. Latent class cluster analysis was performed using a probabilistic mixture model for the registration of medical events in the 30-day period. A hundred such analyses were then combined through consensus clustering which grouped together any two patients that were co-clustered in at least 80 of the 100 individual analyses. For each consensus cluster, a calibrated self-controlled cohort analysis (ICΔ) was used to highlight medical events occurring more often in the 30-day period than expected based on the relative frequency of that medical event within the same patients in two separate control periods: 6–12 months and 1–3 years before the first prescription.

Results: Our analysis identified 41 clusters from the 25,000 patients prescribed etoricoxib. Among the ten largest, three were dominated by single medical event terms: *Pain in joint*, *Gout* and *Knee pain*; while seven clustered patients with a variety of terms, e.g. a back-pain cluster of 1800 records gathering *Pain in lumbar spine (in 33% of the patients)*, *C/O - low back pain (27%)*, *Back pain without radiation NOS (23%)*, *Sciatica (22%)* and *Backache (7%)*. As an illustration of the impact of the self-controlled cohort analysis, it kept e.g. *Osteoarthritis and allied disorders* (22%) and *Enthesopathy of the ankle and tarsus (16%)* while eliminating e.g. *Clearance of external auditory canal* (22%) and *Otalgia (10%)* for a cluster of 470 records relating to osteoarthritis.

Conclusions: Data-driven identification of treatment indication in electronic medical records is feasible. Cluster analysis gathered medical events into clinically coherent indication groups and the calibrated self-controlled cohort analysis successfully eliminated medical events with high background rates, which are less likely to reflect treatment indications. Combining the two methods gave added value.

412 | Evaluation framework to guide model selection and cohort definition in causal inference

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Background: Clinical and cost outcomes from real-world data contain selection bias due to formulary management and provider and patient influences impacting treatment assignment. Causal inference allows learning from real-world data by using observed treatment with corresponding response and adding predicted outcomes given alternative (non-factual) treatments while adjusting for bias and confounding. We sought to develop causal inference models and a framework for evaluating their performance using rheumatoid arthritis (RA) as a use case.

Objectives: To demonstrate the utility of causal inference models in real-world data and develop a framework for evaluating the performance of causal inference in objectively assessing treatment response.

Methods: We used the IBM MarketScan Commercial and Medicare Claims database (2010–2017) to build causal inference models for RA clinical (emergency room visits, outpatient visits, hospitalizations)

and per-patient per-month (PPPM) cost outcomes. We analyzed 27 outcomes for 10 biologic therapies and for conventional therapies as a single treatment group. To evaluate the models, we created 6 visuals that exhibit model precision, consistency, calibration, propensity distribution, covariate balancing, and accuracy.

Results: Using the evaluation framework we were able to detect positivity issues in the data, and construct robust and reliable outcome predictions by: identifying and removing treatment predictions that were not comparable (by calibration plot); modifying models that were too weak for predicting outcomes; discarding methods that were incompatible with causal inference analysis (e. g. random forests); and identifying outcomes for which there wasn't sufficient predictive power. In the context of rheumatoid arthritis, we identified multiple sub-populations that could benefit from a specific treatment over other treatment. For example, we identified that for the population over the age of 65 Etanercept provides the lowest risk of anemia, while Infliximab provides the lowest overall risk for multiple outcomes while also accruing relatively low cost.

Conclusions: Our approach allows multiple directions of analysis to find the best treatment per population, the best responding population for a treatment, as well as clusters of patients that respond similarly across multiple treatments. By analyzing adjusted predictors of treatment response within a disease, formulary decisions can be made to optimize coverage and manufacturers could gain novel insights into which patient populations may best respond to their treatment.

413 | A R-based application to perform distributed regression analysis with vertically partitioned data

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Background: In medical product safety and effectiveness studies, important variables such as exposures, outcomes, and confounders may be collected across multiple databases, requiring researchers to link across multiple data sources. Physical linkage of these so-called vertically partitioned databases raises numerous pragmatic concerns, including the risk of compromising patient privacy. Privacy-protecting analytical methods that do not require physical pooling of disparate databases have been developed to mitigate this concern.

Objectives: To develop an algorithm to perform distributed regression analysis (DRA), a privacy-protecting analytical method that performs multivariable-adjusted regression analysis with only summary-level information, with vertically partitioned data and evaluate its precision and operational performance.

Methods: We developed an R-based algorithm to perform distributed linear and logistic analysis with vertical partitioned data. We used PopMedNet, a data sharing application, to securely transfer summary-level information between the data sites. We evaluated the precision and operational performance of the algorithm with a test case (n = 98,162) in a simulated vertically partitioned data environment, where one data source held the outcome variable and another data partner held 41 covariates. We considered the algorithm successful if the DRA results were precise compared to results from the pooled patient-level data analysis (to at least 10^{-6}). We extracted time stamps from PopMedNet and computed the total execution time.

Results: Distributed linear and logistic regression analysis with vertically partitioned data can be performed using a secure matrix multiplication algorithm to compute the off-diagonal blocks of the covariance matrix. The algorithm produced precise regression parameter and standard error estimates to those from the pooled patient-level analysis. For linear regression, a closed form solution exists, while logistic regression requires iterations of summary-level information exchanges between the data sites until the model converges. On average, it took 12.9 minutes to complete one data exchange cycle. The file transfer process accounted for 97% of the data exchange cycle time. Linear regression in our test case required 64 minutes to compute DRA results, while logistic regression required 251 minutes.

Conclusions: We successfully created a DRA algorithm based in R for vertically partitioned data. Additional work is required to improve operational performance of the algorithm.

414 | Privacy-protecting estimation of adjusted risk ratios using modified Poisson regression in multi-center studies

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Background: Multi-center studies have been increasingly conducted to generate powerful and generalizable evidence using healthcare information collected from a variety of data sources. Privacy considerations and legal restrictions often make it impossible to pool individual-level data across data-contributing sites. With binary outcomes, privacy-protecting distributed algorithms to conduct logistic regression analyses have been previously developed. However, the risk ratio often provides a more transparent measure of exposure-outcome associations than the odds ratio. There are currently no existing distributed algorithms to estimate an adjusted risk ratio while avoiding sharing of individual-level data from data partners.

Objectives: The major objectives of this paper are twofold. First, we propose a new method for making valid and privacy-protecting inference on adjusted risk ratios in multi-center studies. Instead of sharing individual-level data, our method only requires sharing of aggregated information to produce results as if the individual-level data were pooled across data-contributing sites. Second, we provide replication R code of our simulated data example, which can be easily modified by interested readers for their own multi-center analyses.

Methods: Modified Poisson regression was previous proposed to directly estimate the risk ratio and give confidence intervals with the

correct nominal coverage when individual-level data are available. By leveraging the Newton–Raphson procedures, we adapted the modified Poisson approach to estimate the risk ratio using only summary-level information shared from each site. The proposed method was illustrated using both simulated and real data examples.

Results: Our method is guaranteed to produce the same risk ratio estimates and standard errors as the pooled individual-level data analysis without the need for sharing potentially identifiable individual-level data across data-contributing sites.

Conclusions: We propose distributed Modified Poisson regression algorithms for valid and privacy-protecting estimation of the risk ratio in multi-center studies. Replication R code is available online.

415 | Relying on RE-LY to transport effect estimates to patients in routine care

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Background: The RE-LY trial compared dabigatran to warfarin in atrial fibrillation (AF) patients. It is unknown how its findings apply to real-world AF populations with other distributions of effect modifiers (EMs). Further, trial intention-to-treat (ITT) analyses are difficult to compare with studies that require participants remain on treatment.

Objectives: Estimate 2-year as-treated (AT) risk differences (RDs) for dabigatran versus warfarin on ischemic stroke (IS), gastrointestinal bleed (GIB), and death using inverse odds of sampling weights (IOSW) to reweight the RE-LY trial to resemble trial-eligible initiators of dabigatran or warfarin in routine care.

Methods: We estimated AT RDs in the RE-LY participants over 65 via a weighted Aalen-Johansen estimator for risks and bootstraps to estimate RD standard errors using inverse odds of censoring weights to account for potential bias from censoring. We identified target populations with under 15% predicted probability of frailty from 1) dabigatran new users and 2) warfarin new users in a Medicare 20% random sample from January 2010 through October 2015. We estimated odds of sampling onto RE-LY for these users based on EMs, assigned RE-LY participants IOSW from marginal odds of sampling divided by EM-conditional odds, and repeated AT analyses in weighted RE-LY participants.

Results: RE-LY-eligible Medicare patients included 8,500 dabigatran new users and 50,090 warfarin new users. There were 10,018 RE-LY participants over 65 in the 150 mg BID and warfarin arms. RE-LY participants were younger with fewer cardiovascular comorbidities (e.g. diabetes RE-LY prevalence 23% vs. Medicare dabigatran 29% and warfarin 31%). AT 2-year trial RD estimates for IS (−0.81%, 95% CI -1.40%, −0.21%), death (−0.62%, 95% CI -1.60%, 0.36%), and GIB (1.53%, 95% CI 0.78%, 2.27%) were similar to ITT results. IOSW weighting to dabigatran users increased risk of all outcomes but showed similar RDs for IS (−0.74%, 95% CI -1.61%, 0.13%), death (−0.59%, 95% CI -1.98%, 0.81%) and GIB (1.75%, 95% CI 0.56%, 2.94%). IOSW weighting to warfarin users increased variance and pushed the RD for death closer to null (−0.19%, 95% CI -1.95%, 1.57%).

Conclusions: As-treated analyses in the RE-LY trial suggest benefits and harms in line with past work. Attenuation of estimated effect on mortality from a number needed to treat of 162 to 527 when weighting to warfarin users may indicate effect heterogeneity. Despite the large set of possible modifiers that differed between RE-LY and Medicare and an increase in event rates after weighting, weighted trial estimates suggest similar absolute effects in dabigatran initiators in routine care.

416 | An online tool for correcting risk ratio or cumulative incidence estimates for bias due to outcome misclassification

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Background: Insurance claims and electronic medical records databases are not designed for research, and case identification is subject misdiagnosis, miscoding, and recording errors. For any particular study, there is rarely sufficient basis for assuming the magnitude or direction of outcome misclassification bias. Although many researchers acknowledge the possibility of outcome misclassification, its impact on study results is rarely assessed.

Objectives: To develop a user-friendly, open access, web application to correct risk ratio (RR) and cumulative incidence point and interval estimates for bias due to outcome misclassification.

Methods: We used Brenner and Gefeller's methodology (Am J Epidemiol 1993;138:1007–15) to develop a tool to correct RR and confidence interval (CI) estimates for differential or nondifferential outcome misclassification and extended their approach for use with cumulative incidences. The corrected RR uses positive predictive value (PPV) and sensitivity (Se) estimates in exposed (1) and unexposed (0) and is computed as: $RR_{corrected} = RR_{observed} \times (PPV_1/PPV_0) \times (Se_0/Se_1)$.

Results: The tool (http://apps.p-95.com/ISPE/) provides corrected point estimates and CIs based on input of the PPV and Se in each comparison group. For example, given an observed RR of 2.00 (95%CI 1.80 2.20) and assuming non-differential Se, a PPV of 75% in the unexposed and 85% in the exposed gives a corrected RR of 2.27 (2.04, 2.49); a PPV of 85% in the unexposed and 75% in the exposed gives a corrected RR of 1.76 (1.59, 1.94); while the RR remains the same if the PPV is equal in both exposed and unexposed strata. The tool offers a graphic presentation of the corrected RR estimates for a range of hypothetical Se values with specified PPVs and allows users to download graphs and the data sheets.

Conclusions: If Se and PPV are the same across exposure strata, the RR will be unbiased, regardless of its magnitude. With equal Ses across strata, bias depends on the ratio of PPVs across strata. Therefore, validation studies should estimate PPVs in each exposure strata. The practice of seeking PPV across strata with a value above a certain threshold is insufficient to assess bias unless there are no false positive errors. The online tool helps researchers to understand the potential impact of disease misclassification on results.

417 | Clopidogrel drug interactions and serious bleeding: High-throughput screening using the self-controlled case series design

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Background: Drug–drug interactions (DDIs) are a major source of variability in systemic concentrations of clopidogrel. Yet, few population-based studies have examined bleeding associated with clopidogrel DDIs.

Objectives: We aimed to identify medications (i.e., precipitant drugs) taken concomitantly with clopidogrel (i.e., an object drug) that increased rates of hospital presentation for serious bleeding.

Methods: We conducted high-throughput screening of 2000–2015 Optum commercial health insurance claims from the United States. We identified DDI signals by performing confounder-adjusted self-controlled case series studies for clopidogrel + precipitant pairs, examining associations with hospital presentation for gastrointestinal bleeding or intracranial hemorrhage. To help distinguish native bleeding effects of a precipitant from a DDI involving clopidogrel, we reexamined associations using pravastatin as a negative control object drug. We used conditional Poisson regression to generate rate ratios (RRs) with 95% confidence intervals (CIs) and accounted for multiple estimation via semi-Bayes shrinkage.

Results: We identified 431 precipitants frequently co-prescribed with clopidogrel and with pravastatin as object drugs. In confounder-adjusted models, 28 (6.5%) clopidogrel + precipitant pairs were statistically significantly positively associated with serious bleeding after semi-Bayes shrinkage and therefore suggestive of a DDI; precipitants included drugs in commonly-used therapeutic classes, such as anti-infectives, cardiovascular, central nervous system, endocrine/metabolic, gastrointestinal, and nutritional agents. Confounder-adjusted ratios of RRs ranged from 1.13 (95% CI: 1.01–1.26) to 3.94 (1.69–9.20). Among these pairs, 13 (46%) were predictable given that precipitants alone increased and/or were harbingers of serious bleeding. The remaining 15 (54%) pairs constituted DDI signals, none (0%) of which are currently reported in the Micromedex or Lexicomp DDI knowledge bases.

Conclusions: We identified numerous previously undescribed and/or unappreciated potential clopidogrel DDIs associated with serious bleeding. It may be prudent for clinicians to monitor for signs and symptoms of bleeding, adjust clopidogrel dose, adjust precipitant dose, and/or consider therapeutic alternatives in patients concomitantly exposed to clopidogrel-precipitant drug interaction signals identified herein.

418 | Statins and risk of venous thromboembolism

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Background: Statins possess anti-inflammatory and anti-thrombotic effects, but their role in the primary prevention of venous thromboembolism (VTE) is not well-established.

Objectives: To examine the risks of first-time VTE in a cohort of patients initiating statin treatment and in a matched general population comparison cohort.

Methods: We conducted a nationwide, population-based, matched cohort study based on prospectively recorded data from Danish health registries. The study period was from 1 January 2005 to 31 December 2015. We identified a cohort of first-time statin initiators without a history of VTE, myocardial infarction, and ischemic stroke and a sex-, age-, and calendar year-matched (1:3) general population comparison cohort consisting of individuals without a history of statin use, VTE, myocardial infarction, and ischemic stroke. We computed cumulative risks of VTE during follow-up (11 years) and sex-, age-, and comorbidity-adjusted hazard ratios (HRs) using Cox proportional hazard regressions. To examine a potential healthy user effect, we also computed risks and HRs for myocardial infarction and ischemic stroke as secondary endpoints.

Results: Among 601,011 statin initiators and 1,803,033 matched population cohort members during 2005–2015, the cumulative risk after 11 years of follow-up was 2.8% for VTE (both cohorts), 4.7% vs. 2.9% for myocardial infarction, and 7.1% vs. 5.2% for ischemic stroke. After adjustment, however, first-time statin use was associated with a slightly decreased risk of VTE (adjusted HR: 0.95 [95% CI: 0.92–0.97]), driven by a reduced risk of unprovoked VTE (adjusted HR: 0.92 [95% CI: 0.88–0.95]). Expectedly, the adjusted HRs were elevated for myocardial infarction and ischemic stroke. The reduced risk of unprovoked VTE was more pronounced in men than in women and in patients of older age than of younger age. Statin potency did not modify the associations, and the risks of deep vein thrombosis and pulmonary embolism were similar.

Conclusions: Statin use was associated with a moderately reduced risk of VTE, and there were no indications of a healthy user effect. Statins may be considered as an adjunctive therapy in the prevention of VTE.

419 | Antithrombotic treatment preceding ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeds and mortality in patients with atrial fibrillation

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Background: Anticoagulation treatment reduces the risk of stroke but increases the risk of bleeding in atrial fibrillation (AF) patients. There is little data on survival after a stroke or a severe bleed.

Objectives: To analyze 90-day mortality in AF patients after an ischemic stroke, an intracranial hemorrhage (ICH), or a gastrointestinal bleed (GIB) and assess associations with the type of antithrombotic treatment preceding the event.

Methods: From the Stockholm Healthcare database (n = 2.3 million inhabitants) we selected all AF patients suffering from an ischemic stroke, an ICH, or a GIB requiring acute hospital care between July 2011 and August 2018 and assessed 90-day mortality rates. We assessed current use of warfarin, non-vitamin K oral anticoagulants (NOAC), or antiplatelet agents at time of the event. We used a Cox regression to calculate hazard ratios (HRs), adjusting for components of the Charlson Comorbidity Index, the CHADsVASc score, the HAS-BLED score, and comedication, to assess the association between treatment preceding the event and mortality. In addition, propensity score matched analyses were performed. We used an asymmetrically trimmed propensity score matched analyses and an array approach for unmeasured confounding as sensitivity analyses.

Results: Of 105 313 patients with AF, 6 017 were included after an ischemic stroke, 3 006 after an ICH, and 4 291 after a GIB. 90-day mortality rates were 25.1%, 31.6% and 16.2%, respectively. After ICH, there was a significantly increased risk of mortality in warfarin compared to NOAC treated patients (aHR: 1.41 CI: 1.10–1.81). Patients receiving antiplatelets or no treatment had statistically higher mortality rates compared to patients on NOAC treatment, both after an ischemic stroke and a GIB, but there was no significant difference comparing NOACs to warfarin (aHR 0.87 CI: 0.67–1.13 after stroke, aHR 0.96 CI: 0.72–1.29 after GIB). Asymmetrically trimmed propensity score matching yielded similar results. The array approach showed that an unmeasured confounder with a relative risk of 3.0 had to be present in 40% of the warfarin and 10% of the NOAC patients to explain the association after ICH.

Conclusions: Mortality is high in AF patients suffering from an ischemic stroke, an ICH, or a GIB. NOAC treatment was associated with a lower 90-day mortality after ICH than warfarin, but no such association was found after ischemic stroke or GIB. After ischemic stroke and GIB, mortality rates were higher in antiplatelet treated and untreated patients compared to NOAC treated patients.

420 | Pharmacoepidemiologic screening of potential Oral anticoagulant drug interactions and thromboembolic events

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Background: Drug–drug interactions (DDIs) with oral anticoagulants may lead to reduced anticoagulant effect and thus increased risk of thromboembolic events. Warfarin is susceptible to numerous DDIs while few studies have examined DDIs involving direct-acting oral anticoagulants.

Objectives: To identify medications associated with an increased rate of hospitalization of thromboembolic events when taken concomitantly with oral anticoagulants.

Methods: We conducted a high-throughput pharmacoepidemiologic screening study using OptumInsight Clinformatics Data Mart, 2000–2016. We performed self-controlled case series studies among adult oral anticoagulant users (warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban) with at least one hospitalization for thromboembolic events (stroke and/or venous thromboembolism). Among eligible patients, we identified all oral medications frequently co-prescribed with oral anticoagulants as potential interacting precipitants. Conditional Poisson regression was used to estimate rate ratios (RR) and 95% confidence intervals comparing precipitant exposed time vs. precipitant unexposed time for each anticoagulant-precipitant pair. Use of antiplatelet agents and nonsteroidal anti-inflammatory drugs were adjusted as time-varying covariates. To control for within-person confounding by indication for the precipitant and to distinguish a DDI from a native effect of the precipitant on thromboembolism risk, we used pravastatin as a negative control object drug. We calculated the ratio of $RR_{\text{anticoagulant + precipitant vs. anticoagulant}}$ to $RR_{\text{pravastatin + precipitant vs. pravastatin}}$ for precipitants identified in both anticoagulant and pravastatin users. Multiple estimation was adjusted using semi-Bayes shrinkage.

Results: We screened 1,622 oral anticoagulant-precipitant drug pairs and identified 261 (16%) drug pairs associated with a statistically significantly elevated risk of thromboembolism. Using pravastatin as the reference group, we identified 81 potential DDI signals that were associated with statistically significantly elevated ratio of RRs (32 for warfarin, 13 for dabigatran, 22 for rivaroxaban and 14 for apixaban). Among these signals, 40 (49%, 9 for warfarin, 10 for dabigatran, 11 for rivaroxaban and 10 for apixaban) were not documented in DDI knowledge databases Lexicomp and/or Micromedex.

Conclusions: We reproduced some previously documented DDIs, which demonstrated the validity of our approach. The newly identified potential DDI signals need to be examined in future studies.

421 | Non-vitamin K antagonist Oral anticoagulants and angioedema: A cohort and case-crossover study

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Background: Patients taking non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, and apixaban have reported experiencing angioedema in both randomized trials and routine care.

Objectives: To quantify the association between NOACs and angioedema relative to warfarin among routinely treated patients with atrial fibrillation using a cohort study. In order to contextualize the results from the active comparator cohort study, we also compared warfarin users to non-users in a case-crossover study.

Methods: Both designs drew eligible patients from the Truven Health MarketScan Commercial database, the Optum© Clinformatics® Data Mart, and Medicare. Eligible patients must have been previously diagnosed with atrial fibrillation and must not have had a prior dispensing for an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or aliskiren. In the cohort study, we compared the 6-month relative rate of angioedema among new users of NOACs (dabigatran, rivaroxaban, apixaban) and new users of warfarin. Patients contributed person time while they were exposed to the index medication. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) within each database after adjusting for confounders using propensity score stratification, and meta-analyzed the database-specific HRs using a random-effects model. In the case-crossover study, we restricted the study period to the time prior to the introduction of NOACs in October 2010 and pooled cases from each database. We estimated an odds ratio (OR) for the association between warfarin and angioedema by comparing the odds of a warfarin prescription in the 30-day hazard window immediately prior to the case versus an earlier 30-day reference window.

Results: In the cohort study, we observed 249 incident angioedema events among 267,684 NOAC initiators and 281,145 warfarin initiators during a mean follow-up of 89 days across all databases. The absolute incidence rate across all databases was 1.9 per 1,000 person-years. The meta-analyzed HR for angioedema comparing any NOAC versus warfarin was 0.98 (95%CI: 0.76, 1.27). In the case-crossover design, the OR for the association between warfarin and angioedema relative to non-use was 0.91 (95%CI: 0.68, 1.21) based on 431 cases.

Conclusions: Despite suggestions from the pre-approval trials and post-approval individual case safety reports, our estimates were inconsistent with substantial short-term relative increases in the rate of angioedema among NOAC initiators compared to warfarin initiators or among warfarin initiators compared to non-users.

422 | Exposure to Dicloxacillin and Flucloxacillin during warfarin use and risk of ischemic stroke and systemic embolism

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Background: The isoxazolyl penicillins dicloxacillin and flucloxacillin induce cytochrome P450 catalyzed metabolism of warfarin leading to decreased anticoagulant effect as measured by the international normalized ratio. The clinical importance of this drug–drug interaction is unknown.

Objectives: To explore the association between exposure to dicloxacillin or flucloxacillin and risk of ischemic stroke and systemic embolism during warfarin use.

Methods: Using the nationwide Danish registries, we identified all patients receiving warfarin due to atrial fibrillation or mechanical heart valves during 1995–2018 (n = 114,383). Within this population, we performed an active comparator, propensity-score matched cohort study comparing the frequency of ischemic stroke/systemic embolism 7 to 28 days following initiation of dicloxacillin/flucloxacillin to that among initiators of phenoxymethylpenicillin. Hazard ratios (HR) with 95% confidence intervals were estimated using Cox regression. Using the same population of warfarin users, the association was also explored using an untreated comparator (random index dates) and by analyzing the data using a case-crossover design.

Results: A total of 49,392 episodes of dicloxacillin/flucloxacillin use were matched 1:1 to episodes of phenoxymethylpenicillin use. The frequency of ischemic stroke/systemic embolism during the respective episodes were 2.3/1000 episodes and 1.1/1000 episodes, corresponding to a HR of 2.1 (95% CI 1.5–2.9) and a number needed to harm of 833. Results were consistent across patient subgroups. The association was stronger for use of dicloxacillin (HR 2.2; 95% CI 1.6–3.0) than flucloxacillin (HR 1.2; 95% CI 0.5–2.9). Use of an untreated comparator strengthened the association (HR 2.7; 95% CI 1.9–3.9). Finally, the case-crossover analysis gave results similar to the main analysis (Odds Ratio 1.9; 95% CI 1.4–2.6).

Conclusions: Use of dicloxacillin in warfarin users with atrial fibrillation or mechanical heart valves was associated with a clinically relevant increased short-term risk of ischemic stroke and systemic embolism. The absolute risk was, however, low. Dicloxacillin should be used with caution in patients receiving warfarin.

423 | Comparative performance of CIDACS-RL using administrative data sources

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Background: Record linkage has been a common tool to conduct cohort studies using administrative data sources. Despite the development of several linkage tools, availability of datasets of huge volume and complexity still pose a huge challenge in record linkage. Recently, CIDACS-RL has been developed to meet these challenges in building "the 100 Million Brazilian cohort".

Objectives: To evaluate the performance of CIDACS-RL (Centre for Data and Knowledge Integration for Health - Record Linkage) compared to four other linkage tools (AtyImo, Febrl, FRIL, and RecLink).

Methods: We created a gold standard dataset using exact matching of two administrative data sources from the Brazilian Ministry of Health: the Mortality Information System (SIM) and the Live Birth Information System (SINASC). In addition, the Unified Registry for Social Programmes of the Federal Government (CadUnico) and tuberculosis from the Information System for Notifiable Diseases (SINAN-Tuberculosis) from 2001–2013. All datasets contained individual-level data with five attributes in common and were used for linkage: name, mother name, date of birth, municipality and sex. We assessed the accuracy of linkage with standard metrics: sensitivity, specificity, positive predictive value (PPV), and area under receiver operating characteristic (ROC) curve (AUC). To minimize potential implicit bias due to significant differences in several technical choices among the tools, we considered the optimal settings for each method.

Results: Overall, CIDACS-RL algorithm had a superior performance: positive predictive value (99.93% versus AtyImo 99.30%, RecLink 99.5%, Febrl 98.86%, and FRIL 96.17%) and sensitivity (99.87% versus AtyImo 98.91%, RecLink 73.75%, Febrl 90.58%, and FRIL 74.66%). Both AtyImo, RecLink, Febrl and FRIL achieved their best performance by using blocking techniques, nevertheless the CIDACS-RL outperformed them in terms of accuracy and execution time. However, Febrl and FRIL could not be run in this setting hence comparison was not possible with all the tools.

Conclusions: CIDACS-RL algorithm is an innovative linkage tool with higher accuracy, improved scalability, and substantially shorter execution time compared to other existing linkage tools. Also, CIDACS-RL can be deployed for huge datasets on standard computers without the need for high-speed processors and distributed infrastructures.

424 | Swedish National Registries versus electronic medical records: Comparing the completeness of systemic therapy data using data from the SCAN-LEAF study

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Background: Few studies have examined the completeness of drug treatment data in Swedish national registries.

Objectives: The aim was to assess the completeness of systemic anti-cancer therapy (SACT) data in Swedish national heath registries through linkage with hospital electronic medical records (EMR) using data from the SCAN-LEAF study, a retrospective cohort of Non-Small Cell Lung Cancer (NSCLC) patients in Scandinavia.

Methods: EMRs from 2 major Swedish university hospitals, Karolinska and Uppsala, were linked with the Swedish National Cancer Register (NCR), the National Patient Register (NPR), and the Prescribed Drug Register (PDR) forming a cohort of adult patients diagnosed with NSCLC from 2012 to 2015, and followed up until 31 December 2016. Patients with a cancer history were excluded. Ascertainment of systemic therapy in registries was based on procedure (KVÅ) or drug codes (WHO ATC). For PDR which includes community dispensed prescriptions, completeness was assessed for oral SACT only. We calculated sensitivity, specificity and predicted values separately for NPR and PDR, using EMR as the reference standard.

Results: A total of 2,779 NSCLC patients were included. Median age at diagnosis was 70 years (22–96 years); 49% of patients were male, 58% were diagnosed with stage IIIB-IV disease, and 71% had a non-squamous histology. In the NPR, only 265 (9.5%) out of 1,527 patients (55%) identified as SACT-treated in EMR had SACT data. Another 26% (713) of these patients had no SACT data in registries, whereas only 61 patients with SACT data in registries had no SACT data in EMR. NPR had low sensitivity (0.15 [95% CI 0.14–0.17]). This result was not associated with disease stage (I-IIIA vs. IIIB-IV). By contrast, PDR had high sensitivity (0.95 [95% CI 0.91–0.97]), with 230 patients with oral SACT identified in both PDR and EMR.

Conclusions: We observed significant under-reporting of SACT in the Swedish NPR, whereas completeness of oral SACT data in the PDR was high. Investigators using Swedish national health registries to study drug treatment data should exercise caution. Linkage with hospital EMR may overcome some of the limitations of registry-only studies of drug treatment in cancer patients.

425 | Validation of diagnostic algorithms to detect type 1 diabetes mellitus disease using administrative data from a general population from southern Italy

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Background: In Italy, type 1 diabetes mellitus (T1DM), the most common form of DM among children, is about 2–3% of all known cases of diabetes, with an incidence of about 10–11*100,000 persons/year, increasing every year.

Objectives: To validate diagnostic algorithms which allow distinguishing between T1DM and T2DM patients in a general population from Southern Italy, using administrative data from Palermo Local Health Unit (LHU) during 2011–2017. As gold standard, certain diagnoses of T1DM/T2DM in a sample of diabetic patients for whom registries of diabetes ambulatories could be linked to claims data from the same catchment area.

Methods: Among 1.4 million inhabitants from Palermo LHU, 127,590 (9.4%) users of antidiabetic drugs (AD) during the years 2011–2017 in the claims database were identified. Confirmed diagnoses of T1DM/T2DM (gestational diabetes was excluded) were available for a subpopulation of AD users, for whom claims data and registries of diabetes ambulatories could be linked. The first date of AD dispensing during the study period was the Index Date (ID). Age and insulin dispensing at ID and DM-related ICD9-CM codes (T1DM: 250*1/250*3; T2DM: 250*0/250*2) as primary/secondary causes of hospital admissions any time prior to ID were the variables considered for T1DM coding algorithms development. While one algorithm was defined by the user, the other one was based on Recursive PArtitioning and Regression Tree method. Sensitivity (Sn), specificity (Sp), accuracy as well as positive (PPV) and negative (NPV) predicted values were estimated. Such algorithms were then applied to all claims database to identify T1DM.

Results: Among 34,926 AD users with a certain T1DM/T2DM diagnosis, 793 (2.3%) were affected by T1DM. The user-defined algorithm was based on age (i.e., age < 30 years) OR insulin dispensing OR 1 specific T1DM code and showed high Sn (94.2%), Sp (84.0%), accuracy (84.2%), NPV (99.8%), but low PPV (12.0%). The statistical algorithm, based only on age (i.e., age < 22.5 years) and insulin dispensing, showed lower Sn (37.8%), but higher Sp (99.5%), accuracy (98.1%), NPV (98.6%) and PPV (64.1%) than the user algorithm. Applying the two algorithms in the whole sample of 127,590 claims AD users, 22,606 (21.5%) and 1,070 (0.8%) T1DM patients would be identified, respectively. The statistical algorithm was more accurate and achieved high predictive values.

Conclusions: Demographic characteristics in combination with drug-utilization patterns can be used to identify T1DM. Advanced statistical methods may help for a more accurate distinction of T1DM from T2DM.

426 | Validity of claims-based definitions for rheumatoid arthritis, selected cancers and infectious diseases in Japan: Results from VALIDATE - J study

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Background: The National Claims Database (NDB) was launched for research use in 2011. Interest among Japanese academia, industry and government to use the NDB and other large databases is mounting, especially with the increasing interest in real world data and evidence. However, little evidence exists to support the validity of claims-based diagnoses in Japan.

Objectives: To assess the validity of claims-based diagnoses for rheumatoid arthritis (RA), selected cancers and infectious diseases (ID) in Japan.

Methods: We designed a multi-institutional validation study using hospital claims data as identifying and linking patients from large claims databases are prohibited in Japan. We developed various claims-based algorithms for RA, selected cancers and ID: herpes zoster (HZ), *Mycobacterium tuberculosis* (MTB), non-*Mycobacterium tuberculosis* (NTB), and pneumocystis jiroveci pneumonia (PJP), and identified claims-based cases from two large hospitals in Japan between 1/2012–12/2016. The gold standard definitions and standard abstraction forms for RA and ID were developed by a steering committee of Japanese clinical and methods experts. All RA and ID cases were independently reviewed by an adjudication committee. We calculated positive predictive values (PPV) for RA and ID, and PPV, sensitivity and specificity for cancer.

Results: We collected and analyzed data from one hospital. We identified 2,009 RA, 2,272 HZ, 161 MTB, 405 NTB, 162 PJP, and 15,860 cancers. Mean age and % female for RA, all ID, and any cancer were 62; 73%; 64; 54%, and 66; 53%, respectively. PPVs (95% confidence intervals) were RA = 82% (77–88); HZ = 76% (64–88); MTB = 92%

(84–99); NTB = 80% (69–91); PJP = 32% (19–44); Colorectal = 87% (84–90); Breast = 88% (86–89); Lung = 91% (88–93); Pancreas = 90% (85–94); Gastric = 91% (89–94); Melanoma = 46% (28–65); Lymphoma = 82% (78–86); Any malignancy = 84% (83–85). Sensitivity analyses using alternative algorithms in the subsets for RA and ID produced PPVs that were 7–10% higher than those in the main analyses.

Conclusions: PPVs for claims-based algorithms for RA were similar to those reported in US data whereas several cancers had better PPVs than those reported in the US (87% to 91% (Japan) vs 60% to 82% (US)); results for most ID conditions are some of the first ever reported. All algorithms will be invaluable for future claims-based pharmacoepidemiology research in Japan. As the Pharmaceuticals and Medical Device Agency continues to encourage validation studies to support the validity of database research for postmarket surveillance, VALIDATE-J will serve as a model.

427 | ICD-9 to ICD-10 mapping for research in biologics and Biosimilars using administrative healthcare data

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Background: As of October 1st, 2015, the Centers for Medicare and Medicaid Services (CMS) mandated the transition from ICD-9 to ICD-10 codes. Many differences between the two coding systems such as the level of detail and number of codes complicate analysis of data across this transition period. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) uses a distributed research network (DRN) to generate post-marketing evidence for safety and effectiveness of biologics and biosimilars. Active surveillance of products' safety and effectiveness in DRNs requires a robust approach for converting ICD-9 to ICD-10 codes used in defining study populations, covariates and outcomes.

Objectives: To examine three ICD-9 to ICD-10 mapping methods for health conditions (HCs) of BBCIC's interest and compare their incidence identified with ICD-9 versus ICD-10 codes in BBCIC's DRN.

Methods: We applied forward-backward mapping (FBM), using direct links of forward and backward General Equivalence Mappings developed by CMS, to all the 110 HCs. More complicated secondary mapping (SM) and tertiary mapping (TM), based on iterations of FBM, were tested for 7 selected variables. A physician reviewed the relevance of mapped ICD-10 codes and compared the three methods to one another. Incidence of the 110 HCs defined by ICD-9 versus ICD-10 codes was examined in the DRN of data from 5 large healthcare organization partners during the period from three years before the ICD-10 implementation in October 2015 to the latest available data (9/1/2012–3/31/2018). We visually assessed incidence trends before and after October 2015 and used a threshold of 20% level change to examine the performance of ICD-9-to-ICD-10 conversion.

Results: Nearly 4 times more ICD-10 codes were mapped by SM and TM compared to FBM. However, the additional codes identified by SM or TM were mostly irrelevant or too non-specific to be used alone. For distinct conditions such as myocardial infarction, SM or TM did not add any ICD-10 codes to FBM mapping. Through visual inspection, 22% HCs had inconsistent ICD-9 versus ICD-10 trends; in general, ICD-10 algorithms led to a higher incidence. 15% HCs had an incidence level change greater than +/−20% between ICD-9 and ICD-10 algorithms.

Conclusions: FBM is generally the most efficient way to convert ICD-9 to ICD-10 codes, yet manual review of converted ICD-10 codes is recommended for all three methods. No existing guidance is available to compare the performance of ICD-9 versus ICD-10 codes, leading to challenges in empirically determining the quality of conversions.

428 | External validation of an algorithm to identify patients with high data-completeness in electronic health Records for Comparative Effectiveness Research

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Background: Electronic health records (EHR) discontinuity, i.e. receiving care outside the reach of an EHR system, is associated with substantial information loss and bias when using EHR data for comparative effectiveness research (CER). We had developed a prediction algorithm to identify patients with high EHR-continuity to reduce such bias, but its performance across different EHR systems is unknown.

Objectives: To describe EHR-continuity pattern of two demographically distinct US systems and test the performance of the prediction model for identifying patients with high EHR-continuity developed in one system, using the external data.

Methods: Study cohort comprised all patients aged ≥65 in EHR from two EHR systems linked with Medicare claims data from 2007/1/1 to 2014/12/31, one each in Massachusetts (MA) and North Carolina (NC). We quantified EHR-continuity by the Mean Proportion of Encounters Captured (MPEC) by the EHR system when compared to records in the claims data. With predictors available in EHR, we built a prediction model for MPEC by Lasso regression in the MA system and performed external validation in the NC system. Within levels of predicted EHR-continuity, for 40 variables that are typical confounders in a range of CER studies, we quantified misclassification by Mean Standardized Differences (MSD) between the proportions of these variables based on EHR alone vs. the linked claims-EHR data. We compared the combined comorbidity scores in those with high

(defined as top 20% based on literature) vs. low (the remaining population) predicted EHR-continuity.

Results: Based on 104,403 patients in the MA system and 33,205 in the NC system, MPEC was 24% in the MA and 26% in the NC system. Our prediction model yielded a score highly correlated with the measured EHR-continuity (MPEC) in both systems (Spearman correlation = 0.77, 0.72, C-statistic = 0.86, 0.85, respectively). In the validation set, patients in the best predicted EHR-continuity decile had 3.27 (95% confidence interval [CI] 3.25–3.29) fold smaller MSD (i.e. less misclassification), when compared to those in the worst predicted EHR-continuity decile for the 40 key confounding variables. Patients with high EHR-continuity had similar comorbidity profiles when compared to the rest of population (MSD in the comorbidity score categories = 0.02).

Conclusions: Restricting a CER analysis to patients with high predicted EHR-continuity may reduce misclassification of key variables without losing representativeness in terms of their co-morbidity profiles.

429 | Incidence rates of and risk factors for opioid overdoses in new users of prescription opioids among US Medicaid enrollees: A cohort study

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Background: The number of opioid overdoses has been escalating exponentially in the US, particularly in the Medicaid population, yet incidence rates of and risk factors for opioid overdoses among new users of prescription opioids are unknown.

Objectives: To measure the rates of and risk factors for incident opioid overdoses among new users of prescription opioids in the Medicaid population.

Methods: Design - Cohort study. **Setting** - Medicaid population captured by Medicaid claims, supplemented with Medicare claims for dual-enrollees, from California, Florida, New York, and Pennsylvania from 1999 to 2012. Adults (at cohort entry) continuously enrolled in Medicaid for at least 3 years and free of opioid prescriptions and opioid overdoses before cohort entry date (dispensing date of the first observed opioid prescription) were eligible. **Exposure of interest** - Prescription opioid use. **Outcome measure** - Opioid overdoses, identified by ICD-9-CM diagnosis codes appearing in inpatient or outpatient claims. **Statistical analysis** - Incidence rates during 2002–2012 and adjusted hazard ratios (HRs) of opioid overdoses for potential risk factors.

Results: Among new users of prescription opioids identified (1,336,140 persons; 246,466 person-years), the incidence rate of opioid overdoses during 2002–2012 was 247.1 (95% confidence interval (CI): 227.5–266.7) per 100,000 person-years, with about a 3.0% (CI: 1.0%–5.1%) per year of cohort entry relative decrease. A lower hazard for opioid overdose was seen for age 65–80 years (HR = 0.50; CI: 0.37–0.66) and 80–100 years (HR = 0.35; CI: 0.23–0.52) compared to 18–35 years; females (HR = 0.79; CI: 0.67–0.93) compared to males; and other/unknown race/ethnicity (HR = 0.71; CI: 0.54–0.93) compared to whites. A higher hazard was seen for opioid daily dose (in morphine milligram equivalents) 50–100 mg/day (HR = 1.52; CI: 1.24–1.86) and > 100 mg/day (HR = 1.98; CI: 1.55–2.53) compared to <50 mg/day; prior (during 1 year before cohort entry) diagnosis of substance use disorders (HR = 2.30; CI: 1.91–2.79) or mental health disorders (HR = 1.75; CI: 1.47–2.08); and prior (during 30 days before cohort entry) benzodiazepine prescriptions (HR = 1.43; CI: 1.13–1.81).

Conclusions: During 2002–2012 in sampled Medicaid enrollees, the incidence rates of opioid overdoses among apparent new users of prescription opioids declined by cohort entry year. Younger age, white race/ethnicity, higher opioid daily doses, and prior substance use disorders, mental health disorders, and benzodiazepine prescriptions were associated with a higher risk of opioid overdose incidence.

430 | Risk of opioid overdose associated with concomitant use of opioids and muscle relaxants

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Background: The CDC's opioid prescribing guideline cautions against the concomitant prescribing of opioids and muscle relaxants based on the pharmacological theory that muscle relaxants can potentiate the central nervous system depression associated with opioids. However, the clinical importance of this potential drug–drug interaction is not well understood.

Objectives: To compare the risk of opioid overdose hospitalizations or emergency department visits associated with concomitant use of opioids and muscle relaxants versus opioids use alone.

Methods: Using the IBM MarketScan Commercial Claims Database from 2005 to 2015, we assembled two opioid user cohorts based on whether individuals were incident (cohort 1) or prevalent (cohort 2) users. In cohort 1, incident opioid users with concomitant muscle relaxant use were directly compared with incident opioid-only users. In cohort 2, concomitant users were compared with randomly selected (1:3) opioid-only users who filled an opioid prescription on the same calendar date as the concomitant users. We used a validated algorithm to measure opioid overdoses during follow-up. Cox proportional hazards models with propensity score standardized mortality ratio weighting were used to compare the risk between concomitant users and opioid-only users, accounting for 54 potential confounders. Results were measured separately for each cohort and then combined with random effect meta-analysis.

Results: Our study included 1.3 million concomitant users and 13.9 million opioid-only users in cohort 1, and 1.1 million concomitant users and 3.3 million matched opioid-only users in cohort 2. Crude incidence

rates of opioid overdose were 1.2 and 1.0 per 1000 patient-years, respectively, for concomitant users and opioid-only users in cohort 1, and 2.7 and 2.0, respectively, in cohort 2. Adjusted HRs were 1.09 (95% CI: 0.74–1.62) and 1.26 (1.00–1.58) in cohorts 1 and 2, respectively, generating a combined estimate of 1.21 (1.00–1.48). This risk increased with duration of use (<15 days: HR 0.91, 95% CI 0.67–1.44; 15–60 days: 1.37, 0.81–2.37; >60 days: 1.80, 1.30–2.48) and was greater for carisoprodol (1.82, 1.15–2.90) and baclofen (1.84, 1.33–2.56). Patients using daily morphine equivalent opioid dose ≥50 mg (1.50, 1.18–1.92) and patients who had a history of benzodiazepine use (1.39, 1.08–1.79) also had greater risk.

Conclusions: Concomitant use of muscle relaxants and opioids was associated with a slightly increased risk of opioid overdose compared to opioid use alone, which was largely driven by long-term use, use of baclofen or carisoprodol, and use among certain high-risk patient groups.

431 | The association between prescription opioid use and bone fracture: A self-controlled case series study

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Background: Observational studies have reported positive associations between use of prescription opioids and bone fracture. Hypothesized mechanisms include acute central effects, and long-term effects on bone density. Most studies have been limited by potential exposure misclassification, residual confounding and confounding by indication. Alternative study designs are required to overcome these limitations.

Objectives: To estimate the association between prescription opioids and the incidence of bone fracture in adult opioid users.

Methods: Using a self-controlled case series study, adult opioid users registered in the UK Clinical Practice Research Datalink between 2009 and 2017, with a record of first fracture were identified. Opioid users were defined as those prescribed an opioid during the study period, with no record of an opioid prescription in the two years prior to first prescription. First fracture occurrences were defined as the earliest fracture code recorded one year before, or any time following, opioid initiation. Exposed time was categorized into risk periods: the 1st week, 2nd week, 3rd and 4th weeks, and any remaining time; for initial and subsequent periods of exposure. The baseline period consisted of unexposed time: 1-year before first opioid prescription, gaps in exposure, and remaining observation time following the final exposed period. Pre-exposure and post-exposure periods were introduced to eliminate bias arising from event-dependent exposure and residual drug effects. Conditional Poisson regression was used to estimate the risk of fracture during the risk periods as an adjusted incidence rate ratio (IRR), with 95% confidence intervals (CI).

Results: There were 43,639 opioid users with a record of first fracture. Median follow-up time was 4.6 years (IQR: 2.9, 6.3), 61% of the study population were female and the median age was 62 years (IQR: 45, 77). The IRR of fracture during the first week following opioid initiation compared with the baseline period was 6.63 (95% CI: 5.68, 7.73), after adjustment for age, season and opioid dose. The adjusted IRR decreased with time following initiation, the IRR for remaining opioid exposure, at least four weeks after initiation was 2.20 (95% CI 1.89, 2.56) compared to the baseline period.

Conclusions: The results are consistent with the hypothesis that acute central effects of opioids can increase the likelihood of bone fracture and that there may be longer-term effects on bone health. Patients and prescribers need to be aware of the potential increase in fracture-risk associated with opioids, particularly during the initial weeks of use.

432 | The proportion of patients in the United States receiving postsurgical opioids exceeding recommended thresholds increased between 2006 and 2015

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Background: Studies have found that patients routinely receive more opioids than medically necessary for adequate postsurgical pain management. This excess prescribing contributes to unused supply, increasing the risk of diversion and nonmedical use. In response to the US opioid crisis, opioid prescription (Rx) limits have been implemented on a state-by-state basis beginning in 2016, with 32 states currently enforcing prescribing limits.

Objectives: Among a broad cohort of opioid-naïve surgical patients in the US, examine trends in 1) the proportion filling opioid Rxs for postsurgical pain, and 2) the initial volume prescribed.

Methods: We identified patients undergoing surgery in MarketScan (2006–2015) and Medicare (2007–2015) claims. We defined the index opioid Rx for postsurgical pain as the first opioid filled in the week surrounding surgery following 180 days with no prior use. To reflect recent policy recommendations, we examined the proportion of patients whose index opioid Rx exceeded 7 days supply, 40 quantity dispensed (QTY), or 300 morphine milligram equivalents (MME).

Results: We identified 5,148,485 opioid-naïve surgical patients in MarketScan (mean age = 45), of whom 2,957,115 (55%) received an index opioid (median: days supply = 5; QTY = 30; MME = 240). The proportion of all patients with an index opioid Rx increased from 51% in 2006 to 62% in 2013, followed by a decline to 42% in 2015. Among patients receiving an index opioid, the proportion receiving

>7 days supply increased monotonically, nearly doubling between 2006 (11%) and 2015 (19%). Similarly, the proportion of patients receiving >40 QTY more than doubled throughout the study period, rising from 14% in 2006 to 29% in 2015, and the proportion receiving >300 MME rose from 21% in 2006 to 34% in 2015. Parallel analyses in Medicare found that the proportion receiving post-op opioids continued to increase through 2015, with parallel trends of increasing proportions of patients filling index opioid Rxs above defined thresholds throughout the study period.

Conclusions: Between 2005 and 2013, there was an increase in both the probability of opioid receipt for postsurgical pain, and the proportion of Rxs exceeding recommended thresholds. While the proportion of patients filling opioids began to decline in 2014 among the MarketScan population, the proportion of high threshold Rxs continued to increase. Understanding trends in post-surgical prescribing are vital in informing and evaluating policies aimed at reducing unnecessary opioid exposure and curbing the opioid crisis in the US.

433 | Healthcare utilization associated with chronic opioid use among hospitalized patients

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Background: Hospitalized patients are at high risk of chronic opioid use as hospitalization itself may inadvertently be a risk factor to initiating opioids. Inadequate communication of prescribed medications and changes to patient medication history at the time of discharge could lead to inappropriate continuation of opioids post discharge.

Objectives: This study identifies discrepancies in opioid prescribing at transitions in care and quantifies the impact of long-term opioid use on the healthcare system.

Methods: Cohort study using patients admitted to an academic hospital in Montreal (2014–2016) as part of an electronic medication reconciliation trial. Patients were included if they had filled at least one opioid prescription in the community. Provincial health administrative claims were used to measure opioid dispensations in the 1 year post-discharge period as well as hospital re-admissions and ED visits. Time-varying use of opioids was modeled as cumulative and continuous duration of use to differentiate between different opioid risk profiles. Cox models were used for the association between use of opioids and risk of ED visits and hospitalizations, while adjusting for a rich set of clinically important covariates including patient comorbidities, medication history and healthcare system characteristics.

Results: A total of 1525 patients filled an opioid prescription in the 1 year post-discharge, of which the majority (64%) were for oxycodone; 1166 patients received an opioid prescription at discharge, of which 66% were newly written by in-hospital physicians. The remaining 23% of patients had an opioid dispensation post-discharge despite documented evidence of having the opioid stopped in the medical chart. Among patients with previous opioid use, 9.0% had a discontinuation status of their opioid prescription at discharge but had, nevertheless, an opioid dispensation post-discharge. For cumulative opioid use, there was a 41% increase (HR 1.41, 95% CI: 1.11–1.79) in ED visits and re-admissions associated with every additional 30 days of opioid use. When modeling exposure of opioids as continuous use, there was a 21% risk increase, albeit non-significant (HR 1.21, 95% CI: 1.00–1.49).

Conclusions: Our findings reflect a difference in the risk of adverse events associated with distinct profiles of opioid users with increased susceptibility to opioids side effects for patients accumulating opioid use over longer periods of time. Communication of changes to opioid medications may help reduce excess of opioid prescriptions in the community and its associated risk of preventable ED visits and hospitalizations.

434 | High-risk opioid utilization and mortality among hemodialysis patients

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Background: Patients undergoing hemodialysis (HD) frequently report moderate to severe pain and receive three-fold more opioid prescriptions compared to the general United States population. Despite these high rates of opioid utilization, the burden, risk factors, and sequelae of high-risk opioid utilization among HD patients remain unclear.

Objectives: To identify risk factors for high-risk opioid utilization and quantify its association with mortality among patients initiating HD.

Methods: Retrospective cohort study of adults initiating HD in the United States between 2007 and 2014 using national registry data linked to Medicare claims (United States Renal Data System). We used Cox regression accounting for competing risks to identify risk factors for high-risk opioid utilization (≥120 morphine milligram equivalents [MME] & ≥30 days) and adjusted Cox regression with a time-varying exposure to quantify the hazard of all-cause mortality associated with high-risk opioid utilization.

Results: Among 327,344 patients initiating HD, the cumulative incidence of high-risk opioid utilization was 2.1% at six months, 2.9% at one year, and 3.8% at two years. Between 2007 and 2014, high-risk opioid utilization within one year was most common among HD patients with prior drug (7.6% vs. 2.5%; $p < 0.0001$) and tobacco use (5.0% vs. 2.3%; $p < 0.0001$). Among patients with an episode of high-risk utilization, the proportion of days ≥120 MME increased from 3.5% (95% CI: 3.4–3.6) in 2007 to 8.6% (95% CI: 8.5–8.7) in 2014. HD patients who were aged 18–35 years (HR = 2.50; 95% CI: 2.29–2.72), non-Hispanic (HR = 2.31; 95% CI: 2.15–2.49), and in the Far West region of the United States (HR = 3.57; 95% CI: 2.06–6.18) were at increased risk of high-risk opioid utilization. High-risk opioid utilization was associated with a 30% increased risk of death (HR = 1.30; 95% CI: 1.24–1.35).

Conclusions: Efforts designed to prevent high-risk utilization and deaths among HD patients should target HD patients who are younger and non-Hispanic, especially during periods where opioid use exceeds 120 MME for over thirty days.

435 | Opioid prescription use after vaginal delivery and subsequent persistent opioid use and misuse

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Background: Prior studies show that approximately 30% of women in the U.S. fill an opioid prescription after vaginal delivery, making this a common source of exposure to opioids in young women. Limited evidence is available regarding the impact of prescription opioid use after vaginal delivery on the risk of subsequent persistent opioid use and misuse.

Objectives: To evaluate the impact of prescription opioid use after vaginal delivery on the risk of subsequent persistent opioid use and misuse.

Methods: We assembled a nationwide cohort of Medicaid beneficiaries who delivered vaginally between 2009 and 2013 and who were not chronic opioid users/diagnosed with an opioid use disorder (OUD) during pregnancy. We required continuous Medicaid enrollment from ≥90 days before to 365 days after vaginal delivery. We identified prescription opioid dispensings within 7 days of the date of delivery. Persistent opioid use (primary outcome) was defined as ≥10 opioid fills or > 120 days' supply dispensed from 30–365 days after the date of delivery. Newly recorded diagnoses of OUD (secondary outcome) were ascertained during the same interval. We used logistic regression after propensity-score (PS) 1:1 matching to control for potentially confounding. To control for potentially unmeasured confounders, we performed an instrumental variable analysis (IVA) using a 2-stage least squares approach. To define the instrument, facilities were ranked within region according to their opioid dispensing rate after vaginal delivery and divided into deciles.

Results: Among 226,995 vaginal deliveries, 29.9% had an opioid dispensing within 7 days of delivery. Overall, 3,113 of the 67,954 (4.6%) prescription opioid exposed vs. 1,445 of the 159,041 (0.9%) unexposed had persistent opioid use during follow-up, for an unadjusted odds ratio (OR) of 5.2 (95% CI, 4.9–5.6) and a risk difference (RD) of 3.7% (95% CI, 3.5% - 3.8%). After PS matching, the risk remained higher among the exposed, with an OR of 2.7 (2.5–3.0) and a RD of 2.4% (2.3%- 2.6%). This was confirmed by the IVA (pseudo R^2 = 0.3) with an RD of 2.8% (2.5% - 3.1%). For newly diagnosed OUD, the unadjusted OR associated with opioid exposure after delivery was 2.4 (2.2–2.5), which attenuated to 1.5 (1.4–1.6) after PS matching. The adjusted RD was 0.9% (0.7% - 1.0%) after PS matching and 2.1% (1.8% - 2.4%) using IVA.

Conclusions: Opioid exposure following vaginal delivery appears to be a trigger for future persistent opioid use and misuse, independent of confounding factors. Given this risk, prescription opioid use after vaginal deliveries should generally be avoided.

436 | Postpartum opioid prescribing and the risk of persistent opioid use

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Background: Millions of US women are exposed annually to prescribed opioid pain relievers (OPRs) as part of childbirth. The association between postpartum OPR use and the risk of persistent OPR use is unclear.

Objectives: To examine the association of postpartum OPR prescribing with persistent OPR use following childbirth.

Methods: We studied women age 15–44 years enrolled in Tennessee Medicaid with deliveries between 1/1/2007 to 9/30/2015. Women with >1 prescription for an OPR in the 180 days prior to delivery or with diagnoses of opioid use disorder were excluded. We examined OPR prescription fills during the postpartum period (up to 42 days after delivery) and defined OPR exposure groups as 0, 1, 2, or > 2 postpartum fill(s). Follow-up started on day 43 after delivery and continued through the earliest of loss of enrollment, death, identification of opioid use disorder, 1 year post-delivery or becoming a persistent OPR user. We defined persistent OPR use as filling >90 days' supply of OPRs within a 180-day window with no gaps >32 days. We compared the risk of persistent OPR use among postpartum OPR exposure groups using Cox proportional hazards models while adjusting for demographic and baseline clinical characteristics. All data were stratified by cesarean versus vaginal delivery.

Results: Among 231,551 women who met eligibility criteria, 161,175 (69.6%) had vaginal and 70,376 (30.4%) had cesarean deliveries; 58% of women with a vaginal delivery and 91% of women with a cesarean filled ≥1 OPR prescription in the postpartum period. The rate of persistent OPR use with 0, 1, 2, >2 prescriptions was 4.9, 6.4, 27.0, 87.0 per 1000 person-years (py) respectively among women with cesarean and 3.5, 8.2, 37.8, 106.2 per 1000 py respectively among women with vaginal deliveries. After adjusting for additional delivery procedures and postpartum complications, women with cesarean deliveries receiving 1, 2, >2 prescriptions had higher risk of persistent OPR use compared with no prescription (HRs: 1.5 [1.0–2.3], 4.8 [3.2–7.4], 12.5 [8.2–19.0]). Similar findings were observed among women with vaginal deliveries (HRs: 1.9 [1.6–2.3], 6.2 [5.2–7.5], 13.4 [11.0–16.5]).

Conclusions: Postpartum prescription OPR use is strongly associated with risk of persistent OPR use, regardless of delivery route. Reducing

both OPR prescribing following vaginal delivery, and the number of OPR prescriptions in the postpartum period are potential intervention targets.

437 | Prevalence and predictors of ADHD medication use in a cohort of pregnant women

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Background: Attention deficit with or without hyperactivity disorder (ADHD) is common. Increased prevalence of ADHD medication use has been reported in adults and thus its utilization in pregnancy has become a concern.

Objectives: We sought to determine the 1) prevalence and trends of ADHD medication use before and during pregnancy, (2) ADHD medication mean dosages by classes, and prevalence of medication switches, and (3) determinants of ADHD medication use during pregnancy.

Methods: A longitudinal cohort study was performed, using data from the Quebec Pregnancy Cohort (QPC), which includes data on all pregnancies of mothers covered by the provincial prescription drug insurance in Quebec and their children fromJanuary 1998, to December 2015. The cohort entry date was the first day of gestation. Women aged 15–45 years old at cohort entry, and covered by the RAMQ prescription drug plan for at least 12 months before and during pregnancy were eligible. ADHD medication users were defined as those having at least one ADHD medication filling before or during pregnancy overall, and stratified by trimester. Generalized estimating equation (GEE) were used to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs) to identify determinants associated with ADHD medication use during pregnancy.

Results: 428,479 pregnant women were included in the study. A significant increase in the prevalence of ADHD medication use in pregnant women was observed from 0.08% 1998 to 1.2% in 2015 ($p < 0.01$). Methylphenidate, a stimulant, was the most used (70.1% of ADHD medication users). ADHD medication fillings were at optimal dosages 91.8% of the time; 28.1% of women switched to another ADHD medication class or had concomitant multiple ADHD medications use during gestation. Determinants associated with ADHD medication use during pregnancy were being on welfare (aOR 1.27; 95%CI 1.06–1.52), hypertension (aOR 1.85; 95%CI 1.31–2.62), asthma (aOR 1.39; 95%CI 1.13–1.71), psychiatric disorders (aOR 3.28; 95%CI 2.51–4.27), depression (aOR 3.18; 95%CI 2.58–3.93), or other medication use (aOR 3.26; 95%CI 2.36–4.49) in the year before pregnancy; pregnant women were also at increased risk of using ADHD medications during gestation with increasing calendar year (aOR 1.33; 95%CI 1.26–1.41).

Conclusions: Our findings show an increasing trend in ADHD medication use during pregnancy over the past 20 years. Our results are suggestive of a detection bias given the increase in use associated with increasing calendar year.

438 | Interrupted time series analysis to assess prescription filling around conception and implications for misclassification of medication use in pregnancy

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Background: In studies based on administrative data, medication exposures are often defined by one or more prescription fills in pregnancy or first trimester. Harmful exposure effects could be underestimated if there is rapid discontinuation of use after pregnancy recognition. We hypothesized that prescription fills for some psychotropic drugs may decrease rapidly after conception, due to a preference for avoidance of use in pregnancy. Few studies have used a critical biological period as an intervention for interrupted time series analysis (ITSA).

Objectives: To assess the change in the weekly rate of prescription fills before and after conception and the immediate effect of conception and compare with different individual-level exposure definitions.

Methods: Using data from the Norwegian Prescription Database linked the Medical Birth Registry (2005–2015), we linearly modeled the number of prescription fills in each of the 12 weeks before and after conception with ITSA. The "intervention" was the earliest possible date of pregnancy recognition, i.e. 2 weeks after conception. We examined psychostimulants, antidepressants, antipsychotics and antiepileptics (AEDs; separated by use for epilepsy or for other indication). We used relative measures (%) to compare the model coefficients to the predicted values. We also compared the number of pregnancies defined as exposed (yes/no) when the earliest fill was respectively 30 days before the last menstrual period (LMP-30 days), LMP, or conception (LMP + 14 days).

Results: We observed similar patterns for psychostimulants, antidepressants, and AEDs (other indication): a sudden decline in prescription fills from 2 weeks after conception (−47%, −30%, and − 23%) and decreasing fills thereafter (−10.0%, −6.9%, and − 4.2% per week). We also saw similar patterns for antipsychotics and AEDs (epilepsy): The intercept-only model fit the data better with a trend toward a slight increase in prescription fills during the first trimester. Only 77% of pregnancies with fills for psychostimulants from LMP and 58% with fills from LMP-30 days had fills from conception to birth. Similar figures for AEDs (epilepsy) were 99% and 96%.

Conclusions: ITSA can help researchers understand rapid changes in patient behavior around conception that have consequences for exposure misclassification in pregnancy studies. The results suggest that a more conservative definition of exposure prioritizing specificity by avoiding inclusion of prescription fills before conception may be warranted in some cases, e.g. for psychostimulants.

439 | Trajectories of antipsychotic use before and during pregnancy and related maternal and birth characteristics

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Background: Antipsychotics are increasingly being used for a wide array of indications beyond psychotic illness, resulting in increased heterogeneity in patterns of use and characteristics of treated persons. There is no clear guidance antipsychotic use during pregnancy, yet their use in pregnant women is increasing, with a lack of detailed information about variations in treatment patterns.

Objectives: To identify trajectories of antipsychotic use prior to and during pregnancy, and describe the maternal sociodemographic, mental health, and obstetric characteristics, and birth outcomes associated with different trajectories of antipsychotic use.

Methods: We conducted a retrospective cohort study of women who were social security beneficiaries and gave birth in New South Wales, Australia (2005–2012). We estimated the daily dose and duration of antipsychotics in the 450 days prior to conception and during pregnancy using dispensing claims linked to birth records. We used group-based trajectory modeling to identify different patterns of antipsychotic use over time, and characterized women with different trajectories according to maternal sociodemographic characteristics, mental health diagnoses and hospitalisations, use of psychotropic medicines, and birth outcomes.

Results: Of 135 252 women who gave birth, 2741 (2.0%) were exposed to antipsychotics prior to or during pregnancy. We identified six distinct trajectories: in two trajectories, women used low daily doses in the short-term prior to pregnancy only (51.7%), while three trajectories identified women with longer-term use of low (20.7%), moderate (11.0%), and high (2.0%) daily doses continuing in pregnancy. Women in one trajectory (15.0%) had increased use during pregnancy. Women with longer-term use were more likely to have a schizophrenia or bipolar disorder diagnosis, have used mood stabilizers, and have a mental health hospitalization during pregnancy. Compared with women with no antipsychotic exposure, women using antipsychotics had a higher rate of preterm birth, and a baby admitted to intensive care or diagnosed with neonatal abstinence syndrome. Women with the greatest exposure to antipsychotics also had the highest rates of gestational diabetes and hypertension.

Conclusions: Women using antipsychotics around pregnancy are heterogeneous, with varying patterns of use and associated birth outcomes, most likely reflecting underlying differences in the treatment indications and/or severity of illness. This heterogeneity should be considered when developing clinical guidelines and designing safety studies.

440 | Medication use patterns in pregnant women with migraine

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Background: Potential risks from medications taken during pregnancy are traditionally assessed through post-approval prospective pregnancy registries, which often struggle to meet enrollment targets, providing limited power to evaluate outcomes. Large administrative databases are a potential alternative data source to evaluate drug safety during pregnancy. Migraine, with peak prevalence around reproductive age, represents a population who may have increased medication exposure during pregnancy.

Objectives: To describe the use of three classes of medications commonly used for migraine prevention (anti-epileptic drugs [AED], antidepressants [AD], and beta blockers [BB]), before and during pregnancy in a cohort of women with migraine in the MarketScan commercial claims US database.

Methods: Women with migraine and a pregnancy resulting in a livebirth between 1/1/2010 and 9/1/2015 were identified. Women were required to have 180 days continuous enrollment prior to their estimated date of conception (EDC) through childbirth. Multiple pregnancies per woman were included. We described medication use 180 days before EDC and by pregnancy trimester.

Results: Among the 88,084 women with evidence of migraine and a livebirth during the study period, 98,155 unique pregnancy episodes were evaluated. The average age at EDC was 31 years (14% were 18–24 years; 63% were 25–34 years; 21% were 35–40 years). AEDs were filled by 2.3% of women within 180 days before EDC, dropping to 1.1% during pregnancy. Of the pregnancies with AED exposure, 79%, 32%, and 27% had AED filled in the 1st, 2nd, and 3rd trimesters, respectively. Similarly, 2.8% of women filled an AD within 180 days before EDC, compared with 1.7% during pregnancy. Of the pregnancies with AD exposure, 77%, 40%, and 34% had AD filled in the 1st, 2nd, and 3rd trimesters, respectively. Within 180 days before EDC, 1.4% of pregnant women filled a BB, increasing to 2.8% during pregnancy. Of 2,642 pregnancies with BB exposure, 50%, 54%, and 70% had BB filled in the 1st, 2nd, and 3rd trimesters. Older women were more likely to receive these 3 classes of medications during pregnancy than younger women.

Conclusions: Use of migraine prevention medications was low in the months leading up to and during pregnancy. However, due to the large size of the underlying database, over 1,000 women filled each class of medication during pregnancy. The low frequency of medication use may help explain some of the difficulties of identifying and enrolling women in pregnancy registries and suggests that healthcare

databases may offer a more practical approach to evaluating potential safety concerns during pregnancy, particularly for rare exposures.

441 | Baclofen decreases alcohol consumption in real world clinical populations

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Background: Randomized trials demonstrate that baclofen, a GABA beta-receptor agonist used for spasticity, decreases alcohol use in substance use treatment-seeking individuals with alcohol use disorder (AUD).

Objectives: To determine if baclofen, prescribed for any indication, was associated with changes in alcohol consumption among treatment-seeking and non-treatment-seeking patients, with and without AUD, and by baseline levels of drinking and baclofen dose.

Methods: We used real-world data from the US Veterans Birth Cohort (n = 4.5 million). We included patients with Alcohol Use Disorder Identification Test - Consumption (AUDIT-C) scores >0 who received >1 pharmacy fill of baclofen (BACLO+) for ≥60 consecutive days for any indication from 2009 to 2015, and compared them to 1:5 propensity score (PS)-matched, baclofen unexposed (BACLO-) patients. Index date was defined as prescription release date for BACLO+ patients and a randomly selected outpatient visit date for BACLO-. Change in pre and post AUDIT-C scores were compared using difference-in-difference analysis. Pre-index AUDIT-C scores were closest to index date, and post-index scores were closest to end of exposure or < 90 days after. A 1-point change in AUDIT-C was considered clinically meaningful. We defined three mutually exclusive groups: those with AUD (defined by validated ICD codes) and baseline substance use disorder treatment clinic visit (AUD-SUD), those with AUD and without a baseline SUD clinic visit (AUD-OTH), and those without AUD. We examined the association of baclofen with change in AUDIT-C in these groups overall, and by baseline AUDIT-C and baclofen dose.

Results: There were no demographic or clinical differences between 5,120 BACLO+ and 14,047 BACLO- PS-matched patients (all standardized differences <0.1). Median age was 58 years (IQR: 53–63), most were male (92%) and European-American (69%), 27% were AUD-SUD, 10% were AUD-OTH, and 63% did not have AUD. Among AUD-SUD prescribed ≥30 mg, the difference-in-difference (DiD) estimate of the additional decrease in AUDIT-C scores between BACLO +/− was significant and potentially clinically meaningful (DiD 0.73, 95% CI 0.30, 1.16). Similar estimates were observed among AUD-OTH patients who reported heavy drinking (AUDIT-C ≥ 6) (DiD 0.73, 95% CI 0.24, 1.22). Among patients without AUD, estimates were not clinically meaningful (DiD 0.16, 95% CI 0.08, 0.24).

Conclusions: Provision of baclofen for any indication is associated with significant decreases in AUDIT-C scores in real-world patient populations, and clinically meaningful decreases among those with AUD and heavy drinking.

442 | Long-term effect of interferon and Glatiramer acetate in real-world settings use on multiple sclerosis disability progression: Input of time-dependent propensity score

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Background: The long-term effect of beta-interferon (IFN) and glatiramer acetate (GA) on multiple sclerosis (MS) disability progression showed controversial results, maybe due to lack of appropriate control of confounding.

Objectives: To better assess the long-term effect of IFN and GA on disability progression in relapsing onset MS patients from the Rennes expert MS centre, France using a time-dependent propensity score (PS).

Methods: This retrospective observational study is based on a series of patients collected in the European Database for Multiple Sclerosis (EDMUS). All patients with relapsing onset MS before 31/12/2005 and treatment-naïve before 30/11/1995 (date of approval for IFN) were included in the present study. Moreover, a minimal follow-up of 2 years from MS onset and a minimal of 3 visits were required. We used a time-dependent PS matching procedure. This procedure consists of a Cox model to assess the time from MS onset to treatment start to get the hazard of being treated at each time. The model was adjusted for sex, age at onset and two time-dependent covariates, i.e. disability progression and relapse activity. The linear predictor of this Cox model was used as time-dependent PS; an IFN/GA-treated patient was matched to a not yet treated patient at the same time and having the same hazard of being treated. A nearest neighbor matching at random, with a caliper of 0.2 of the standard deviation and without replacement has been used. The restricted mean times to reach a moderate level of disability were compared between the two groups in an intention-to-treat analysis. Bootstrap interval has been estimated to handle the randomness of the matching procedure.

Results: Among the 1300 included patients, 627 were treated. Among them, 409 were matched with a not yet treated patient. The median follow-up duration was 15 years (Interquartile range (IQR): 11–18) for IFN/GA-treated patients and 18 years (12–23) for IFN/GA-not

yet treated patients. Over 15 years, the mean time before reaching a moderate level of disability was 12.8 years in the treated group and 11.2 years for in the not yet treated group. Thus, the time to reach the outcome was significantly delayed by 1.6 year (95%CI: [0.40; 2.83]) in the IFN/GA-treated group.

Conclusions: Our results tended to show that starting IFN and GA earlier delayed disability progression. This time-dependent PS seems relevant to well balance the two groups over time while conventional PS ignores the temporal features of the therapeutic decision. In the future, we plan to explore the use of marginal structural models.

443 | Ethnic inequalities in prescribing quality for patients with dementia: A cohort study using electronic health records

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Background: The number of Black and Minority Ethnic People (BAME) with dementia in Western countries is rising: in the UK it is projected to increase seven-fold in the next 40 years. Appropriate prescribing to patients with dementia can be measured by high rates of anti-dementia drugs where indicated and low rates of antipsychotic, anticholinergic, and hypnotic and anxiolytic drugs, which are associated with risk of cognitive decline. It is unclear whether ethnicity is associated with appropriate prescribing in patients with dementia.

Objectives: To determine whether differences exist by ethnicity in prescribing of anti-dementia drugs where indicated, and in prescribing of antipsychotic, anticholinergic, and hypnotic and anxiolytic drugs.

Methods: Retrospective cohort using electronic longitudinal primary care medical records from The Health Improvement Network (THIN), a broadly representative database of UK general practices (GP). Patients with dementia were identified by diagnosis or prescription of an anti-dementia drug, were aged between 50 and 105, and were followed up for up to two years between 1 January 2014 and 31 December 2016. The primary outcome measures were a prescription for: an anti-dementia drug where indicated; an antipsychotic drug; a hypnotic or anxiolytic drug; and two or more prescriptions in one year for a drug with a definite anticholinergic burden. Multiple imputation by chained equations was used to impute missing ethnicity. Poisson regression was used to calculate prevalence rate ratios of each outcome by ethnicity.

Results: We analyzed data from 53,715 people with dementia. Compared to people from White ethnic groups, Asian people with dementia were less likely to be prescribed anti-dementia drugs when indicated (adjusted prevalence rate ratio 0.86 (95% CI 0.75–0.98)), and more likely to be prescribed anticholinergic drugs (1.22 (1.04–1.44)), after controlling for gender, age and level of deprivation. People from Black ethnic groups were less likely to be prescribed an anxiolytic or hypnotic drug (0.58 (0.43–0.79)). Compared to people from White ethnic groups, there was no difference in prescribing of antipsychotic drugs between patients from Asian (0.94 (0.78–1.13)) or Black (0.99 (0.77–1.28)) ethnic groups.

Conclusions: Compared to people from White ethnic backgrounds, people with dementia from Asian backgrounds appear to receive less good quality prescribing. These results may identify a target for improvement in primary care.

444 | Nested case–control study of antidepressant drug use and subdural hematoma risk

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Background: Studies have raised concerns as to whether use of selective serotonin reuptake inhibitors (SSRIs) increases the risk of bleeding. We investigated whether use of antidepressants is associated with subdural hematoma (SDH), a specific type of intracranial hemorrhage.

Objectives: To investigate the relationship between use of antidepressant drugs and risk of SDH, and whether this risk is influenced by concomitant use of antithrombotic drugs or nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods: We identified 10,885 patients (median 72 years; 65% men) discharged from Danish hospitals with a first-ever SDH diagnosis in 2000 to 2016. For each case, we selected 40 age-, sex- and period-matched population controls. We used conditional logistic regression to estimate odds ratios (OR), adjusted for comorbidity, co-medication, education level, and income (aOR).

Results: Current use of SSRI (aOR 1.60, 95%CI: 1.50–1.71) or 'other' antidepressants (aOR 1.35, 95%CI: 1.25–1.47) was linked to SDH risk. For both groups of antidepressants, risk of SDH was inversely related to duration of current use, e.g., <1 month of current use of antidepressants yielded an OR of 2.55 (95% CI: 2.07–3.15) for SSRI and 1.88 (95% CI: 1.46–2.41) for 'other' antidepressants whereas >3 years of current use returned ORs of 1.04 (95%: 0.93–1.17) and 1.12 (95%CI: 0.98–1.28), respectively. Combined use of antidepressants with either antithrombotics or NSAIDs yielded similar ORs to those observed for single use of antithrombotics or NSAIDs. For instance, SSRI combined with DOAC returned a risk of SDH of OR 0.84, 95%CI: 0.42–1.68), while SSRI combined with VKA yielded OR 3.79, 95%CI: 2.66–5.42), results that were similar to single use of DOAC 1.20, 95%CI: 0.87–1.65), or single use of VKA (OR 3.01, 95%CI: 2.62–3.46). The highest risk of SDH was observed in patients receiving therapy of antidepressants together with both VKA and NSAIDs (combined with SSRI: OR 5.51, 95%CI: 2.70–11.22; combined with 'other' antidepressants: OR 6.81, 95%CI: 2.37–19.60). Supplementary analyses of single use (i.e.,

excluding concomitant users), new users, sex and age stratification, and other groupings of antidepressants yielded similar results as in the main analyses. In analyses of specific single use of antidepressant drugs, estimates ranged from an OR of 1.04 (95%CI: 0.84–1.29) for mianzerine to an OR of 1.95 (95%CI 1.52–2.50) for fluoxetine.

Conclusions: Compared with non-use, antidepressant use was associated with higher risk of SDH, more so for SSRI than 'Other' antidepressants. In absolute terms, the observed excess risk of SDH was small and declined after prolonged drug use.

445 | Co-occurring neuropsychiatric diagnoses and use of psychotropic drugs in children with autism Spectrum disorder

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Background: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder. Co-occurring psychiatric and neurological comorbidities are common, and many children with ASD receive psychotropic medications with uncertain efficacy and safety.

Objectives: In a nationwide Norwegian sample of children (2–17 years old) in 2014 we aimed to calculate lifetime prevalence of ASD. For the individuals with an initial diagnosis of ASD in the registry in 2014 we aimed to estimate the proportion of co-occurring psychiatric and neurological diagnoses and to investigate use of psychotropic drugs according to ASD subtype, age and gender. Further we aimed to explore the relationship between co-occurring diagnoses and CNS active drug use.

Methods: Individual-level registry data from the Norwegian Patient Registry and Norwegian Prescription Database were linked using the unique personal identity number assigned to all individuals living in Norway. We calculated the proportion who were dispensed selected groups of psychotropic drugs during the 365 day period after the date of the first diagnosis.

Results: In 2–17 year old children, the ASD lifetime prevalence was 0.76%. Of the children who received an initial ASD diagnosis in 2014 (n = 1234), 64.8% had one or more co-occurring neuropsychiatric diagnosis. Children with autistic disorder were mainly prescribed hypnotics: 16.3 and 17.3% of the girls and boys, respectively. Children with Asperger's syndrome were mainly prescribed stimulants (25.2 and 23.3% of girls and boys) and hypnotics (25.2 and 18.2% of girls and boys), while there was a disparity in the use of antidepressants: they were prescribed to 16.5% of girls and only 7.2% of boys. Children with atypical or unspecified autism were mainly prescribed stimulants (16.9 and 19.9% of girls and boys) and hypnotics (19.1 and 17.6% of boys and girls). There was a relatively good match between prescription of stimulants/ADHD drugs, antiepileptic drugs, and antidepressants, and co-occurring diagnoses for which these drugs are indicated. In contrast, a small proportion of children who received treatment with antipsychotic drugs had a diagnosis where such treatment is indicated. The children who had ASD, but non of the studied neuropsychiatric comorbidities, received very little psychotropic drugs in general.

Conclusions: Use of psychotropic drugs was common among children with ASD and co-occurring neuropsychiatric and neurological diagnoses, and most children who usied medications had a diagnosis for which the drug was indicated. Drug use among children without co-occurring conditions was low.

446 | Concurrent use of Neurocognitively-active medications and alcohol increases risk of community-acquired pneumonia

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Background: Accumulating evidence suggests that some neurocognitively-active potentially inappropriate medications (NC-PIMs) have immunosuppressive properties and increase risk of infections, including community-acquired pneumonia (CAP). Concurrent alcohol use may exacerbate this effect.

Objectives: To evaluate the independent and interactive effects of concurrent alcohol use and NC-PIM exposure on the risk of CAP.

Methods: From a base cohort using real-world data from the Veterans Birth Cohort (n = 4.5 million), we conducted a nested case–control study from 2008 to 2015. Cases with CAP requiring hospitalization (n = 52,122) were 1:5 matched to controls without CAP (n = 260,610) at the time of event by age, sex, race/ethnicity, baseline year, and duration of observation time. Index date was event date for cases and match date for controls. Exposure to NC-PIMs, including anticonvulsants, antidepressants, antipsychotics, muscle relaxants, prescription opioids, and sedatives, was assessed in the 45 days prior to index date. Odds ratios (OR) and 95% confidence intervals (CI) for the independent and interactive effects of NC-PIMs (overall and by class) and alcohol use were estimated with conditional logistic regression models. Alcohol use was measured using Alcohol Use Disorder Identification Test - Consumption (AUDIT-C, 4–5 = moderate and $\geq$ 6 = heavy drinking). Models were adjusted for VACS Index (i.e., physiologic frailty), number of outpatient medications, smoking

status, steroid receipt, influenza and pneumonia vaccination status, previous CAP, and comorbidity.

Results: Among 312,732 patients, median age was 59 years (IQR: 55–61), 96% were male, 71% were white, and median follow-up time was 3 years (IQR: 1–5). Cases were more likely to be prescribed at least one NC-PIM (70% vs. 53%) and ≥ 5 NC-PIMs (11% vs. 4%) than controls ($p < 0.0001$). Exposure to ≥5 NC-PIMs (OR 1.72, 95% CI 1.61–1.84) and heavy alcohol use (OR 1.57, 95% CI 1.48–1.67) independently increased the risk for CAP. Concurrent exposure increased risk even further (OR 3.29, 95% CI 2.76–3.92). Exposure to anticonvulsants, antipsychotics, opioids, barbiturates, or benzodiazepines independently increased risk for CAP and had significant interactions with moderate and heavy alcohol use (all $p < 0.001$). Antidepressants, muscle relaxants, and other sedatives were not associated with CAP.

Conclusions: NC-PIMs, including anticonvulsants, antipsychotics, opioids, barbiturates, and benzodiazepines, especially in the context of heavy alcohol use, were associated with CAP in a national healthcare system.

447 | Patient-, disease- and treatment related factors that impact values attached to drug effects: A preferences study among patients with type 2 diabetes

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Background: About 50% of patients with type 2 diabetes do not reach their glucose (HbA1c) treatment targets. Incorporating patient preferences at the time of prescribing may improve treatment satisfaction, adherence, and subsequently outcome. Preferences may be influenced by patient-, disease- and treatment-related characteristics.

Objectives: To evaluate to what extent patient-, disease- and treatment-related factors affect the importance patients attach to certain drug effects.

Methods: A cross-sectional survey was administered to type 2 diabetic patients aged between 57 to 80 years who received ≥1 prescription of an oral anti-diabetic drug in the last 4 months. The survey comprised patient- (age, sex, BMI, education), disease- (diabetes duration) and treatment- (adverse drug events (ADEs), HbA1c levels) related questions and a discrete choice experiment (DCE) to elicit patients' preferences for hypothetical anti-diabetic agents described in terms of six attributes: HbA1c decrease, cardiovascular risk reduction, weight change, gastrointestinal (GI) ADEs, hypoglycemic events and bladder cancer risk. A latent class logit model was used to model preference heterogeneity and identify factors associated with class membership probabilities.

Results: The 199 patients were on average 67 (SD 4.4) years old, 54% were male, had a BMI of 29 (SD 4.8) and 20% were higher educated. The mean diabetes duration was 9 (SD 8.8) years. ADEs were reported by 23% of the patients. The analyses identified two classes. Class 1 attached more importance to decreasing HbA1c levels, reducing cardiovascular risk, maintain body weight and no increasing risk of cancer. Class 2 allocated more importance to decreasing GI ADEs and reducing hypoglycaemic events. Characteristics with the strongest influence of belonging to class 2 were male gender (OR: 0.51; 95% CI: 0.34–0.77), BMI (OR: 0.90; 95% CI: 0.87–0.94) and diabetes duration (OR 0.93; 95% CI: 0.91–0.94).

Conclusions: Males with high BMI and long diabetes duration preferred agents with larger effects on HbA1c reduction and cardiovascular risk reduction, that maintain body weight and do not increase the risk of cancer despite an increase in GI ADEs and hypoglycaemic events. The observed heterogeneity among patient preferences should be acknowledged when prescribing new - and or additional - drugs.

448 | Impact of medicines regulatory risk Communications in the United Kingdom on prescribing and clinical outcomes: Systematic review, re-analysis and meta-analysis

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Background: Risk communications about medicines from regulatory bodies are important to ensure medication safety, but their impact is often uncertain.

Objectives: The aim of this study was to systematically review studies measuring the impact of United Kingdom risk communications and quantify their effect on medication use and other outcomes.

Methods: Systematic review and overview of published studies reporting prescribing and/or health outcome data relevant to the regulatory risk communication. Data were extracted and re-analyzed using interrupted time-series regression analysis to quantify the impact on prescribing and health outcomes twelve months following the date of the regulatory intervention. Effect estimates for mean changes were pooled using a random effects generic inverse variance method to examine the impact of the following risk communication subgroups: drug withdrawals; restrictions/changes in indications; 'be aware' messages without specific recommendations for action; communication via Direct Healthcare Practitioner Communications (DHPCs); communication via drug bulletins.

Results: After screening 11,466 articles, 40 studies were included examining 25 separate UK regulatory risk communications using variable methods of analysis. At 12 months post-risk communication, product withdrawals, restriction in indications and 'be aware' communications were associated with mean relative changes of −78% (95%CI -60% to −96%), −34% (95%CI -12 to −55%) and − 11% (95%CI -8% to −15%) in targeted drug prescribing respectively. DHPCs were associated with a mean relative change of −47% (95%CI -27 to −68%) compared to −13% (95%CI -6 to −20%) for drug bulletins. Regulatory risk

communications were associated with a 8% (95%CI 4 to 11%) change in clinical outcomes examined.

Conclusions: UK medicines regulatory risk communications were associated with significant changes in targeted prescribing and potentially significant changes in clinical outcomes. Communication using direct letters was associated with greater change compared with via drug bulletins. Further research is needed to more systematically study the impact of regulatory interventions.

449 | Risk minimisation studies outcomes and process indicators

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Background: Good Pharmacovigilance Practice (GVP) Module XVI recommends the evaluation of additional risk minimisation measures (aRMMs) with process indicators and outcomes. Outcomes are difficult to assess and most evaluations study only process indicators.

Objectives: To describe risk minimisation (RM) evaluation plans that assess both process and outcome indicators.

Methods: The EU Register of Post-Authorisation Studies (EU PAS Register) was used to identify survey studies evaluating the effectiveness of aRMMs in EU and any outcome studies linked to the surveys.

Results: From 1189 studies in the EU PAS Register as of October 2017, 106 were risk minimisation studies, of which 98 were conducted in ≥1 EU country. The number of RM studies with survey component was 52 of which 15 also assessed outcomes (28.9%; 46.7% included in the same protocol). One RM plan included a survey and two drug utilization studies. While all surveys were cross-sectional, the outcome studies included retrospective (75.0%), cross-sectional (18.8%) and prospective (6.3%) designs that assessed aRMMs pre/post-implementation (37.5%) or only after implementation (62.5%). Data sources for outcomes consisted of EMR databases (43.8%), medical chart review (25.0%), drug safety databases (12.5%), primary data collection (12.5%) and a prescription questionnaire (6.3%). The most frequently assessed outcomes were: off-label/on-label use (8), rate of spontaneous adverse events (2), proportion of prescriptions (2) and rate of infections (2). A correlation between survey results and outcomes was reported in five studies. Two studies attempted to correlate aggregate survey results with spontaneous reporting rates, two with outcomes recorded in the clinical records at an individual patient level, and one with prospectively collected events. Key limitations of the research methods included: for EMR databases, no information on rationale for metabolic monitoring and missing information on treatment duration and doses; for spontaneous reporting databases, only ecological correlations were possible which are affected by underreporting and the lack adjustment for confounding; for chart reviews, bias in extrapolating current survey results with past events, small sample size and missing data; for prescription questionnaires, recall bias.

Conclusions: A minority of RM studies assessed both process indicators and outcomes with varying degrees of success. Further innovative hybrid studies to overcome these limitations are needed to meet expectations from regulators.

450 | Ivabradine drug utilization study in five European countries: A pass to assess effectiveness of risk-minimization measures

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Background: Ivabradine hydrochloride, a pure heart rate lowering agent, was first granted marketing authorization in Europe in October 2005 for the treatment of symptomatic chronic stable angina pectoris. Following the SIGNIFY study, which evaluated ivabradine at higher starting and maintenance doses than the recommended and showed an increase of cardiovascular events in a sub-group of patients, the benefit–risk ratio of ivabradine was re-assessed in 2014 and new risk-minimization measures (RMM) were implemented.

Objectives: To evaluate prescribers' compliance with the RMMs.

Methods: This was a multinational (France, Germany, Italy, Spain, and the United Kingdom), retrospective, chart review-based, drug utilization study with pre- and post-RMM study periods. Patients were identified by general practitioners (GPs) and cardiologists sampled from very large source lists. Data were collected at ivabradine initiation and during ≤6 months of treatment start. The primary outcome was the compliance with the following RMMs: use in patients with a heart rate ≥ 70 bpm at initiation, no doses higher than those recommended in the Summary of Product Characteristics (SmPC) (starting and maintenance doses should not exceed 2.5 and 5 mg twice daily, respectively), and no concomitant use of verapamil or diltiazem. The differences between proportions of the study outcomes in the pre- and post-RMM periods were calculated as estimates of the changes using the Newcombe score.

Results: Out of 60,675 contacted sites, 522 were interested in participating and 68 were active. Overall, 711 and 506 eligible patients were included in the pre-RMM and post-RMM periods, respectively. The percentage of patients for whom ivabradine prescriptions were compliant with all above mentioned RMMs increased in the post-RMM period (70.6% pre-RMM and 78.4% post-RMM; p-value = 0.0035). The compliance increased for each individual component: patients with heart rate ≥ 70 bpm at initiation (79.4% pre- and 85.2% post-RMM; p-value = 0.0141), no dose higher than the SmPC doses at initiation and during follow-up (92.8% pre- and 94.1% post-RMM; p-value = 0.3957), and no concomitance with verapamil or diltiazem (96.1% pre- and 99.2% post-RMM; p-value = 0.0007). The increase in RMMs compliance was observed in both GPs and specialists and in all countries except Italy.

Conclusions: The RMMs for ivabradine were well implemented across the participating European countries ensuring a favorable benefit–risk balance of ivabradine in chronic stable angina pectoris.

451 | Comparative effectiveness of risk mitigation strategies to prevent fetal exposure to mycophenolate

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Background: In 2012, the Food and Drug Administration approved a Risk Evaluation and Mitigation Strategy (REMS) program to prevent fetal exposure to mycophenolate products (MPA). Prior to the implementation of the REMS, which includes training for prescribers and a pregnancy registry, the teratogenic risk was solely mitigated via a black-box warning in the label and a medication guide (2008–2012). To date, there is no evidence on the effectiveness of the REMS for MPA.

Objectives: To compare the proportion of women who were pregnant on the day of MPA initiation (study 1) and the risk of pregnancy onset during an MPA treatment episode (study2) before and after REMS implementation.

Methods: We conducted a retrospective cohort study using the IBM MarketScan® Research Databases for Commercial Claims (2007–2015). Study enrollees were women aged 15 to 44 who filled &ge 1 MPA prescription and without medical encounters indicating infertility. For outcome 2, we further excluded patients who were pregnant or who used medications with pregnancy contraindication on MPA initiation. We extracted demographics, clinical indications, and comorbidities within a 6-months look-back period. Pregnancy episodes and conception were measured with an algorithm based on diagnosis and procedure codes for pregnancy outcomes or screening services. We used Poisson and Cox proportional hazard regression with inverse probability of treatment weighting to estimate the rates, relative risk/hazard ratio, and absolute risk differences.

Results: We identified 38,098 treatment episodes of which, 24,899 were eligible for the study. Tissue disorders and kidney transplant were the most common indications for MPA (67.9%). For study 1, we included all eligible treatment episodes from 12,501 unique women and found 73 pregnancies at the point of MPA initiation. The risk of pregnancy was reduced during the REMS period: adjusted risk ratio 0.42 (95% confidence interval 0.23, 0.76) and adjusted risk difference − 2.1 pregnancies (−3.4, −0.8) per 1000 treatment initiations. For study 2, we examined 20,381 treatment episodes from 10,277 women. We found 106 pregnancies over 8,592 MPA treatment-years. The REMS period showed a non-significant reduction in pregnancy risk: hazard ratio 0.78 (0.52, 1.18) and adjusted risk difference − 3.0 (−.7.2, 2.1) per 1000 person-years.

Conclusions: While the REMS program has been successful in preventing MPA initiation during pregnancy compared to the use of only the black-box warning and a medication guide, its effectiveness in preventing pregnancy during MPA treatment might not be superior.

452 | Post-authorisation amendments to additional risk minimisation measure requirements of medicines authorized in the EU: A cohort study

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Background: Additional risk minimisation measures (aRMMs) may be required to strengthen the benefit–risk profile of medicines that are associated with serious risks. ARMMs may be required at the time of authorisation, but risks may also become evident during the life cycle. Moreover, the recommended actions in the aRMMs may become part of clinical practice and aRMMs may therefore no longer be required. There is limited information about post-authorisation amendments (PAA) to aRMMs of medicines authorized in the European Union (EU).

Objectives: The aim of this study is to describe PAA to aRMMs for medicines authorized in the EU.

Methods: We performed a retrospective cohort study that included all new active substances authorized through the EU centralized procedure between January 1st 2006 and December 31st 2017. Medicines were followed up until July 1st 2018, when data extraction took place. We extracted the following data from European Public Assessment Reports (EPARs) available on the website of the European Medicines Agency (EMA) on www.ema.europa.eu: active substance, Anatomical Therapeutic Chemical (ATC) classification, date of Marketing Authorisation, presence (yes/no) of aRMMs at the time of MA, PAA to aRMMs (yes/no) and type of PAA to aRMMs (introduction/discontinuation), and date of PAA. Descriptive statistics were used to analyze frequency data.

Results: There were 476 medicines authorized during the study period with a total of 32.514 months of follow-up. Median follow-up time was 60 months (range 8–150). At the time of marketing authorisation, aRMMs were required for 27.3% of the medicines. During the study period, 19 (4%) medicines were identified with PAA to aRMM including introduction of aRMM for 15 products (79%) and discontinuation of existing aRMMs for four products (21%). The median time to PAA to aRMM was 46 months for introduction, 90 months for discontinuation. All products with PAA to aRMM were approved between 2006 and 2013. No PAA to aRMM occurred between 2006 and 2008; introduction of aRMMs in the post-authorisation phase occurred since 2009, while the discontinuation of aRMMs occurred since 2015. The ATC groups with the highest proportion of PAA were “Blood and

blood-forming organs" (15.8%), "Musculoskeletal system" (15.4%) and "Various" (8.0%).

Conclusions: The proportion of medicines with PAA to aRMM was low (4%) and the majority of amendments to aRMM concerned introductions of new aRMMs. Notably, the proportion of discontinuation of aRMMs post-authorisation is very low.

453 | Effect of a novel pharmacist-delivered behavioral intervention for patients with poorly-controlled diabetes: The enhancing outcomes through goal assessment and generating engagement in diabetes mellitus pragmatic, database-randomized controlled trial

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Background: Many factors contribute to suboptimal diabetes control, including insufficiently-intensive treatment and non-adherence to medication and lifestyle. Determining which of these is most relevant for individual patients is challenging. Patient engagement techniques may help identify contributors to poor control and address barriers (using motivational interviewing) and help facilitate choices among treatment augmentation options (using shared decision-making). These methods have not been used in combination to improve diabetes outcomes.

Objectives: The study objective was to evaluate the impact of a telephone-based patient-centered intervention on glycated hemoglobin (HbA1c) control and medication adherence.

Methods: ENGAGE-DM was a two-arm, pragmatic, database-randomized controlled trial of 1,400 US commercially-insured participants (18–64 years old) with poorly-controlled type 2 diabetes. Eligible patients were identified via administrative claims and linked laboratory data and randomized to usual care or a pharmacist-delivered phone intervention that consisted of an integrated brief negotiated interview and shared decision-making to identify patient goals and options for diabetes management. The primary outcome was change in HbA1c from baseline. Secondary outcomes were medication adherence measures. Outcomes were evaluated using intention-to-treat principles with routinely-collected claims and lab data; multiple imputation was used for missing HbA1c values in the 12-month follow-up. We also conducted as-treated analyses using propensity score matching to identify similar patients in the usual-care arm as those in the treatment arm who received the intervention.

Results: Participants had a mean (SD) age of 54.7 (8.3) years and baseline HbA1c of 9.4 (1.6). Change in HbA1c was −0.79 (2.01) in the usual-care arm and − 0.75 (1.76) in the intervention arm (difference: +0.04, 95%CI: −0.22, 0.30). There were no significant differences in adherence to medication. In as-treated analyses, the intervention significantly improved diabetes control (−0.48, 95%CI: −0.91, −0.05) in the 30% of patients in the intervention arm who received it versus usual care.

Conclusions: A novel telephone-based patient-centered intervention did not improve HbA1c in patients with poorly-controlled diabetes, although as-treated analyses suggest that the intervention was effective when balanced for potential confounders.

454 | Reduced healthcare utilization in patients using Empagliflozin: An interim analysis from the Empagliflozin comparative effectiveness and safety (EMPRISE) study

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Background: The efficacy of Empagliflozin (EMPA) for reducing the risk of cardiovascular (CV) death (HR 0.62; 95% CI 0.49–0.77) and hospitalization for heart failure (HHF) (HR 0.65; 95% CI 0.50–0.85) was demonstrated in the EMPA-REG OUTCOME trial in adults with type 2 diabetes (T2D) and established CV disease. EMPRISE is a study program on the comparative effectiveness, safety and health care resource utilization (HCRU) of EMPA for T2D patients in routine care across a spectrum of CV risk in two US commercial (Optum and MarketScan) and Medicare claims datasets (2014–2019).

Objectives: To compare HCRU among EMPA versus dipeptidyl peptidase-4 inhibitor (DPP4i) users observed during the first two years of EMPRISE (08/2014–09/2016).

Methods: In this interim analysis,we identified a 1:1 propensity-score-matched cohort of T2D patients ≥18 years initiating either EMPA or a DPP4i, and assessed balance on ≥140 covariates including clinical, HCRU, and cost-related covariates at baseline using absolute standardized differences (aSD). We compared risk of first hospitalization, risk of first emergency department (ED) visit, hospital length of stay (LOS), and number of hospital admissions, office visits and ED visits in EMPA and DDP4i users.

Results: We identified 17,549 matched pairs in the three data sets with mean follow-up of 5.4 months. All baseline characteristics were well balanced (with aSD < 0.1) after propensity matching. The mean age was 59 and 47% were female. Approximately 24% of patients had history of CV disease and mean HbA1c was 8.6%. Risk of first hospitalization [hazard ratio (HR) = 0.84; 95%CI: 0.76–0.92] and ED visit (HR = 0.83; 0.73–0.94) was lower in EMPA than DDP4i users

as was the number of all hospital admissions (12% and 15% per member per year [PMPY]; Incidence rate ratio (IRR) = 0.78; 0.72–0.86). LOS was 0.52 days PMPY in EMPA compared to 0.75 days in DDP4i group (Diff = −0.23, 95% CI = −0.38- -0.08). Number of ED visits (0.07 and 0.09 PMPY; IRR = 0.80; 0.71–0.89) and number of office visits (8.03 and 8.39; IRR = 0.96; 0.95–0.98) were also lower in EMPA than DPP4i initiators. Our findings in the pooled data were consistent across individual databases; however, rate ratios for risk of first hospitalization and first ED visit only reached statistical significance in Medicare databases in this first analysis.

Conclusions: We observed significantly lower HCRU in EMPA compared to DDP4i initiators in the pooled dataset within the first two years of EMPRISE. The findings in each individual database were consistent with the overall results in the pooled analysis.

455 | The effectiveness of glucagon-like Peptide-1 receptor agonists in preventing hospitalizations for chronic lower respiratory disease

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Background: Limited evidence supports tailoring antidiabetic regimens for patients with type II diabetes (T2DM) and chronic lower respiratory disease (CLRD). Animal and ex-vivo human studies have demonstrated positive effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in reducing pulmonary exacerbations, providing potential benefits over other antidiabetic regimens for patients with comorbid CLRD and T2DM.

Objectives: To evaluate the effectiveness of GLP-1RAs in preventing CLRD-related hospitalizations in a population with T2DM and CLRD using real-world data.

Methods: About 6.5 million antidiabetic users were identified in the IBM MarketScan Commercial Claims database between 2006–2017. Patients who initiated second-line therapy were categorized into GLP-1RAs or non-GLP-1RAs, which comprised sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones (TZDs). Non-insulin users with CLRD and T2DM and no T1DM diagnoses within one year before drug initiation were included. We followed the patients up to one year to compare incidence rates of CLRD hospitalizations between GLP-1RAs and non-GLP-1RAs users. We used stabilized inverse probability treatment weighting (SIPTW) to adjust for confounders including age, prescriber specialty, insulin use, healthcare utilization, comorbidities, CLRD regimens and the adapted diabetes complications severity index. We used absolute standardized differences (ASD) with a threshold of 10% to evaluate SIPTW performance. Sensitivity analyses were conducted to compare GLP-1RAs against each of the following: sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors and TZDs.

Results: The study sample comprised 8,600 and 88,709 users of GLP-1RAs (median age of 53) and non-GLP-1RAs (median age of 55), respectively. The largest ASD after applying SIPTW was 7.8% showing well-balanced covariates. The CLRD-hospitalizations incidence rate was 13.3 and 20 per 1000 patient-years for GLP-1RAs and non-GLP-1RAs users, respectively. The unadjusted rate ratio (RR) was 0.67 (95% CI: 0.55–0.81, p-value <0.01). After applying SIPTW, the RR was 0.74 (95% CI: 0.61–0.90, p-value <0.01). Sensitivity analyses were consistent with the main analysis except for SGLT-2 showing non-significant difference.

Conclusions: GLP-1RAs demonstrated potential benefits in preventing CLRD-related hospitalizations. Further studies including randomized clinical trials are needed to provide evidence for the causality of GLP-1RAs.

456 | Risk factors for progression to vision threatening diabetic retinopathy

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Background: While numerous studies have examined the risk factors of diabetic retinopathy progression, none have taken an all-encompassing approach accounting for systemic medical conditions, laboratory values and current prescription medications in the same study.

Objectives: To assess all factors that are associated with the hazard of progression from non-proliferative diabetic retinopathy (NPDR) to vision-threatening diabetic retinopathy (VTDR), proliferative diabetic retinopathy (PDR), or diabetic macular edema (DME).

Methods: This is a time updating retrospective cohort study using medical claims data from a large U.S. insurer. Cohorts were created from all NPDR patients who had lab values from 2002–2016. Exclusion criteria consisted of any previous diagnosis of VTDR, proliferative vitreoretinopathy or treatment used for VTDR. Patients were also excluded if they had a diagnosis of VTDR within 2 years of insurance plan entry, regardless of when NPDR was first noted in the plan. The main outcome was a new diagnosis of VTDR (defined as either PDR or DME), DME or PDR individually. Cox proportional hazard regression was used to determine demographic, systemic medical conditions, laboratory values and prescription drug usage (assessed in a time-updating manner based on date of prescription fill and days of medication supplied. Anemia (hemoglobin) levels and kidney function (eGFR level) were based on laboratory values and were also time-updated.

Results: 69,982 NPDR patients were included for analysis, of which 12270, 2162, 10322 progressed to VTDR, PDR and DME, respectively. After controlling for all covariates, both mild and moderate/severe (mod/sev) anemia were associated with an increased hazard for progression to VTDR (mild HR:1.10,95%CI:1.04–1.16,p < 0.001; mod/sev HR:1.20,95%CI:1.12–1.29,p < 0.001), to PDR (mild HR:1.29,95%CI:1.13–1.46,p < 0.001; mod/sev HR:1.43,95%CI:1.21–1.69,p < 0.001), and to DME (mild HR:1.06,95%CI:1.00–1.13,

p < 0.001; mod/sev HR:1.14,95%CI:1.05–1.24,p < 0.001). Fenofibrates were associated with a protective effect for VTDR (HR:0.89,95%CI:0.82–0.98,p = 0.01) and PDR (HR:0.71,95%CI:0.56–0.91,p = 0.006), but not DME (HR:0.96,95%CI:0.87–1.06,p = 0.39). Statin use was not associated with VTDR (HR = 0.98, 95%CI:0.94–1.02,p = 0.26) or DME (HR = 1.01,95%CI:0.97–1.06,p = 0.48), but showed an increased hazard for PDR (HR = 1.12,95%CI:1.02–1.23, p = 0.01).

Conclusions: Anemia, independent of kidney function was associated with increased risk of VTDR progression. Use of fenofibrates was protective for PDR, but not DME. Statin use was not associated with DME, but showed an increased risk for PDR.

457 | Dipeptidyl Peptidase-4 inhibitors and risk of inflammatory bowel disease: Real world evidence in US adults

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Background: A recent cohort study raises the concern that dipeptidyl peptidase-4 inhibitors (DPP4i) are associated with increased risk of inflammatory bowel disease (IBD).

Objectives: Evaluate the association between new use of DPP4i vs other antihyperglycemics and IBD risk.

Methods: We implemented an active comparator, new user cohort study using two US administrative claims databases for commercially-insured (MarketScan) and elderly (Medicare fee-for-service, 20% random sample) patients from January 2007 to September 2015. We identified patients, aged 18+, who initiated DPP4i vs sulfonylureas (SU), or DPP4i vs thiazolidinediones (TZD), and without prior diagnoses, treatments or procedures potentially related to IBD. The primary outcome was incident IBD, defined by IBD diagnosis preceded by colonoscopy and biopsy within 30 days before diagnosis, and followed by IBD treatment within 30 days after diagnosis. Secondary analyses assessed the risk of incident Crohn's disease (CD) and ulcerative colitis (CD). Follow-up started 180 days (latent period) post the 2nd prescription to account for diagnostic delay of IBD, continued 180 days (the carry-over period) after treatment changed or stopped. We used standardized mortality/morbidity weighted Cox proportional hazards models to estimate propensity score adjusted hazard ratios (aHRs [95% CI]) censoring treatment change. We performed random-effects meta-analysis models with inverse variance weighting to pool aHRs across cohorts. We stratified analyses by age at cohort entry (MarketScan: <50/ ≥50 years; Medicare: <75/ ≥75), sex, duration of use (<1/ ≥1 year) and pre-existing gastroenterological disease. Sensitivity analyses applied different latent and carry-over periods (0, 90, 365 days, respectively), no censoring for treatment change, relaxed outcome definitions, relaxed exclusion criteria, and multivariable-adjusted Cox regression.

Results: We identified 839,949 eligible initiators of DPP4i, SU or TZD; IBD incidence rates ranged from 13.4–35.4 per 100,000 person-years. Over a median treatment duration of 1.04–1.45 years, DPP4i were not associated with increased IBD risk across comparisons. Pooled aHRs for IBD were 0.89 (95% CI: 0.56–1.41) comparing DPP4i (n = 146,691) vs SU (n = 285,724), and 0.66 (0.40–1.08) comparing DPP4i (n = 183,698) vs TZD (n = 83,264). Overall, results were robust across secondary and sensitivity analyses.

Conclusions: Our population-based cohort study of US adults with diabetes suggests that DPP4i treatment for approximately one year does not increase IBD risk.

458 | Dipeptidyl Peptidase-4 inhibitors and the risk of bullous pemphigoid among patients with type 2 diabetes: A population-based cohort study

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Background: There are concerns that dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of second- to third-line antidiabetic drugs, may be linked to the development of bullous pemphigoid, a rare but potentially severe autoimmune blistering skin condition.

Objectives: To assess whether the use of DPP-4 inhibitors, when compared with the use of other second- to third-line antidiabetic drugs, is associated with an increased risk of bullous pemphigoid in patients with type 2 diabetes.

Methods: Using the United Kingdom Clinical Practice Research Datalink we conducted a population-based cohort study, thereby including all patients initiating antidiabetic drugs between January 1, 2007 and March 31, 2018. We used time-dependent Cox proportional hazards models to estimate adjusted hazard ratios with 95% confidence intervals of incident bullous pemphigoid associated with current use of DPP-4 inhibitors, compared with current use of other second- to third-line antidiabetic drugs. We also investigated whether there was a duration-response relation modeling duration of use as a continuous variable using restricted cubic splines. Finally, we conducted a propensity score-matched analysis to further assess the impact of residual confounding.

Results: Among 168,774 patients initiating antidiabetic drugs and during 711,311 person-years of follow-up, 150 patients were newly diagnosed with bullous pemphigoid (crude incidence rate, 21.1 per 100,000 person-years). Current use of DPP-4 inhibitors was associated with an increased risk of bullous pemphigoid (47.3 versus 20.0 per 100,000 person-years; hazard ratio, 2.21; 95% confidence interval, 1.45 to 3.38) when compared with current use of other second- to third-line antidiabetic drugs. Hazard ratios gradually

increased with longer duration of use, reaching a peak after 20 months of use (hazard ratio, 3.60; 95% confidence interval, 2.11 to 6.16). Similar results were obtained in the propensity score-matched analysis (hazard ratio, 2.40; 95% confidence interval, 1.13 to 4.66).

Conclusions: In this large population-based study, the use of DPP-4 inhibitors was associated with an at least doubling of the risk of bullous pemphigoid in patients with type 2 diabetes.

459 | Identifying drug classes whose initiation may be a proxy for frailty

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Background: Frailty is a potentially important confounder, not well measured in insurance claims data. Attempts to find proxies for frailty have largely omitted drug use variables or focused on prevalent drug use. Since drug initiation is driven by the treatment indication and expectation of benefit, it may serve as a better proxy for frailty than prevalent drug use.

Objectives: To identify drug classes whose initiation is associated with high or low short-term mortality and may therefore be a proxy for frailty.

Methods: Using U.S. Medicare data from 2009–2010, we identified initiators of drug classes defined by the second level of the Anatomical and Therapeutic Classification coding system (e.g. C03 Diuretics) and randomly sampled outpatient visits from all beneficiaries to create a general population comparator. For all groups, we required people to be ≥65 years old, with ≥1 year of prior continuous Parts A, B and D coverage. We assessed demographics, the components of a common comorbidity score and the components of a frailty score for each person. Since frailty was unavailable, we assessed 30-day mortality as the outcome, assuming that frailty would increase short-term mortality. We compared mortality between each group of initiators and the comparator group using logistic regression, controlling for all baseline covariates.

Results: The 62 initiator groups larger than 5,000 people were considered, resulting in a range from 5,033 (M02, Topical products for joint and muscular pain) to 528,354 (J01 Systemic antibacterials) people. Crude mortality was 0.41% for the comparator group and ranged from 0.09% (J07 Vaccines) to 13.84% (B05 Blood substitutes and perfusion solutions) for the initiator groups. J07 Vaccines, D10 Anti-acne preparations and G03 Sex hormones and modulators of the genital system were the drug classes with the most reduced odds of death, with adjusted odds ratios of 0.41 (95% CI: 0.28, 0.60), 0.65 (0.42, 0.99) and 0.81 (0.63, 1.05) respectively. B05 Blood substitutes and perfusion solutions, A04 Antiemetics and antinauseants and A15 Appetite stimulants were the drug classes with the most increased odds of death, with adjusted odds ratios of 14.4 (12.6, 16.4), 12.1 (10.8, 13.5), and 10.0 (8.8, 11.3) respectively. Most drug classes showed increased odds of death relative to the comparator.

Conclusions: Several commonly used drug classes were associated with high or low short-term mortality. While these associations are not causal and reflect both treatment indications and prescribing patterns, initiation of these drug classes may serve as markers of poor or good health to improve confounding control in pharmacoepidemiologic studies.

460 | Validation of a five-year mortality prediction model among US Medicare beneficiaries

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Background: A recent claims-based five-year mortality prediction model was developed including comorbid conditions and indicators of frailty, disability, and functional impairment. The model was developed and internally validated in a 2008 cohort of North Carolina (NC) Medicare beneficiaries.

Objectives: We aimed to externally validate this new model in a nationwide sample of US Medicare beneficiaries.

Methods: From a 20% random nationwide sample of US Medicare beneficiaries, we created a cohort of beneficiaries 66 years and older with an office visit in 2008, not receiving hospice care, and at least one year of continuous pre-visit Medicare A/B enrollment. Residents of NC were excluded. The outcome was 5-year all-cause mortality determined from enrollment files. We applied model estimates derived in the original study cohort and computed the predicted probability of 5-year morality for each beneficiary. For comparison, we also ran a model using a Charlson and Elixhauser combined comorbidity score. To assess discriminatory performance, we calculated c-statistics with 95% confidence intervals. To evaluate improvement in reclassification between the new model and the comorbidity score model, we computed the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for the change in the difference of the average predicted probabilities between those who died and those who survived. For both metrics, a positive number indicates improved classification.

Results: The cohort included 1,116,745 beneficiaries of whom 284,154 (25%) died within 5-years, similar to the original study cohort. The mean age was 76.0 years (SD 7.3) and 65% of the cohort was female. Based on the new model, 27% of the cohort had a predicted probability of death of <10% and 8.6% had a predicted probability of death of >80%. Predictions from the new model slightly overestimated the 5-year mortality. The c-statistic for the new model was nearly identical to that obtained in the internal validation (0.823 [95% CI 0.823, 0.824] and 0.825 [95% CI 0.823, 0.828], respectively) and higher than that from the comorbidity score

(0.795 [95% CI 0.794, 0.796]). The new model improved reclassification of death at five years compared to the comorbidity score: NRI 11.9% and IDI 9.2%.

Conclusions: Our results provide external validation for the new five-year mortality prediction model. Using US Medicare beneficiaries, the model had strong discrimination and generally improved classification compared to a combined comorbidity score model, although the new model slightly overestimated 5-year mortality.

461 | The impact of polypharmacy definitions on the estimation of polypharmacy prevalence in older individuals: A population-based evaluation

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Background: There are numerous definitions of polypharmacy. Yet, there is little data on how these definitions influence estimates of polypharmacy prevalence in a single population.

Objectives: To assess the impact of different definitions of exposure to medications on the mean count of medications used and on the proportion of individuals exposed to polypharmacy at a population-level.

Methods: We created a population-based cohort of individuals ≥65 years insured by the universal public drug plan in Quebec, Canada, between April 1, 2016 and March 31, 2017. We extracted all medications used by a random sample of 10% of the population (*n* = 120,652) and described their medication use according to five definitions: 1) simultaneous polypharmacy: number of medications used on a single day; 2) cumulative polypharmacy: number of distinct medications over a 3-month period; 3) weighted polypharmacy: number of distinct medications weighted according to the duration of exposure; 4) persistent polypharmacy: number of distinct medications used over the first 3 months that were still used in the last 3 months; 5) persistent polypharmacy without interruption: number of distinct medications used persistently without gaps. We used descriptive statistics and performed sensitivity analyses by varying grace periods between refills.

Results: With the simultaneous definition of polypharmacy, the mean number of medications used was 4.44 (SD:3.45). Cumulative counts resulted in a mean of 4.98 (3.65) medications, while weighted count totaled 4.43 (3.44). Persistent polypharmacy definition yielded a mean of 4.16 (3.43) medications, while it was 2.85 (3.09) for the persistent polypharmacy without gaps. According to the definitions, the proportions of individuals using at least 5 medications were respectively 44.0% (1&3), 49.4% (2), 42.9% (4) and 36% (5), while the proportion of those using at least 10 medications were 8.9% (1&3), 12.3 (2), 8.0% (4) and 4.0% (5). Sensitivity analyses yielded similar results.

Conclusions: Prevalence of polypharmacy varies according to definitions, but graphic representations show similarity in medication use patterns. There is a need to explore which definitions best predict outcomes and what cut-off should be used for polypharmacy. As one-third to one-half of the population is exposed to at least five medications, this threshold would be of little use for a population polypharmacy indicator whose purpose is to predict health outcomes.

462 | Measuring frailty in administrative claims data: Comparative performance of four claims-based frailty measures in the United States Medicare data

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Background: Administrative claims data are a valuable data source to inform clinical and public health policy decisions for older adults. Recently, 4 claims-based models were developed to measure frailty in the United States Medicare data. Comparative performance of claims-based frailty measures has not been examined.

Objectives: To evaluate the performance of the 4 claims-based frailty measures in identifying older adults with frailty and at high risk for adverse health outcomes.

Methods: This retrospective cohort study included 2,326 community-dwelling Medicare beneficiaries who had at least 1 health care encounter within 6 months of their 2008 assessment in the Health and Retirement Study. The claims-based frailty measures by Davidoff, Faurot, Segal, and Kim were estimated from claims data and compared against clinical measures of frailty (gait speed, grip strength) and adverse health outcomes (e.g., mortality, hospitalization, activities-of-daily-living disabilities) over 2 years. The associations between claims-based frailty measures and outcomes were examined using correlation coefficients and C-statistics after adjusting for age and sex.

Results: The correlation coefficients with gait speed for Davidoff, Faurot, Segal, and Kim indices were − 0.19, −0.33, −0.37, and − 0.37, respectively. Age and sex adjustment attenuated the correlation to −0.17, −0.22, −0.18, and − 0.33, respectively. The corresponding correlation coefficients with grip strength were − 0.17, −0.27, −0.35, and − 0.24, which attenuated to −0.09, −0.14, −0.05, and − 0.23 after age and sex adjustment, respectively. The models that included age, sex, and each of Davidoff, Faurot, Segal, and Kim indices showed C-statistics of 0.67, 0.71, 0.71, 0.75 for mortality (versus C-statistic for age and sex: 0.66); 0.59, 0.64, 0.63, 0.70 for hospitalization (versus C-statistic for age and sex: 0.58); and 0.64, 0.63, 0.63, 0.70 for activities-of-daily-living disabilities (versus C-statistic for age and sex: 0.61), respectively.

Conclusions: The choice of a claims-based frailty measure results in meaningful variations in the identification of frail older adults at high

risk for adverse health outcomes. Claims-based frailty measures that included demographic variables offer limited additional risk adjustment beyond age and sex alone.

463 | Predictive modeling in patients with heart failure: A comparison of machine learning and traditional statistical approaches

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Background: Accurate risk-stratification in heart failure (HF) with respect to clinically-important outcomes is critical to effectively deploy targeted interventions including palliative care and to guide prognostic discussions with patients.

Objectives: To compare machine learning approaches including classification and regression trees (CART), random forests (RF), gradient boosting modeling (GBM), least absolute square shrinkage operator (LASSO) regression with traditional logistic regression in predicting 1-year mortality in patients with HF.

Methods: We linked Medicare claims (2007–2014) to electronic medical records (EMRs) from two academic medical centers in Boston, MA to construct a cohort of HF patients based on a recoded diagnosis in claims and a recorded ejection fraction (EF) measurement within 30 days from EMRs. Patients were followed for the outcome of all-cause mortality for 1 year. Predicted probabilities were calculated from logistic regression, LASSO, CART (in conditional inference framework), RF, and GBM. Predictors were sequentially added to these models with claims-based variables first (demographics, HF related variables, co-morbid conditions, frailty score, and a socioeconomic status index) and subsequently EMR-derived variables (EF, natriuretic peptides, serum creatinine, blood urea nitrogen). All models were constructed using data from Center 1 and validated using data from Center 2. The performance was reported based on C-statistics, calibration plots, and Brier score in validation data.

Results: A total of 9502 HF patients were included; 6113 from Center 1 and 3389 from Center 2, with 1-year mortality of 20.6% and 22.6%, respectively. In claims-only models, the performance of various approaches was similar except for CART, which underperformed compared to all other models (C-statistics for logistic, LASSO, CART, RF, GBM: 0.724, 0.725, 0.678, 0.723, and 0.725, respectively; Brier scores: 0.158, 0.157, 0.165, 0.156, 0.157, respectively). Addition of EMR variables markedly improved performance for all models, especially for GBM (C-statistics for logistic, LASSO, CART, RF, GBM: 0.746, 0.747, 0.703, 0.748, and 0.756, respectively; Brier scores: 0.152, 0.152, 0.160, 0.152, 0.151, respectively). Visual inspection of the calibration plots revealed generally better calibration with LASSO, RF, and GBM.

Conclusions: Machine learning methods offered limited improvement over traditional methods in predicting mortality in HF. Clinical parameters from EMRs may offer enhanced risk prediction information beyond claims-based data.

464 | Performance of machine learning algorithms for hysterectomy risk prediction among women with endometriosis in the United States

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Background: Machine learning algorithms are increasingly used in healthcare delivery research, yet have not been used to identify women at risk for surgical management of endometriosis.

Objectives: To compare the performance of machine learning algorithms for estimating the 1-year risk of hysterectomy among women with endometriosis.

Methods: Women aged 18–49 years were identified in Optum® data from January 1, 2006 through December 31, 2016. Patients had a laparoscopic procedure plus an endometriosis code within the 90 days before or 14 days after the procedure. The index date was the latter of the two dates. Patients were censored for hormone replacement therapy initiation, disenrollment, or reaching age 50, and inverse probability of censoring weights were used in the model. We identified 50 covariates to use in the prediction models, including demographics, comorbidities and medications found in the relevant lookback period (i.e. either all available data or 1 year before index, depending on the variable). We used the H20 machine learning package in R to fit the following algorithms to predict 1-year risk of hysterectomy: generalized linear model (penalized elastic-net logistic), distributed random forest, gradient boosted classification trees, deep learning, a stacked ensemble of these methods, and H20's automated algorithm. The data were randomly split 80/20 into training and testing sets, and 10-fold cross-validation was used on the training set. Area under the receiver operator curves (AUC) and log loss statistics were used to compare methods. A model-agnostic variable importance metric was used to measure each covariate's influence on a model's predictive ability.

Results: We identified 23,358 eligible women, of whom 1,975 (8.5%) had a hysterectomy within 1 year of index. The AUC for the different models in the testing data ranged from the lowest performing model at 0.65 (random forest) to the best fitting algorithm at 0.77 (stacked ensemble). The automated machine learning had similarly high predictive ability (AUC = 0.74). Log loss statistics suggested a similar pattern. Within the auto machine learning method, the stacked ensemble models had the highest AUC. Age was the most influential predictor of hysterectomy risk.

Conclusions: Combining multiple machine learning algorithms (e.g. stacked ensemble) resulted in substantially better prediction than any of the individual methods in this data set. When using machine learning methods in healthcare research, assessing the performance

of different algorithms is an important step to maximize a model's predictive ability.

465 | Inferring mortality in claims data

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Background: Mortality is an important outcome in many epidemiological studies. However, deaths are not reported in many databases, and are under-reported in others. We hypothesize that machine learning based approaches can be used to accurately identify likely mortalities in claims data, thus enabling the use of death as an outcome in studies.

Objectives: To assess the feasibility of inferring deaths in claims data when mortality is not reported.

Methods: We used data from the Optum Clinformatics® Data Mart, a nationally representative de-identified claims dataset that includes near-complete patient level mortality information prior to September of 2011. We developed and assessed a classifier to identify which disenrollment events are due to death on training and testing sets prior to 11/2011. Classifiers based on diagnosis and procedure codes (any and count), demographics, and utilization-based variables in the month prior to disenrollment were developed from logistic regression and several probabilistic machine learning approaches including random forest (RF), and gradient boosted trees (GBT). Analyses were performed in Apache Spark MLLib. Each model's performance was evaluated based on sensitivity, specificity, positive predictive value, and negative predictive value, and the area under receiver curve (AUC) and bootstrapped-based standard deviations (StD) were calculated. Models were developed for the general population as well as for condition-based cohorts: chronic obstructive pulmonary disease (COPD), metastatic and non-metastatic tumors, congestive heart failure (CHF), and chronic kidney disease (CKD).

Results: The full cohort comprised over 36 million patients, and nearly 600,000 reported deaths. Several methods led to models with good properties, but GBT followed by RF performed the best. GBT classified deaths with specificity of 0.99 when sensitivity was higher than 0.8, and AUC of 0.97 with a StD of 0.0017. Age, place of service, number of days in the hospital, total medical cost, as well as diagnosis codes indicating cardiac arrest, respiratory failure, or the count of diagnosis codes for hypertension, fatigue and shortness of breath were strong predictors of death in the general population. The models for the disease-based cohorts performed well, with specificity that ranged from 0.98 for COPD and non-metastatic tumors, to 0.90 for CKD and CHF (with sensitivity greater than 0.8). Strong predictors were similar, with place of service surpassing age as the most important in the cancer, CKD, and CHF cohorts.

Conclusions: Our results suggest that mortality events can be inferred in claims data using machine learning approaches, with very high accuracy.

466 | Federated learning for predicting clinical events with distributed patient data sets

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Background: There is a growing research effort in using machine learning to predict clinical events among hospitalized patients. Sharing sensitive patient data across hospitals to create a large central database is difficult due to privacy concerns, single point of failure, and high latency, making large-scale learning difficult.

Objectives: To demonstrate a novel approach based on federated learning, wherein a global predictive model is trained on local data residing at hospitals, without ever sharing the raw data.

Methods: We used a public benchmark data generated from MIMIC-III (2001–2012), an electronic health data set from intensive care units (ICUs) in a tertiary hospital. All adult subjects (age > = 18) were included, excluding those who transferred between units or had insufficient data. The benchmark data had 714 features based on physiological variables from the first 48 hours of data. Logistic regression (LR) and support vector machine (SVM) predicting in-hospital mortality were trained and evaluated for performance, using both centralized and federated learning methods. Centralized learning results were averaged over 10 iterations with 7:3 train and test data split. In federated learning, we either randomly divided data into 5 sites or divided by 5 different ICU types, using the second-largest ICU type (n = 3,665) as the test set, and updated model coefficients over 10 rounds of aggregation.

Results: The final data set had 21,139 ICU stays with a mortality rate of 13.23%. In centralized learning, the accuracy and AUC was 0.88 (standard deviation +/−0.01) and 0.62 (+/−0.03) for SVM and 0.88 (+/−0.002) and 0.64 (+/−0.02) for LR, respectively. In random-split federated learning, the accuracy and AUC for SVM was 0.86 (+/−0.002) and 0.64 (+/−0.006) and those for LR was 0.84 (+/−0.003) and 0.64 (+/−0.02), respectively. When data was split by ICU types, the accuracy and AUC from centralized learning for SVM was 0.94 (+/−0.008) and 0.68 (+/−0.04) and those for LR was 0.95 (+/−0.004) and 0.68 (+/−0.02), respectively. Federated learning across 4 different ICU units generated accuracy and AUC of 0.94 (+/−0.60) and 0.65 (+/−0.001) for SVM and 0.81 (+/−0.02) and 0.82 (+/−0.004) for LR. The low mortality at test ICU site contribute to higher accuracy compared to random split experiment.

Conclusions: We show that federated learning can achieve comparable predictive performance to centralized learning, while preserving data privacy. This approach is applicable for predicting clinical events or predicting adverse drug reactions without sharing patient data across hospitals.

467 | Using machine learning to predict risk of opioid overdose in Medicare

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Background: Current approaches to identify individuals at high risk for opioid overdose have major limitations, leading to burdensome interventions that are targeting many patients who are not truly at high risk.

Objectives: To apply machine learning approaches to claims data to improve the accuracy of identifying individuals at varying risks for opioid overdose.

Methods: A retrospective cohort study included 560,057 fee-for-service Medicare beneficiaries without cancer, who filled ≥1 opioid prescription from 2011–2015. We randomly and equally divided beneficiaries into training, testing, and validation samples. Potential predictors (*n* = 268) including socio-demographics, health status, patterns of opioid utilization, and provider- and regional-level factors, were measured in 3-month windows starting from 3 months before initiating opioids until loss of follow-up or end of 2015. We identified diagnosis-based opioid overdose (fatal or nonfatal) episodes from inpatient and emergency department claims. We applied multivariate logistic regression (MLR), least absolute shrinkage and selection operator-type regression (LASSO), random forests (RF), gradient boosting machine (GBM), and deep neural network (DNN) to predict overdoses in the subsequent 3 months. We assessed prediction performance using the C-statistic and other metrics (e.g., sensitivity, specificity, number needed to evaluate to identify one overdose [NNE]). We used the Youden index to identify the optimized threshold of predicted score that balanced sensitivity and specificity.

Results: The training (*n* = 186,686), testing (n = 186,685), and validation (n = 186,686) samples had similar characteristics (mean age = 68.0 ± 14.5; female = 63.1%; white = 82.2%; ≥1 overdose = 0.60%). In the validation sample, DNN (C-statistic = 0.91, 95%CI = 0.88–0.93) and GBM (C-statistic = 0.90, 95%CI = 0.87–0.94) outperformed LASSO (C-statistic = 0.84, 95%CI = 0.80–0.89), RF (C-statistic = 0.80, 95%CI = 0.75–0.84), and MLR (C-statistic = 0.75, 95%CI = 0.68–0.81) for predicting overdose. When at the optimized sensitivity and specificity, DNN had a 92.3% sensitivity, 75.7% specificity, and NNE of 542. The DNN classified patients into low, medium, and high-risk subgroups (76.2%, 18.6%, and 5.2% of the cohort, respectively), with only 1 in 10,000 in the low-risk subgroup having an overdose. Over 90% of overdoses occurred in the high and medium-risk subgroups.

Conclusions: Machine learning algorithms achieved excellent performance for risk prediction and stratification of opioid overdose, especially in identifying low-risk subgroups that have minimal risk of overdose.

468 | Dual-trajectories of opioid and Gabapentinoid use and risk of subsequent drug overdose among United States Medicare beneficiaries

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Background: Increasing opioid (OPI) overdose deaths involving gabapentinoids (GABAs) in the US has raised concerns of misuse/abuse of GABAs. Little is known about the patterns of concurrent opioid and gabapentinoid use (hereafter OPI-GABA) most associated with drug overdose risk.

Objectives: We examined the association between OPI-GABA dose and duration trajectories and subsequent drug overdose risk among Medicare beneficiaries.

Methods: This retrospective cohort study included Medicare beneficiaries with fibromyalgia, low back pain, neuropathy, and/or osteoarthritis who newly initiated prescription OPIs and/or GABAs from 2011–2016. We used dual group-based trajectory models to identify distinct OPI-GABA use patterns, based on average daily morphine milligram equivalent for OPI and standardized daily dose for GABA, within the first year of OPI and/or GABA initiation (i.e., index-year). We used inverse probability of treatment weighted multivariable Cox proportional model to estimate the risk of time to the first drug overdose episode within 12 months following the index-year, adjusting for socio-demographics and health factors.

Results: Among 71,005 beneficiaries (mean age ± SD = 65.5 ± 14.5, female = 68.1%), 10 distinct trajectories were identified (3 OPI-only trajectories, 3 GABA-only trajectories, and 4 OPI-GABA trajectories). Compared to OPI-only early discontinuers (40.6% of the cohort), the 1-year drug overdose risk varied by trajectory group: consistent low-dose OPI-only users (16.6%; HR = 1.50, 95%CI = 1.21–1.84); consistent high-dose OPI-only users (1.8%; HR = 4.33, 95%CI = 2.99–6.27); GABA-only early discontinuers (12.5%; HR = 1.43, 95%CI = 1.13–1.81); consistent low-dose GABA-only users (11.0%; HR = 1.46, 95%CI = 1.14–1.87); consistent high-dose GABA-only users (3.1%; HR = 1.60, 95%CI = 1.07–2.38); early discontinuation of OPI and consistent low-dose GABA users (6.9%; HR = 1.25, 95%CI = 0.91–1.70), consistent low-dose OPI-GABA users (3.4%; HR = 2.23, 95%CI = 1.61–3.11); consistent low-dose OPI and high-dose GABA users (3.2%; HR = 2.18, 95%CI = 1.55–3.07); and consistent high-dose OPI and moderate-dose GABA users (0.9%; HR = 4.56, 95%CI = 2.82–7.37).

Conclusions: Subsequent overdose risk varied substantially by different OPI-GABA trajectories among Medicare beneficiaries. High-dose

OPI-only users and all consistent OPI-GABA users, especially high-dose OPI and moderate-dose GABA users, were associated with more than doubled drug overdose risk.

469 | Estimates of prolonged opioid use following surgery vary by orders of magnitude across various definitions

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Background: Chronic opioid use has been reported as the most common post-surgical complication. Methods to accurately define prolonged opioid use in claims data are needed to quantify the impact of measures that target this outcome. As opioids are typically prescribed on an as-needed basis (PRN), values listed for 'days supplied' on prescription (Rx) claims may not represent actual consumption patterns.

Objectives: Among a cohort of women undergoing hysterectomy, we examined the impact of varying definitions of prolonged opioid use on estimates of prolonged opioid use post-surgery.

Methods: We identified women undergoing hysterectomy in MarketScan insurance claims, 2005–2015. We defined the index opioid Rx for postsurgical pain as the first opioid filled in a perioperative window beginning 30 days prior and extending 7 days post-surgery, with no baseline opioid Rx in the 180-day washout. We examined two categories of prolonged opioid use definitions: 1) Continuous Use definitions based on reported Rx date and days supplied, allowing varying grace periods (GP) between Rx fills; 2) Time Window definitions counted any Rx within specific target windows during follow-up. To compare with published estimates, we also report the proportion with an opioid Rx 90–180 days post-op. We report estimates of prolonged use following surgery based on the array of definitions.

Results: A total of 414,544 women meeting our inclusion criteria underwent a hysterectomy, of whom 348,590 (84.1%) filled a perioperative opioid Rx (median days supplied: 4, IQR: 3, 5; median qty dispensed: 30, IQR: 25, 40). Among women with a perioperative opioid Rx, the proportion with a continuous supply of opioids through 90 days post-op ranged from 0.09% using a 7-day GP to 0.69% using a GP of two times the days supplied. In contrast, the proportion of women with evidence of an opioid Rx occurring in the 4th month of follow up (90–120 days) was 2.7%. Finally, defining prolonged use as evidence of any opioid Rx 90–180 days post-op identified 6.8% of women.

Conclusions: When analyzing prolonged opioid use, continuous use measures resulted in drastically different estimates compared to methods based on fills within target windows during follow-up. Overall, continuous use measures found a small proportion of hysterectomy patients had prolonged opioid use following surgery. Meanwhile, defining prolonged use as evidence of an Rx occurring 90–180 days after surgery resulted in estimates 10 to 80 times higher. Irregular consumption patterns with PRN medications complicate our ability to define periods of drug exposure and examine prolonged use in claims data.

470 | Concurrent use of opioids and strong metabolic inhibitors and the risk of serious infections

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Background: Opioid use, including the use of methadone, is associated with an increased risk of serious infections. The concurrent use of methadone and strong inhibitors of its main metabolic pathways would increase methadone levels and increase its toxicity. Cytochrome P4530A4 (CYP3A4) was previously postulated to play a role in the metabolism of methadone, yet whether the concurrent use of CYP3A4 inhibitors impacts the risk of serious infections associated with methadone use remains unclear.

Objectives: To compare the risk of serious infection among patients using methadone during periods with and without concurrent use of CYP3A4 inhibitors.

Methods: We conducted a retrospective cohort study among adult Tennessee Medicaid enrollees initiating use of methadone (1995–2015). Hospitalizations for serious infection were identified using validated coding algorithms for pneumonia, bacteremia/sepsis, pyelonephritis, meningitis/encephalitis, osteomyelitis/septic arthritis, endocarditis, and cellulitis. We compared the risk of infection during periods of methadone use with and without concurrent use of CYP3A4 inhibitors not indicated for treatment of HIV and fungal infections (i.e., diltiazem, verapamil, nefazodone). We used multivariable Poisson regression to calculate adjusted incidence rate ratios (aIRR). Analyses accounted for demographics, opioid dose, calendar year, prior medication use, comorbidities, frailty indicators and healthcare utilization history measured in the prior 366-day period for each day of follow-up using exposure propensity scores. We conducted similar comparisons among long-acting morphine users as a negative control.

Results: We identified 691 serious infections among 10,210 person-years (py) of long-acting methadone use, including 437 py (4.3%) of concurrent CYP3A inhibitor use. The absolute rate of infections was highest during periods of concurrent methadone and CYP3A inhibitor use compared to no concurrent use (9.4 vs. 6.7 per 100 py). However, after adjustment, the use of CYP3A inhibitors was not significantly associated with an increased risk of infections among methadone users [aIRR: 1.23 (95% CI: 0.88–1.71)]. No association was observed for concurrent metabolic inhibitor use among morphine users [aIRR: 0.97 (95% CI: 0.90–1.12)].

Conclusions: Preliminary evidence suggests certain medications previously thought to impact the metabolism of methadone do not increase the risk of serious infections associated with its use, though larger studies may increase the precision of our preliminary estimates.

471 | Methods to account for time-varying medication use when developing a model for patient prognosis

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Background: Prognostic models can help clinicians make decisions over whether to prescribe certain medications for individual patients. For this purpose, models should estimate what a patient's outcome risk would be if they were to remain unexposed to a certain treatment. However, data used to develop prognostic models typically include treated individuals and standard methods fail to account for this.

Objectives: To compare methods for utilizing routinely collected information on medication use in prognostic model development and assess the benefits for risk prediction, using the prescription of selective β-blockers (SBBs) in chronic obstructive pulmonary disease (COPD) patients as a case study.

Methods: Clinical and prescription information on COPD patients were identified from the Utrecht General Practitioners (UGP) database. We compared 7 approaches to model time-varying treatments: 1) ignoring treatment, 2) excluding treated patients, 3) censoring treated patients, 4) inverse probability of treatment weighting after censoring (IPTW), modeling treatment as a 5) binary or 6) time-varying covariate and 7) marginal structural modeling (MSM). First, directed acyclic graphs (DAGS) were used to assess the theoretical properties of the different approaches. Next, models to predict 5-year mortality risk without SBB use were developed in the UGP data using the 7 approaches. The absolute risk predictions and overall performance (calibration slope, c-statistic, Brier score) of the models were compared.

Results: Based on DAGs, we found IPTW and MSMs have the best theoretical properties, as they can account for the effects of treatment and avoid selection bias. In our case study, 1906 patients were included in the analysis and 325 received SBBs during follow-up. Compared to ignoring SBBs, approaches (2) and (5) provided predictions that were 1% and 2% higher on average. Measures of model performance varied minimally between approaches.

Conclusions: We found IPTW and MSMs are preferred in theory, but found little difference between methods in our case study. Future studies should consider using data on time-varying medication use to better model prognosis.

472 | Using the reverse waiting time distribution with random index dates to estimate prescription durations with seasonal variation

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Background: The reverse Waiting Time Distribution (rWTD) has been shown to provide valid estimates of prescription durations expressed as the time within which 80% of the current users have redeemed a new prescription. The method considers each patient's time since last prescription redemption before an index date. This index date must be chosen independently of the individual redemption processes. This is, however, violated if rates of prescription redemptions exhibit seasonal variation and a fixed index date is used.

Objectives: To modify the rWTD to provide valid estimates of prescription durations when redemption rates have seasonal variation.

Methods: We selected a one-year sample window supplemented with a preceding period of equal length. For each patient we uniformly sampled a random index date within the sample window and identified the last prescription, if any, within one year prior to the index date. From this, we estimated prescription durations using the parametric rWTD. We conducted a simulation study where we generated log-normal distributed prescription durations, but with a longer average duration when filled within the last two months of the year. This mimicked a situation where patients stockpile medication at the end of the year. We generated 2,500 datasets such that on average 15,000 patients had prescriptions each year, of whom 25% stopped treatment. We analyzed the simulated datasets with the new method and with the rWTD with fixed dates of Nov 1 and Jan 1 the subsequent year. For each method, the data were analyzed using a single log-normal distribution and we estimated the relative bias and coverage probability of nominal 95% confidence intervals. As a real-world example, we applied the methods to Norwegian data on prescription redemptions of warfarin in 2014.

Results: In simulations, the method with random index dates had a low relative bias (−0.1%) and retained nominal coverage (94.4%), even though the model is misspecified due to prescription durations originating from a mixture of two log-normal distributions. Using Nov 1 and Jan 1 the following year as index dates led to substantial relative bias (<−5.1%) and coverage probabilities close to 0%. For warfarin prescriptions in Norway 2014, the estimated duration was 130 (128; 131) days with random index dates and 122 (121; 123) with index date Nov 1 2014 and 101 (100; 102) days with Jan 1 2015.

Conclusions: In case of seasonal stockpiling the rWTD method with fixed index dates yields biased estimates of prescription duration. This bias can be mitigated using random index dates.

473 | Exploring longitudinal trajectories to model paternal exposure in evaluating risk of adverse outcomes in their offspring

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Background: New analytical methods have been developed to enable more precise descriptions of drug exposure during pregnancy and distinguish different profiles of exposure which may vary in their teratogenic or long-term health impact on the mother's offspring. Such methods for evaluating drug exposure during the 3-month spermatogenic cycle of the father immediately prior to conception and corresponding impact of exposure on the offspring has yet to be examined.
Objectives: To explore the feasibility of defining clusters of paternal exposure to medicines prior to conception.
Methods: A dataset of 5000 males was simulated using posology of an antiepileptic drug as the motivational example. Using this sample size a hazard ratio of 2 should be detectable with 5% significance and 80% power when the risk of the outcome in the reference group is 1%. Prescription data were introduced using normal and uniform distributions for each month for 3 months. Representing real-world situations, 7 patterns of longitudinal drug exposure were created: constant use (n = 440[0), start of use at month 2 (n = 100), start of use at month 3 (n = 100), end of use after month 1 (n = 100), end of use after month 2 (n = 100), increasing usage (n = 100) and decreasing usage (n = 100). K-means longitudinal clustering analysis (KmL) was then conducted to determine homogeneuous exposure trajectories based on the monthly cumulative dose and patterns of drug exposure. Calinski-Harabasz criterion values were used to evaluate the optimal number of clusters (1–10). All analysis were conducted in R (kml package).
Results: Through conducting KmL, the optimal number of clusters in which to partition men exposed during the 3 month pre-conception period was 7, each representing a unique trajectory of exposure: 3 levels of constant use (high n = 1130, intermediate n = 2070, low n = 1350), start of use at month 2 (n = 96), start of use at month 3 (n = 104), end of use after month 1 (n = 127), and end of use after month 2 (n = 121).
Conclusions: This simulation suggests that the application of KmL cluster analysis can facilitate the description of paternal exposure patterns over time. Specifically designed to deal with longitudinal data, KmL shows its potential for investigating the relationship between adverse outcomes in offspring of fathers exposed to medications in the 3-month period of highest risk pre-conception. As with most algorithmic clustering methods, KmL is mainly an exploratory technique and the determination of the optimal cluster number still can be challenging. Sensibility assessment is therefore recommended.

474 | Using machine learning algorithms to predict medication initiations and discontinuations

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Background: Current treatments for chronic kidney disease (CKD) focus on slowing disease progression but do not address the underlying inflammation and cause of kidney disease. Mineralocorticoid receptor antagonists (MRA) include spironolactone and eplerenone. A new MRA may have some beneficial effect on CKD patients. There was previously little information about treatment patterns, initiation and discontinuation of MRA in CKD patients.
Objectives: To predict and determine factors associated with initiation and discontinuation of MRA in CKD patients in the UK CPRD.
Methods: A retrospective cohort of CKD patients was created from the CPRD GOLD dataset (Jan 2008-Mar 2012) linked with Hospital Episode Statistics and the Office of National Statistics for mortality. Inclusions were age $\geq$ 18 years, CKD diagnosis, $\geq$1 year baseline history, and $\geq$ 2-year follow-up. The cohort was divided into a derivation cohort (70%) and a validation cohort (30%). For all models, the set of predictors included patient demographics, lifestyle factors, laboratory tests, CKD stages, time from the first CKD diagnosis, co-morbidities, and co-medications. Gradient Boosting Classifier (GBC), LASSO, and Random Forest (RF) were used to predict and determine factors associated with the risk of the initiation and discontinuation of MRA. Average (95% CI) AUC was used to evaluate the performance of the methods.
Results: There were 11,053 CKD patients with diabetes with median age of 72 (mean 70.4) years old. GBC and LASSO outperformed RF in predicting MRA initiation, with an average AUC of 0.836 (95% CI: 0.835–0.838) and 0.843 (95% CI: 0.841–0.845) compared to 0.807 (95% CI: 0.805–0.809), respectively. Predictors that increase MRA initiation included longer CKD history, older age, A&E visits, and prior use of ARB, CCB, BB, ACEI, and diuretics. Similarly, among 729 naïve MRA users in CKD patients without diabetes, GBC and LASSO outperformed RF in predicting MRA discontinuation, with an average AUC of 0.743 (95% CI: 0.740–0.747) and, 0.741 (95% CI 0.738–0.745) compared to 0.714 (95% CI: 0.710–0.718), respectively. Predictors that increase the risk of MRA discontinuation included hyperlipidemia, hyperkalemia, dialysis, and A&E visits.
Conclusions: GBC and LASSO models performed better than the RF model in term of AUC in predicting the risk of MRA initiation and discontinuation. Variables of importance for MRA initiation and discontinuation were determined. These findings support the potential of incorporating machine learning models into a study cohort to inform treatment pattern, medication initiation and discontinuation.

475 | Assessing differences in treatment effects: Interactions with propensity score splines

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Background: Assessing heterogeneity of treatment effects (TEs) is important for regulatory decision-making. A recent study compared effectiveness and safety of three non-vitamin K antagonist oral anticoagulants (NOACs), and warfarin in Medicare patients with nonvalvular atrial fibrillation. Subgroup analyses suggested that TEs may vary by age, sex, and calendar year. Since 65% of warfarin users were excluded via propensity score (PS) matching, the benefit–risk for those patients similar to excluded warfarin users was unknown. We explored using PS spline (nonlinear) regression models to adjust for confounders, while allowing valid estimation of TEs under limited PS overlap (in terms of relative frequencies), and assessed TE variation by different values of PS.

Objectives: To investigate using PS splines to identify variation in TEs in a study evaluating risk of major extracranial bleeding in beneficiaries initiating a NOAC (apixaban, dabigatran, or rivaroxaban) vs. warfarin.

Methods: A multinomial regression model, including nearly 100 patient and provider characteristics, was used to estimate three PSs. The logit of PSs was included in a Cox regression model as cubic splines and interacted with treatment. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) across values of the warfarin propensity score (PS_w). We added important covariate interactions with treatment to the model to explore variation in TEs across subpopulations.

Results: The PS spline model showed substantial variation in TEs across PS_w when comparing dabigatran vs. warfarin: HR = 0.78 (95% CI 0.68–0.9) and HR = 1.77 (95% CI 1.47–2.13) when PS_w was 0.5 and 0.9 respectively. This implies that dabigatran users had significantly higher bleeding risk compared to warfarin if they had a higher likelihood of receiving warfarin, and significantly lower bleeding risk otherwise. When two-way interactions of treatment with age spline and sex were added to the model, the difference in TE across PS values decreased: HR = 0.96 (95% CI 0.81–1.14) and HR = 1.39 (95% CI 1.10–1.74) when PS_w was 0.5 and 0.9 respectively. A model further interacting calendar year with treatment showed strong evidence for TE variation by year.

Conclusions: Models with PS splines interacted with treatment offer an alternative to other methods of confounding adjustment in subgroup analyses for assessing variation in TE. This approach allows all patients to be included in the model, including those with limited PS overlap. Additionally, it allows one to easily assess whether any heterogeneity exists, by estimating TEs over different values of the PS.

476 | A challenge of real world data: How to assign individuals to a treatment strategy when their data are consistent with several treatment strategies at baseline

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Background: When using real world data to emulate a hypothetical target trial, eligible individuals are assigned to a treatment strategy at time zero (baseline). However, when the exposure strategy involves timing, the information available at baseline may be insufficient to determine an individual's treatment strategy, that is, for some individuals, the baseline data could be consistent with more than one strategy. For example, in emulating a target trial of stopping vs. continuing annual mammograms among elderly women, many subjects have baseline data that could be consistent with either strategy.

Objectives: To compare two approaches for the assignment of individuals to treatment strategies at baseline: random assignment and cloning.

Methods: The simplest way to allocate women to a screening strategy when their data are consistent with both strategies is to randomly choose at baseline one of the two strategies: "stop" or "continue" screening. A second option is cloning the eligible women and assigning one clone to each strategy. While both approaches are unbiased, cloning is expected to be more efficient. However, the relative efficiency of the two approaches has not been studied in real data. Under both approaches, we censored women when they stopped following the assigned strategy (i.e., when receiving a screening mammogram if assigned to "stop" and at month 14 after the last mammogram if assigned to "continue"). We estimated the breast cancer-specific mortality hazard ratio for "continue" vs "stop" screening using a pooled logistic regression that included the screening strategy, time and baseline covariates. To adjust for the potential selection bias due to censoring, the model was inverse probability weighted using weights that depended on baseline and time-varying variables.

Results: 1,235,459 eligible women aged 70–74 years received a screening mammogram at baseline. Using the random assignment approach, we randomly assigned half of the women to each strategy: continue screening for 8 years vs. stop screening. The hazard ratio (95% CI) of breast cancer mortality was 0.74 (0.57–0.96) for continuing vs. stopping screening. When we repeated the procedure 100 times, the hazard ratios varied from 0.62 (0.48–0.79) to 0.94 (0.72–1.22), with an average hazard ratio of 0.79. Using the cloning approach, we created and assigned 1,235,459 clones to each strategy and the corresponding hazard ratio was 0.78 (0.64–0.96).

Conclusions: Cloning individuals is more efficient than randomly assigning them to strategies that have overlapping initial follow-up.

477 | Development and validation of algorithms to estimate live birth gestational age in Medicaid analytic extract data

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Background: While healthcare utilization data are a useful source for post-marketing surveillance of drug safety in pregnancy, the date of last menstrual period is generally not recorded and has to be estimated using diagnostic codes indicative of gestational age at birth (GA). Well performing predictive algorithms (ALG) are available, but none are specific to U.S. Medicaid Analytic eXtract (MAX).

Objectives: To develop and validate an ALG for estimating GA among live births specific to the Medicaid insured population.

Methods: From the existing 1999–2010 MAX cohort linked to birth certificates (BC) for Florida, Texas, and New Jersey, we identified mothers with continuous Medicaid enrollment from ≥12 months prior to delivery to 1 month post-delivery and infants enrolled for ≥3 months after birth unless they died sooner. We used the clinical/obstetric estimate of gestation on the BC as the gold standard. Four different approaches to estimate GA were developed based on: ALG 1 - preterm codes; ALG 2 - pre−/post-term codes; ALG 3 - timing of prenatal screening tests; ALG 4 - prediction via multiple linear regression, LASSO regression and random forests, using pre-specified predictors from ALG 1–3 plus additional predictors selected based on clinical relevance or their prevalence and strength of association in the dataset. ALG performance was assessed based on the mean squared error (MSE) and the proportion of deliveries with estimated GA within ±1 and 2 weeks of the BC GA in the full cohort and the subset of preterm deliveries (10-fold cross-validated for ALG 4).

Results: We identified 114,117 eligible deliveries with a valid BC GA. Among ALG 1–3, ALG 3 performed the worst (63.5% within 1 week, 80.7% within 2 weeks of BC GA), while ALG 2 had the highest agreement (79.7% and 93.9% respectively). Estimated GA based on the multiple linear regression model of ALG 4 was within 1 week of the BC GA for 84.0% of the deliveries and within 2 weeks for 96.1% (MSE: 1.5; R^2: 0.6). LASSO regression performed similarly to the multiple linear regression model. Random forests including all 255 predictors performed the best: 98.4% of estimated GA within 1 week and 99.6% within 2 weeks of BC GA (MSE: 0.3, R^2: 0.9). Of note, random forests also performed the best for the subset of preterm deliveries (91.4% within 1 week, 97.7% within 2 weeks, MSE: 1.0, R^2: 0.9).

Conclusions: Using a random forests approach, we were able to develop a highly accurate ALG for estimating GA among live births in MAX, both for term and preterm infants. This algorithm performs substantially better than existing validated algorithms based on GA related diagnostic codes.

478 | Utility of prenatal tests to estimate pregnancy start in sentinel

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Background: Pregnancy start among live births can be accurately estimated using gestational age-specific ICD-CM codes. The general absence of this information for non-live birth outcomes in electronic healthcare data often precludes evaluation of medications potentially associated with these outcomes. Algorithms using prenatal tests routinely performed during specific gestational windows may provide a proxy for pregnancy start in the absence of gestational age information.

Objectives: To evaluate whether the performance of algorithms based on combinations of prenatal tests can accurately estimate pregnancy start in the Sentinel live birth pregnancy cohort.

Methods: Using ICD-9-CM and ICD-10-CM codes we selected 16 prenatal tests and procedures clinically recommended within specific windows of gestation. A reference estimate of gestational age and pregnancy start was assigned to each live birth pregnancy based on a previously validated algorithm. We then assessed the prevalence of each prenatal test and the distribution of the timing of gestational age at each test. The proportion of tests that occurred within two weeks of the most common gestational day for each test based on the distribution (i.e., sensitivity within the two-week window) was calculated. Tests were added stepwise to 3 algorithms in order of performance within the two-week window. For each algorithm, we calculated 1) the proportion of pregnancies with ≥1 test in the algorithm and 2) the mean difference between the reference pregnancy start estimate and the algorithm-based pregnancy start estimate.

Results: In over 4.7 million live birth pregnancies, the sensitivity of each test ranged from 20.9% (1st trimester ultrasound) to 90.6% (nuchal translucency). Our final algorithms included 12 tests with >50% sensitivity within the two-week window. When adding these tests stepwise in order of performance, algorithm 1 included 6 tests, each of which had a sensitivity of ≥80%. Most (81.9%) of live birth pregnancies had at least one of these tests. The mean (median) difference between the reference- and test-based pregnancy start was −5.5 days (0 days). Algorithms 2 and 3, based on sensitivity cut-off points of ≥70% and ≥ 60%, respectively, included 87.6% and 97.9% of pregnancies with mean differences of −4.4 days (0 days) and − 3.7 days (0 days), respectively.

Conclusions: In a population of primarily commercially-insured pregnant women, certain prenatal tests implemented according to our algorithms can accurately identify pregnancy start. These results may

be particularly useful for non-live birth outcomes, for which algorithm validation is underway.

479 | Estimation of the beginning of pregnancies ending in stillbirths

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Background: In studies based on claims data, the beginning of pregnancy is usually estimated by subtracting a median length of pregnancy from the date of birth. Due to the variability in pregnancy lengths, this results in non-negligible errors, especially in stillbirths where the individual pregnancy lengths typically have a high variability. It has been shown that he expected delivery date (EDD), which can be coded in German claims data, allows to reliably estimate the beginning of pregnancy for live births.

Objectives: To assess the whether the EDD can be used to reliably estimate the beginning of pregnancy in stillbirths by examining the availability, consistency and plausibility of the EDD information in the German Pharmacoepidemiological Research Database (GePaRD).

Methods: We included data of all pregnancies in GePaRD ending in a stillbirth between 2006 and 2015 in women of childbearing age (12–50 years). For each pregnancy, we searched for EDDs coded in the three quarters before and in the quarter of the end of pregnancy. We determined the number of EDDs coded per pregnancy and their concordance if more than two EDDs were coded. For the assessment of consistency, we also examined the differences between discordant EDDs. The beginning of pregnancy was estimated by subtracting 280 days from the EDD or from the most frequently coded EDD (if ≥2 discordant EDD). To assess the plausibility of the EDD, we examined the resulting length of pregnancy and assessed whether the gestational age at which prenatal examinations were coded was plausible.

Results: We identified 3,333 pregnancies ending in a stillbirth (about 0.3% of all pregnancies). In 82% of these pregnancies at least on EDD was available. In most of these pregnancies (70%) two or more EDDs which were all concordant were coded, in 14% only one EDD was identified and in 16% ≥ 2 EDDs which were not all concordant were identified. The maximal difference between discordant EDDs was in median 6 days (25%–75%: 3–11 days). The median length of pregnancy was 224 days (25%–75%: 179–264, 5%–95%: 154–282) and the timing of prenatal examinations was plausible.

Conclusions: A key prerequisite for studies on the safety of drugs during pregnancy is the correct assessment of drug exposure in vulnerable gestational windows. By using the EDD, the beginning of pregnancy and thus gestational age at exposure can plausibly be estimated in more than 80% of stillbirths.

480 | Validation of ICD-9-CM coding algorithms to identify non-live birth outcomes in an automated database

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Background: Observational studies using automated databases, such as the Medicaid Analytic eXtract, play a major role in generating evidence on drug safety in pregnancy. Such studies are often restricted to live births, mainly due to lack of established algorithms to identify non-live births.

Objectives: To develop and validate ICD-9-CM coding algorithms for the ascertainment of stillbirth, spontaneous abortion (SAB) and termination in healthcare utilization databases.

Methods: We used the Partners Research Patient Data Registry (RPDR) 2000–2014, a registry of electronic medical record data for patients receiving care at a Partners affiliated hospital in Boston, to assemble a cohort of women enrolled in Medicaid with a non-live birth outcome. We identified 1) stillbirths based on ≥1 inpatient ICD-9 diagnosis (Dx) codes 656.4x, V27.1, V27.4 or V27.7; 2) SAB based on ≥1 inpatient/ ≥ 2 outpatient Dx codes 632.xx, 634.xx, 637.xx or CPT4 procedure (Px) codes 01965, 59812, 59820–1, or 59830; 3) terminations based on ≥1 inpatient/ ≥ 2 outpatient Dx codes 635.xx, 636.xx, 779.6x or CPT4 Px codes 01966, 59840–1, 59850–1, 59852, 59855–7, 59866 or ICD-9 Px codes 69.01, 69.51, 74.91, 75.0x. We randomly sampled 100 cases each for validation. In sensitivity analyses, we 1) excluded cases with codes for other live/non-live birth outcomes within ±5 days of the outcome of interest, and 2) relaxed the definitions for SAB and termination by allowing cases with 1 outpatient diagnosis only. Cases were adjudicated based on medical chart review. We estimated the positive predictive value (PPV) for each non-livebirth outcome and for the composite of any non-livebirth outcome. Validated algorithms will be converted to ICD-10.

Results: The PPV was 71.0% (95% CI, 61.1–79.6) for stillbirths; 79.0% (69.7–86.5) for SABs, and 93% (86.1–97.1) for terminations. When excluding cases with adjacent codes for other birth outcomes, the PPV increased to 80.6% (69.5–88.9) for stillbirth, 86.4% (75.0–94.0) for SAB and 97.7% (91.8–99.7) for termination. Relaxing the definition while removing cases with adjacent codes did not affect the PPV substantially: 86.6% (80.5–91.3) for SAB and 94.9% (91.1–97.4) for termination. For the composite outcome, the PPV was 94.4% (92.3–96.1).

Conclusions: Algorithms for all three non-live birth outcomes using ICD-9 codes had high PPVs, suggesting these outcomes can be validly identified and studied in healthcare utilization databases. The improvement in performance after excluding cases with adjacent codes for other birth outcomes highlights the need for hierarchical algorithms to distinguish specific birth outcomes.

481 | Immortal time bias in comparative drug safety studies in pregnancy

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Background: The presence and consequences of immortal time bias in drug safety studies of pregnant women remains poorly understood, particularly in the presence of an active comparator.

Objectives: To describe the occurrence of immortal time bias in studies examining the comparative safety of prescription drugs during pregnancy and its impact on estimated treatment effects.

Methods: We identified a retrospective cohort of pregnant women using the Pregnancy Register of the Clinical Practice Research Datalink (CPRD) as part of a Canadian Network for Observational Drug Effect Studies (CNODES) distributed protocol study that included seven databases. We examined the risk of fetal death, defined as a composite of spontaneous abortion or stillbirth, for: 1) ondansetron versus other antiemetics; and 2) fluconazole versus other antifungals. Inclusion in the study cohorts was restricted to pregnancies involving women who received the exposure or comparator of interest during the pregnancy. Treatment effects were estimated using time-fixed and time-dependent Cox proportional hazards models, both adjusted using high-dimensional propensity scores.

Results: The ondansetron cohort (n = 10,460) included 862 fetal deaths, and the fluconazole cohort (n = 42,165) included 2,153 fetal deaths. The median gestational age at the time of first exposure was 85 days (interquartile range: 67, 108) for ondansetron and 70 days (interquartile range: 54, 100) for other antiemetics. In contrast, the median gestational age at the time of first exposure was 34 days (interquartile range: 17, 82) for fluconazole and 160 days (interquartile range: 96, 217) for other antifungals. Compared with the use of other antiemetics, the hazard ratio (HR) of fetal death with ondansetron was 0.68 (95% CI 0.47, 0.98) when using a time-fixed model and 0.99 (95% CI 0.68, 1.43) when using a time-dependent approach. Compared with other antifungals, the HR of fetal death with fluconazole was 5.25 (95% CI 4.67, 5.89) when using a time-fixed model and 1.75 (95% CI 1.56, 1.97) when using a time-dependent approach. We observed similar differences between time-fixed and time-dependent models in analyses conducted in the pregnancy cohorts across other CNODES sites.

Conclusions: The use of time-fixed exposure definitions can result in substantial bias in comparative safety studies in pregnancy. Importantly, this bias can go in either direction in the presence of an active comparator, depending on the relative timing of the study drugs. The use of a time-dependent approach is essential to ensure validity.

482 | Comparing the use of propensity and disease risk scores in signal detection for prematurity on medico-administrative database

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Background: Pregnant women are often excluded from clinical trials despite their need to use drugs. So, there is a lack of information of drugs adverse effects during pregnancy. Administrative databases are a promising tool for post-market surveillance in this population and confounder summary scores can improve signal detection.

Objectives: To evaluate signal detection performance for drug induced prematurity and compare strengths and limits of propensity and disease risk scores using several ways to build them.

Methods: Using the French national health insurance database, we included all pregnancies identified by ICD-10 codes in the hospitalization database, lasting more than 24 weeks of amenorrhea and whose delivery occurred between 01/01/2019 and 12/31/2016. Scores were calculated on delivered drugs according to trimester of pregnancy and on associated diseases occurring during the study period by two methods: cross validated lasso logistic regression and cross validated extreme gradient boosting. Effect of variable preselection algorithm was studied. Scores were used through adjusting, 1:1 matching and weighting. Score computation times and prediction AUCs were analyzed. Signal detection pertinence was evaluated through Pubmed literature review and a pharmacovigilant expertise.

Results: Computation times of the disease risk score were lower than the propensity score whose computation times depended heavily of the exposure prevalence. Disease risk score AUCs were more homogeneous than propensity score AUCs but the latter reached greater values for certain drugs. Boosting took 1.5 to 10 times longer computation time than lasso, especially when the number of initial variables increased. Regarding signal detection, adjustment allowed the best detection performance especially when coupled with boosting. False positive signals due to indication bias were reduced and certain classes such as antivirals and antidepressants appeared particularly at risk in our analysis.

Conclusions: High dimensional preselection algorithm is an effective way to reduce computation time without loss of performance and detection rate. Disease risk scores for the exploration of many drugs with different levels of exposure allow a better stability than propensity scores. Adjusted analysis with boosting disease risk scores leads us to think that some classes of drugs such as antivirals and antidepressants should be further investigated for their risk of prematurity.

483 | Pneumococcal vaccine safety surveillance using three statistical methods: Disproportionality analysis, tree-based scan statistics, and empirical Bayes geometric mean

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Background: Concerns on the safety profile of pneumococcal vaccine (PV) have been raised due to increased spontaneous adverse event (AE) reports over the recent years in South Korea. Empirical Bayes geometric mean (EBGM) and tree-based scan statistics were introduced newly in local AE database to generate safety signals compared with disproportionality analysis.

Objectives: To identify safety signals after pneumococcal vaccination using disproportionality analysis, tree-based scan statistics, and EBGM, and to compare detected signals across statistical methods to confirm the consistency of results.

Methods: We conducted a vaccine safety surveillance study by applying the three statistical methods in the Korea Institute of Drug Safety & Risk Management-Korea adverse event reporting system database (KIDS-KD) between 1989 and 2017. The following statistical methods were used for signal detection: disproportional analysis using proportional reporting ratio, reporting odds ratio and information component simultaneously; EBGM using the lower bound of the 90% posterior probability interval; tree-based scan statistics at a significance level of 0.05. We repeated signal detection for pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV) to identify the difference among the subtypes of PV.

Results: A total of 20,156 spontaneous reports were related to any vaccine, and 1,272 spontaneous reports were related to PV. We identified 111 AE-pairs, and signals detected by disproportionality analysis, tree-based scan statistics, and EBGM were 21 (18.9%), 14 (12.6%), and 11 (9.9%), respectively. Only six signals (5.4%) were simultaneously detected by three statistical methods: fever (369); injection site discharge (218); cellulitis (52); oedema (19); injection site inflammation (14); angioedema (12). We identified 79 and 77 AE-pairs from PPSV and PCV, and different number of signals were detected by the three methods, respectively: PPSV (13 (16.5%), 14 (17.7%), 7 (8.9%)); PCV (14 (18.2%), 5 (6.5%), 3 (3.9%)). Cellulitis was the only AE detected simultaneously from PPSV and PCV by all statistical methods.

Conclusions: Discrepancy in the detected signals were observed among the three statistical methods. Compared to disproportionality analysis, EBGM generated the least signals, and tree-based scan statistics generated either less or equal number of signals; both seems to calibrate noise. Nonetheless, the difference of results should be interpreted with caution due to lack of gold standard of signal detection.

484 | Early season self-controlled risk interval analyses of Guillain-Barré syndrome risk following influenza vaccination using claims delay adjustment

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Background: The U.S. Food and Drug Administration monitors the risk of Guillain-Barré syndrome (GBS) following influenza vaccination using a multilayered approach. This includes end-of-season self-controlled risk interval (SCRI) analyses to compare GBS rates in post-vaccination risk windows (days 8–21 and 1–42) with the rate in a control window (days 43–84), using Medicare claims data. However, due to the delay in the observation of GBS hospitalized cases, results from these end-of-season analyses are often not available in time to inform decisions regarding next season's vaccinations.

Objectives: Develop and assess the performance of a methodology to conduct SCRI analyses to evaluate the GBS risk following influenza vaccination earlier in the season, accounting for the differential delay in claims between risk and control windows.

Methods: We conducted a simulation study using SCRI methods. We used claims data of beneficiaries enrolled in Medicare Parts A and B during the 2017–18 influenza season to identify influenza vaccinations and reported GBS hospitalized cases. To account for claims delay, we estimated the probability of observing a case using historical data and used it to adjust the follow-up time in the offset term of the conditional logistic model. We simulated seven scenarios varying the surveillance assessment between weeks 15 and 25. For each scenario we ran three SCRI models, one with claims delay adjustment, one without adjustment, and one with end-of-season data. We compared the difference in the log odds-ratio estimates from the models versus the true value used in the simulation (bias), as well as the variance and coverage.

Results: By surveillance week 20 (by December 29, 2017), the average bias of the log odds-ratio for the adjusted SCRI model was 0.014, ~95% less than the bias for the unadjusted model (0.286). The variance of the log odds-ratios were comparable (0.111 vs 0.108) and the coverage of the 95% confidence interval with adjustment was 96% versus 87% without adjustment. The SCRI adjusted model had comparable performance to the model using end-of-season data by week 20.

Conclusions: Our results suggest that, in an SCRI analysis using claims data, the delay in observation of GBS cases may be controlled for without substantially increasing bias or variance. This adjustment, if used during the past season, would have allowed us to obtain risk estimates 20 weeks earlier than an end-of-season analysis. This approach may provide reliable and timely interim analysis results to support regulatory decisions for future seasons.

485 | Comparative effectiveness of high-dose versus standard-dose influenza vaccine among patients on chronic hemodialysis

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Background: The standard-dose influenza vaccine (SDV) may not prevent influenza-related outcomes in patients on chronic dialysis. Little is known about the comparative effectiveness of high-dose influenza vaccine (HDV) versus SDV in this population.

Objectives: To compare the risk of all-cause mortality, hospitalization due to influenza or pneumonia, and influenza-like illness during the influenza season among adult recipients of HDV versus SDV.

Methods: We performed a cohort study using Medicare data from the United States Renal Data System (USRDS) for patients with end-stage renal disease (ESRD). We constructed yearly cohorts of adults with ESRD undergoing in-center hemodialysis during five individual influenza seasons (2010/11 to 2014/15). We required vaccination to occur prior to the start of each influenza season. Baseline covariates were ascertained during the 6-month period prior to vaccination. Follow-up began at the start of influenza season. Patients were eligible for inclusion in multiple yearly cohorts, thus our unit of analysis was the influenza-season. To examine the relationship between vaccine dose and effectiveness outcomes, we estimated risk differences (RD) using propensity score weighting of Kaplan–Meier functions, accounting for a wide range of patient- and facility-level characteristics. For non-mortality outcomes, we used competing risk methodology to account for high mortality in the dialysis population. Patients were censored at the earliest of a competing risk event (death for non-mortality outcomes), loss of Medicare Parts A or B, kidney transplant, peritoneal dialysis, subsequent influenza vaccine, or end of influenza season. The primary analysis was conducted in adults aged ≥65 years, and a secondary analysis was conducted in adults aged <65 years.

Results: We identified 255,281 eligible adult patients who contributed 507,552 unique patient-seasons. Within 225,215 patient-seasons among adults aged ≥65 years, 97.4% received SDV and 2.6% received HDV. We observed similar risk estimates for HDV and SDV recipients for mortality (RD, −0.1%; 95% CI, −0.9% to 0.8%), hospitalization due to influenza or pneumonia (RD, 0.2%; 95% CI, −0.7% to 0.9%), and influenza-like illness (RD, 0.0%; 95% CI, −1.5% to 1.1%). Our findings were similar among adults aged <65, as well as within subgroups defined by influenza season, age group, years on dialysis, month of vaccination, and vaccine valence.

Conclusions: HDV does not appear to provide additional protection beyond the SDV against all-cause mortality or influenza-related outcomes in the adult dialysis population.

486 | Effect of age on relative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries ages 65 years and older

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Background: Influenza causes substantial morbidity and mortality, and influenza-related hospitalization and death disproportionately affects older adults. Several studies have found that the high-dose (HD) influenza vaccine has higher relative vaccine effectiveness (RVE) compared to standard-dose (SD) vaccines in some seasons.

Objectives: This multi-season study investigates effect modification by age on the RVE of HD versus SD influenza vaccines among Medicare beneficiaries ≥65 years.

Methods: This retrospective six-season cohort study from August 2012 to August 2018 using Medicare claims and enrollment data included beneficiaries ≥65 years of age who received inactivated HD or a SD influenza vaccine in a community pharmacy setting prior to January 31st of an influenza season. The primary outcome was influenza hospital encounters, defined by inpatient hospitalizations or emergency department visits listing an influenza code. Linear function and cubic splines of continuous age were used to explore linear and non-linear relationships. We used a series of Poisson regression models interacting age with vaccine status to evaluate the effect of age on the RVE of HD versus SD influenza vaccines.

Results: A total of 35,156,602 (42%) HD and 47,760,909 (58%) SD influenza vaccinations were recorded in our study period (HD/SD ratio increased over time). After applying inclusion criteria, there were 13,770,207 (69%) HD and 6,151,913 (31%) SD vaccinations from eligible Medicare beneficiaries. The RVE estimates indicate that the HD vaccine was at least as effective as SD vaccines in preventing influenza hospital encounters across all seasons, and was more effective in the 2012–13 (RVE 23.1%, 95% CI 17.7–28.3%), 2013–14 (RVE 15.3%, 95% CI 7.8–22.3%), 2014–15 (RVE 8.9%, 95% CI 5.6–12.1%), and 2016–17 (RVE 12.6%, 95% CI 6.3–18.4%) seasons. We found a slightly increasing trend in RVE for HD versus SD vaccines with age in all seasons. The cubic spline model, which fit the data best, indicated notable improvement in RVE among those ages ≥80 years. For example, the predicted RVE increased from 4.8% (95% CI -10.9-18.2%) among 65-year-old beneficiaries to 15.0% (95% CI 8.3–21.2%) among 85-year-old beneficiaries in the 2016–17 season. We also found that the HD vaccine was consistently more effective than SD vaccines for people ages ≥85 years across all seasons.

Conclusions: This six-season study showed that RVE of the HD versus SD influenza vaccines increased slightly with age across seasons, and

that the HD vaccine was consistently more effective for people ages ≥85 years.

487 | Risk of pneumonia after varicella vaccination

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Background: Post-marketing surveillance data suggested that live attenuated varicella vaccine may be associated with post-vaccination pneumonia.

Objectives: To exam the risk of pneumonia after administration of varicella vaccine.

Methods: This nationwide study was based on linkage of the Taiwan National Health Insurance data and National Immunization Information System from January 2004 through September 2014. Since January 2004, varicella vaccination has been included in public vaccination program for all children older than 12 months and born after 2003. The study population was 12- to 35-month old children who received varicella vaccine, excluding those were coadministered with other vaccines on the same day. Exposure date was the day of varicella vaccine administration. Incident pneumonia was defined as patients with relevant ICD-9-CM diagnosis codes for hospitalization (052.1, 480.8, 480.9, 483.8, or 485) without the same diagnosis during the previous 14 days. The distribution of incident pneumonia was evaluated through 84 days after vaccination. We conducted a self-controlled risk interval analysis with a risk period for pneumonia incidence in 1 to 42 days after vaccination, and a reference period in 43 to 84 days for the same individual. Incidence rate ratio (IRR) of pneumonia was evaluated by conditional Poisson regression with adjustment of age (13–24, 25–36 month) and seasonal (1–3, 4–6, 7–9, 10–12 month) effects. The risk for fractures (ICD 800–829), which were unlikely to be associated with varicella vaccination, was also assessed as a negative control. Sensitivity analysis was performed with different conditions: excluding patients having the same diagnosis 28 days before outcome of interest, first-ever diagnosis, and a risk period of 8–42 days postvaccination.

Results: Of the 2,263,242 varicella vaccinees during study period, 1,194,189 (59.9%) were eligible for study cohort and 10,188 incident pneumonia episodes were observed 1–84 days after vaccination. The numbers of events were evenly distributed within 84 days, except in the first week, when fewer cases occurred. The crude IRR of pneumonia during 1–42 days was 0.94 (95% confidence interval (CI), 0.90 to 0.97), and the adjusted IRR was 0.97 (95% CI, 0.93 to 1.01). For the negative control, fractures, no association was observed with varicella vaccine (adjusted IRR: fracture 1.06 (95%CI, 0.79 to 1.41)), as expected. Sensitivity analysis of different scenarios showed similar results.

Conclusions: Our study showed no increased risk of pneumonia following varicella vaccination.

488 | No increased risk of Kawasaki disease among young children in 28 days after PCV13 vaccination

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Background: The US Vaccine Safety Datalink compared the risk of Kawasaki disease within 28 days of 13-valent pneumococcal conjugate (PCV13) vaccination with the historical risk after 7-valent PCV vaccination, using chart-validation. A relative risk of 2.38 (95% CI: 0.92, 6.38) was found. Concurrently, a post-licensure safety review by the US Food and Drug Administration identified cases of Kawasaki disease after PCV13 through adverse event reporting.

Objectives: To assess the existence and magnitude of any increased risk of Kawasaki disease in the 28 days after PCV13 vaccination.

Methods: The study population was children 0–23.99 months old from participating Sentinel data partners in 2010–2015. PCV13 vaccinations were identified in claims data by CPT, HCPCS, and NDC codes. Potential cases of Kawasaki disease were identified by ICD-9 code 446.1 or ICD-10 code M30.3 in the inpatient setting. Medical records were sought for potential cases and adjudicated by board-certified pediatricians. The primary analysis used chart-confirmed cases in a self-controlled risk interval (SCRI) design, which controls for time-invariant potential confounders. The pre-specified risk interval was Days 1–28 after vaccination; a 28-day-long control interval followed. The varying background risk by age was adjusted for in logistic regression using offset terms obtained by modeling the risk of Kawasaki disease by age in 2009 hospitalization data from the Healthcare Cost and Utilization Project. Sensitivity SCRI analyses without age adjustment, with possible cases included, and with alternative control intervals were conducted. A secondary analytic approach used a cohort design and Poisson regression, with alternative risk intervals of Days 1–28 and 1–42 and age adjustment based on the study population. Temporal scan statistics were used to look for clustering of onsets during Days 1–56.

Results: In the primary analysis, there were 43 confirmed cases of Kawasaki disease in the risk interval and 44 in the control interval. The age-adjusted risk estimate was 1.07 (95% CI: 0.70, 1.63). The results of all secondary and sensitivity analyses were also null. Temporal scan statistics found no statistically significant clustering of cases.

Conclusions: With more than 6 million doses of PCV13 administered, no evidence was found of an association between PCV13 vaccination and Kawasaki disease onset in the 4 weeks after vaccination nor of an elevated risk extending or concentrated beyond 4 weeks. These null results were consistent across alternative designs, age-adjustment methods, control intervals, and categories of Kawasaki disease case included.

489 | Reaplicating clinical trial data using RWD

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Background: As part of the FDA's efforts to lay the groundwork for using RWE on product effectiveness and safety to support regulatory approval for new or expanded indications, several demonstration projects were initiated to assess the feasibility, utility and methodological challenges of replicating clinical trial results using real-world data (RWD) stemming from claims and electronic health records. The idea is to first demonstrate the validity of the use of RWD analysis techniques by replicating clinical trial results that were already known; then the evidence on the utility of these techniques can be expanded for RWD usage to predict clinical trial results or to serve as an external control arm for single arm trials. In addition to the FDA project, several demonstration projects by other sponsors also have been presented and showed promising results. This symposium is intended to have focused presentations and panel discussion with panel members who have been contributing in the various initiatives in this area to provide updates on their projects and insights gained from the work so far. In addition, the regulatory implications of these findings and insights will be discussed.

Objectives: 1. To provide an overview of completed and ongoing projects replicating clinical trial results using RWD a. To discuss the methodologies that were used in the various projects b. To identify important considerations for control of bias and confounding when conducting such analyses **2. To provide insights on the potential applications of the methodologies and learnings from the various projects for regulatory submissions using RWE** a. From regulator's perspective b. From researcher's perspective.

Description: The symposium will start with a brief introduction of the background and objectives of the symposium (Solomon Iyasu, 5 minutes). An overview of the landscape, updates of the demonstration projects and regulatory applications will be provided (David Martin, 20 minutes). The findings of the demonstration projects will be discussed (Jessica Franklin, 20 minutes). Methodologic and study design considerations will be discussed (Miriam Sturkenboom, 20 minutes). Panel discussion (all, 20 minutes) and a brief conclusion will then follow (Solomon Iyasu and Kai-Li Liaw, 5 minutes).

490 | Data diversity in multi-database Pharmacoepidemiologic studies and its role in outcome misclassification: A curse or a blessing?

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Background: Pharmacoepidemiologic studies can be conducted on multiple data sources, which may be profoundly heterogeneous. This may cause different levels of outcome misclassification. Misclassification can be burdensome to quantify so is often neither measured nor accounted for, as was shown by a review of outcome misclassification in published studies conducted by the ISPE Database SIG (DB SIG).

Objectives: To highlight issues of resource diversity and outcome misclassification and to describe and demonstrate how this diversity can be leveraged to estimate misclassification in the absence of a gold standard and to correct the point estimate.

Description: The session will be chaired by two coauthors and feature the following topics and presenters, followed by discussion. *(a)* Highlight diversity between databases used in Pharmacoepidemiology research including those generated in North America, Europe, Australia and Asia, with a focus on diversity in outcome recording and ascertainment *(b)* Review the literature on bias from outcome misclassification, and on methodologies to address this bias using estimates of positive predictive value (PPV) and sensitivity (SE), with a focus on the meaning and consequences of differential misclassification*(c)* Describe a novel methodology to quantify outcome misclassification bringing together a) and b). By simultaneously using multiple data sources, and leveraging on their diversity, the method incorporates existing validation studies to allow estimation of PPV and SE of outcomes in the absence of a gold standard, and to support or challenge the assumption of non-differentiality between exposed and non-exposed. Some examples will be used to illustrate the methodology: an acute disease (acute myocardial infarction), a chronic disease (type 2 diabetes), and an infectious disease (pertussis) *(d)* Demonstrate how point estimates can be adjusted using PPV and SE from exposed and unexposed strata, using a publicly available online tool developed by the DB SIG. Examples will include cumulative incidence adjusted using indices generated from the work in point c), as well adjustment of relative risk.

491 | Characterizing patient experience data in medical product development: What is it, what is expected, and how can you contribute based on anticipated regulatory guidance?

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Background: In response to mandates of the 21st Century Cures Act and other initiatives, regulators are working to ensure that patient experiences are meaningfully captured in medical product development and evaluation via the use of patient experience data (PED). This includes engaging patients on trial design, endpoint development, clinical outcome assessment (COA) [e.g., patient reported outcomes], preference data, as well as other data collected from patients using qualitative, quantitative, or mixed method approaches; however, not all PED are equal. The FDA is issuing a series of PED guidances to outline expectations for scientifically sound methods to collect robust, meaningful, and sufficiently representative patient input to consider in regulatory decision making. The ISPE community needs to increase awareness of FDA and EMA expectations regarding the inclusion of PED in medicines development so that epidemiologists can contribute to and incorporate expected practices into any trial or observational studies being planned.

Objectives:

1. To understand regulators' intent and expectations related to PED data, including how anticipated guidances may change our approach to patient reported outcomes and benefit–risk.
2. To review examples of PED, including those that raise unanswered questions or potential gaps in our understanding on how and when to engage regulators.
3. To discuss opportunities to contribute to the science and guidances on PED.

Intended audience: Epidemiologists who would like to better understand and contribute to PED methods and its use in medical product development for regulatory decision making.

Description: This session will be organized as follows:

- The introduction will introduce issues related to current regulatory policy development that motivates incorporation of patient input to inform medical product development, regulatory decision-making, and post-marketing surveillance. (10 min: RD).
- Regulators will present intent and maturing expectations about the use of PED in decision making including anticipated guidance series. (~30 min: LLJ, PM).
- Examples of patient input in trial design, endpoints, COAs, and patient preference information will be reviewed in the context of engaging regulators and understanding evolving expectations. (~30 min: CG, BH).
- An interactive discussion with audience participation including questions, discussion about potential barriers to inclusion of PED, and opportunities to contribute to best practices (20 min: CG, LLJ).

492 | Existing databases for drug utilization research in Latin American and African countries

Maribel Salas[1,2]; Björn Wettermark[3]; Luciane Cruz Lopes[4]; Raquel Herrera Comoglio[5]; Joseph O. Fadare[6]; Olayinka O. Ogunleye[7]; Macarius M. Donneyong[8]; Dan Kajungu[9]; Anahi C. Dreser Mansilla[10]

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Background: Knowledge of the quantitative and qualitative patterns of drug use is a key element for a health care system either from the economic perspective and/or public health perspective. Drug utilization research (DUR) can provide such information including the estimation of exposed population, indication and duration of treatment derived from different sources. Data sources to be used in DUR include primary (e.g. data collected prospectively) and/or secondary sources. The measures of drug exposure will differ in each of the healthcare settings. DUR has been recognized as an important area for cross-national (CNC) comparisons of drug use and also to describe and measure the patterns, extent, and determinants of drug exposure between/within countries. Therefore, we understand that valid CNC studies can only be performed if the available data sources can deliver valid data. There is the urgent need to identify databases for DUR in Latin American and African countries that at the end can be used for decision making.

Objectives: To provide an overview of key information of databases for DUR and describe the current status of existing databases for DUR of some Latin American and African Countries. Researchers, payers and regulators involved in the development, interpretation and use of databases on drug utilization would be benefit from the symposium.

Description: The Symposium will be moderated by Maribel Salas. Björn Wettermark will present the key information in databases in DU research followed by presentations on the current status of databases for DUR in Latin American and African countries. Each speaker will present the challenges and potential solutions of current databases in their countries. For Latin America, Luciane Cruz Lopes will present the situation in Brazil, Anahi Cristina Castro in Mexico, and Raquel Herrera Comoglio in Argentina. For Africa, Joseph O. Fadare will present the situation in Nigeria, Macarius Donneyong in Ghana and Dan Kajungu in Uganda. All presenters and Olayinka O. Ogunleye from Nigeria will participate in the discussion.

493 | Introducing lactation real world data to ISPE

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Background:

At last year's ICPE in Prague, ISPE's Medications in Pregnancy Special Interest Group (SIG) was renamed the Medications in Pregnancy *and Lactation* SIG, because real world data (RWD) should be used to better understand the safety of medications in infants who are exposed through breastfeeding. Pregnant women who require treatment for a chronic condition will generally need to continue treatment in the post-partum period and can face the dilemma of deciding whether to breastfeed. In addition, breastfeeding women may need to initiate treatment for acute or chronic conditions. The safety of medications in breastfeeding infants have not been well studied. There are short and long-term benefits of breastfeeding both to the mother and the infant, and these factors are important in the overall risk–benefit decision making process. Therefore, it is important that ICPE has a symposium (for the first time) to address this important issue.

Objectives: The objective of this symposium is to understand how real world data can be used in the assessment of the safety of medications in breastfeeding infants.

Description: This symposium will provide an overview of the use of medications by breastfeeding mothers and identify the gaps in knowledge. The session will also discuss the use of strategies (e.g., modeling and simulation) to evaluate the utility of RWD in assessment of the safety of medications used during breastfeeding. The experience of harmonizing safety data collection in breastfeeding infants with ongoing pregnancy registry studies, and the experience of developing a human milk repository will be presented. A case example will provide the industry experience of real world data collection and submission to the FDA to inform labeling. Additionally, the FDA perspective about the assessment and integration of available data into drug labeling to inform risk–benefit considerations in breastfeeding women will be discussed. The symposium will provide a platform for discussion for researchers and industry to develop methods to assess the safety of medications and biologics in breastfeeding infants. Audience participation will be encouraged.

494 | Structured benefit–risk assessment of prophylactic subcutaneous C1-esterase inhibitor for hereditary angioedema management

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Background: The first subcutaneous C1-esterase inhibitor (C1-INH [SC], 60 IU/kg) for routine prophylaxis to prevent hereditary angioedema (HAE) was approved in the United States and Canada in 2017. To improve transparency and consistency of the benefit–risk decision-making process, a structured framework was employed.

Objectives: Utilize a structured framework to quantitatively assess the benefits and risks of C1-INH [SC] plus possible on-demand treatment as compared to on-demand treatment alone in patients with an average of 2 or more attacks per month.

Methods: A cross-functional team employed the Centre for Innovation in Regulatory Science Benefit–Risk Action Team (CIRS-BRAT) framework to establish the decision frame and identify key benefit and risk outcomes relating to prevention of HAE attacks, control of HAE symptoms, global assessment of response to therapy (GART) and treatment emergent adverse events (TEAEs). Risk differences (RD) for each outcome were calculated per 100 patients as proportion of C1-INH [SC] plus possible on-demand treated patients minus proportion of on-demand treatment alone patients using data from the pivotal, double-blind cross-over study COMPACT (NCT01912456) and displayed in a forest plot.

Results: The value tree was refined iteratively to allow for dichotomous expression of outcomes and to eliminate redundant outcomes. Using the intent-to-treat population (N = 45), RDs for reduction of HAE attacks to less than 1 per month and free of any attack was 76 (95% Confidence Interval (CI) = 62–89) and 40 (95% CI = 26–54) respectively and favored C1-INH [SC]. Investigator graded "none/mild" attacks (RD = 56, 95% CI = 41–71), no days with HAE symptoms (RD = 40, 95% CI = 26–54), or good/excellent subject (RD = 53, 95% CI = 36–71) and investigator (RD = 78, 95% CI = 65–91) GART were higher for C1-INH [SC] than for on-demand alone treatment. In the safety population (N = 43), no significant differences were detected for other TEAEs, no thromboembolic and anaphylaxis events were confirmed, and a favorable safety profile was observed.

Conclusions: Benefits of options to treat HAE attacks favors prophylactic C1-INH [SC] treatment while risks are low and comparable to on-demand treatment alone. A structured framework for assessing the benefit–risk profile and resulting visual outputs can facilitate balanced and improved communication of benefits and risks to clinicians and patients.

495 | Impact of complex drug approval decision-making processes on safety-related regulatory actions for drugs approved by the European medicines agency

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Background: Although regulators make a binary decision at initial drug approval, decision-making processes vary widely in complexity. Whether greater complexity as a proxy for greater uncertainty leads to more safety-related regulatory actions post-approval is unknown.

Objectives: To assess associations between complexity of drug approval decision-making processes and regulatory actions concerning new safety issues.

Methods: We performed a retrospective cohort study of 40 innovative drugs approved by the European Medicines Agency (EMA) in 2009–2010, excluding influenza vaccines. For these, we identified revocation, suspension, non-commercial withdrawal, non-renewal, Direct Healthcare Professional Communications (DHPCs) and new restrictions of indications, contraindications and warnings in the product information until 31 Oct 2017. Complexity was assessed as 'low', 'medium', or 'high', based on presence of significant concerns regarding clinical trial data, procedure duration, whether consensus was reached, and negative initial opinion. Data were extracted from regulatory sources. A recurrent time-to-event model was applied to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs), comparing levels of complexity, and adjusted for pre-approval patient exposure.

Results: We identified no revocations, suspensions, non-commercial withdrawals and non-renewals, 14 DHPCs, and 222 product information changes, of which 72 concerned new restrictions of indications, contraindications and warnings. Complexity was 'low' for 11, 'medium' for 16, and 'high' for 13 drugs. When considering complete follow-up (median 7.9 years), we did not identify a significant association (medium/high vs. low aHR 1.23 [0.63–2.42]; medium vs. low aHR 1.42 [0.71–2.82]; high vs. low aHR 1.00 [0.34–2.92]). However, post-hoc analyses restricted to the first 2.5 years suggest an increased hazard (medium/high vs. low aHR 4.31 [0.96–19.33]; similar for medium and high vs. low), in contrast to a slightly reduced hazard during later follow-up (medium/high vs. low aHR 0.80 [0.42–1.54], which was even more pronounced for high vs. low).

Conclusions: Complexity of drug approval decision-making processes does not lead to more safety-related regulatory actions post-approval. This may indicate that risk minimisation processes have been adequately implemented, as also suggested by the differential timing of regulatory actions between levels of complexity.

496 | The occupational hazards of measuring risk tolerance: Convergent validity in preference elicitation

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Background: Phenylketonuria (PKU) leads to an accumulation of phenylalanine (Phe) in the blood and subsequent neurologic, cognitive, psychiatric, and behavioral dysfunction. Many patients report social isolation and decreased quality of life. Pegvaliase is an enzyme substitution therapy that reduces blood Phe levels in patients with PKU and is associated with a risk of hypersensitivity reactions.

Objectives: Given there is no consensus about the best way to elicit patients' preferences, this study empirically test the consistency of responses to two different preference elicitation methods. Such research has been encouraged by the FDA and is one of the key motivators of the Innovative Medicine Initiative funded Patient Preferences in Benefit–Risk Assessments during the Drug Life Cycle project (PREFER).

Methods: Two methods, thresholding and adapted swing weighting (ASW), were adopted to elicit patients' minimum acceptable benefit (MAB) for pegvaliase, a treatment for phenylketonuria (PKU). Both elicitation methods used the same attributes and associated levels: the ability to lower phenylalanine (Phe) levels, and the likelihood of experiencing allergic reactions. To enable the reasons for differences in MAB obtained from these two exercises the participants were asked to outline their rational for their choices.

Results: Patients would require a minimum likelihood of 22.67% (ASW) to 34.4% (thresholding) of achieving a Phe level less 360 μmol/L before they would tolerate the risks. This is less than the benefit generated by pegvaliase. There was no relationship between MAB and patient's current Phe level, perception of PKU control, or satisfaction with treatment. Seven participants had their MAB increase significantly between the ASW and the thresholding exercise. In four cases, this was explained by their refusal to take an injectable, which was an aspect highlighted in the introduction to the thresholding but not in the ASW exercise.

Conclusions: The insight generated by both methods supported patients would be willing to take pegvaliase despite its risks, and both methods drew the same conclusions with regards to treatment preference. However, this study highlights the impact of the elicitation format and framing of questions on the elicited trade-offs. The introduction of the treatment characteristic could explain most of the discrepancies between the MABs in the two exercises.

497 | Determinants for safety issue coverage by lay and social media

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Background: Drug safety issues communicated by Direct Healthcare Professional Communications (DHPCs) may receive substantial media coverage, e.g. thrombosis risk of oral contraceptives. However, what triggers media coverage in general is unknown.

Objectives: What are determinants for media coverage of DHPCs in the Netherlands?

Methods: Newspaper articles covering issues mentioned in 387 DHPCs issued from 2001 till 2015 were retrieved from Lexis Nexis Academic™, a repository of newspaper and magazine articles. Articles published two months before to two months after the DHPC was

issued were retrieved. Web postings were retrieved from Coosto™, a repository of social media, for 220 DHPCs issued from 2010 till 2015. We retrieved postings mentioning the drug/brand name from 14 days before to 14 days after the DHPC was issued. Media coverage in newspapers and in social media were defined as binary outcomes. As potential determinants ATC code (first level), date of DHPC (years), month of DHPC, type DHPC message (i.e. safety issue, shortage/delivery, defect/recall), withdrawal yes/no, drug age (≤2 years, 3–5 years, 6–11 years, and > 11 years (ref)), amount of users (low/unknown use (<1000), moderate use (1000–10000), wide use (>10000) (ref)), specialist drug (yes/no) were collected. We used Multivariate logistic regression analyses to evaluate which determinants were associated with media coverage, showing adjusted odds ratio (ORadj) and 95% confidence interval (95% CI).

Results: Of the issues mentioned in 387 DHPCs, 55 (14.2%) were covered in newspaper articles in the four months around the DHPC was issued. Shortages or delivery problems (ORadj 4.90; 95% CI [1.36–17.65]), drug age (3–5 years ORadj 0.24; 95% CI [0.06–0.91], 6–11 years ORadj 0.20; 95% CI [0.06–0.65]) and amount of users (low/unknown ORadj 0.16; 95% CI [0.06–0.43], moderate ORadj 0.28; 95% CI [0.09–0.83]) were all associated with newspaper coverage. DHPCs issued more recently were less likely to be covered by newspapers (ORadj 0.86; 95% CI [0.78–0.95]). 143 (65%) drugs mentioned in 220 DHPCs were covered by the social media in the month the DHPC was issued. Drugs with a safety message (ORadj 4.04; 95% CI [1.51–10.83]) and non-specialist drugs (ORadj 2.57; 95% CI [1.05–6.26]) were associated with social media coverage.

Conclusions: Determinants associated with media coverage differed for newspapers and social media. Newspapers focused more on old drugs, those that are widely used, or shortages or delivery problems, whereas social media coverage was more related to non-specialist drugs and safety messages.

498 | Monitoring benefits and risks of medicines for overactive bladder in primary care; building a bridge between daily practice and research

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Background: Monitoring benefits and risks of medicines in the post-marketing phase is important for a safe and effective treatment of patients. Aim of this project is to develop a flexible infrastructure with general practitioner's (GP) routine electronic health records triggering the collection of patient reported outcomes (PROs) regarding the effect and adverse reactions (ADRs) of pharmaceutical treatment.

Objectives: To evaluate the feasibility of acquiring real world data to monitor the effects and ADRs of medicines.

Methods: For this pilot study, two general practices in the Netherlands were included. Overactive bladder (OAB) was used as a use case. OAB patients were flagged in electronic health records data that are collected by Nivel on a weekly basis. The GPs checked whether the patient was eligible for the study. PROs were obtained by an electronic survey, using the Lareb Intensive Monitoring system. Questions involved bladder complaints, treatment (physiotherapeutic interventions and medicines), ADRs, therapy compliance, and quality of life.

Results: 109 OAB patients were flagged in the electronic health records data. After revision by the GPs, an invitation to participate was sent to 82 (75%) patients. Reasons for excluding patients were: patient cannot work with a computer or questionnaire (10x), cognitive/mentally not fit to fill in questionnaire (10x), patient in hospital (3x), patient died/moved (2x). GPs were enthusiastic about the study procedure. Nineteen patients (23%) filled in the questionnaire. Average age was 63 years (38–79 years) and 14 of them were women. Patients reported an average score of 4.0 for urogenital complaints, on a scale from 1 (none) to 10 (very much). Eleven patients received physiotherapeutic interventions and 5 received medicines to treat the OAB. Of these, 3 patients experienced ADRs.

Conclusions: The developed infrastructure is successful in providing clear information about patients' perspective of the benefit and ADRs of their treatment at relatively low effort. The pilot shows that information about effectiveness and ADRs of medicines can be acquired using this system. The system is designed to be applied to any new medication on the market and has several advantages above more traditional monitoring instruments like longer follow-up, and a real life setting.

499 | Effectiveness of risk evaluation and mitigation strategies to prevent maternal exposure to a Topiramate weight loss product

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Background: In 2012, the Food and Drug Administration (FDA) approved a combination product for weight loss (phentermine/topiramate (PT)) with a Risk Evaluation and Mitigation Strategy (REMS) to prevent maternal exposure and mitigate topiramate teratogenicity. However, the evidence on the effectiveness of such REMS programs is scarce.

Objectives: To evaluate the effectiveness of the REMS program for PT to prevent maternal exposure to topiramate compared to other anti-obesity medications (AOMs).

Methods: We conducted a retrospective cohort study using IBM MarketScan® Commercial Claims Databases (2011–2017) to compare the risk of pregnancy during exposure to PT versus other AOMs approved for long-term use (naltrexone/bupropion, lorcaserin, liraglutide, orlistat). Females of child-bearing age 14–50 with &ge 12 months continuous enrollment before the first prescription fill and not having diagnoses or procedures indicating infertility were included. Multiple treatment episodes were allowed if the gap

between fills was >14 days. The outcome was defined as conception identified by an algorithm based on diagnosis and procedure codes indicating &ge 2 medical encounters for pregnancy or screening tests. Other teratogenic drug use, hormonal contraception, and comorbidities were measured as potential confounders. Patients were followed up to two years and were censored due to infertility, drug discontinuation, conception, or end of the study. We used Cox proportional hazard regression with inverse probability of treatment weighting to compare the study groups, accounting for multiple treatment episodes.

Results: We included 14,517 treatment episodes for PT and 47,173 episodes for other AOMs. Mean age was 39.7 (7.5) vs. 39.9 (7.5) in the PT and other AOMs groups, respectively. The median follow-up time was comparable (30.0 (43.0) vs. 30.0 (34.0), respectively). Hypertension (26.0%) and hyperlipidemia (21.3%) were the most common comorbidities. Use of hormonal contraception within two months before and one month after the index date was 16.9% in the PT and 16.0% in other AOMs groups. The adjusted conception rate was 7.1 per 1000 person-years in the PT group and 11.0 in other AOMs group. The unadjusted and adjusted hazard ratios were 0.70 (0.43, 1.14) and 0.66 (0.40, 1.08), respectively. Sensitivity analyses including varying assumptions to estimate conception and assuming discontinuation of drug exposure before the last fill showed minimal changes in the risk estimates.

Conclusions: The REMS program for PT appears to have limited effectiveness in preventing maternal exposure.

500 | Agomelatine post-authorization safety studies program: Comprehensive results

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Background: Agomelatine, indicated from 2009 in Europe to treat major depressive episode, is covered by a risk management plan including hepatotoxic reaction as an important identified risk. Risk-minimisation measures (RMMs) were implemented from marketing authorization, and consist of contraindications in patients with hepatic impairment and precautions of use in patients at risk of liver injury; liver testing at several time points, as well as a prescriber's guide and a patient booklet. Two information letters were distributed to prescribers in 2012 and 2013.

Objectives: Five post-authorization safety studies were conducted in 9 countries overall allowing a diverse geographic representation of Europe, to further characterize agomelatine hepatic risk or measure effectiveness of these RMMs.

Methods: A prospective observational cohort assessed the safety of agomelatine in current medical practice as the drug was launched, with focus on hepatic reactions. A pharmacogenomics study aimed at identifying genomic biomarkers associated with agomelatine-induced liver injury. A prescription survey assessed prescribers' knowledge on the risk of hepatotoxicity. A chart review evaluated the adherence to the liver test requirements and compliance with contraindications and precautions of use, and a patient survey assessed reasons for non-compliance with the liver testing. A case–control study nested in an antidepressant new users cohort quantified the risk of acute liver injury (ALI) comparing agomelatine to citalopram.

Results: The incidence rate and type of hepatic events observed in the prospective cohort were comparable to what was observed in clinical trials. No genomic biomarkers were identified to be associated with agomelatine-induced liver injury. The prescription survey suggested that physicians, with up to 80% of the psychiatrists and up to 51% of GPs, have a good knowledge of the safety concerns associated with agomelatine. The chart review showed that after the last RMMs were implemented 16% of patients treated with agomelatine had one test at initiation and during treatment (25% had a test at initiation and 61.5% during treatment) and 99% of patients were treated with respect to the contraindications. The nested case control study showed that, in the context of the current RMMs, the risk of ALI among agomelatine users is not higher than that for citalopram users.

Conclusions: These studies allowed to better characterize the agomelatine hepatotoxic risk and to assess the effectiveness of the RMMs, showing that altogether these RMMs with the current level of adherence are effective in preventing ALI among agomelatine users.

501 | Area-level linkages to enrich primary care electronic health data for research

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Background: Clinical Practice Research Datalink (CPRD) collects de-identified patient data from a network of general practitioner (GP) practices across the UK. These longitudinal data, encompassing >35 million patient lives, are available for research into drug safety, use of medicines, health policy, health care delivery and disease risk factors. Linkage of these primary care data to a range of health and health-relevant contextual data further enriches their research value.

Objectives: To describe area-level linkages recently made available in CPRD and review their application in research studies of drug safety, care utilization and public health.

Methods: Patient and GP practice postcodes were mapped to lower layer super output area (LSOA, England/Wales, average 1,600 population), super output area (SOA, Northern Ireland, average 2,100 population) or datazone (DZ, Scotland, population 500–1,000). Linkage to practice-level Rural–Urban classification was made to support research where access to services, employment and educational opportunities might be an important confounder. Inclusion of the individual domains of the Index of Multiple Deprivation (IMD) - housing, employment, income, access to services, education, crime, and living environment - was implemented to facilitate research requiring a more nuanced adjustment for aspects of material deprivation; within

England, correlations between practice-level quintiles of IMD and the IMD domains range from 0.36–0.89. Linkage to Carstairs Index provided an alternative index of material deprivation covering England, Wales and Scotland.

Results: 1615 GP practices contributing to CPRD's primary care database (January 2019) were linked to these area-level measures, representing 19.5, 18.2, 10.8, and 7.9% of GP practices in England, Wales, Scotland and Northern Ireland, respectively. Since being made available in June 2018, protocols requesting linkage to these area-level variables have included a study looking at the influence of patient and practice-level factors associated with vaccine uptake, and a study assessing the social and demographic characteristics of high cost patients in primary and secondary care. The next release of linkage data will include linkage of these area-level measures to patient postcode.

Conclusions: The research value of electronic health datasets, like those held by CPRD, can be enhanced via linkage to other health and health-relevant datasets. Area-level data can provide a context within which health care is delivered, act as a proxy for socioeconomic status, and support the planning and targeting of health and social care services.

502 | Role of health plan administrative claims data in participant recruitment for pragmatic clinical trials - an ADAPTABLE (aspirin dosing: A patient-centric trial assessing benefits and long-term effectiveness) example

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Background: The utility of longitudinal claims to identify eligible patients across health systems provides an innovative and valuable potential solution for large pragmatic clinical trial recruitment.

Objectives: This study sought to evaluate the HealthCore/Anthem Research Network (HCARN) recruitment outreach, compare member of visits to the ADAPTABLE study's recruitment portal, and assess enrollment rates for different outreach strategies.

Methods: Setting/intervention: We conducted outreach to health plan members identified by a previously validated PCORnet common data model computable phenotype and their providers utilizing HCARN administrative claims data, during 11/2017 — 08/2018. Provider outreach preceded member outreach, and allow the provider to opt out their patients. We conducted two phases of member outreach, phase 1 consisted of 2 batches of email/mail and 1 phone call, phase 2 compared two equal batches of either email/mail or brochure and 1 phone call. Main outcome: The main outcomes were whether outreached members visited the study portal or enrolled into ADAPTABLE study. Additionally, we compared our different outreach strategies across the two phases of outreach. Statistical analysis: Rates of portal visit and enrollment were reported by phases and by outreach methods. Descriptive statistics were used to examine outreached members, portal visitors and enrollees' demographic and clinical characteristics.

Results: We outreached to 28,593 providers in phase 1 and an additional 5,077 providers in phase 2. In phase 1, 301,375 mixed e-mail/mail were delivered to 133,373 members, followed by 90,481 phone calls. In phase 2, post randomization 51,777 members to email/mail or brochure groups, 51,623 communications were sent to 25,914 members via mail/e-mail, and 50,160 brochures to 25,863 in the brochure group. Following 2 waves of mail/e-mail or brochure outreach, 16,608 and 16,600 calls were made to the groups, respectively. Overall, 1,549 HCARN members visited the study portal; resulted in 355 enrollments. Brochures drove more portal visits in Phase 2, but less conversion to enrollment. Recruitment was better in Phase 2 — 2.3 vs 1.8 enrollees per 1,000 outreach members in Phase 1.

Conclusions: This study showed that a health plan within PCORnet has the ability to identify potential study participants with administrative claims and facilitate recruitment and enrollment for pragmatic clinical trials facilitating pragmatic pharmacoepidemiology research.

503 | Impact of length of pre-index enrollment criterion on patient characteristics in a cohort of heart failure patients using a large U.S. Medicare advantage claims database

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Background: When designing retrospective claims database studies, researchers must define the pre-index enrollment criterion for the cohort. This decision is often driven by optimizing availability of data and limiting patient attrition.

Objectives: This study aimed to examine the impact of the selected lengths of pre-index period on the characteristics of a heart failure patient cohort.

Methods: A cohort of patients diagnosed with heart failure was identified in a large Medicare Advantage database. The index date was defined as the first heart failure diagnosis. Key demographic and clinical characteristics were examined using data from varying pre-index periods (including ≥3 months, ≥ 6 months, ≥ 12 months, ≥ 18 months, and ≥ 24 months). Comorbidities and comorbidity burden were assessed based on diagnosis codes and prescription records/procedures, respectively. Descriptive analyses were performed to assess the impact.

Results: A total of 269,586 patients were identified. 239,054 (88.7%) had ≥3 months of pre-index enrollment, 170,697 (63.3%) had ≥12 months, and 129,001 (47.9%) had ≥24 months. Demographic characteristics, including gender and average age, were similar (mean age 76 or 77, male ranging from 50.4% to 49.7%) across the varying pre-index study periods. As expected, the longer the pre-index period, the higher the observed prevalence of comorbidities. However, the increase in comorbidity prevalence was most pronounced between patients with ≥3 months vs. ≥ 6 months pre-index enrollment (e.g., hypertension 83.4% vs 89.7%), and likewise for ≥6 months vs. ≥ 12 months (89.7% vs 93.9%), but was marginal for the comparisons of longer time periods after ≥12 months (93.9% vs 94.0% vs 94.1%). Comorbidity burden showed similar estimates across the varying pre-index periods.

Conclusions: Choice of pre-index time can affect the prevalence estimates of pre-index comorbidities and clinical variables. These results suggest that periods longer than 12 months may only provide marginal additional detail on patient medical history while reducing available sample size.

504 | Predicting the likelihood of 30-day hospital readmissions among stroke patients: An application of machine-learning techniques

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Background: Understanding the patients most at risk for hospital readmission is of great interest to clinicians and policymakers. Stroke patients are known to have a substantial risk for early hospital readmission, but prior studies show fairly low predictive accuracy.

Objectives: The objective of this study was to assess the accuracy of standard techniques along with machine-learning (ML) approaches in predicting 30-day readmissions among ischemic stroke patients.

Methods: This single cohort retrospective analysis used the HealthCore Integrated Research Database (HIRD), an administrative claims database with over 50 million members. The study cohort consisted of patients with a first-listed diagnosis of ischemic stroke between 1/1/08 and 3/31/15, one year of eligibility prior to the stroke hospitalization ("Index"), and at least 30 days of eligibility following discharge from the index stay. Predictors (e.g., demographics, comorbidities, characteristics of the index stay) of all-cause hospital readmission were pre-specified based on the results of a literature review and in consultation with the study physician. Additional features were generated automatically based on the frequency of medications, diagnoses, and procedures summarized to a CCS or Multum level for the one year prior to index and during the index stay. Five models were generated, including logistic using the LACE score ("LACE"), logistic based on pre-specified measures ("standard L"), and 3 ML models with all features ("ALL"). The models used a 15% holdout with a 75%/25% train/validation split. All analyses were undertaken using the Instant Health Data (IHD) platform (BHE, Boston, MA, USA).

Results: A total of 79,642 ischemic stroke patients were identified (median age: 67 yrs; 49.9% female), of whom 17.9% were readmitted within 30 days. AUC values were 58.8% (LACE), 70.6% (standard L), 73.1% (Lasso regression, ALL), 73.2% (feed-forward neural net, ALL), 73.3% (logistic, ALL), and 73.7% XGBoost (ALL). We picked XGBoost for the final holdout test, which had: Accuracy: 77.3%, AUC: 73.4%, Recall: 67.3%, Precision: 42.4% and F1: 0.52.

Conclusions: In this cohort of almost 80,000 ischemic stroke patients, ML techniques provided a modest benefit in terms of AUC. Further testing and evaluation would be useful in a database that includes additional structured clinical measures and unstructured clinical notes.

505 | New automated signal detection methods in pharmacovigilance combining medico-administrative database controls and spontaneous reporting cases

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Background: Pharmacovigilance aims to detect early adverse reactions of marketed drugs. Classically, it relies on large spontaneous reporting databases (SRD), which is a collection of case reports of suspected adverse drug reactions. Statistical methods have been proposed to mine these large databases and highlight suspicious drug-adverse event (AE) associations, called signals. With these approaches, controls for a given AE are cases of other AEs.

Objectives: We aim to develop new signal detection methods by building a control group from the general population using hospital and healthcare claims databases. An empirical assessment with a real application on "acute liver injury" (ALI) is conducted.

Methods: We constructed an hybrid database (HB) with the ALI cases from the French national SRD and a large set of controls from the *Echantillon Généraliste des Bénéficiaires*, a representative sample of the French population's healthcare claims data. In HB and SRD, we implemented i) a classical univariate signal detection method: the reporting fisher's exact test (RFET) and ii) a logistic lasso. We also investigated detection rules based on various outcome combinations from HB and SRD. Finally, we evaluated approaches derived from the adaptive lasso in which statistics (e.g. log (OR) or p-values) from the HB detection are included as prior weights in a lasso performed on SRD. Performances were mainly measured in terms of sensitivity and false discovery proportion on the basis of a published reference set for ALI. Methods were compared at identical number of generated signals.

Results: For the same number of generated signals, RFET showed comparable performances. The lasso in HB showed a better sensitivity for large number of signals. We observed that a decision rule based on the union of the signals lasso-generated in each database slightly improved performance compared to the same procedure in the SRD. Finally, our "adaptive lasso" had a better sensitivity compared to the classical lasso in the SRD and shows a lower false discovery proportion.

We also observed that a significant proportion of HB and SRD signals were different.

Conclusions: From this empirical evaluation, we conclude that signal detection using controls from medico-administrative databases is a complementary approach to signal detection on SRD only.

506 | Total hip or knee replacement surgery and risk of thromboembolic outcomes: A retrospective cohort study

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Background: Patients undergoing total knee or hip replacement (TKR/THR) surgeries are at high risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). Detailed risk characterizations in this population are limited.

Objectives: To estimate incidence rates (IRs) of DVT/PE across multiple risk windows (RWs) among adults undergoing TKR/THR in United States (US), stratified by potential risk factors.

Methods: A retrospective cohort study using 2007- mid 2018 Optum EHR data was conducted. Patients aged 18–85 years with ≥183 days of enrollment prior to TKR/THR and met study inclusion/exclusion criteria were included. Two cohorts (TKR and THR), 2 outcomes (DVT and PE), and selected clinical characteristics for stratifications were defined based on ICD-9/10 codes. IRs and 95% confidence intervals (CIs) were estimated in the following 6 RWs: during surgical hospitalization and ≤ 10, 30, 90 180, or 365 days post-operation.

Results: 168,785 TKR and 88,284 THR patients were eligible for the study. The IRs and 95% CIs for DVT following TKR and THR per 1000 person-years ranged from 828.99 [787.46, 872.72] and 554.77 [507.58, 606.35] during surgical hospitalization to 43.23 [42.14, 44.35] and 33.92 [32.58, 35.31] ≤ 365 days post-operation; and for PE, they were 529.20 [496.26, 564.33] and 281.52 [248.51, 318.91] during surgical hospitalization to 17.23 [16.55, 17.94] and 13.02 [12.21, 13.89] ≤ 365 days post-operation. These IRs decreased consistently across all RWs (mean surgical hospitalization = 3 days) in both cohorts. Stratified analyses revealed that older patients (≥66 years), males, or those with longer hospital stays (LHS), diabetes, allogenic blood transfusion, or prior medical history of DVT/PE had a higher IRs of DVT and PE in both cohorts. The LHS could be a consequence of these events. Higher IRs of DVT in both TKR and THR patients with implanted material during surgery, prior permanently implanted device, or history of ankylosing spondylitis were observed. Higher IRs of PE in black patients with TKR, and THR patients with prior permanently implanted device were also observed. Revisional surgery status revealed no substantial differences in DVT/PE in either cohort.

Conclusions: Using a large US EHR database, we show that IRs of DVT and PE in TKR/THR patients are highest during surgical hospitalization and attenuated with prolonged risk periods. Sub-populations with higher IRs of DVT and PE in TKR/THR patients were also identified. Future analyses may benefit from further confounder adjustment, effect modifier identification, medical chart review to confirm outcomes, and estimation with other databases.

507 | Validation of cancer diagnoses in electronic health Records in Catalonia: Preliminary results from the information system for research in primary care (SIDIAP)

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Background: The Information System for Research in Primary Care (SIDIAP) includes electronic health records of >6 million people living in Catalonia assigned to a primary healthcare centre of the Catalan Institute of Health. SIDIAP may be a useful tool for cancer research, but the recorded diagnoses need to be validated.

Objectives: To validate 25 types of incident cancer cases in SIDIAP using the population-based cancer registries of Girona (CRG) and Tarragona (CRT) as gold-standard and to assess the time-difference in the date of diagnosis between SIDIAP and the registries.

Methods: We performed a cross-sectional study during 2009–2015 including the SIDIAP adult population (≥18 years) of Girona and Tarragona. We identified 25 types of incident cancer cases in SIDIAP (using the registered ICD-10 codes and date of diagnosis) and compared them to those from the CRG (2009–15) and the CRT (2009–13). We used cases registered during 2005–08 to exclude prevalent cases. For each cancer type, we calculated the sensitivity, positive predictive values (PPV) and the time-difference in the date of diagnosis in SIDIAP vs. the registries.

Results: In SIDIAP, we identified 497,331 persons living in Girona and 289,187 in Tarragona in 2016. Out of 22,785 registered incident cancer cases in SIDIAP, we confirmed 9,296 (57%) cases in Girona and

4,389 (67%) in Tarragona. The sensitivity for all cancer types was 74% in Girona and 70% in Tarragona. Breast (90%), colorectal (82%), and prostate (81%) had the highest sensitivity in Girona and breast (86%) prostate (81%), and malignant skin melanoma (76%) in Tarragona. Bone (54%) and gallbladder and biliary tract (32%) had the lowest sensitivity in Girona, and head and neck (37%) and gallbladder and biliary tract (20%) in Tarragona. In both regions, trachea, bronchus, and lung (72% in Girona and 81% in Tarragona) and stomach (71% and 78%, respectively) had the highest PPVs. Most cancer diagnoses were first reported in the registries than in SIDIAP with less than two months of difference.

Conclusions: Out of 25 cancer types validated in SIDIAP using the population-based cancer registries as gold-standard, 22 had a sensitivity >60% in Girona, and 18 in Tarragona. Overall, SIDIAP reports cancer cases with less than two months of difference than the registries. Our results support the use of SIDIAP cancer diagnoses for research on most common cancer types in Catalonia. Low PPVs could be due to cases treated in centres outside the study reference area, but more research is needed to understand the potential false positive cancer diagnoses recorded in SIDIAP.

508 | Quality and completeness of diagnoses recorded in the new CPRD aurum database: Evaluation of pulmonary embolism

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Background: The first studies using what is now Clinical Practice Research Datalink (CPRD) GOLD were published around 1990. Since that time the database has been repeatedly validated, has grown and evolved to contain electronic patient records on millions of UK residents, and has been the basis for thousands of important epidemiology studies reporting on many health outcomes. CPRD is now providing data from a new medical record database, CPRD Aurum. Like CPRD GOLD, CPRD Aurum contains electronic medical record data recorded by GPs, but the data is captured using a different GP patient management software, EMIS. Evaluating the quality and completeness of this new database is important for future studies.

Objectives: To assess the quality and completeness of data present in CPRD Aurum for research purposes by evaluating presence of pulmonary embolism (PE) diagnoses recorded in CPRD Aurum compared to a gold standard data source, Hospital Episode Statistics (HES).

Methods: We identified a sample of patients in CPRD Aurum with linkage to HES data (1997–2017), a database that contains information on hospitalizations in England. We confirmed PE diagnoses recorded in CPRD Aurum using HES and report positive predictive values (PPV). We further evaluated completeness of CPRD Aurum data by identifying primary or secondary PE diagnoses in HES and report the proportion of these diagnoses also present in CPRD Aurum.

Results: Among the 50,000 patients evaluated, there were 593 patients with a PE diagnosis in CPRD Aurum, of whom 431 also had a PE diagnosis in HES (PPV = 72.7%). The proportion confirmed was higher when we restricted the analysis to patients with a PE diagnosis and concomitant anticoagulation therapy in CPRD Aurum (PPV = 76.8%). Of the 378 patients with a primary PE diagnosis in HES, 299 (79.1%) also had a PE diagnosis in CPRD Aurum, whereas of the 254 patients with a secondary PE diagnosis in HES only 132 (52.0%) had a PE diagnosis in CPRD Aurum. In patients with complicated medical conditions (e.g. cancer) or who were close to death, PE diagnoses were less likely to be recorded in both data sources. Because CPRD Aurum data are newly available, these results are preliminary.

Conclusions: This preliminary evaluation of PE recording in CPRD Aurum is reassuring and suggests that the quality and completeness of these data are promising. However, detailed assessment is underway and further discussion will be provided at ICPE. PE is a serious outcome that requires medical attention, but there are reasons that could explain differential recording between the two data resources.

509 | Use of Joinpoint regression in drug utilization research: Post-tonsillectomy codeine use in pediatrics, United States (2005–2016)

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Background: Drug utilization researchers often evaluate effects of policy or other interventions on secular trends via before and after comparisons. The change point is determined a priori based on assumptions regarding immediate change or predefined lag time. Joinpoint regression methods offer an opportunity to identify deviations in secular trends without a preconceived notion on specific break points in the data. Use of codeine in pediatric patients in absence of pharmacogenomic testing emerged as unsafe practice in the literature and was subsequently addressed in guidelines and via labeling changes. Evaluating prescribing trends using real-world data in this patient population can help explore the utility of the methodology in future drug utilization research.

Objectives: To evaluate trends of codeine prescribing in pediatric patients undergoing tonsillectomy procedures by applying joinpoint regression.

Methods: We conducted an ecological study using data from the IBM MarketScan Commercial Database 2005–2016. The study population included patients aged 2–17 undergoing tonsillectomy with and without adenoidectomy identified by ICD-9, ICD-10, and CPT procedure codes. We calculated the monthly proportion of tonsillectomy patients with a dispensing claim for codeine within 7 days of surgery. We used the NCI Joinpoint regression software v4.6 to find significant months associated with a rise or fall of codeine utilization. The joinpoints were obtained by permutation tests using Monte Carlo samples, and we

specified a maximum of 4 points for computing efficiency. We compared the obtained joinpoints and their respective 95% CI with the dates of regulatory action by the FDA on codeine products.

Results: There were 666,824 pediatric tonsillectomies in our study period. The monthly proportion of patients undergoing tonsillectomy that had a claim for codeine decreased from 41% at the start of 2005 to 4% at the end of 2016. We found four months associated with significant shifts in the trend: Aug 2008 (95% CI 03/2006, 01/2017), Feb 2009 (95% CI 05–07/2009), May 2012 (95% CI 02–09/2012), and Jul 2013 (95% CI 03–10/2013). The latter two joinpoints, which bordered the period with the largest decline, appeared soon after an FDA issued safety communication on the use of codeine in Aug 2012 and introduction of a black box warning for these products in Feb 2013.

Conclusions: We detected significant time points of shifting trends in codeine use using joinpoint regression. This method captured early reaction to emerging evidence and highlighted regulatory action as the greatest influence of shifts.

510 | Clinical evaluation of benzodiazepine and Z-drug use duration among adults with anxiety and sleep disorders in primary care

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Background: Long-term use of benzodiazepines and Z-Drugs remains an ongoing concern in the treatment of anxiety and sleep disorder. Understanding factors related to potentially inappropriate use is important for reducing adverse events.

Objectives: i) To measure the incidence of 'long-term' benzodiazepines/Z-Drug (BZD) use among a cohort of Canadian adults with anxiety and/or sleep disorders.

ii) To determine factors associated with progression to long-term BZD use.

Methods: Linked administrative data from 1996–2016 was used to conduct an incident user cohort study. Individuals were deemed eligible for the cohort if they were adults at the time of their first prescription, had an ICD-9/10 diagnosed anxiety, mood or sleep disorder and did not have co-existing seizure disorder, cancer or palliative condition. Prescription records were used at the individual level to longitudinally track duration of use and enumerate 'use' episodes. Covariates, measured at baseline, comprising demographic, socio-economic, provider and prescription level variables were analyzed in a multiple variable logistic regression model. Sensitivity analysis was used to measure variance in the estimate of 'long-term' use given the range of definitions available.

Results: i) Of 206.933 individual patients meeting the cohort criteria, only 4.5–9.6% progressed to 'long-term' use within their first treatment episode. The proportion of 'long-term use' increased to 15.6%–35.1% after all subsequent episodes for each user were accounted for in an individualized 'duration of use' average.

ii) Factors statistically associated with 'long-term' use in the first treatment episode include; being male (OR = 1.33), age $\geq$ 65 (OR = 5.15), receipt of income assistance (OR = 1.68), previous psychotropic (OR = 1.93) or opioid prescription use (OR = 1.16), high comorbidity score (OR = 1.43), high healthcare resource use score (OR = 1.46), first prescription from psychiatrist (OR = 2.11) and having the first prescription later in the study period (OR = 2.99).

Conclusions: Less than one in ten patients become 'long-term' BZD users in their first treatment episode. However, with repeated BZD treatment, between one in every 3 to 6 patients go on to become 'long-term' users in primary care. Clinicians should carefully consider baseline factors associated with progression to 'long-term' BZD use in individual patients' benefit–risk equation.

511 | Use of non-insulin diabetes medicines after insulin initiation: A retrospective cohort study

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Background: Clinical guidelines recommend that metformin be continued after insulin is initiated among patients with type 2 diabetes, yet little is known regarding how often metformin or other non-insulin diabetes medications are continued in this setting.

Objectives: Among patients with type 2 diabetes initiating insulin, to characterize rates and use patterns of six classes of non-insulin diabetes medications: biguanides (metformin), sulfonylureas, thiazolidinediones (TZDs), glucagon-like peptide 1 receptor agonists (GLP1 receptor agonists), dipeptidyl peptidase 4 inhibitors (DPP4 inhibitors), and sodium-glucose co-transporter inhibitors (SGLT2 inhibitors).

Methods: We conducted a retrospective cohort study using the 2010–2015 MarketScan Commercial Claims and Encounters data to examine 72,971 patients with type 2 diabetes aged 18–65 years old who initiated insulin and had filled a prescription for a non-insulin diabetes medication in the 90 days prior to insulin initiation. Our primary outcome was the proportion of patients refilling the various non-insulin diabetes medications during the first 90 days after insulin initiation. We also used time-to-event analysis to characterize the time to discontinuation of specific medication classes.

Results: Metformin was the most common non-insulin medication used prior to insulin initiation (*N* = 53,017, 72.7%), followed by sulfonylureas (*N* = 25,439, 34.9%) and DPP4 inhibitors (*N* = 8,540, 11.7%). More than four out of five patients (*N* = 65,902, 84.7%) refilled prescriptions for any non-insulin diabetes medications within 90 days after insulin initiation. Within that period, metformin remained the most common medication with the highest continuation rate of 84.6%, followed by SGLT2 inhibitors (81.9%) and TZDs (79.3%).

Sulfonylureas were the least likely medications to be continued (73.6% continuation) though they remained the second most common medication class used after insulin initiation. The median time to discontinuation varied by therapeutic class from the longest time to discontinuation of 26.4 months among metformin users to the shortest (3.0 months) among SGLT2 inhibitor users.

Conclusions: While metformin was commonly continued among commercially insured adults starting insulin, rates of continuation of other non-insulin diabetes medications were also high. Further studies are needed to determine the comparative effectiveness and safety of continuing insulin secretagogues and newer diabetes medications after insulin initiation.

512 | Feedback to general practitioners on inadequate statin prescriptions results in a lower prevalence of statin use and no change in the incidence of Ischaemic heart disease or stroke: An interrupted time series analysis

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Background: There is controversial evidence on the risk–benefit of statin therapy in primary prevention. The Catalan Health Institute launched a feedback programme for affiliated general practitioners to discourage statin primary prevention therapy in patients with low estimated risk.

Objectives: we aimed to test the impact of the feedback programme on the use of statins in low (<5%) vs high (>10%) cardiovascular risk patients, and on their incidence of vascular events.

Methods: patients registered in the SIDIAP database in the study period and with a 10-year REGICOR cardiovascular risk, a re-calibrated equation based on the Framingham score, recorded were included. SIDIAP includes primary care records for >6 million people (>80% of the population) from Catalonia, linked to pharmacy dispensations. Previously validated ICD10 codes were used to identify ischemic heart (IHD) and cerebro-vascular (CVD) events separately; ATC codes were used to identify statin dispensations. Monthly prevalence of statins use and monthly incidence rates (IR) of IHD and CVD were estimated for the period 1/1/2013 to 31/12/2018 for people aged 35 to 74 years old. ARIMA models were used to estimate the impact of the feedback programme (established in May 2014, with a 12-month lag) on the secular trends of statin use, IHD, and CVD.

Results: A median of 755,518 low risk subjects and 36,674 with a high risk were included. A median of 1,800,095 and 220,695 were excluded due to lack of data on estimated risk or a previous cardiovascular history. The prevalence of statins in low risk patients was already in decline before the intervention but declined further immediately after the feedback programme ($p < 0.001$), and continued to decline in the following years ($p < 0.001$) shifting from a pre-intervention mean prevalence of 23% to 17% post-intervention; pre-existing slow increases in IHD and CVD rates did not change after the intervention. The prevalence of statins use in high risk patients was stable at 45% before the feedback programme, followed by a continued decline in use in the following 4 years ($p < 0.001$) to a 43% mean prevalence after; no change in the secular trends of either IHD or CVD were observed.

Conclusions: Electronic feedback to general practitioners resulted in a progressive reduction in the prevalence of use in low risk patients (inappropriate prescription), and a progressive decrease in use in high risk subjects. No change in the secular trends of IHD or CVD were observed in neither of low or high-risk patients.

513 | Pregabalin use outside subsidy restrictions in Australia

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Background: In March 2013, pregabalin was subsidized on Australia's Pharmaceutical Benefits Scheme (PBS) for neuropathic pain after treatment failure with other medicines. Since its public subsidy, pregabalin use skyrocketed, raising questions about the appropriateness of its use.

Objectives: We detail patterns of pregabalin initiation, discontinuation, and consistency with PBS subsidy restrictions.

Methods: We performed a retrospective cohort study of people initiating pregabalin using dispensing claims for a 10% sample of Australians (2013–2018). We examined patterns of initiation including dispensing of other prescribed analgesics prior to initiation, and treatment discontinuation in the first year. We used logistic regression and Cox regression to identify predictors of initiation without prior use of analgesics, and time to discontinuation, respectively.

Results: During our study period 142,910 people initiated pregabalin (median age 61 years, 56.8% female). Initiation was constant over time, from 25,604 in 2013/14 to 24,632 in 2017/18. In the 180 days prior to pregabalin initiation, dispensing of other first-line medicines for neuropathic pain was low: tricyclic antidepressants (12.2%), SNRIs (8.5%), and gabapentin (0.4%). However, dispensing of other prescribed analgesics was common: weak opioids (30.6%), strong opioids (28.3%), and NSAIDs (30.4%). Overall, 81.5% (n = 107,147) had not been dispensed a first-line treatment, and 35.8% (n = 47,002) had not been dispensed any analgesic, which increased from 29.2% in 2013/14 to 40.3% in 2017/18. Predictors of initiation without prior dispensing of analgesics included: male sex (adjusted OR (aOR) = 1.17, 95% CI 1.14–1.19), and both age < 45 years (vs 65–84 years)

(aOR = 1.12, 95% CI 1.09–1.16) and ≥ 85 years (aOR = 1.11, 95% CI 1.06–1.17). In the year after initiation, 83.1% discontinued, with 46.3% discontinuing after the first dispensing. Predictors of discontinuation were younger age, initiating in 2016/17 (vs 2013/14) (aHR = 1.23, 95% CI 1.21–1.26), no prior dispensing of neuropathic pain medicines (aHR = 1.32, 95% CI 1.30–1.34) or other prescribed analgesics (aHR = 1.19, 95% CI 1.18–1.21), and initiating on 75 mg (vs 300 mg) (aHR = 1.42, 95% CI 1.33–1.53).

Conclusions: Few people initiating pregabalin had used recommended first-line neuropathic pain medicines, and more than one third had not been dispensed any PBS-subsidized analgesics. This suggests that prescribers are not adhering to subsidy restrictions, which is increasing over time. Further, high rates of discontinuation may indicate poor tolerability or use in patients where the medication is not effective or appropriate.

514 | Impact of tramadol classification on the prescribing of other pain medicines commonly related to drug-misuse deaths in UK

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Background: Tramadol was classified as a Controlled Substance in the United Kingdom (UK) in June 2014 due to increased mortality related to tramadol. Since then, there has been a decrease in tramadol prescribing, but a concern was raised about a potential substitution effect between tramadol and other pain medicines which are also associated with drug-misuse deaths (DMDs).

Objectives: This study aimed to evaluate the impact of tramadol classification on the utilization of other pain medicines commonly related to DMDs in the UK.

Methods: A cross-sectional study was conducted by using practice-level dispensing data from the UK National Health Service Digital and the estimated population size from the Office for National Statistics between August 2010 and July 2017. Primary care practices prescribing pain medicines commonly related to DMDs during the study period were included. Pain medicines were categorized into opioids (excluding tramadol), benzodiazepines (BZDs), z-drugs, antipsychotics, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and gabapentinoids (GABAs). Monthly utilization was measured as the number of Defined Daily Doses/1000 registrants/month for each category of medicines. Interrupted time-series analysis was used to evaluate the impact of the intervention (tramadol classification) on the utilization of each category of medicines after adjusting autocorrelation by an auto-regressive integrated moving average model.

Results: After the intervention, the trend of increasing (β1: 2.4, $p < 0.001$) monthly opioids utilization did not change, but the trend of increasing monthly utilization significantly elevated for SSRIs (β3: 3.2, $p = 0.004$) and SNRIs (β3: 0.18, $p = 0.025$). Furthermore, the decreasing trend of monthly BZDs utilization (β1: −1.6, $p < 0.001$) significantly raised (β3: 0.49, $p < 0.001$) after the intervention, while increasing trend of monthly GABAs utilization (β1: 2.9, $p < 0.001$) did not change and utilization consistently escalated.

Conclusions: After tramadol classification, the increasing trend of utilization of SSRIs, SNRIs and BZDs implies a potential substitution but the increasing prescribing of GABAs in England is not related to tramadol classification. Further studies should apply individual patient data to clarify the switching between tramadol and these medicines and evaluate the impacts of this substitution on DMDs in the UK.

515 | Mortality and hospitalization following initiation of Sacubitril/valsartan in the Medicare population

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Background: In 2015, sacubitril/valsartan received approval as a treatment for chronic heart failure with reduced ejection fraction (HFrEF). Few population-based studies have characterized early users of the drug.

Objectives: To describe a population-based cohort of patients initiating sacubitril/valsartan in terms of their baseline characteristics and subsequent clinical outcomes.

Methods: This study used claims data from a 20% general Medicare sample for patients with Medicare Parts A/B (fee-for-service) and Part D (prescription drug) coverage. We included all patients initiating sacubitril/valsartan in 2015–2016, with the first prescription fill date defined as the index date. We used claims from 2007–2016 to identify baseline covariates and required patients to have at least one year of fee-for-service coverage prior to the index date. We estimated the rates of hospitalization with HF as the primary discharge diagnosis (HF hospitalization), cardiovascular death, and all-cause death through the end of follow-up. The underlying cause of death was determined via linkage with the National Death Index.

Results: 4,111 patients initiating sacubitril/valsartan were included in the study, with mean age 72.6 (range: 28–97) years, 33% female, and 80% white. Patients had a high burden of comorbidities, including histories of hypertension (98%), diabetes (61%), atrial fibrillation (60%), myocardial infarction (54%), and cerebrovascular disease (43%). Patients were first diagnosed with HF an average of 5 years before the index date, and 22% had a prior HF hospitalization. The most common starting dose of sacubitril/valsartan was 24/26 mg (63%), followed by 49/51 mg (29%) and 97/103 mg (8%). Over a mean follow-up of 5.7 months, patients had an average of 4 fills of sacubitril/valsartan (including the index fill), constituting an average drug supply of 5 months. Treatment interruption (discontinuation or a gap

between prescriptions of more than 45 days) occurred in 25% of patients. The rates per 100 person-years of clinical outcomes were 16.8 (95% confidence interval [CI] 15.0, 18.8) for the composite of cardiovascular death and HF hospitalization, 7.9 (95% CI 6.8, 9.3) for cardiovascular death, 10.2 (95% CI 8.9, 11.8) for HF hospitalization, and 11.9 (95% CI 10.5, 13.5) for all-cause death.

Conclusions: In this study, sacubitril/valsartan users had a high baseline comorbidity burden and experienced a high rate of mortality and hospitalization, as would be expected for patients with chronic HF. Future work should assess the effectiveness and safety of sacubitril/valsartan in population-based studies.

516 | Negative control outcomes to control for unmeasured confounding in device safety research: A clinical example

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Background: Negative control outcomes have been proposed to adjust for uncontrolled confounding in drug safety research. There is seldom experience on their use in medical device epidemiology.

Objectives: We aimed to demonstrate the use of negative control outcome calibration after propensity score matching. We tested this in the study of post-operative infections following partial (PKR) compared to total knee replacement (TKR).

Methods: -Design: Propensity score matched multi-database parallel cohorts. -Setting and participants: Data was obtained from 4 US claims (IBM MarketScan® Commercial Database (CCAE), IBM MarketScan® Medicare Supplemental Database (MDCR), Optum ® de-identified Clinformatics ® Datamart, Extended - Date of Death (Optum) and PharMetrics) databases. All these were mapped to the OMOP common data model. Subjects undergoing PKR or TKR in any of these databases from 2005 onwards at age 40 or older were included. -Exposures: PKR and TKR were compared. -Outcomes: post-operative infections of the surgical area or the prosthesis within 60 days post-surgery were considered. -Statistical analysis: Propensity score matching with a 0.02 SD caliper width was used to minimize confounding. Cox regression models were fitted to calculate Hazard Ratio (HR) and 95% Confidence Intervals [95CI] for infection according to device type, using TKR as the reference group. A list of 39 negative control outcomes was pre-specified and results used to calibrate the obtained HRs. All analyses were run separately for each of the databases [Schuemie MJ et al. Stats Med 2014] using a common R package.

Results: Propensity score matching worked to reduce confounding for all observed variables below the pre-specified threshold of a standardized difference of <0.1. In CCAE, 96/7,779 (1.23%) PKR and 845/58,290 (1.45%) TKR subjects had the outcome of interest; compared to 58/4,093 (1.42%) PKR and 613/34,836 (1.76%) TKR in MDCR; 71/5,750 (1.23%) PKR and 795/43,612 (1.82%) TKR in Optum; and 141/12,777 (1.10%) PKR and 1,638/98,516 (1.66%) in PharMetrics. Cox models in the propensity-matched cohorts suggested a consistent reduction in risk of infection with PKR, with HR [95CI] ranging from 0.66 [0.55–0.78] in PharMetrics to 0.85 [0.68–1.05] in CCAE. Calibration after negative control outcomes attenuated this and resulted in non-significant associations in any of the 4 databases, with HR ranging from 0.73 [0.45–1.24] in PharMetrics to 1.04 [0.77–1.43] in CCAE.

Conclusions: Calibration for negative control outcomes was useful to adjust for residual confounding (for unobserved variables) after propensity score matching.

517 | Tramadol analgesic use as a screening tool for Total hip arthroplasty implant survival: A population-based cohort study

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Background: The need for effective screening tools to monitor implant performance and identify poorly performing implants early has been highlighted by recent failings of metal-on-metal devices.

Objectives: To investigate whether tramadol utilization in the first year following total hip arthroplasty (THA) surgery is associated with long-term implant survival.

Methods: A retrospective observational cohort study was conducted. Data was used from the Catalan Joint Registry (RACAT) linked to primary care records and pharmacy invoice data in the SIDIAP Database (www.sidiap.org). All participants registered in both SIDIAP and RACat undergoing primary THA between 2005 and July 2012 were eligible (n = 17,034). Patients under the age of 40 and revisions in the first-year post-operation were not included. Fine & Gray models were used to investigate the association between tramadol use and implant survival adjusting for age, gender, Charlson comorbidity index, socio-economic status, cardiovascular disease, atrial fibrillation, hypertension, diabetes, depression, cancer, indication, previous fixation, fracture, BMI, alcohol, smoking. Multiple imputation by chained equations was used to adjust for missing values for the BMI, alcohol and smoking variables.

Results: 16,433/17,034 (96.5%) patients were eligible. Of these 158/16,433 (1.0%) revisions were observed after a median of 2.25 (1.22–3.74) years follow-up. Tramadol use following THA surgery was significantly associated with revision rate. Adjusted sub-hazard ratio (SHR) was 2·42 [95%CI 1.74–3.35, p < 0.001].

Conclusions: This study demonstrates an association between tramadol use within the first post-operative year following THA surgery and subsequent revision rates. Tramadol prescriptions can, through linkage to arthroplasty registries, potentially be used as an early surrogate to identify patients and implants at high risk of device failure.

518 | Long-term outcomes following mid-urethral mesh sling surgery for stress urinary incontinence

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Background: Midurethral mesh slings are the gold standard surgery for stress urinary incontinence (SUI). However, following FDA safety notifications regarding risks of vaginal mesh surgery for other indications, concerns have been raised about midurethral slings, with regulatory agencies banning or restricting this surgery in some countries. Women who undergo mesh sling procedures may need another procedure to remove the sling due to complications, such as visible mesh exposure or urinary retention, or a repeat SUI surgery for recurrent symptoms.

Objectives: To determine the long-term risk of sling removal for either mesh exposure or urinary retention and the risk of repeat SUI surgery after initial sling surgery in a U.S. based population and to identify potential predictors of these outcomes.

Methods: Using a population-based cohort of commercially insured individuals, we identified women aged 18 and older who underwent a sling procedure between January 1, 2001 and September 30, 2015. We estimated the cumulative risk (95% confidence interval [CI]) of sling removal and repeat SUI surgery annually using Kaplan–Meier survival curves and evaluated predictors of sling removal and repeat surgery using Cox proportional hazards models. Predictors included age, year of initial sling surgery, region, and other concurrent procedures for SUI.

Results: We identified 305,970 mesh sling surgeries. Median age was 53 (IQR: 45–61). The 10-year cumulative risk of sling removal was 5.5% (95%CI, 5.3–5.7). The proportion of sling removals due to mesh exposure was 59.1%, with a 10-year risk of 3.6% (95%CI, 3.5–3.8), and the proportion due to urinary retention was 37.4%, with a 10-year risk of 1.7% (95%CI, 1.6–1.8). For repeat SUI surgery, the 10-year risk was 12.9% (95%CI, 12.6–13.2). The 10-year risk of any subsequent surgery (removal or repeat SUI surgery) was 16.4% (95%CI, 16.1–16.7). Women aged 18–29 had an elevated risk for both sling revision and repeat SUI surgery compared to women over 70, with hazard ratios of 1.55 (95%CI, 1.48–1.63) and 1.66 (95%CI, 1.58–1.74), respectively.

Conclusions: In this population-based analysis, the 10-year risks of sling removal and repeat surgery were 5.5% and 12.9%, respectively. These findings are consistent with the results of previous studies reporting relatively low risk of complications following these widely used procedures, including a lower 10-year odds of repeat surgery compared to women who underwent Burch colposuspension. These and other recent findings may provide critical data for women and providers considering mesh sling surgery for SUI to support informed decisions.

519 | Machine learning for probabilistic phenotypes and exploration of complex coding patterns in large real-world healthcare databases: An applied example in conversion from minimally-invasive to open Sigmoidectomy

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Background: Conversion from minimally-invasive to open surgery is a marker of adverse clinical circumstances and an important outcome in surgical research; however, conversion codes may be unavailable or under-coded in real-world healthcare databases.

Objectives: We applied machine learning techniques to a high-dimensional US EHR dataset to develop an exploratory phenotypic predictive model of conversions in patients undergoing sigmoidectomy. We sought to identify factors that co-occur with conversion codes as candidates for inclusion in improved conversion identification algorithms for use in future research.

Methods: We extracted electronic health records from the Optum Pan-therapeutic database for patients aged≥18y undergoing inpatient sigmoidectomy between 10-01-2016—12-31-2017 (first admission = index). The outcome was defined as a documented code for conversion (ICD-10-CM = Z53.3x) during index. We constructed a high-dimensional dataset comprising demographics, individual binary indicators for every observed diagnosis, procedure, and ingredient-level medications recorded at index. We utilized regularized lasso regression to develop and internally-validate a prediction model (75%/25% split model training/testing) based on the high-dimensional dataset.

Results: The analysis included 3,386 patients, of whom 501 (14.8%) experienced conversion. In testing, the final model possessed good discriminative accuracy (area under the curve [AUC] = 0.902, 95% CI = 0.869–0.936) with poor sensitivity, but otherwise good diagnostic accuracy (at predicted probability = 0.5: specificity = 0.987, sensitivity = 0.559, ppv = 0.880, npv = 0.927). Of 12,067 covariate candidates considered for inclusion in the model, 245 were selected by lasso logistic regression. The three covariates most strongly associated with increased risk of conversion were "Inspection of Lower Intestinal Tract, Percutaneous Approach," "Accidental puncture and laceration of a genitourinary system organ or structure during a genitourinary system procedure," and "Inspection of Peritoneum, Percutaneous Endoscopic Approach"; these covariates appear to represent factors that co-occur (inspection procedures) or necessitate (accidental puncture/laceration) conversions.

Conclusions: Our findings suggest that machine learning techniques may be valuable for hypothesis-generating exploration of complex coding patterns in large healthcare databases.

520 | Application of propensity scores odds to visualize clinical equipoise for robotic assisted surgery from 2003 to 2015

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Background: Robotic assisted surgery (RAS) revolutionized surgical practice since the early 2000s. Urology and gynecology appear to be at a RAS adoption steady state in the USA. We define channeling bias as the preference for a certain surgical approach and clinical equipoise as the point of parity for RAS versus more traditional approaches for a given patient-hospital-procedure (PHP) profile. Given the diversity of possible PHP profiles, characterizing the evolution of channeling bias and clinical equipoise over time remains a challenge.

Objectives: To evaluate a method for visualizing channeling bias of PHP profiles receiving robotic versus standard surgery.

Methods: This was a retrospective population-based cohort study utilizing the Premier Healthcare Database. Individuals >18 years old who underwent prostate (*n* = 199,704) or uterus (n = 1,476,595) surgery between July 2001 and July 2015 were included. RAS utilization was identified by either ICD9 codes 17.4x or charge file text-search. 5 discrete adoption periods were identified using diffusion of innovations theory. Clinical equipoise occurs when the odds of a PHP profile receiving RAS compared to other approaches is 1:1. We use propensity scores (PS) due to its unidimensional simplicity and population comparability. Kernel densities of the PS distributions were log-scaled to number of persons to better visualize and interpret population shifts. The ratio of these two distributions is termed PS-odds.

Results: The 5 discrete adoption periods for prostate and uterus respectively were 2002-'03, '03-'05, '05-'07, '07-'11, '11-'15 and 2001-'06,'06-'08,'08-'10,'10-'12, and'12-'15. For the first 3 periods, the PS-odds favored the non-RAS groups by a mean of 59.6, 4.21, 3.00 and 64.1, 26.7, 4.32 odds for prostate and uterus, respectively. Only in the last 2 periods did clinical equipoise begin to occur for select PHP profiles. Mean PS-odds still favored non-RAS in these last 2 periods (1.98, 2.48 prostate and 2.67, 2.19 uterus). Splitting by PS-odds favoring RAS versus non-RAS, the mean PS-odds for prostate were: .433 RAS vs 3.71 non-RAS in period 4 and .498 vs 5.14 in period 5; for uterus: .555 RAS vs 3.58 non-RAS in period 4 and.451 vs 4.82 in period 5.

Conclusions: Patient propensity-score odds is a useful tool for measuring channeling bias and its evolution in the adoption of new surgical technologies. In the example of robotic assisted surgery, clinical equipoise first occurred from 2007-'11 in prostate and 2010-'12 in uterus. Compared to uterus, prostate RAS procedures appear to have more channeling towards specific patient hospital profiles.

521 | Does operating room time affect the rate of superficial, deep and organ system post-surgical infections in Total knee replacement?

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Background: Post-surgical infections are significantly associated with postoperative morbidity and mortality. Prolonged operating room time may increase the risk of infections due to increased surgical wound exposure and contamination, increased damage to tissue and bleeding. However, there is very limited data on relationship between operating room time and type of post-surgical infections (superficial, deep and organ system) after total knee replacement (TKR).

Objectives: To evaluate the association between operating room time and types of post-surgical infections (superficial, deep and organ system) after unilateral TKR.

Methods: This was a retrospective observational cohort study. Through data partnership with Mercy-Technology-Services, patients who underwent unilateral TKR surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. The main independent variable was operating room time for TKR. The dependent variable was absence or presence of post-surgical infection by types, superficial, deep or organ system within 3 months of TKR. A Multinomial logistic regression was constructed controlling for patient demographic and clinical characteristics. Odds ratios (OR) along with 95% confidence intervals (95% CI) and p-values were reported.

Results: A total of 21,584 patients with mean (SD) age 66.8 (9.9) years, 61.8% females and mean (SD) Elixhauser score 2.8 (1.9) were included in the analysis. Of these, 1.2% patients developed superficial infections, 0.60% patients developed deep infections and 5.19% patients developed any organ system infections within 3 months after TKR. The adjusted multinomial logistic regression showed that with a 10-minute increase in operating room time the odds for superficial infection increased by 9% (OR, 1.09, 95% CI, 1.06–1.12), the odds for deep infections increased by 10% (OR, 1.10, 95% CI, 1.06–1.12) and the odds for any organ system infections increased by 5% (OR, 1.05, 95%CI, 1.03–1.07) (all $P < 0.0001$) as compared to patients without infections.

Conclusions: This study found that increase in operating room time was associated with an increased risk of superficial, deep and any organ system infections after TKR. The study suggests that efforts to lower the operating room time, thereby reducing the length of time the surgical wound is open would reduce the rates of post-surgical infections.

522 | Utilization of intrauterine device in Europe - prescription patterns in routine medical practice

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Background: A variety of intrauterine devices are available on the European market, including devices of different shapes, sizes, composition and mechanism. Guidelines identifying the appropriate intrauterine device (IUD) for an individual, only exists for mechanism of action (i.e. hormonal vs. copper).

Objectives: To describe prescription patterns of IUDs in routine medical practice in Europe and to identify women's characteristics that may influence the choice of IUD.

Methods: Analyses were based on the multinational, prospective, non-interventional "European Active Surveillance Study on LCS12" (EURAS-LCS12). Participants were recruited from eight European countries - Germany, Austria, United Kingdom, France, Poland, Finland and Sweden via health care providers. The association between women's baseline characteristics and IUD characteristics were analyzed by multiple linear and logistic regression models.

Results: Approximately 48,000 women were included in the analysis. Prescription patterns differed by country. Across all countries observed, parity was consistently identified as having an influencing effect on the choice of IUD characteristics. Parous women used larger copper IUDs with a longer 'duration of use'and larger copper surface area, compared to nulliparous women. Omega- and Y-shaped devices and additional coatings of gold and silver, respectively were also more likely to be used in this subgroup. Nulliparous women more frequently used copper sleeves or -beads. Other influencing factors for some IUD characteristics were age, education, monthly household income, previous use of hormonal contraceptives and intrauterine devices. Although trends in prescription pattern could be observed, there are only a few hormonal intrauterine systems (IUSs) currently marketed having similar characteristics. Therefore, trends could not be clearly differentiated.

Conclusions: Parity of women is consistently an influencing factor for the choice of copper IUD and hormonal IUS characteristics in all observed European countries.

523 | Administrative burden of the Brazilian rule that contributes to Price transparency in the medical device market

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Background: The lack of transparency in the market is one of the main factors for the great variation in prices of medical devices. In Brazil, the Brazilian Health Regulatory Agency (Anvisa) published a rule (RDC No. 185/2006) with the purpose of reducing the asymmetry of information on prices of strategic medical devices for the public health system. The prices are declared by the companies and are published in a dashboard on the Anvisa website.

Objectives: The aim of this study was to estimate the administrative burden of the RDC No. 185/2006 imposed on companies of information and reporting obligations.

Methods: It was used the Standard Cost Model to measure the administrative burden of information and reporting obligations requested by RDC No. 185/2006 and sent to Anvisa in the period from 2014 to 2017. Nine companies were contacted to respond to the instrument of data collection. The basic parameters used in this measurement were: i) price; ii) time; and iii) quantity. We used the Shapiro–Wilk test to evaluate if the sample data presented a normal distribution and the Grubbs test was performed to verify the presence of outlier. The final estimate of the administrative burden is presented in annual monetary value in dollars.

Results: Seven companies participated in the study, representing 10.4% of 67 who submitted 651 reports of economic information on medical devices to Anvisa in the period from 2014 to 2017. The data presented a normal distribution (W = 0.9655; p-value = 0.8643) and according to the Grubbs test the extreme observations of the sample were not considered discrepant values. Thirteen information obligations were identified in the rule, resulting in an estimated average annual administrative burden of $ 315,202.17. Companies spend more resources to comply with the following information obligations: (i) Familiarization with the rule; (ii) Price of the medical device practiced in other countries; and (iii) List of substitute medical devices accompanied by their respective prices.

Conclusions: This is a pioneer study assessing administrative burden of the Brazilian rule that contributes to price transparency in the medical device market. The results should be considered in a future revision of the RDC No.185/2006, with the purpose of reducing the administrative burden for companies, if the information obligations are not essential to minimize the problem of asymmetry of information in the Brazilian market.

524 | Validation of algorithms for identifying pulmonary hypertension patients using diagnostic predictive modeling in large claims databases

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Background: Pulmonary hypertension (PH) is a progressive fatal disease with multiple etiologies. There is no consensus on its incidence

and prevalence. Claims databases provide potential for real-world study of PH, but identifying PH patients based on administrative codes (ICD-9/10 and others) is challenging.

Objectives: To test a series of algorithms for identifying PH patients in claims databases, using the PheValuator, a diagnostic predictive modeling tool.

Methods: We used 4 US administrative claims databases: Optum© De-Identified Clinformatics® Data Mart Database, IBM® MarketScan® Multi-State Medicaid, Medicare Supplemental Beneficiaries, and Commercial Claims and Encounters (data from 2010–17). Using PheValuator in each database, we developed a diagnostic predictive model for PH, which was applied to 2 million random subjects to estimate the probability of each subject being a PH case or non-case. These probabilities were then used to validate several PH algorithms for patient identification. The tested algorithms included 1) ≥1 occurrence of a PH diagnosis code in the subject's record [≥1DX], 2) ≥1 occurrence of a PH diagnosis in a hospital inpatient setting [≥1DX-IP], 3) a procedure code for right heart catheterization or echocardiography (RHC/Echo) followed by a PH diagnosis [RHC/Echo +DX], and 4) a PH diagnosis followed by a RHC or Echo and another PH diagnosis [DX + RHC/Echo+DX].

Results: The proportion of patients identified as having PH was higher in retired subjects, with variations by PH algorithm. The algorithm [≥1DX] yielded an average proportion of 1.64% across the databases (range: 0.25%–3.80%), showed the lowest positive predictive value (PPV) (average: 83.4%, range: 74.3–92.5%) but highest sensitivity (average: 99.8%, range: 99.7–99.9%). The most complex algorithm that requires PH diagnoses before and after diagnostic test, [DX + RHC/Echo+DX], yielded an average proportion of 0.14% (range: 0.02%–0.35%), showed highest PPVs (average: 91.4%, range: 83.6–96.4%) but lowest sensitivities (average: 9.2%, range: 8.6–10.3%). The performance characteristics of other algorithms fall between these extremes. Specificities were high for all algorithms (>99%).

Conclusions: All the tested algorithms identified PH patients with high specificity, but sensitivity and PPV varied widely. While sensitivity substantially decreased with algorithm complexity, PPV tended to increase. Model-based tools like the PheValuator can help evaluate and prioritize algorithms for PH patient identification in claims databases to meet different research purposes.

525 | Incidence of systemic sclerosis. An epidemiological study in a large insured population in the US

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Background: Systemic Sclerosis (SSc), also called scleroderma, is a very rare, chronic autoimmune disease, which can affect the skin, as well as internal organs. Incidence estimates vary widely, which could be due to the rarity of the disease, the wide range of possible symptoms, different disease definitions used as well as geographical variation.

Objectives: To estimate the contemporary incidence of SSc, using a large US-based claims database.

Methods: We conducted a retrospective cohort study in the IBM Watson Health MarketScan Commercial Claims and Encounters Database, containing data from over 50 million patients from over 150 large employers geographically distributed throughout the US. Study period was 01. Jan 2010 until 31. Dec 2015. Following manual review of electronic patient profiles from a sample of patients with SSc in MarketScan, cases of SSc were defined using the following inclusion criteria based on the ICD codes:

-Raynauds Syndrome and two SSc outpatient diagnosis (at least 30 days apart) or -Three SSc outpatient diagnoses (two of these diagnoses should be at least 30 days apart) or-One SSc inpatient diagnosis plus one SSc outpatient diagnosis (on different dates).

Yearly incidence estimates and 95% confidence intervals were calculated for each calendar year from 2010 until 2015. Incident cases were required to have no recorded claim of SSc any time before the entry date.

Results: Overall 4782 incident cases of SSc were identified over the study period. Incidence rates per 100,000 person-years (95% C.I.) decreased from 4.49 (4.19–4.80) in 2010 to 2.73 (2.48–2.97) in 2015. In the adult population (>18 years) incidence rates in females decreased from 9.13 (8.46–9.80) to 5.52 (4.99–6.06) and in males from 1.38 (1.10–1.65) to 0.83 (0.61–1.04) over the same time-period. Results for the pediatric population have been published previously (Michel A et al, *Arthritis & Rheumatology*, *2018*, *70(S9):1576–1577*).

Conclusions: Incidence estimates of SSc in the MarketScan database are higher than previously reported from field studies in the USA, but in the same range as reported from another claims database in the USA (Furst et al. J Rheumatol 2012;39:784–6). A conservative case definition has been used in our study, since SSc is a complex disease often requiring considerable time to be diagnosed. However, this case definition may have led to the decrease in incidence seen over the study time period, since patients diagnosed at the end of the time window had less opportunity to fulfill the definition compared to those diagnosed during the first years. Such artifacts need to be considered in database studies of similar conditions.

526 | Incidence of Vaso-occlusive crisis and setting of Care in Patients with sickle cell disease from 2013 through 2017 in the United States

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Background: Despite an evolution in the care of patients with Sickle Cell Disease (SCD), the incidence rate of vaso-occlusive crisis (VOC) in patients with SCD has not been estimated with recent data. The availability of large insurance claims and Electronic Health Records (EHRs) data allows for a rapid reassessment of VOC in these patients.

Objectives: 1. Estimate the recent incidence rate of VOCs in patients with SCD in large US insurance claims and EHR databases. 2. Examine distribution of incident VOC events according to the setting of care.
Methods:
Design: Patients were followed longitudinally from their diagnosis of SCD to the end of the study period, loss of enrollment, or a VOC event.
Setting: SCD patients were identified in 3 US databases: the (1) Truven Health Market Scan® Multistate Medicaid database, the (2) Optum EHR, and (3) the Optum claims-based Clinformatics® Data Mart from 2013 through 2017. These databases were selected because of the high completeness of their health records and the inclusion of the Medicaid data in the Truven database.
Exposures: Follow up began at the first of 2 diagnoses of SCD, which were defined by diagnostic code, and a 30 day enrollment period where patients were free of a VOC diagnosis.
Outcome: VOC events were were defined as a first diagnostic code for a SCD crisis following the first qualifying SCD diagnosis. Treatment setting included any hospital inpatient admission, emergency department visit, or outpatient clinic visit that started within the 7 days following the incident VOC event.
Statistical Analysis: The incident rate of VOC events and proportions of patients in each setting of care was estimated. Analyses were conducted with Safety Works® V.6.5.0 and R V.3.5.0.
Results: VOC incidence rates were 0.64 per person*year (95% Confidence Interval [CI]: 0.63, 0.66) in the Truven-Medicaid data, 0.49 per person*year (95% CI: 0.47, 0.51) in Optum Claims, and 0.32 person*year (95% CI: 0.31, 0.33) in the Optum EHR data. The proportion of patients receiving any care in the outpatient setting following the VOC ranged from 48.5% to 68.2%.
Conclusions: In these recent data, the incidence of VOC ranged from 0.32 to 0.64 per person*year which was lower than the last comparable estimate of 0.8 pain episodes per person*year in data from 1979 to 1988. Treatment in outpatient clinics shortly after the VOC was common and warrants further examination. These results provide a much needed contemporary perspective on VOC incidence and treatment, as well as, highlighting the need for further assessments of the generalizability of these estimated across multiple data sources.

527 | The use of real-world data in health technology assessment of medications for rare diseases

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Background: Challenges exist when assessing the risk and benefit of new therapy for rare diseases: small populations make assessing safety and efficacy in controlled trials difficult, idiosyncratic presentations are frequent, and collecting rigorous comparative data is costly. Both health services researchers and decision makers are advocating the consideration of real-world data (RWD) - data derived from sources such as electronic health records, disease registries, and claims databases - in the health technology assessment (HTA) of medications. However, how such data are being presently used for is unclear, as is whether their inclusion impacts decision-making.
Objectives: To characterize the use of RWD in HTA decision-making for medications for rare diseases in the United Kingdom (UK), and explore whether its inclusion was associated with favorable HTA recommendations.
Methods: All rare diseases with a prevalence of 10 to 50 per 100,000 were identified from Orphanet. Those with published National Institute for Health and Care Excellent (NICE) technical appraisals for medications within the last 10 years were selected for review, data extraction, and analysis. From the published appraisals, the proportion including RWD was assessed, types of RWD submitted were classified, and whether submissions with RWD received favorable recommendations was tabulated. RWD were also classified according to whether they provided support for clinical effectiveness, cost effectiveness, safety and tolerability.
Results: Twenty-one of 205 rare diseases (10%) had ≥1 published appraisal in NICE over 10 years, corresponding to 62 individual technology appraisals (Jan 2019). Overall, 23 (40%) submissions included RWD; they were included in submissions for 40% of recommended products and 7% of those not recommended. Types of RWD were most frequently (75%) observational studies (for non-comparative evidence of clinical effectiveness), with a few preference or quality-of-life studies (contributing to cost-effectiveness evidence). Among the published appraisals using RWD, almost all (96%) had a favorable recommendation.
Conclusions: Among HTA submissions for medications for rare diseases, RWD remain relatively infrequent; most often providing non-comparative evidence of the effectiveness of existing therapies. However, among published appraisals where RWD were included, almost all submissions had a favorable recommendation. While these results suggest that RWD are becoming more frequent in NICE submissions, their incorporation in other HTA submissions, and how the use of these data will change over time, remains unclear.

528 | Identification of inherited metabolic disorders using temporal data and recurrent neural network models

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Background: Inherited metabolic disorders are often left undiagnosed due to either a lack of or ineffective newborn screening. Applying deep learning techniques to electronic health records (EHR) can help identify patients with these rare genetic disorders. Patients may not

show symptoms for years to decades after birth and clinicians often do not have experience with the rare disease to recognize or even consider the disorder.

Objectives: We present different classification approaches, including a novel approach that we developed for identification of a rare inherited metabolic disorder - Hereditary Hemochromatosis.

Methods: For this analysis, we used the IBM MarketScan® Commercial Claims database that included patients enrolled from 2006 to 2016. The IBM MarketScan® database contains administrative claims in the United States for commercially insured working-age adults and their dependents. The database encompasses the full continuum of care across settings with longitudinal tracking at the patient level. We applied three approaches to classify patients: one hot-encoded data, sequential diagnosis data, sequential diagnosis data along time difference between the diagnosis. Finally, we built a novel model to predict the presence of Hereditary Hemochromatosis a year before the clinical diagnosis.

Results: We identified 9,926 patients diagnosed with Hereditary Hemochromatosis. Patients had to have an outpatient encounter with an ICD9/10 primary diagnosis code for Hereditary Hemochromatosis. We randomly selected an equal number of patients from the general population to include in the dataset as controls. Data were used from the beginning of enrollment to one year prior to diagnosis or index data. The final feature set included over 28,000 diagnosis and procedure codes. The model AUCs ranged from 0.817 for the k-nearest neighbor model to 0.90 for our novel model approach which included features for event sequence and timing.

Conclusions: In our model, we mimic the clinician's differential diagnosis approach by implementing a RNN framework that incorporates the timing and sequence of events. This approach provided the best AUC and we believe could be generalized to other rare disease.

529 | Prevalence of Friedreich ataxia in the United States: Analysis of two large US insurance claims databases

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Background: Friedreich ataxia (FRDA) is a rare autosomal recessive inherited disorder that progressively causes damage to the nervous system, and in many cases, is associated with scoliosis, heart disease, and diabetes. Although several epidemiological studies have been conducted in European countries suggesting the prevalence ranged from 0.1 to 5 per 100,000, no such study has been conducted in the United States (US).

Objectives: To estimate the prevalence of FRDA and describe patient characteristics in the US using two large nationwide administrative claims databases.

Methods: A retrospective cross-sectional study was conducted using two US administrative claims databases separately: 1) Truven Health MarketScan® Research Database and 2) Optum Clinformatics® Data Mart Database. 334.0, a specific ICD-9-CM code, was used to identify FRDA cases. Considering FRDA is a life-long disease with no cure, the disease prevalence was calculated by dividing the numbers of patients who had at least two diagnoses of FRDA on separate dates before or on December 31, 2014, by the total numbers of patients in the database on December 31, 2014. Only patients who had continuous health plan enrollment throughout 2014 were included. Descriptive analyses were used to summarize the demographics for the patients with FRDA.

Results: In the Truven MarketScan analysis, 444 patients diagnosed with FRDA were identified from the 27,632,078 enrollees. The crude prevalence of FRDA in 2014 was estimated as 1.6 per 100,000 persons (95% confidence interval [CI]: 1.46–1.76). Of the FRDA patients, 52.7% were female (n = 234) and the mean age was 49.0 years in 2014 (standard deviation [SD]: 23.2). In the Optum analysis, 317 patients diagnosed with FRDA were identified from the 9,768,738 enrollees. The crude prevalence in 2014 was 3.3 per 100,000 persons (95% CI: 2.9–3.6). The FRDA patients identified from the Optum database included 183 female patients (57.7%), and the average age was 60.3 years (SD: 21.0) in 2014.

Conclusions: The prevalence of FRDA among privately insured patients ranged from 1.6 to 3.3 per 100,000 in the US in 2014. The prevalence of FRDA calculated using the large US claims databases was relatively higher than most estimates previously reported in Europe. FRDA patients included in this study also included more elderly patients. These differences may result from geographic differences in disease prevalence, measurement errors in the claims database, or improved disease diagnosis and management in the US.

530 | Clinical manifestation of adult onset Still's disease using administrative claims database

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Background: Adult Onset Still's Disease (AOSD) is a rare inflammatory disorder of unclear clinical manifestation. The U.S. Centers for Medicare & Medicaid Services (CMS), requires the use of an ICD-10-CM code such as M06.1 to file reimbursement claims with a date of service on or after October 1, 2015.

Objectives: This exploratory study is to describe a cohort of AOSD patients by utilizing large retrospective insurance claims' data based on the adapted Yamaguchi criteria.

Methods: We used data from the Truven Claims and Encounters database, from January 1, 2009 to December 31, 2017. This study analyzed complete longitudinal records of inpatient and outpatient services and prescription drug claims with associated billing codes from ICD9/ICD10, Current Procedural Terminology (CPT) codes, and National Drug Codes (NDC). The cohort is defined as patients aged 18 or older with one or more diagnostic codes for AOSD (M06.1). For the adapted Yamaguchi criteria, this study diagnoses, if 4 or more

criteria are met with 2 or more being major criteria. Baseline data includes patient demographics (age, gender), duration of follow-up, and Charlson Comorbidity Index (CCI) scores. In addition, cumulative data was captured based on major AOSD treatment categories including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), non-biological disease-modifying antirheumatic drugs (nbDMARDs), immunosuppressants, IL-1/IL-1R blockers, anti-TNFs, and non-TNF bDMARDs In addition, we included ferritin, C-reactive protein, erythrocyte sedimentation rate, and bone biopsy. Major complications such as severe infection, macrophage activation syndrome (MAS), acute respiratory distress syndrome (ARDS), interstitial lung disease (ILD) were also measured. Descriptive statistics are calculated with means and standard deviations or medians as appropriate.

Results: After we applied a 6 month washout period and more than 30 days of follow-up criteria, we identified 517 AOSD patients who had M06.1. The mean age was 46.31 (std = 14.72) with female predominance (60.4%) and a mean CCI of 1.27. At baseline, the major clinical manifestations include fever (16.6%), arthritis (24%), rash (13.5%), sore throat (10.1%), lymphadenopathy (3.1%), and hepatomegaly (1.6%). During the study period, we found that therapeutic markers had increased by 2% in comparison to the baseline data. Interestingly, we found that only 7.4% of the AOSD cohort met the adapted Yamaguchi criteria.

Conclusions: Existing diagnostic criteria is not comprehensive so adding procedural and drug codes could improve the accuracy of AOSD cohorts in claims research.

531 | Prediction model for identifying patients with lipodystrophy in electronic health records

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Background: Lipodystrophy is a rare disorder that is often difficult to diagnose or undetected.

Objectives: The objective of this study was to develop a prediction model to assist general practitioners (GP) to identify patients with lipodystrophy based on electronic health records (EHR).

Methods: EHR from the GP Database of the PHARMO Database Network were obtained for unsupervised feature learning and to evaluate predictive performance of the model; 91 patients with a GP note that included the word 'lipodystrophy', 200 randomly selected patients and 100 patients with a clinical presentation similar to lipodystrophy patients (anorexia nervosa, thyrotoxicosis or Cushing's syndrome) were included. The model was deployed in two steps. First, a simple filter (predefined database queries) was applied to the complete GP Database to identify patients whose records exhibit two attributes ('filtered EHR'): conditions common in obese patients presenting in a patient with healthy/moderate BMI; diagnosis codes suggesting possible confusion on the part of examining clinicians. In the second step the prediction model was applied to all filtered EHR, yielding the predicted probability that each of these patients has lipodystrophy. A threshold of 65% predicted probability for the cut-off was used, based on confidence of the model and natural breakpoint in the probabilities. Model performance was evaluated using prediction accuracy and area under the receiver operator characteristic curve (AUC).

Results: The model achieved an accuracy of 90.8% and AUC of 93.0%. The model identified 36 patients with a predicted probability of lipodystrophy above the threshold of 65% and of these, 20 patients were identified as especially promising through outlier analysis. Of these 20 patients, four patients were identified as 'likely lipodystrophy', ten as 'possible lipodystrophy' and six as '(highly) unlikely lipodystrophy'.

Conclusions: The results show that the prediction model, learned through lipodystrophy-related GP records, was able to identify high potential lipodystrophy candidates using EHR.

532 | Gender differences in the Management of Chronic Obstructive Pulmonary Disease: Effect of a clinical audit in a Sicilian general practice setting

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Background: COPD is considered a predominantly male disease, but recent studies reported increasing diagnoses in women. Gender differences in quality of care (QOC) of chronic obstructive pulmonary disease (COPD) have not yet been described.

Objectives: To measure gender differences among COPD patients' QOC before and after educational interventions in a general practice setting.

Methods: In this prospective cohort study COPD patients were identified from electronic medical records of 33 Sicilian general practitioners (GPs) using validated algorithms. Twelve process indicators concerning diagnosis, preventative measures and therapeutic process were developed by GPs, pneumologists and clinical pharmacologists. Educational interventions consisted of clinical audits on COPD QOC indicators at baseline, and after 12 and 24 months, plus continuous remote education, i.e. disseminating important COPD-related information through a dedicated app. Patient characteristics and QOC indicators were stratified by gender. Gender-specific baseline QOC indicators values were compared at 12 and 24 months.

Results: Of 46,326 people registered with GPs, 1,465 COPD patients (3.2%) were identified; of these, 536 (36.6%) were women. The median age (interquartile range) was 74 (66–81) and 74 (64–82) in males and in females, respectively. Hypertension was the most common comorbidity in both sexes (59.4% males; 61.4% females; p-value: <0.001); osteoporosis was more frequent in females (38.6% vs. 6.7%; p-value: <0.001). Baseline QOC indicators were more positive for men. Interesting cases include having a spirometry test anytime (64.3% males; 51.9% females; p-value: <0.001) and a recorded medical history of smoking (80.0% males; 70.0% females; p-value: <0.001). Baseline QOCs concerning low adherence to long-acting COPD therapy also favored men: 56.6% vs. 71.4% (p-value: <0.001). The gender disparity in QOC at baseline largely remained unchanged at 12 and 24 months.

Conclusions: QOC gender disparity among COPD patients was observed in a Sicilian general practice setting, with better disease management in men, even following an educational program, highlighting the need to improve recognition of gender-specific signs and symptoms and therapeutic response.

533 | Changes in persistent asthma care and outcomes from 2006 to 2016 in France

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Background: Changes in asthma care need to be documented at arrival of biotherapies.

Objectives: To characterize changes in asthma care and outcomes in patients with persistent asthma.

Methods: Repeated transversal analyses were conducted on a historical cohort using the French national claims data over 10 years. Patients aged 18–40 years with either ≥1 (any use [AU] population) or ≥ 4 yearly dispensings (high use [HU] population) of controller therapy were selected. Clinical and demographic features were characterized, and comparisons were made between 2006 and 2016 to assess temporal changes in asthma therapy, healthcare resource utilization, and outcomes.

Results: In 2016, prevalent use of controller therapy was 5.2% (AUP) and 0.8% (HUP) of the population aged 18–40 years. In the AU population, the use of long-acting β-agonists (LABA) in monotherapy, and inhaled corticosteroids (ICS) decreased (1.7 and 40.3% in 2016, respectively), whereas the use of fixed-dose combinations (FDCs) increased (56.4%). In both populations, visits to respiratory or hospital physicians and pulmonary function testing increased with time, in parallel to a decreasing number of general practitioner visits; in addition, oral corticosteroids (OCS) use, and incidence of emergency room (ER) visits increased. However, asthma hospitalizations and mortality remained low and stable in both populations.

Conclusions: Changes in persistent asthma care included replacement of ICS by FDCs, decreased use of LABAs as a monotherapy, and increased involvement of secondary care physicians. In parallel, despite stable figures for hospital admissions and mortality, overall use of OCS and incidence of ER visits have increased over the last decade.

534 | Comorbid conditions in chronic obstructive pulmonary disease patients: A retrospective analysis of a large United States electronic health record database

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Background: Chronic Obstructive Pulmonary Disease (COPD) refers to a group of progressive lung diseases that cause airflow blockage and breathing-related problems. COPD often co-exists with multiple comorbidities which impact the quality of life, and furthermore, complicates management of the disease.

Objectives: The main objective of the present study was to evaluate COPD patients, their demographics, and presence of comorbid conditions.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All visits involving adult patients (≥ 18 years) with an ICD-9/10 diagnosis for COPD between 2014 and 2017 were analyzed. Comorbid conditions were characterized by corresponding ICD9/10 diagnosis codes following a medical review of the EHR data.

Results: The study included 998,912 patients with COPD with a total of 2.7MM (45% male vs. 55% female) patient visits. It was observed that the highest percentage of COPD patients were in the age group of '>65 years' (53.1%), compared to 44.3% in the '36–65 years' age group and 2.6% in the '18–35 years' age group. Within visits where race was specified, majority were Caucasian (81.3%), followed by African-American (12.2%), Asian/Pacific Islander (0.9%), and Hispanic (0.1%). Given the major phenotypes of COPD, 17.2% of the visits had a diagnosis of chronic bronchitis, 9% had emphysema, while the majority had other forms of COPD (77.8%). The most prevalent comorbid conditions among COPD patients were depression (9.8%), pneumonia (7.8%), respiratory infections (4.3%), lung cancer (2.7%), and pulmonary hypertension (2.1%).

Conclusions: This retrospective analysis examined EHR data from a large COPD patient cohort to better understand real-world patient characteristics as well as comorbidities. Identification of these characteristics can potentially help develop new strategies to treat COPD patients.

535 | Assessment of asthma severity and patient comorbidities: A retrospective analysis of a large United States electronic health record database

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Background: Asthma is a chronic disease that affects the airways in the lungs which makes breathing difficult. Asthma attacks can range from mild intermittent to severe. Severe asthma attacks can be life-threatening, significantly impairing quality of life. Several comorbidities are associated with asthma, making it harder to control, and may influence disease management.

Objectives: The main objectives of the present study were to evaluate asthma patients by their demographics, asthma severity, and their comorbid conditions.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All inpatient visits (age $\geq$ 18 years) between 2014 and 2017 with a principal ICD9/10 diagnosis of asthma were evaluated in this study. Comorbid conditions were characterized by corresponding ICD9/10 codes.

Results: A total of 293,744 patients with asthma were identified in the database corresponding to 434,096 inpatient visits. It was observed that 70.9% of asthma patient visits were female. Half of the visits were in the '36–65 years' age group (50.4%), 29.7% in the '>65 years' age group, and 19.9% in the '18–35 years' age group. Majority of patient visits were Caucasian (63.8%), followed by African-American (25.8%). Number of patient visits with a diagnosis of mild intermittent asthma was higher as compared to those with mild persistent asthma (43.6% vs. 13.3%). Moderate persistent asthma was present in 25.2% of patient visits, while 17.9% of visits had severe persistent asthma. The most prevalent comorbid conditions among asthma patient visits were obesity (49%), followed by depression (20.2%), respiratory failure (12.2%), and pneumonia (10.8%).

Conclusions: The large database analysis provides insights into real-world evidence on the demographics, severity levels, and comorbid conditions in asthma patients. Identification of these patient characteristics can potentially help guide decision-making for new asthma treatment initiatives.

536 | Anemia and clinical outcomes in patients with severe chronic kidney disease: A Danish population-based study

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Background: Routine clinical care evidence is limited on clinical outcomes associated with anemia in patients with chronic kidney disease (CKD).

Objectives: To examine the association of anemia with risk of dialysis, adverse cardiovascular events (CVEs), hospitalization, and death in patients with severe CKD.

Methods: We linked population-based medical databases to identify all individuals with severe (stage 4 or 5) CKD (eGFR <30 mL/min/1.73m^2) in Northern Denmark from 2000 to 2016. We classified patients as non-anemic or anemic (categorized into anemia grade 1, 2, or 3+), using the lowest hemoglobin (Hgb) value in the year before study inclusion. Patients were stratified by dialysis status and followed for incident dialysis; first adverse CVE (hospitalization with myocardial infarction, unstable angina pectoris, stroke, or heart failure); all-cause acute hospitalization; and all-cause death. We derived risk curves through cumulative incidence functions and computed incidence rates and adjusted hazard ratios (HRs) using Cox proportional hazards regression.

Results: Among 28,510 patients whose profiles showed severe CKD, 14% had no anemia, 35% had grade 1 anemia, 44% had grade 2 anemia, and 17% had grade 3+ anemia. Rates of incident dialysis, CVE, acute hospitalization, and death increased markedly with increasing anemia grade. Adjusted HRs for non-dialysis-dependent patients with grade 3+ anemia, compared to patients with no anemia, were substantially elevated for dialysis (1.91, 95% CI 1.61–2.26), any acute hospitalization (1.74, 95% CI 1.57–1.93), all-cause death (1.82, 95% CI 1.70–1.94), and CVE (1.14, 95% CI 1.02–1.26). For CVE the strongest associations were observed for hospitalization with heart failure (1.24, 95% CI 1.09–1.41) and any fatal CVE (1.42, 95% CI 1.19–1.68). Similar HRs were observed among dialysis-dependent patients.

Conclusions: Among patients with severe CKD receiving routine clinical care, presence and severity of anemia were associated with increased risks of incident dialysis, CVE, acute hospitalization, and death. The findings emphasize the need for attention to anemia in CKD and the underlying disease.

537 | Duration of follow-up of chronic condition cohorts in the sentinel system

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Background: The US FDA's Sentinel Initiative uses a distributed data network to conduct active surveillance on medical product safety using administrative and claims data. Observable person-time in the indicated population is instrumental to drug safety analyses. While median length of observation time for members in commercial insurance claims databases is <2 years, variation by chronic conditions is unknown.

Objectives: To assess duration of follow-up of chronic condition cohorts in the Sentinel System.

Methods: We identified prevalent and incident cohorts of 24 chronic conditions in the Sentinel System from 2008–2018. We operationalized the Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse condition algorithms by including members with evidence of at least 1 inpatient or 2 ambulatory claims with qualifying diagnosis codes (exceptions of claim count and care setting apply). We followed cohorts from the first qualifying diagnosis date to the earliest occurrence of disenrollment, death, or end of data.

We report follow-up time for each condition cohort overall and stratified by sex, age, and data partner (DP) type.

Results: Sample size ranged from 412,572 (endometrial cancer) to 50,788,725 (hypertension) members in the prevalent cohorts. Hypertension and hyperlipidemia had the highest prevalence (26.3% and 23.9%), while all 5 cancers assessed had low prevalence (0.2–1.5%). Median follow-up ranged from 0.8 (lung cancer) to 2.7 years (hyperlipidemia). Conditions with shorter follow-up time had a higher proportion of members censored due to death (55% vs 11% for lung cancer vs hyperlipidemia). The proportion of members with 3+ years follow-up time ranged from 17% (lung cancer) to 45% (glaucoma, hyperlipidemia, and osteoporosis). Follow-up was consistent across sex but longer for members 65+ vs 19–64 years old (50% vs 35% of members with hypertension had 3+ years follow-up). Integrated delivery systems had longer follow-up time than claims-based DPs (59% vs 43% of members with prostate cancer had 3+ years follow-up). Incident cohorts had similar follow-up, with a few exceptions (e.g., median follow-up 2.4 vs 1.7 years in prevalent vs incident ischemic heart disease cohorts).

Conclusions: We found that conditions with higher mortality had shorter follow-up, suggesting that disease prognosis impacts available observation time in claims data. The Sentinel System may provide sufficient person-time to observe many outcomes of interest in claims-based drug safety evaluations in chronic condition patient cohorts, although this ability will vary by chronic condition, patient age, and data source.

538 | Incidence and prevalence of alopecia Areata in the US and UK

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Background: Global incidence and prevalence data for alopecia areata (AA), an uncommon autoimmune disease that causes hair loss ranging in severity from limited patches to the entire body, have relied on outdated US population-based studies or convenience samples from single hospitals or dermatology practices; severity of AA, if available, is inconsistently defined.

Objectives: To estimate the incidence rates (IRs) and prevalence of AA among adult and pediatric patients, using electronic healthcare records (EHR) and claims data in the United States (US) and United Kingdom (UK), stratified by severity.

Methods: A retrospective cohort study was conducted using 2 EHR databases (DBs; The Health Improvement Network [THIN] from the UK, and US Optum EHR) and 2 US commercial health insurance claims DBs (Truven Health MarketScan® and Optum) via SÆfetyWorks™, an analytic tool. ICD-9/10 codes for the US data (704.01, L63*) and analogous Read Codes for UK THIN were used to identify AA patients. Patients were eligible with ≥6 mo of enrollment in the DB before the Index date (Jan 2016 or date of eligibility thereafter); observation ended mid-2017 depending on data availability for each DB. Patients were required to have ≥2 AA diagnoses ≥6 wk apart. Two subcohorts were created: AT/AU [alopecia totalis (AT) and/or alopecia universalis (AU)], and Non-AT/AU. Additional stratification by age (including pediatric groups), and sex was performed. IRs of AA were calculated for the cohort overall and sub-cohorts. Prevalence (%) was calculated using any AA diagnosis within 2 yrs prior to the index date and any time in the study period after index date.

Results: The IR of AA per 1000 person years (PYs) was 0.01–0.25 (0.22–0.25 in US claims data; 0.01–0.08 in UK and US EHR). The IR for the AT/AU cohort was 0–0.015 (0.014–0.015; 0–0.006), and Non AT/AU cohort was 0.01–0.24 (0.20–0.24; 0.01–0.08). In general, IRs of AA and AT/AU were lowest among children aged ≤5 and higher among females across age groups. The period prevalence (%) of AA was 0.01–0.10 (0.08–0.10 in US claims data; 0.01–0.04 in UK and US EHR), and in the AT/AU cohort was 0–0.003 (0.003; 0–0.002).

Conclusions: Using large US and UK healthcare data, we found that the IRs and prevalence estimates were generally comparable with those in the literature (i.e. IRs = 0.20–0.21 per 1000 PYs in 1975–89 and 1990–2009, respectively, and prevalence = 0.1–0.2%). The observed variation in the estimates may be due to the differences in data type (claims vs. EHR) and region (US vs. UK) as well as other underlying population characteristics, which highlights the importance of multiple database analyses. Future studies are warranted to confirm these findings.

539 | Do alopecia Areata patients differ by severity?

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Background: Alopecia areata (AA) is an uncommon autoimmune hair loss disorder that generally starts as patchy hair loss on the scalp. It can progress to total loss of scalp hair, (alopecia totalis [AT]) or to total loss of body hair (alopecia universalis [AU]). Little is known about the epidemiology of AA, including whether there are differences by subtype, because the literature is old, not population-based, or nonexistent.

Objectives: To describe the prevalence and characteristics of patients with AA, both overall and stratified by sex, age, and severity (AT/AU vs. non-AT/AU).

Methods: A retrospective cohort study was designed using the HealthCore Integrated Research Database (HIRD), which contains healthcare and prescription data from US commercial insurance plans. Cohort eligibility required at least 1 day of health plan coverage in the most recent 5-year (yr) period and was defined as patients with ICD9 (1/06–9/15, 704.01, AA only) or ICD10 (Oct 2015+) that had relevant codes for AA, AT, or AU (L63*). We separately evaluated patients with ≥1, ≥2, or ≥ 2 diagnoses including ≥1 by a dermatologist. We further stratified the groups as any AA, AT/AU, and non-AT/AU, and by sex

and age (0–5, 6–11, 12–17, 18–64, 65+ yr). The top 10 most common dermatologic procedures by Current Procedural Terminology (CPT) and top 20 medications by Generic Product Identifier (GPI) class in patients with ≥2 diagnoses were described for each population. Statistical analyses were descriptive only; prevalence calculations were generated with 95% CI. Primary analysis focused on the most recent 5-yr period (7/13–6/18).

Results: Between 7/13 and 6/18, there were 31 M individuals with ≥1 day of health plan coverage in HIRD; the overall prevalence of ≥2 diagnoses of AA, AT/AU and non-AT/AU was 89.0, 4.2, and 77.0 per 100,000 respectively, with narrow 95% CI; AT/AU accounted for 5.2% of the total AA burden. AA (overall and by severity) had a female predominance (60.3–68.2%) and skewed younger (92.6–94.0% were < 65 yrs; 12.3–15.2% were < 18 yrs). Thyroid medications and premalignant lesion removal were observed among the 20 most common medications and 10 most common dermatologic procedures for the AT/AU subgroup but not the non-AT/AU subgroup. Other differences in the proportion and rank order of other medications and procedures were also identified.

Conclusions: Estimates of AA are generally consistent with the existing literature; however we observed a clear female predominance and detected differences in GPI medication classes and dermatologic procedure patterns that may indicate important variation in the autoimmune profile of AT/AU vs. non-AT/AU patients. These differences merit further research.

540 | Defining heat exposure in a climate-drug interaction study: A Pharmacoepi approach

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Background: Heatwaves kill people. Many medications may interact with the effect of extreme heat, exacerbating health outcomes in vulnerable older adults with multimorbidities and polypharmacy. To precisely assess the interaction between heat and medications applying high-resolution cohort design in pharmacoepidemiology, the initial step is to better understand the effect of extreme heat in the vulnerable population, as no standard definition of heatwave currently exists.

Objectives: To understand the health effect of heatwaves defined by various durations of maximum temperature (Tmax) at selected cut offs.

Methods: We identified adults aged > = 65 linking Medicare Current Beneficiary Survey (MCBS) from 2007 to 2013 via zip codes of residence with the Parameter-elevation Relationships on Independent Slopes Model (PRISM) daily temperature grid data. We assessed the health effect of extreme heat with different lengths, i.e., one day, two days and > = 3 days, and various cut offs, i.e., Tmax > = 95th, 97th, and 99th percentile (Tmax95, Tmax97, Tmax99) based on 30-year climatologies. Outcomes of interest included all-cause mortality and all-cause hospitalization. We used multivariate Cox regression to adjust for demographics, socioeconomic factors, comorbidities, and physical/cognitive function.

Results: Among 26,325 older adults (mean age 71; 45% male; 85% White) accrued 80,151 person-years (PYs) of follow-up, 39% (7,356) were exposed to > = 1 day of Tmax95 (1,887 exposed PYs). We observed 2,697 deaths and 18,577 hospitalizations. The mortality/hospitalization rate using Tmax95 was 58/523, 42/433, and 40/349 per 1,000 PYs for 1 day, 2 days, and > = 3 days. The overall mortality for any extreme heat exposure was 45, 27, and 61 per 1,000 PYs for Tmax95, Tmax97, and Tmax99. The adjusted hazard ratios (HR) for exposure to Tmax95 > = 1 day on mortality and hospitalization were 1.5 (95% confidence limit [CI] 1.2–1.8) and 1.4 (95%CI 1.3–1.5), respectively. Defined as Tmax95 > =3 consecutive days, effects of extreme heat were diminished: HR = 1.3 for mortality and 1.2 for hospitalization.

Conclusions: Older adults had the highest risk for mortality and hospitalization at 1-day exposure to extreme heat with this risk diminishing with longer duration definitions. We observed a dose response to a higher Tmax cutoffs in the mortality risk. While no standard definition of heatwave exists, most previous studies defined heat waves as > = 2 consecutive days. Our findings suggest using > = 2 days to define heat waves may underestimate the effects of extreme heat among vulnerable adults in the climate-medication interaction study.

541 | Identification of risk factors in chronic kidney disease: A retrospective analysis of a large United States electronic health record database

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Background: Chronic Kidney Disease (CKD) is a condition characterized by a gradual loss of kidney function over time which can lead to kidney failure. Adults with chronic comorbidities like diabetes and/or hypertension are at a high risk of developing CKD. In addition, patients suffering from acute conditions like Acute Kidney Injury (AKI) are also at risk for CKD.

Objectives: The main objective of the present study was to identify patients in different CKD stages, assess risk factors, and explore the relationship between AKI and CKD.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All inpatients (≥ 18 years) between 2009 and 2016, with an ICD9/10 diagnosis of CKD, were evaluated in this study. Hypertension and diabetes were

identified using ICD9/10 diagnosis codes within Elixhauser Comorbidities. AKI stages were based on KDIGO guidelines and were evaluated using time-stamped laboratory results.

Results: The study included 878,048 patients (51.1% male) with CKD, 61% of patients over 65 years of age. By race, 72.4% of patients were Caucasian, followed by African-American (17.0%). In patients where CKD stages were available (*N* = 447,744), most were in stage 3 (65.5%), followed by 14.6% in stage 4. CKD was diagnosed in 13.6%, 18.1%, and 24.8% of patients with hypertension (*N* = 5,751,488), diabetes (*N* = 2,528,992), and a combination of hypertension and diabetes (*N* = 1,760,992), respectively. Thirty-four percent of all AKI patients had some form of CKD. Patients with AKI stage 3 were more likely to be in stage 5 CKD (5.6%) as compared to AKI stage 2 (0.3%) and AKI stage 1 (0.9%) patients.

Conclusions: This real-world analysis confirms that patients with chronic comorbidities, such as hypertension and/or diabetes, are at higher risk for CKD. This analysis also demonstrates the interconnected relationship CKD has with AKI.

542 | Association of Diagnosis Code-Based and Laboratory Results-Based Kidney Disease with development of vision threatening diabetic retinopathy

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Background: Studies have shown in diabetics that decreased renal function is strongly associated with retinopathy. In some administrative medical claims databases, both diagnosis code and laboratory results are available to identify decreased renal function, but no study has evaluated whether there are differences in their associations with retinopathy.

Objectives: In this study, we compared the association of kidney disease (KD) identified through diagnosis code to lab value-based identification of KD with development of vision threatening diabetic retinopathy (VTDR).

Methods: A national administrative medical claims database was used for this retrospective observational study. All individuals age ≥ 18 years with diagnosed nonproliferative diabetic retinopathy (NPDR) were followed longitudinally. ICD9/10 CKD diagnoses from outpatient claims were used to classify KD without or with end stage renal disease (ESRD). Serum creatinine results were used to calculate estimated glomerular filtration rates (eGFR) which were categorized based on the National Kidney Foundation's levels of disease. VTDR was defined as any new diagnosis of diabetic macular edema or proliferative diabetic retinopathy. Multivariate Cox models were used to assess the associations of KD diagnosis and eGFR (modeled as time-dependent variables) with progression to VTDR, controlling for demographics and time-updating covariates (systemic health, laboratory values, insulin use). Hazard ratio (HR), C-statistic(a measure of model discrimination) and their 95% confidence intervals (CI) were calculated.

Results: Among 69,982 enrollees with NPDR, 12,770(18.2%) developed VTDR during a median of 1.5 years follow-up. In multivariate analysis, lower eGFR was associated with higher risk of VTDR (eGFR 15–29:HR = 1.14;95%CI:1.02–1.27,*p* = 0.02; eGFR<15: HR:1.37;95%CI:1.25–1.50,*p* < 0.001) compared to patients with eGFR ≥90. Whereas a diagnosis of ESRD was associated with higher risk of VTDR (HR = 1.07,95%CI:1.01–1.13,p = 0.02), but a diagnosis of KD without ESRD was not (HR = 0.97,95%:0.92–1.03,*p* = 0.35) when compared to normals. C-statistic was 0.60(95%CI:0.59–0.60) for the model with eGFR and for the model with KD diagnosis.

Conclusions: Both diagnosis-based and lab value-based KD were associated with development of VTDR. There was no difference in their ability to predict development of VTDR.

543 | A Clinico - epidemiological study of acute poisoning cases in emergency Department of Tertiary Care Hospital, Warangal, India

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Background: "Poisoning is a critical condition. In developing countries adverse outcomes from poisoning are more frequent than in developed countries because of weak regulation and limited healthcare services".

Objectives: To evaluate the rate of deviations from WHO guidelines and adverse drug reactions occurring due to lack of specific antidotes in poisoning cases and outcomes with alternative treatment in MGM HOSPITAL, India.

Methods: A prospective and observational study of organophosphorus poisoning, snake bite, scorpion sting, multiple tablet intake, house hold poisoning, unknown insect sting has been conducted in tertiary care hospital, India. In the period of April 2018–October 2018. A suitable data collection form was prepared and data was collected accordingly, all the poison intake cases were included in the study. Extent of deviation in treatment plan were compared from the standard (WHO) treatment guidelines. ADRs were assessed using Naranjo scale and drug–drug interactions were checked through Micromedex.com.

Results: 365 Patient's data were collected, of these 195(53.42%) patients were females and 170(46.57%) were male.22% cases are deviated in (82) OP poisoning, 23% cases are deviated in (52)snake bite, 53% cases are deviated in (56)scorpion sting, 22% cases are deviated in (45) Multiple tablet intake, 6% cases are deviated in (119) house hold poisoning, there is no deviation(0%) found in (11) unknown insect sting poisonings. Out of 365 patients 235(64.3%) were intentional poisoning and 133(36.4%) were accidental poisoning. Occupation wise farmer(32.32%) remain predominant followed by daily wage workers(20%) and house wife(17.26%).Out of 365 patients 155(42.4%) have undergone first aid and 210(57.5%) have not taken first aid before admission. 148 (30 types) Adverse events occurred: 18 headache, 14giddiness, 10 atropine psychosis were prominent;

assessed on the basis of Naranjo scale. 13 types of drug–drug interactions were found by using Micromedex.com, most prominent include (55) Tetanus toxoid+ Hydrocortisone, (13) Ringer lactate+ Ceftriaxone, (11) Atropine +5%Dextrose.

Conclusions: This study findings suggests extent of deviation in treatment is high based on antidote administration.Awareness on first aid to educate the people is required and availability of antidotes in developing countries is needed & there is a need to improve patient stability by administering specific antidote, thereby reducing, morbidity mortality and pharmacoeconomic burden by identifying, assessing, monitoring and reporting ADRs and drug interactions.

544 | Chronic kidney disease in the real-world: Rationale and Design of the Global Discover CKD program

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Background: Chronic kidney disease (CKD) is a global health problem associated with adverse clinical consequences and impaired quality of life (QoL). Real-world data on the journey of patients with CKD, specifically pertaining to clinical management, metabolic control, treatment patterns, disease progression, QoL and diet are limited.

Objectives: This study aims to create a global cohort of patients with CKD to provide robust data to address epidemiological knowledge gaps and to understand determinants of clinical progression of CKD across multiple geographic regions over time.

Methods: DISCOVER CKD will have an enriched hybrid study design approach, utilizing a novel cloud-based IT platform to integrate primary and secondary data from nephrology-referred patients with CKD stage 3 (estimated glomerular filtration rate < 60 ml/min/1.73 m^2) through to end stage kidney disease (ESKD, eGFR <15 ml/min/1.73m^2) from the UK, US, Sweden, Denmark, China and Japan. Primary data will be prospectively captured over a 3-year period from >1,000 CKD patients followed for at least 1-year via electronic case report form (CRF) entry during routine clinical visits and via patient questionnaires, mobile apps and interviews for patient reported outcomes (PROs). Secondary data will be retrospectively captured from >100,000 CKD patients from existing datasets and registries (via electronic health record (EHR) database linkage and data extraction).

Results: The DISCOVER CKD program will capture patient demographics, biomarker and laboratory measurements, medical history, clinical outcomes, healthcare resource utilization, medications, diet, physical activity, and other PROs, including QoL. Initial results are anticipated in late 2019.

Conclusions: The DISCOVER CKD program will establish a global cohort of patients with CKD with high quality retrospective and prospective data to provide real-world insights into the current management and disease progression of patients with CKD.

545 | Treatment patterns of targeted therapies among patients diagnosed with rheumatoid arthritis in the United States

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Background: Rheumatoid Arthritis (RA) is a chronic disease and the most common autoimmune inflammatory arthritis in adults with a significant negative impact on the ability to perform daily activities and health-related quality of life. Treatment often involves long term targeted therapy (T-Rx). This study evaluates current T-Rx patterns in the real world setting and provides information for future drug development.

Objectives: The main objective of this study was to assess patterns of T-Rx among RA patients.

Methods: This retrospective cohort study was conducted among all US adults (≥18 years) using IBM® MarketScan® Research database (2012–2017). All eligible patients with continuous enrolment for at least 2 years and minimum of 2 RA diagnoses at least 30 days apart were included in the study. Patients were followed for 2 years after the index date (date of first T-Rx claim post RA diagnosis) to assess patterns of T-Rx treatment. T-Rx was defined as claim of etanercept, adalimumab, infliximab, tofacitinib, rituximab, golimumab, certolizumab, tocilizumab or anakinra. After excluding all patients with a history of T-Rx prior to the index date the final cohort consisted of 9,630 RA patients. This study generated treatment sequence, identified treatment switches and discontinuation. Sankey charts and

sunburst plots were developed to describe lines and order of T-Rx claims filled in the cohort. This study was funded by GSK.

Results: The cohort was mainly females (80%) with mean age of 53 (±12) years. The most common T-Rx within 2 years of follow-up were etanercept (29%) and adalimumab (28%). Over 2 years of follow up 32% of all RA patients reported switching T-Rx. 19% had 1, 8% had 2 and 5% had over 3 or more switches. While assessing lines of T-Rx therapy, the most commonly prescribed T-Rx were etanercept (34%), adalimumab (33%) and abatacept (7%) among first line; adalimumab (21%), etanercept (18%) and abatacept (15%) among the second line; and abatacept (20%), tofacitinib (18%) and tocilizumab (13%) among the third line. Only 6% of the cohort report tofacitinib claims as first line, but they increase to 11% and 18% in second and third line use respectively.

Conclusions: This study estimates assesses lines of T-Rx among RA patients. Over half of all RA patients fill a prescription claim for etanercept and/or adalimumab which are the choice of drugs for initiation of RA treatment. Over 32% patients switch treatment within the first 2 years of targeted therapy initiation, with some patients switching 3+ times indicating the difficulty in obtaining optimal treatment for RA patients.

546 | A descriptive analysis of Florida medical marijuana registry patients from 2016–2017

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Background: The Compassionate Medical Cannabis Act of 2014 (CCA) legalized medical marijuana (MM) in the state of Florida. This legislation mandated providers to submit treatment plan forms to the University of Florida's College of Pharmacy (UF COP) for safety and efficacy review.

Objectives: To describe the characteristics of Florida MM registry patients including demographics, medical conditions for seeking treatment with MM, and prescription medication usage among this population.

Methods: An Initial Treatment (IT) Plan form and a Follow-up Treatment (FUT) Plan form were created to meet the CCA's requirements. Providers submitted forms electronically via a secured portal maintained by the UF COP. Data elements collected on the forms cover information on patients, providers, and the cannabis order. We retrospectively analyzed IT and FUT plan forms submitted between August 2016 to July 2017 (N = 12,798). Records were excluded if data were invalid or incomplete.

Results: 7,963 IT and 2,075 FUT plans were available for the analysis. At the initial visit for MM evaluation, patients were mostly white (83.7%), on average 52.3 years (SD 16.4) of age, and were assessed as at least moderately ill (42.9%) by the prescribing physician. At the time of MM initiation, about one in four patients (26.3%) reported concurrent use of prescription opioids. Antidepressants (24.2%) and anxiolytics including benzodiazepines (23.7%) were the second and third most frequently used medications, respectively. The top three identified medical complaints for seeking MM were musculoskeletal disorders including spasms (54.7%), chronic nonmalignant pain (42.7%), and multiple sclerosis (33.3%) with at least one condition per patient possible. Chronic nonmalignant pain and multiple sclerosis are explicitly allowed by current law. Musculoskeletal disorders were interpreted by the provider as meeting other qualifications allowed. At a follow-up encounter after MM initiation, providers' assessments of patients' conditions showed that 31.7% were much improved and 30.1% were minimally improved while 25% were unchanged and less than 3% were worse. MM discontinuation was reported by 5.0% of patients and 1.7% reported indicators of adverse reactions to cannabis.

Conclusions: Results suggest that patients with serious medical conditions sought treatment with MM despite pharmacological options and out-of-pocket expenses. Furthermore, the data suggests that a significant number of patients may benefit from MM therapy. This study adds to the limited information available on the individuals and their conditions who seek MM treatment.

547 | Hydroxychloroquine in systemic lupus: Drug tapering/discontinuation and clinical outcomes

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Background: Hydroxychloroquine (HCQ) is a cornerstone drug to control disease activity in Systemic Lupus (SLE). Since concern exists regarding the safety of long-term HCQ use, it may be tapered or stopped to potentially lengthen the period over which patients may benefit.

Objectives: We evaluated associations between tapering/discontinuing HCQ and SLE outcomes.

Methods: We used data from a clinical cohort of adult SLE patients exposed to HCQ at least once between January 2006 and October 2018 in Montreal, Canada. Baseline was defined as the first visit with HCQ exposure. At the first follow-up visit (one year after baseline), we examined the percent of patients who tapered HCQ dose, discontinued HCQ therapy, or did not change therapy. Logistic regressions were conducted to examine whether HCQ taper/discontinuation was associated with poor outcomes at the second follow-up visit (defined as an increase of $\geq$4 points in the SLE Disease Activity Index, SLEDAI-2 K, and/or hospitalization for SLE, and/or augmented SLE therapy). Analyses were controlled for age, sex, and race/ethnicity, and stratified by education, SLE duration, and baseline SLEDAI-2 K.

Results: Of 469 potentially eligible patients, 412 completed at least 2 annual visits and were therefore included. In the first year of follow-up, 15.3% of patients tapered HCQ, 8.7% discontinued HCQ, and

the remainder did not change therapy. Among the 367 patients with outcome information, 48.5% had at least one poor outcome at the second follow-up visit. The proportion of patients having a poor outcome was slightly higher for those tapering/stopping HCQ, versus those maintaining therapy (difference of 11.9%, 95%CI 0.0%, 23.4%). Having tapered or discontinued HCQ within the first year of follow-up was associated with experiencing a poor outcome at the subsequent follow-up visit (one year later) independently of potential confounders (OR = 1.69; 95%CI 1.02, 2.80). Stratified analyses showed that reducing/discontinuing HCQ was associated with poor outcomes particularly for those with low educational level (OR = 3.06; 95%CI 1.29, 7.30), those within two years of SLE diagnosis (OR = 2.02; 95%CI 1.03, 3.96), and those with high SLEDAI-2 K (≥4 points) at baseline (OR = 2.28; 95%CI 1.09, 4.77).

Conclusions: Though some SLE patients do well after tapering or discontinuing therapy, others have poor outcomes including lupus-related hospitalization. Tapering/discontinuing HCQ may be particularly problematic in patients with low educational level, recent SLE diagnosis or unstable disease. These issues are likely important in personalizing decisions for tapering/discontinuing HCQ in SLE.

548 | TNF-alpha inhibitor treatment patterns in patients with rheumatic diseases and those with inflammatory bowel disease

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Background: TNFα inhibitors are the first line biological treatment for patients suffering from rheumatic diseases (RD) and inflammatory bowel disease (IBD). Limited information is available about long-term treatment patterns of patients starting a TNFα inhibitor and whether these differ between patients suffering from RD and IBD.

Objectives: To compare treatment patterns of patients with RD and IBD starting a TNFα inhibitor.

Methods: Included were all patients starting (i.e. no prior use of a biological) with a TNFα inhibitor (ATC code: L04AB) between 1 July 2012 and 1 July 2017 at a Dutch general teaching hospital (the Spaarne Gasthuis, Haarlem/Hoofddorp) and with a RD or IBD diagnosis. All patients were followed for at least one year. Outcomes at one year of follow-up were: continuous use of the first TNFα inhibitor, switch to a different TNFα inhibitor or to a biological with another mode of action, or discontinuation. In addition, median duration of first TNFα inhibitor treatment were compared for patients with RD and IBD using the Kaplan Meier method. Data were analyzed by Pearson's chi square and Kruskal Wallis test.

Results: 646 patients were included (median age 46 years, 84% female), of which 63.9% (n = 413) received a TNFα inhibitor for RD and 36.1% (n = 233) for IBD. After 1 year, 60.1% of patients continuously used their first TNFα inhibitor, 13.4% switched to another biological and 26.5% discontinued treatment. Significantly less RD patients continued their TNFα inhibitor compared to IBD patients (54.4% versus 70.0%, RR 0.78, 95% CI 0.69–0.88) and RD patients discontinued treatment more frequently than IBD patients (33.0% versus 15.0%, RR 2.19, 95% CI 1.57–3.06). 12.6% of RD patients and 15.0% of IBD patients had switched, most patients (71.1% of RD switchers and 91.4% of IBD switchers) to a second TNFα inhibitor.

The median treatment duration of the first TNFα inhibitor was significantly (p < 0.01) lower for RD patients (437 days, IQR 686 days) when compared with IBD patients (728 days, IQR 988 days).

Conclusions: RD patients discontinue their first TNFα inhibitor significantly more often than IBD patients and have a shorter duration of treatment, patterns of switching are equal in both indications. These findings show the importance of underlying disease in classification of exposure to TNFα inhibitors and this should be taken into account in future pharmacoepidemiologic studies.

549 | Comorbidities, infections and treatment patterns in psoriasis patients: A retrospective analysis of a large United States electronic health record database

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Background: Psoriasis is an immune mediated, chronic skin disease marked by red patches covered with white scales. Several comorbid conditions may exist with psoriasis, some of which may worsen psoriasis, significantly impacting quality of life. Psoriatic patients are prone to infections, a leading cause of death. Multiple therapeutic options are available for treatment of psoriasis.

Objectives: The objective of the present study was to examine comorbid conditions, infections, and treatment techniques in psoriatic patients.

Methods: This retrospective study examined data from a US electronic health record database (Cerner Health Facts®). All visits, including inpatient (age ≥ 18 years), between 2012–2016 with a principal ICD9/10 diagnosis of psoriasis were included in the analysis. ICD9/10 diagnosis codes were used to identify comorbid health conditions and prevalence of infections. Type of treatment provided was identified via medication names as well as procedure codes.

Results: The study included a total of 244,512 psoriasis-related visits (51.8% female), majority in the '36–65 years' age group (64.7%). Psoriatic arthritis (21.7%), type 2 diabetes (12.2%), kidney disease (4.5%), and cardiovascular disease (3.9%) were the most commonly seen concomitant diseases. The most prevalent infections among psoriatic-patient visits were skin infections (2.7%), fungal infections (2.1%), urinary tract infections (2%), hepatitis C (1.4%), upper respiratory infections (1.4%), pneumonia (1.13%), herpes zoster (0.16%),

hepatitis B (0.12%), and tuberculosis (0.03%). More than half of psoriasis patient visits were prescribed topical treatments (56.5%) as compared to light therapy (25.3%), and systemic medications (18.2%). The most commonly prescribed systemic medication was methotrexate (67.2%), followed by biologics (15.6%), cyclosporine (12.5%), and retinoids (4.7%).

Conclusions: This large database analysis examined various comorbidities and types of infections associated with psoriasis and provides insights into current pharmacological and other treatment strategies.

550 | Characterization of rheumatoid arthritis (RA) in Puerto Rico: Prevalence, demographics, and prescribing trends among beneficiaries of the government sponsored health care plan (GSHCP)

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Background: Rheumatoid arthritis (RA) is a debilitating disease characterized by irreversible joint destruction. RA generally affects more women than men, and incidence increases with age. The latest American College of Rheumatology Guidelines recommend nonbiologic disease modifying antirheumatic drug (DMARD) monotherapy for the initial treatment of RA. Biologic agents include IFN inhibitors and are generally reserved for refractory RA due to their high cost. Unfortunately, there are no studies describing the prevalence, sociodemographic distribution, and pharmacotherapeutic treatment patterns of RA in Puerto Rico.

Objectives: This study aims to describe the prevalence, sociodemographic features, and pharmacotherapeutic patterns of RA patients in Puerto Rico.

Methods: A longitudinal retrospective review of RA medical and pharmacy claims from Puerto Rico's GSHCP was performed. Demographic features of age and gender were determined for each region in Puerto Rico and prevalence was calculated following a previously validated algorithm. Pharmacy claims were used to determine the frequency that patients were prescribed nonbiologic DMARDs and biologic agents.

Results: A cohort of 40,473 RA beneficiaries was generated from October 1, 2015 to December 31, 2016. The average age of beneficiaries was 59 years. Females were 3 times as prevalent as males and regions West and East had the highest prevalence of RA. The calculated prevalence of RA in Puerto Rico's GSHCP was 0.4%. 41% of beneficiaries filed a claim for a biologic agent while 77% filed a claim for a nonbiologic DMARD.

Conclusions: Demographic characteristics of RA in Puerto Rico follow expected trends for RA; however, prevalence is higher in Puerto Rico than other areas of the world. As suggested by guidelines, majority of patients are taking nonbiologic DMARD therapy. Medication data should be further analyzed to determine prescribers' adherence to guidelines.

551 | The importance of reliable data collection: Using electronic medical records to study lower extremity injuries in elite football

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Background: Lower extremity injuries impact the majority of elite American football players over the course of their careers, and some of these injuries can be career-ending. Previously published studies describing lower extremity injuries among National Football League (NFL) players often rely on convenience samples from publicly-reported injury information, often from the lay press, which may be inaccurate, incomplete, and biased towards more severe injuries.

Objectives: Accurately characterize incidence and impact of lower extremity injuries in NFL athletes through use of a high quality, closed electronic medical record (EMR) data collection system, and to compare findings to previously published studies that utilized publicly-reported injury information.

Methods: All 32 NFL teams report injuries into the league-wide EMR under mandated, consistent data collection guidelines. Lower extremity injuries reported during 2015–2017 regular season games were included, with. Injury data were linked with game statistics and player participation, including the number of plays each player participated in for each game. Rates per 1,000 game-plays and 10,000 player-plays were calculated along with 95% CI for injuries overall, by specific lower body injury, and stratified by characteristics such as roster position and play type. Descriptive statistics were generated for number of days missed from football participation for each injury. Findings were compared to previously published results in the same population.

Results: Lower extremity injuries that resulted in missed time occurred at a rate of 21.5 (21.0,22.0) injuries per 1,000 plays (n = 3538 over 3 seasons). Incidence of the most severe injuries was similar to that reported from publicly available data; for example, occurrence of 34 game-related Achilles ruptures across 5 years was captured in both the EMR and a publication based on public reports (Krill et al, 2017). However, injuries such as Jones fractures, which range in severity and impact, were more likely to be underestimated; one published study (Parekh et al, 2017) reported only 53.8% of the Jones fractures that were reported in the EMR.

Conclusions: Use of a closed EMR, in this case within the NFL, linked with game statistics and player participation, provides the ability to capture reliable injury occurrence and player exposure, which are necessary for incidence and impact assessment of these important injuries. This system can be extended more broadly to health systems interested in characterizing adverse event rates or for performing surveillance and risk management.

552 | Prescribing pattern of Janus kinase inhibitors drugs in rheumatoid arthritis patients in Taiwan

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease. When patients are untreated, RA causes pain, joints damage and disability. It also increases disease mortality in infection or osteoporosis. RA cannot be cured; therefore, the goal of treatment is to achieve a state of clinical remission or low disease activity. Tofacitinib is an oral Janus kinase inhibitor and a higher average cost per month than other drugs in our hospital. In addition, little research has focused on JAKIs treatment strategies for routine care in Taiwan.

Objectives: Our aim was to evaluate trends in use of prescription JAKIs among RA patients and the changes in patterns of JAKIs as monotherapy or combination conventional DMARDs utilization.

Methods: We used the electronic medical records of 2018 Jan to Dec in hospital claims databases to establish research cohorts. We included patients who are diagnosed RA by ICD 10 and prescribed JAKIs at the same time. We defined the date of first-prescribe JAKIs as index date and observed cDMARDs prescribing patterns at every month after the index date.

Results: Drug consumption data presents that 62 patients were RA. The mean age was 57 years and the average proportion of woman patients was 80.6%. The percentage of patients initiated on JAKIs in combination with any cDMARDs was 79%, while combination with hydroxychloroquine (HCQ) was about 45.1%, with methotrexate (MTX) was about 32.2%. About 75.8% of RA patients were co-prescribing oral steroids. A continuous decrease in combination cDMARDs therapy was observed by months in 14.3% patients after prescribed JAKIs. HCQ and MTX were the two most prescribed cDMARDs.

Conclusions: This study indicated that trend towards more aggressive management of RA in our hospital. The utilization of JAKIs in combination with cDMARD major is HCQ. It is a difference from combination with MTX in an international guideline. The consideration of treatment strategies is not only patient tolerance of drug property individually but also cost of average per course of therapy.

553 | Effect of reimbursement restriction policy on the use of benzodiazepines in the Netherlands: An interrupted time series analysis

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Background: Use of benzodiazepines has serious health risks. Reimbursement was restricted in the Netherlands from 1 January 2009 onwards with the goal to reduce chronic use and healthcare expenditures.

Objectives: The aim of this study is to assess the initial and long-term effects of this policy on benzodiazepine use.

Methods: Setting: Benzodiazepine dispensings by out-patient pharmacies between January 2002 and August 2015 were obtained from the PHARMO Database. This database comprises GP and specialist prescribed medication and covered a catchment area representing about 3.6 million residents in 2015. Participants: 2,500,800 benzodiazepine prescriptions from 128,603 (66.6% female) patients were included. Intervention: Reimbursement restriction policy from 1 January 2009 onwards. Design: A 10% random sample of PHARMO database was obtained and analyzed. Interrupted times series design, segmented regression models, Kaplan–Meier survival analysis and Cox-proportional hazard analysis were used to compare the use of benzodiazepines before and after the reimbursement restriction policy. Main outcome measures: Changes in the volume of dispensed prescriptions and doses, as well as in the incidence and prevalence of incidental, regular and chronic use and changes in discontinuation rates of benzodiazepines.

Results: The calculated volume of dispensed prescriptions and doses decreased by 12.5% respectively 15.1% in January 2009 compared to December 2018. A clear initial effect on the overall incidence (−14.7%) and the prevalence of incidental (−17.8%), regular (−20.0%) and chronic (−16.0%) use was observed. A statistical long-term effect was observed for the overall incidence (−0.017) and the prevalence of incidental use (−3.624) but not for regular (−0.304) and chronic (0.136) use. Patients who started treatment post-policy had a slightly higher probability of discontinuation (HR = 1.013; 95%CI, 1.004–1.022).

Conclusions: The reimbursement policy had a significant initial effect on the volume, incidence and prevalence of BZD use. In addition, there is a long-term effect on overall incidence and on the prevalence of incidental use. No long-term effect on chronic use of BZD, the main purpose of the reimbursement restriction, could be proven.

554 | Differences in patterns of prescribing medications for depression in obese and Normal weight patients

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Background: Patients with obesity often have more severe depression than normal weight patients and may respond poorly to pharmacological treatment. Certain depression medications can increase weight (are obesogenic) contributing to the high prevalence of obesity in patients with depression. Presently, it is unknown whether healthcare providers account for body weight when they prescribe obesogenic

medications for depression. It is, therefore, important to evaluate prescribing patterns of obesogenic depression medications for patients with depression and excess weight.

Objectives: Using a national primary care practice database, to examine the association between obesity and prescribing medications for depression, focusing on obesogenic medications.

Methods: Study sample was extracted from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) Electronic Medical Records database for 2011–2016. Adult patients (18 years of age and older) diagnosed with depression were included. Measures were prescribing of depression medications (outcome) and body mass index (BMI) to categorize patients into weight groups (exposure). Data were analyzed cross-sectionally using multivariable binary logistic regression adjusting for age, sex, and the comorbidities.

Results: Among 61699 patients with depression, 41389 (67.1%) had a prescription for at least one medication for depression. Compared with normal weight patients, obese patients were more likely to receive a prescription for at least one depression medication (adjusted Odds Ratio [aOR] = 1.21; 95% Confidence Interval [CI]: 1.16–1.26). Obese patients were less likely to receive obesogenic antidepressant mirtazapine, belonging to the norepinephrine- and specific serotonergic group (aOR = 0.64; 95% CI: 0.58–0.70); however, compared with normal weight patients, obese patients were more likely to receive other obesogenic depression medications: tricyclic antidepressant amitriptyline (aOR = 1.26; 95% CI: 1.15–1.38), selective serotonin reuptake inhibitor paroxetine (aOR = 1.19; 95% CI: 1.06–1.34) and atypical antipsychotic quetiapine (aOR = 1.09; 95% CI: 1.00–1.18).

Conclusions: Compared with normal weight patients, obese patients with depression appear to be more likely to be prescribed at least one medication for depression and to receive obesogenic depression medications amitriptyline, paroxetine and quetiapine. While causality cannot be inferred, these prescribing patterns may contribute to the issue of obese patients who are at higher risk for severe depression and poor response to treatment.

555 | Trends in prescribing and dispensing of common insomnia drugs as compared to National Guideline Recommendations

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Background: Insomnia is often treated with medication, including on-label (eg, Z-drugs) and off-label (eg, trazodone) drugs. In 2017, the American Academy of Sleep Medicine (AASM) released its first-ever clinical guideline for the pharmacologic treatment of insomnia, recommending that physicians consider using Z-drugs and consider not using trazodone.

Objectives: To measure trends in the prescribing and dispensing of four medications commonly used for insomnia (trazodone + three Z-drugs: zolpidem, eszopiclone, zaleplon) and to compare the findings to the 2017 AASM recommendations.

Methods: Cross-sectional analysis of two nationally representative US data sources: 1) the National Ambulatory Medical Care Survey (NAMCS), and 2) a 1% sample of the MarketScan® Research Databases. NAMCS data were used to measure prescribing trends among office-based visits for insomnia from 2009 to 2015, while the MarketScan data were used to measure dispensing trends among privately-insured patients with insomnia from 2011 to 2016. The unit of analysis in the NAMCS and MarketScan data was the insomnia visit and patient, respectively. We calculated the annual percent of visits/patients where each drug was prescribed/dispensed. In the MarketScan data, we used dose information to restrict to trazodone claims for <50 mg/day. We used multivariable logistic regression to estimate adjusted yearly odds ratios (ORs) for the likelihood of each drug being prescribed/dispensed. For the NAMCS data, we used SAS survey analysis procedures to calculate weighted national estimates and account for the complex survey design.

Results: Among a national weighted average of 10.4 million insomnia-related visits/year from 2009 to 2015 in NAMCS, the annual percent of visits where trazodone was prescribed rose from 7.0% (95% CI 3.4%–10.5%) to 21.2% (11.0%–31.3%), while the annual percent of visits where zolpidem was prescribed fluctuated widely around an average of 21%. In the MarketScan data, among an average of 8,000 insomnia patients/year from 2011 to 2016, the annual percent of patients with low-dose trazodone dispensed increased from 4.5% (4.0%–5.0%) to 7.3% (6.7%–7.8%) and fell from 32.9% (31.8%–34.0%) to 26.3% (25.4%–27.2%) for zolpidem and from 4.8% (4.3%–5.3%) to 3.6% (3.2%–4.0%) for eszopiclone. Zaleplon was dispensed/prescribed infrequently. In both data sources, the adjusted ORs supported a statistically significant increase in trazodone prescribing/dispensing over time among insomnia patients.

Conclusions: Contrary to the AASM guidelines, the off-label use of trazodone for insomnia appears to be increasing over time.

556 | Long-term outcomes of early use of long-acting injectable antipsychotics in schizophrenia

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Background: Patients in the early stage of schizophrenia may be the ideal candidates for long-acting injectable (LAIs) antipsychotics. However, no studies examined the long-term comparative effectiveness between patients who added or switched to LAIs during the treatment and those remaining on oral antipsychotics (OAPs).

Objectives: To assess whether patients adding or switching to LAIs in early schizophrenia are associated with decreased risk of psychiatric inpatient and emergency room (ER) visits and improved mortality.

Methods: Using Taiwan National Health Insurance Research Data from 2008–2016, we formed a cohort by identifying all participants from the base population of OAPs initiators who subsequently added

or switched to a LAIs during hospitalization and further prescribed LAIs at least 6 times in 1-year post discharge. For each patient adding or switching to LAIs, we identified a matched reference patient who also was a OAPs initiator but remained on OAPs, using a prevalent new-user design. The potential reference patients were selected from the corresponding exposure sets namely from the OAPs initiators in the base cohort who spent the same duration of time in base cohort as the exposed patients (defined as the period from the first prescription of OAPs to first prescription of LAIs) and remained on OAPs when exposed patients added or switched to LAIs. Survival and conditional negative binomial regressions were adapted to estimate the risk of mortality, psychiatric inpatient and ER visits associated with LAIs and OAPs.

Results: In patients adding or switching to LAIs within 3 year of OAP initiated, their all- and natural- cause mortalities were significant lower than those remaining on OAPs. The hazard ratio (HR) was 0.45 (95% Confidence Interval [CI]: 0.27–0.87) and 0.30 (95% CI: 0.15–0.60) for all- and natural- cause, respectively. The unnatural cause mortality was lower in the LAIs groups comparing with those remaining on OAPs, but the HR did not reach a statistical significance. Patients who added or switched to LAIs had a lower risk to have an inpatient visit (IRR = 0.56, CI = 0.45–0.69), to have a psychotic inpatient visit (IRR = 0.63, CI = 0.50–0.81) and to have a psychotics ER visit (IRR = 0.58, CI = 0.45–0.75) than patients remaining on OAPs. The improvement in survival and disease control is not observed in patients who added or switched to LAIs in late phase of their diseases.

Conclusions: Using LAIs in early schizophrenia has a profound impact on mortality. Our results provide an important piece of evidence to support the idea that early phase schizophrenia patients may benefit the most from LAIs.

557 | Concurrent use of gabapentin, benzodiazepines and opioids: Prevalence and risk factors among commercially insured United States adults

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Background: Off-label use of gabapentin within the United States is rapidly increasing, ranging between 83 to 95%. Gabapentin, opioids and benzodiazepines are commonly co-prescribed, raising concerns about an increased risk of central nervous system depression and abuse. Little is known about factors potentially associated with co-prescription of these medications.

Objectives: To estimate the prevalence of co-prescription of opioids, gabapentin, and benzodiazepines (OGB) among adults ages 18 through 64, and evaluate associated risk factors.

Methods: We conducted a retrospective cohort study derived from a 1% random sample of enrollees within the IQVIA™ PharMetrics Plus adjudicated claims database during January 1, 2007 to December 31, 2015. The index date was defined as the first opioid prescription within the study period. We constructed a 3-level categorical measure of concurrent use based on medication receipt in the 12-month post-index period: OGB, opioids and gabapentin only (OG), and opioids only. Concurrent OGB exposure was defined as having at least one day overlap of days supplied for gabapentin and benzodiazepine with an opioid prescription. Clinical and demographic characteristics including age, chronic pain, sedatives, muscle relaxants, mental health and substance use disorders were assessed in the 6-month pre-index period. We estimated the prevalence of concurrent OGB use, and used a multinomial logistic regression (AOR; 95 CI) to estimate the association of clinical and socio-demographic factors with concurrent use.

Results: Among 125,904 adult opioid users, 1588 (1.3%) and 451(0.3%) had concurrent use of gabapentin (OG) and gabapentin and benzodiazepines (OGB), respectively. The prevalence of concurrent OGB use was higher among middle-aged adults (46–55) with diagnosis of chronic pain, mental health (MH), and substance use disorder (SUD) when compared to OG and opioid-only users ($p < 0.01$.) After adjusting for other demographic and clinical factors, back pain (2.53;2.06–3.10), depression (2.33;1.86–2.76), anxiety (2.63;2.08–3.36), mood disorders (1.95;1.43–2.65), and opioid-related substance use disorders (10.90;5.9–13.8) were the strongest predictors of concurrent OGB use.

Conclusions: Although prevalence of gabapentin is low among opioid users, close to one third of OG users also use benzodiazepines. Despite their increased vulnerability to opioid related adverse outcomes, adults with MH and SUD are more likely to be OGB users.

558 | Real-world evidence of disease progression and treatment pattern of patients diagnosed with Parkinson's disease

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Background: Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting 1–2 per 1000 of the population at any time. As treatment algorithms and therapeutic options have been continuously updated by the neurology community, it is important to understand current PD diagnosis and treatment patterns using real-world data. Although large claims databases can be a valuable data source for epidemiological studies, they are limited by the lack of information on disease stage.

Objectives: To explore potential proxies for PD stage and disease progression by delineating longitudinal treatment patterns and comorbidity profiles of a PD patient cohort in a US administrative claims database.

Methods: A retrospective cohort study was conducted using the Truven Health MarketScan® Research Database, a US administrative claims database from 2001–2017. PD patients were included if they had health plan coverage for at least one year before and one year

after the initial diagnosis of PD. Patient demographics, comorbidities and PD therapies at baseline were summarized by descriptive analyses. The median time to pharmacological therapy and deep brain stimulation were also calculated. The incidence of comorbidities and different PD therapies were estimated for each year after the initial diagnosis of PD for up to 6 years.

Results: The cohort included *n* = 100,239 patients diagnosed with PD from 2001–2017. Mean age was 72.4 years and about half of the patients were over 60 years old. The cohort featured relatively more male patients (55.2%), Medicare enrollees (41.3%) and more patients from north central (33.7%) and southern (31.2%) US regions. The median time to pharmacological therapy and deep brain stimulation were 8.4 and 41.2 months respectively. The incidence rates of dual and triple therapy increased over time, and the greatest increase was seen in year 3. In the last year of follow-up, incidence rates of dual and triple therapy were 45.2 and 14.7 per 100 person-years respectively. Over time, patients experienced an increased diagnosis rate of constipation, heart failure, diabetes, atrial fibrillation and peripheral vascular disease, but a decreased diagnosis rate of depression, cerebral vascular disease and dyslipidemia during follow-up.

Conclusions: Trends in treatment patterns and changes in incidence rates of PD related comorbidities were described in this study. As disease progressed more complicated treatment regimens and different comorbidity profiles were observed, which may be used as potential disease severity indicators.

559 | Concomitant drug use among frequent users of insomnia medications: A US claims database study

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Background: Prior studies have reported polypharmacy with sleep hypnotics but there is limited evidence from database studies supporting concomitant drug use. The ability to detect evidence of concomitant drugs using an administrative database is challenging given the high PRN use of insomnia medications.

Objectives: To describe concomitant drug use for frequent new users of suvorexant (suvo), zolpidem (zol), temazepam (tem), and ramelteon (ram).

Methods: A new user cohort study was conducted using the Optum Research Database with patients having ≥2 prescriptions for the index drug identified between January 01, 2015 to September 30, 2017, with ≥12-months of follow-up and baseline data. Given challenges with detecting concomitant medication use for drugs frequently used on a PRN basis, the cohort was further restricted to more chronic drug users defined as those with a refill ratio (RR) ≥0.8 with RR defined as cumulative days' supply/time between the first and last prescription. Concomitant drug use was defined as having ≥1 overlapping prescriptions of the index drug and a second (non-index) insomnia drug, with a sensitivity analysis defining it with ≥2 overlapping prescriptions. Non-index drugs also included low dose doxepin and trazodone which is commonly used for insomnia. Given the potential for channeling with newer medications, a subgroup analysis was performed for those with no prior insomnia medication use. Descriptive statistics were used.

Results: The sample included 4,182 suvo, 46,400 zol, 15,217 tem, and 1,144 ram new users with ≥2 prescriptions. Among the cohort, 62%, 31%, 54%, and 69% of suvo, zolp, tem, and ram new users, respectively, had an overall RR ≥0.8, with 12%, 20%, 25%, and 19% also having no evidence of prior insomnia drug use. Concomitant drug use, overall and for the subgroup with no prior insomnia drug use, respectively, was 33.6% and 12.7% for suvo, 17.5% and 11.3% for zol, 28.8% and 16.9% for tem, and 37.7% and 19.4% for ram. When requiring evidence of ≥2 overlapping prescriptions, the proportions were further reduced to 4.5% and 0.4% for suvo, 0.9% and 0.4% for zol, 2.5% and 0.8% for tem, and 5.6% and 2.3% for ram.

Conclusions: Although evidence of overlapping insomnia medications exists, the analysis demonstrates that database analyses are very sensitive to the algorithm used to define concomitant drug use. When attempting to control for baseline imbalances in important prognostic factors by excluding prior insomnia drug users, there is still evidence of concomitant drug use. However, the rates of concomitant use are lower with greater numerical balance among users of different insomnia drugs.

560 | Antidepressant use in Denmark, Germany, Spain, and Sweden from 2009 to 2014: Incidence and comorbidities of antidepressant initiators

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Background: Antidepressants are among the most prescribed drugs in Europe. Antidepressant choice is influenced by factors related to the

specific antidepressant as well as patient-related factors. No studies have described the use of antidepressants and characteristics of adult users in Europe since 2012.

Objectives: To describe patterns of use and characteristics of adult users of 10 antidepressants from 2009–2014 in four European countries.

Methods: The antidepressants were citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, mirtazapine, and agomelatine. This included different classes of commonly used antidepressants in the participating countries. Agomelatine was selected for regulatory reasons. Adult initiators of each study antidepressant from 2009–2014 were identified in the Danish and the Swedish National Registers, GePaRD (Germany), EpiChron (Aragon, Spain), and SIDIAP (Catalonia, Spain). Cumulative incidence of antidepressant initiation was calculated. Initiators were characterized at the start of treatment episode according to age, sex, and presence of comorbidities. Patterns of use, including use of antidepressants prior and during the current episode, were also assessed.

Results: The study included 4.8 million initiators of antidepressants. Citalopram had the highest cumulative incidence (users per 1,000) in all populations except in Aragon, ranging from 65 in Denmark to 38 in Catalonia. Agomelatine (fewer than 10), and paroxetine had the lowest cumulative incidence. Women (> 60%) comprised the majority of antidepressants initiators. Mirtazapine was used among older initiators (median age range 54 years in Denmark - 67 years in Aragon) with higher prevalence of comorbidities, and fluoxetine was used among younger and healthier initiators (median age range 38 years in Sweden - 50 years in Aragon). The most prevalent comorbidities among initiators were hypertension, diabetes, hyperlipidaemia, and obesity. The results indicated that citalopram and amitriptyline were the most common first-line treatments, whereas agomelatine and duloxetine were mostly used in the second line. Agomelatine, venlafaxine, and duloxetine were mostly used in combination therapy.

Conclusions: This study suggests that citalopram and mirtazapine were the most commonly prescribed antidepressants in the populations studied during 2009–2014. Age, presence of comorbidities, and patterns of use in adult initiators differed between antidepressants.

561 | Comparability of antipsychotic-treated and non-treated patients with schizophrenia and the assessment of mortality in Taiwan

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Background: Treatment versus non-treatment comparisons are often performed to evaluate drug safety or effectiveness.

Objectives: To assess comparability of antipsychotic (AP)-treated and non-treated patients with schizophrenia when evaluating mortality.

Methods: A retrospective cohort study estimated the risk of all-cause, sudden death, and cardiovascular (CV) mortality among AP-treated and non-AP-treated patients with schizophrenia. The study population covering a period of 2001–2015 was identified using the linkage of the Taiwan National Health Insurance (NHI) claims and National Register of Death databases. In as-treated and intention-to-treat (ITT) analyses, incidence density estimates were calculated in AP-treated and non-AP-treated patients with schizophrenia. The study population included patients with at least one inpatient or at least two outpatient diagnosis codes of schizophrenia, and the subset of AP-treated patients were those with 2 or more AP prescriptions within a 90 day period.

Results: A total of 68,348 and 8,959 AP-treated and non-AP-treated patients with schizophrenia, respectively, were included in the study. Demographic and clinical characteristics for non-AP-treated patients with schizophrenia were inconsistent with the medically accepted profile of patients with schizophrenia. Non-AP-treated patients compared to AP-treated patients, respectively, were substantially older (mean ages 47.4 and 39.1 years old), were more likely to be male (55.5% and 49.3%), and had more comorbidity (mean Charlson comorbidity scores 0.49 and 0.15). In AP-treated as-treated analyses, AP-treated ITT analyses, and non-AP-treated patients, respectively, mortality outcome estimates per 1,000 patient-years were: all-cause mortality (16.4, 14.5, and 27.4); sudden death (2.7, 2.4, and 2.8); CV death (0.7, 0.6, and 2.1); all estimates were highest among non-AP-treated patients.

Conclusions: This analysis of a key outcome in a schizophrenia population demonstrates how lack of comparability between populations may be misleading. The results also suggest the need to closely scrutinize criteria for schizophrenia diagnoses, and potentially validate these diagnoses in NHI by linkage to the Catastrophic Illness Registry. For comparative effectiveness pharmacoepidemiology studies of patients with a diagnosis of schizophrenia, AP treatment versus non-treatment comparisons without validation, matching, and other adjustment strategies should be conducted with caution due to fundamental differences in these patient groups, which may bias effect estimates.

562 | Real-world treatment patterns among attention-deficit/hyperactivity disorder patients who initiated extended-release treatment

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Background: Attention-deficit/hyperactivity disorder (ADHD) affects 7.8%–11.0% of children and 4.4% of adults in the U.S. Extended-release (ER) and immediate-release (IR) medications are commonly prescribed for ADHD, with ER formulations gaining popularity in recent years.

Objectives: To assess the real-world treatment patterns of ER ADHD medications among commercially-insured adolescents and adults in the U.S.

Methods: Patients aged ≥12 years with ≥1 ADHD diagnosis and ≥ 2 ER or IR prescriptions (covering ≥60 days within the first 90 days of treatment) were identified in a large US claims database from 2011 to 2017. Patients had ≥6 months of continuous enrollment pre- and ≥ 12 months post-treatment initiation and were followed until discontinuation (60-day treatment-free interval), enrollment end or 24 months post treatment initiation. Patients were untreated within the 6-month baseline period and grouped based on the first recorded treatment as ER monotherapy, IR monotherapy or ER/IR combination.
Results: A total of 209,342 ADHD patients (49.7% female, median age 24 years) met the study inclusion criteria. Of these, 127,362 (60.8%) initiated with ER, 80,600 (38.5%) with IR and 1,380 (0.7%) with ER/IR combination. Of patients that initiated ER, 15,599 (12.2%) switched to or added another ER, 12,333 (9.7%) switched to IR or multiple IR, and 5,898 (4.6%) added an IR to an ER regimen. The median time on ER therapy prior to any modification was 165 days. The most frequent therapy modifications were generic ER amphetamine salts to Adderall XR (16.5%) and from Vyvanse to generic ER amphetamine salts (11.3%). The proportion of ER patients who switched or modified an existing regimen increased with age among adults <40. The median age for modifiers was 25 while those that remained on therapy was 22 ($p < .001$). The five most prevalent comorbidities of these patients are depression (23.5%), anxiety (6.6%), insomnia (3.7%), bipolar disorder (3.1%), and substance use disorder (2.9%). Depression (28.0% vs 21.9%, p < .001), anxiety (8.2% vs 6.0%, p < .001) and insomnia (4.6% vs 3.4%, p < .001) were significantly higher in patients who modified their regimen.
Conclusions: In this population, a higher number of patients were initially treated with ER compared to IR therapy and more likely to remain on the same treatment they initiated for the duration of the study. Most ER patients who modified their regimen switched to another ER. Age and the presence of psychological comorbidities may play a role in the treatment management of certain ADHD patients.
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563 | Use of antidepressants and anxiolytics among patients with chronic diseases in the Netherlands

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Background: In the Netherlands, around 8,8 million people suffer from some form of chronic disease. Comorbid depression and axiety are often found in patients suffering from chronic immune disease. Untreated and undetected anxiety and depressive symptoms may increase physical disability and morbidity and may affect health-care utilization. The risk of comorbid depression in patients with other chronic diseases has not been fully explored. Understanding the use of antidepressants among patients suffering from different chronic diseases may lead to new methods of (mental) treatment for patients suffering from chronic diseases.
Objectives: To understand the relation between chronic use of medication for different diseases and the use of antidepressants and anxiolytics.
Methods: The NControl database containing prescription data of 800 pharmacies and over 7 million patients in The Netherlands was used. Patients that received frequent dispensings of COPD medication, statins (cardiovascular disease), oral glucose lowering medications (type II diabetes mellitus), dermatology medications (anti-psoriatics and eczema treatments) and patients that received DMARDS (rheumatic arthritis) were analyzed for concomitant chronic dispensings of antidepressants and anxiolytics. The WHO Anatomical Therapeutic Chemical (ATC) codes were used to identify these medications. Patients of age 55+ that received 2 or more of these drugs per year between 2014 and 2018 were included. We also included two control groups of patients aged 55+: the first with patients that received medication in at least 2 out of these 5 years and that were not included in the groups of chronic patients, and one control group of patients with dispensed medications in less than 2 years and that were not included in any of the previous groups.
Results: We found that patients that suffer from the studied chronic diseases have a higher risk of using anti-depressants or anxiolytics than patients in the control groups. 49.9% of all patients that are treated for dermal problems, 48% of patients that receive COPD treatment, 44.9% of patients that receive DMARDS, 40.1% of patients that received oral blood glucose lowering medication, and 39.5% of all patients that receive statins are also treated for depression or anxiety, compared to 31.2% of our first control group, and 15.6% of our second control group.
Conclusions: Patients that suffer from chronic diseases have a higher risk of also being treated for depression and anxiety.

564 | Factors associated with deep brain stimulation surgery for Parkinson's disease: Examining medication use and patient characteristics

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Background: Prior studies have shown that deep brain stimulation (DBS) is superior to medical management alone for severe motor complications of Parkinson's disease (PD), and may enhance activities of

daily living and quality of life. Currently, there are limited data on PD medication use prior to DBS surgery.

Objectives: The objectives of our study were (1) to describe the use of PD medications in the 2-year period prior to surgery for DBS cases and matched controls and (2) to examine whether patient factors, including use of multiple PD medication classes, were associated with undergoing DBS surgery.

Methods: We used several health administrative datasets (Ontario, Canada) to examine DBS surgery within a cohort of individuals diagnosed with incident PD between 1995–2009 at age 40 years or older. Patients undergoing DBS surgery were matched with up to 4 non-DBS controls by age, sex, and time with PD. Analyses of prior use of PD medications were restricted to a subset of the matched cohort who were 67 years of age or older at their surgery/index date. Associations between patient characteristics and receipt of DBS surgery for PD were estimated using conditional logistic regression models.

Results: There were 46,237 individuals with PD in our cohort, with 747 patients (155 DBS cases, 592 controls) included our analyses of PD medications. Compared to controls, patients receiving DBS surgery were more likely to have used individual PD medication classes in the previous 2-year period, including levodopa (92.3% vs. 70.4%), non-ergot dopamine agonists (56.1% vs. 26.2%), ergot dopamine agonists (11.6% vs. 6.1%), monoamine oxidase B inhibitors (12.9% vs. 10.5%), catechol-o-methyltransferase inhibitors (38.1% vs. 16.0%), anticholinergics (7.7% vs. 5.7%), and amantadine (45.2% vs. 17.2%). Relative to patients treated with fewer medications, those treated with a greater number of unique PD medication classes in the previous 2 years were more likely to undergo DBS surgery (5+ vs. 0–2 PD medication classes: adjusted odds ratio = 4.95, 95% CI = 1.85–13.25). Other factors, such as neighborhood ethnic concentration, were also found to be associated with DBS surgery.

Conclusions: Patterns of PD medication use may serve to identify eligible candidates for DBS surgery. Future studies should examine whether identified disparities in DBS surgery are attributed to patient preference, established care and referral pathways, or differences in the biological need for DBS.

565 | The utilization of first and second-generation antipsychotic drugs in Denmark from 1999 to 2017: A study using population-based data

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Background: Both first generation antipsychotics (FGA) and second-generation antipsychotics (SGA) may cause serious adverse events ranging from metabolic disorders to possible changes in brain structure and volume or desensitization of dopamine receptors, that may eventually cause relapses of the psychotic disorders. Despite the wide usage of antipsychotic drugs and the approval and marketing of several new substances during the last two decades, little information is available on longitudinal utilization patterns and the use in specific age groups.

Objectives: To analyze the consumption of antipsychotic drugs in Denmark with a focus on the transition from FGA to SGA and the utilization pattern of SGA.

Methods: Nationwide data on outpatients' purchase of antipsychotic drugs was obtained from national statistics on the total drug sales in Denmark (Medstat.dk) during the period 1999 to 2017. The annual use in million DDDs (MDDD) and the number of users was retrieved for FGA, SGA, and single substances (ATC codes), stratified on 5-year age groups and sex. The one-year prevalence of use and average consumption in DDD/user/year was calculated for all strata.

Results: The total consumption of FGA decreased from 9.180 MDDD in 1999 to 2.743 MDDD in 2017. Conversely, SGAs consumption significantly increased from 3.481 to 18.209 MDDD. During the study period, among the five most highly used SGA clozapine, olanzapine, quetiapine, aripiprazole and risperidone, there was a distinct increase in preference towards quetiapine and aripiprazole when compared to the other SGA. Clozapine use was slightly decreasing throughout the period. Age-specific prevalences and annual average use revealed a middle-aged population treated with higher doses/longer duration and an elderly population treated with lower doses/shorter duration. Considerable variation in use was observed among the drugs.

Conclusions: Our study explored the longitudinal use of antipsychotics showing a transition from FGA to SGA and an increasing preference for quetiapine and aripiprazole during later years. Furthermore, populations with distinct utilization patterns were identified: younger and middle-aged patients (likely with chronic psychosis, e.g. schizophrenia) and elderly (probably with acute psychosis or symptoms related to dementia).

566 | Real-world evidence for treatment patterns of patients diagnosed with depression in the United States

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Background: Understanding treatment patterns is vital to understand how patients are treated in the real world, and to identify potential non-responders who might require alternative or new treatment options.

Objectives: To describe the current patterns and duration of medication use for the treatment of depression and its symptoms in patients diagnosed with depression.

Methods: We identified patients diagnosed with depression from a large national claims database of commercially insured individuals. The index date was the first observed medical claim in the database with a diagnosis of depression. Patients were required to have continuous enrollment in the database at least one year prior to and three years following the index date. Patients were excluded if they had evidence of treatment for depression more than 30 days prior to index.

Treatment patterns were captured at the class level and included selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), anxiolytics, hypnotics/sedatives, and antipsychotics. Treatment patterns were captured during all available follow-up, a minimum of 3 years.

Results: We identified 102,738 patients diagnosed with depression. The median patient age was 58 years [interquartile range = 35 to 70 years] and 66% were female. One quarter (26%) of patients did not receive any pharmacological treatment during follow-up. Of the treated, 56% received ≥2 different classes of therapy, while 25% received ≥3 classes and 8% received 4 or more. Sixty-four percent of patients first received an SSRI or SNRI, however 34% received an anxiolytic, hypnotic/sedative, or antipsychotic as the first treatment prior to any antidepressive treatment. Anxiolytics and SNRIs were the most common 2nd and 3rd treatments received, while antipsychotics were the most common 4th treatment, received by 24% of patients with at least 4 different treatments. Patients remained on their first treatment for an average of nine months.

Conclusions: More than a third of patients received a non-antidepressant as their first treatment. More than half of patients received more than one type of antidepressant or a completely different treatment class - anxiolytics, hypnotics, or antipsychotics - during the study follow up, suggesting that the first treatment received may not be optimal for most patients.

567 | Levodopa misuse/abuse among patients with Parkinson's disease

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Background: Levodopa, often combined with carbidopa or with carbidopa/entacapone to improve its bioavailability, is indicated to treat symptoms of Parkinson's disease (PD). A small portion of PD patients are thought to misuse/abuse levodopa, developing a pattern of compulsive self-medication called Dopamine Dysregulation Syndrome (DDS), in which patients increase their dosage despite experiencing harmful consequences of high levodopa dosage.

Objectives: To describe prevalence, risk factors, and trends of levodopa misuse/abuse among PD patients.

Methods: We extracted published epidemiologic studies on DDS or misuse/abuse of levodopa using PubMed on June 18, 2018 using search terms related to [Parkinson's disease] and [levodopa] and [(dopamine dysregulation syndrome) or (misuse) or (abuse)]. We analyzed patterns of US poison center exposure calls (2008–2017) related to levodopa from the National Poison Data System (NPDS) and U.S. outpatient retail utilization patterns for levodopa-containing products from IQVIA™ (2013–2017) to provide context for misuse/abuse calls over time.

Results: Twenty-eight studies reported incidence, prevalence, or risk factors for misuse/abuse of levodopa among PD patients. Among the general PD population, reports of levodopa misuse/abuse prevalence ranged from 0–7.4%. High-risk sub-populations, including patients with compulsive behavior disorders (4–58.8%) and candidates for surgical sub-thalamic stimulation (0–20.6%), reported higher prevalence of misuse/abuse. Patient characteristics associated with levodopa misuse/abuse included: male gender, early onset PD, history of drug abuse or compulsive behaviors, mood disorders, and high daily dose of levodopa. U.S. retail drug utilization data showed the number of patients taking levodopa in the outpatient setting ranged from an estimated 541,000 patients in 2013 to 580,000 in 2017; including long-term care pharmacies, the number of tablets dispensed increased from 570 to 721 million tablets during the same span. We identified 11,985 NPDS exposure calls related to levodopa from 2008–2017, including 230 (1.9%) misuse/abuse calls. From 2013 to 2017, the years with available drug utilization data, the rate of levodopa misuse/abuse calls increased from 3.5 to 5.7 calls per 100,000 patients with a prescription for levodopa.

Conclusions: The epidemiologic literature and epidemiologic data suggest misuse/abuse of levodopa occurs among some PD patients. However, one summary estimate for PD patients may not be appropriate, as prevalence varies substantially based on patient characteristics.

568 | Regional variation and increasing Gabapentinoids prescribing in England

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Background: Gabapentinoids (GPNs; i.e. gabapentin and pregabalin) will be classified as controlled substabces in the United Kingdom (UK) from April 2019, due to increasing concerns of probable drug-misuse deaths. Medication use is often linked with geographical variation and health inequality, but variations of GPN utilization is still not fully understood in the UK.

Objectives: This study aimed to quantify the amount and trend of prescription GPNs in England and identify the geographical variation in use.

Methods: This cross-sectional study applied practice-level dispensing data from the UK National Health Service Digital and the estimated population sizes from the Office for National Statistics between January 2011 and December 2017. GPNs prescribed by general practitioners in England were identified from the dispensing data. The annual utilization of GPNs dispensed in England was calculated in the number of defined daily doses (DDD)/1000 registrants. In 2017, the 7467 general practices were grouped into 207 clinical commissioning groups (CCGs) and ranked by the GPN utilization. Descriptive statistics were used to report annual utilization and its trend from 2011 to 2017. The CCG regions with top GPN utilization in 2017 were identified.

Results: The annual DDD/1000 registrants of prescribed GPNs significantly increased 140% from 1847 in 2011 to 4450 in 2017, with an

increasing annual rate of 442 DDD/1000 registrants per year. The increasing trend is consistent when stratified into gabapentin and pregabalin. In 2017, the median DDD/1000 registrants across the 207 CCGs was 4247 (interquartile range: 2857, 5302). The majority of CCGs with the highest GPNs utilization was in the North of England. Five of the top 10 ranking CCGs of GPN utilization were situated in the North West.

Conclusions: The prescribing of GPNs markedly and steadily increased in England. There is a North–South divide in prescribing GPNs with the North having a larger use than the South, which is potentially related to socioeconomic status. Further study is needed to identify the determinants of increasing GPNs prescribing and the associated harms.

569 | Characterization of gabapentin use in Kentucky

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Background: Due to high prevalence of gabapentin among Kentucky (KY) drug overdose decedents and concerns for possible misuse in communities, gabapentin was reclassified as a Schedule V controlled substance (CS) in KY, effective July 2017.

Objectives: The purpose of this study was to characterize gabapentin use in KY.

Methods: We used Kentucky All Schedule Prescription Electronic Reporting (KASPER) data (Oct 2017-Sep 2018). Gabapentin use was defined as having received at least one gabapentin prescription during the study period. Gabapentin use rates, including by age, sex, and region, were calculated based on 2017 annual estimates of the resident population. Choropleth maps were created to examine regional variations in county-level gabapentin rate. Concurrent use of gabapentin with opioids, pregabalin, and benzodiazepines (BDZ) with 7+ continuous overlapping days was assessed.

Results: The overall state rate of gabapentin use was 66.3 per 1,000 residents, with highest rates among residents 55–64 years of age (133.4/1,000). Rates of gabapentin use were significantly higher in females vs. males [rate ratio (RR): 1.47; 95% confidence interval (CI): 1.46–1.48]. The prevalence of gabapentin use was significantly higher in eastern Kentucky counties, Appalachian region vs. Central region [RR: 1.73; 95% CI: 1.72–1.75] and Appalachian region vs. Delta region [RR: 1.36; 95% CI: 1.34–1.37]. The median days' supply of gabapentin during study period was 179 days and the median daily dose was 911.0 mg. The median days' supply of gabapentin and the median daily dose was significantly higher in Appalachian region [227 days; 1200 mg] than Central region [153 days (p-value: <0.001); 900 mg (p-value: <0.001)] and Delta region [170 days (p-value: <0.001); 900 mg (p-value: <0.001)]. Among gabapentin users, 44.6%, 19.5%, and 1.8% had 7+ continuous overlapping days with opioids, BDZ, and pregabalin, respectively.

Conclusions: Given that gabapentin use is more frequent in vulnerable populations (older age, female, and eastern Kentucky counties), further studies should examine the factors related to gabapentin prescribing and risk of having overlapping days with other CS.

570 | New treatments for comorbidities after diagnosis with multiple sclerosis (MS): A study in the UK clinical practice research datalink (CPRD) GOLD

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Background: Patients with MS have an elevated risk of many comorbid conditions. Few studies have examined patterns of new treatment use for these conditions after MS diagnosis.

Objectives: To describe the patterns of new treatments for comorbid conditions in MS patients compared with matched non-MS patients.

Methods: We conducted a cohort study in the UK CPRD GOLD. Each MS patient diagnosed from 2001–2015 with ≥1 year of pre-diagnosis history was matched with up to 10 non-MS patients on age, sex, general practice and record history length before cohort entry (MS diagnosis/matched date). We compared new use of treatments for comorbid conditions in years 0 to <2 and 2 to <4 after cohort entry using a chi-square test. Prevalent users (patients with at least one prior prescription in the year before cohort entry) were excluded separately from each treatment category.

Results: 6932 MS patients were identified and compared with 68,526 non-MS patients (female, 70%; median age at cohort entry, 43 years). In both time periods, MS patients had higher use of antihypertensives (years 0–2: 7.9% vs. 5.3% [$p < 0.0001$] and years 2–4: 5.9% vs. 5.1% [$p = 0.03$]), immunosuppressants for non-MS autoimmune disorders (years 0–2: 1.2% vs. 0.5% [p < 0.0001] and years 2–4: 0.6% vs. 0.4% [$p = 0.01$]), proton pump inhibitors (PPIs) (years 0–2: 14.9 vs. 7.6% [p < 0.0001] and years 2–4: 10.8 vs. 7.7% [p < 0.0001]), antibiotics (years 0–2: 39.1 vs. 31.7% [p < 0.0001] and years 2–4: 30.2 vs. 24.9% [p < 0.0001] and sexual dysfunction treatments (males) (years 0–2: 11.0 vs. 1.6% [p < 0.0001] and years 2–4: 6.2 vs. 1.8% [p < 0.0001]). Anticoagulant use was higher in years 0–2 (0.5% vs. 0.3% [$p = 0.013$]) but not years 2–4 (0.4% vs. 0.4%). MS and non-MS patients had similar new use of asthma/COPD treatments, but the percentage of new users changed over time (years 0–2: 5.2 vs. 5.0% [$p = 0.66$] and years 2–4: 3.2 vs. 3.6% [$p = 0.10$]). Use of the following drug categories were similar for MS and non-MS patients and percentage of new users was consistent over time: statins (~2.5%),

other CVD treatments (~0.7%), insulin (~0.2%), and other hypoglycemics (~0.8%) [all $p > 0.05$].

Conclusions: In the UK CPRD GOLD, MS patients had a higher incident use of antihypertensives, autoimmune treatments, PPIs, antibiotics and sexual dysfunction treatments than matched non-MS patients. Use of anticoagulants was higher in the first 2 years after MS diagnosis.

571 | Comorbid conditions and medications in post traumatic stress disorder patients: A retrospective analysis of a large United States electronic health record database

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Background: Post Traumatic Stress Disorder (PTSD) is a mental health condition which develops after experiencing a traumatic event. Epidemiologic studies have demonstrated that over 90% of people with PTSD have at least one lifetime comorbid mental disorder which may influence the treatment choice for PTSD.

Objectives: The main objective of the present study was to evaluate mental health conditions and treatments of PTSD patients.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All outpatient visits (age ≥ 18 years) between 2012 and 2016 with a principal ICD9/10 diagnosis of PTSD were evaluated in this study. Chronic and acute PTSD were defined as a duration of symptoms of >3 months, and 1–3 months respectively. Complications were identified by the corresponding ICD9/10 diagnosis codes. Medications were classified into categories (antidepressants and anti-anxiety) for further examination.

Results: A total of 46,560 patients with PTSD were identified in the database, corresponding to 197,856 outpatient visits, likely indicating multiple visits per patient. Chronic PTSD was diagnosed in 43.2% of visits, while 1.9% of visits were associated with acute PTSD. The majority of visits (74.1%) comprised female patients. It was also observed that the highest percentage of PTSD patients were in the age group of '36–65 years' (67.2%). Other mental health conditions prevalent in PTSD patients were depression and anxiety (49.0%), followed by issues with drugs, substance, and alcohol use (18.3%), eating disorders (2.6%), and suicidal thoughts and actions (0.1%). Prescriptions combining anti-anxiety medications and antidepressants (41.3%) were the most common, followed by anti-anxiety medications only (39.1%) and antidepressants only (19.6%).

Conclusions: This large database analysis provides insight into the real-world evidence of mental health conditions that pose as both risk factors and/or complications of PTSD, and their impact on medication prescribing to treat PTSD patients.

572 | Predictors for methylphenidate initiation in young individuals in the Netherlands

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Background: Methylphenidate is widely used to treat children with attention deficit hyperactivity disorder (ADHD), but the reason to initiate pharmacological treatment remains unclear. Multiple factors may contribute to the decision to start treatment, including parents. However, relatively little is known about their characteristics as predictive factors for treatment initiation.

Objectives: To examine the parental characteristics as predictors for initiating pharmacological treatment with methylphenidate among children.

Methods: A follow-up study in a cohort of children within a large prospective population-based cohort investigating children's health from fetal life onwards in Rotterdam, the Netherlands. Children were included if their mother gave full consent for postnatal follow-up. Children were excluded if no pharmacy records could be obtained. The outcome was defined as having a dispensing pharmacy record of methylphenidate for the first time since birth. We evaluated parental characteristics as potential determinants of methylphenidate initiation through univariable and multivariable logistic regression analysis. A Cox proportional hazard model was used to evaluate these potential determinants among children whose mother have completed the Child Behavior Check List at the age of 18 months, 1.5, 5 and 9 years.

Results: Overall, we found that these 4,243 children were less likely to receive methylphenidate when mothers have a Turkish/Moroccan (OR_{adj}: 0.43, 95%CI: 0.21–0.86) or Surinamese/Antillean background (OR_{adj}: 0.35, 95%CI: 0.17–0.74) compared to Dutch mothers, or if they had received a lower education (OR_{adj}: 1.57, 95%CI: 1.12–2.21) or if they were smoking during pregnancy (OR_{adj}: 1.52, 95%CI: 1.01–2.28). Similar results were observed for fathers. Of children where the questionnaire was completed, we found that children with elevated ADHD symptoms born to a Turkish/Moroccan (OR_{adj}: 0.19, 95%CI: 0.06–0.62) or other non-western (OR_{adj}: 0.17, 95%CI: 0.05–0.55) mother, were less likely to receive methylphenidate treatment than children of Dutch mothers. ADHD symptoms were more present in these groups (Turkish/Moroccan OR: 1.60, 95%CI: 1.56–1.64; Surinamese/Antillean OR: 2.22, 95%CI: 2.16–2.27; other non-western OR: 1.90, 95%CI: 1.85–1.94).

Conclusions: Our study indicates that children were less likely to receive methylphenidate prescriptions when their mothers have an ethnic minority background, were lower educated or were smoking during pregnancy. ADHD symptoms were more frequently reported in ethnic minority groups, but they were less likely to receive methylphenidate.

573 | Use of atypical antipsychotics in the Brazilian health system: Profile of users and their self-perception of health

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Background: Psychotic disorders are relatively common mental disorders and are usually treated with antipsychotics, which mainly aim to minimize the loss of functionality of individuals. In Brazil, in the scope of the national health system, there are policies that direct the health care of people with mental disorders, promoting the guarantee of integral care and access to medicines, among which are atypical antipsychotics.

Objectives: To describe the profile of atypical antipsychotic users and their self-perception of health in a public pharmacy in Brazil.

Methods: A cross-sectional study was conducted with users of atypical antipsychotics in a public pharmacy in Brazil. The patients were invited to the interview and answered the questionnaire, after free and informed consent. Sociodemographic, economic and clinical data were collected. Self-reported health status was measured by a visual analog scale, where "zero" was the worst and "100" the best possible state of health. The survey was conducted between September-2017 to March-2018 and data processed in November-2018.

Results: This study included 388 individuals who met the eligibility criteria. For the sociodemographic characteristics, a majority of male (55.2%; *n* = 214) and mean age of 46.1 years (SD 11.8) were identified. Most of the individuals had no spouse (77.3%; *n* = 300) and studied until high school (68.0%; *n* = 264). It was observed that only 16.2% of the individuals were working at the time of the interview and that 81.7% had a monthly family income of up to US$ 1,002.74. For the clinical characteristics, 49.0% of the interviewees reported having no disease other than psychotic disorder, most (50.3%) performed their psychiatric consultations in the public health sector, 35.5% had undergone an abortion and 34.8% % of respondents have already made at least one suicide attempt. The majority of the patients reported using olanzapine (35.6%, *n* = 138), followed by quetiapine (18.6%, *n* = 72), ziprasidone (18.3%, *n* = 71), clozapine (16.8%, *n* = 65) and risperidone (10.8%, *n* = 42). For the state of health, a better self-perception was associated with the use of clozapine, with a mean VAS of 75.0 (SD 20.3), while for the other atypical antipsychotics a mean VAS of 65.2 was reported (SD 24.7 $p = 0.008$).

Conclusions: The importance of knowing the profile of the population with psychotic disorders and identifying the factors that interfere in the health of these individuals is to enable the prioritization of more efficient policies to guarantee the improvement of health care and quality of life of this population, often in a situation of vulnerability.

574 | Benzodiazepine drugs utilization studies at few Indian hospitals

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Background: Benzodiazepine group of drugs are frequently prescribed for treatment of patients with anxiety and insomnia as anxiolytics, hypnotics, tranquilizers, anticonvulsants, etc. Owing to their diverse usages in different clinical specialities, there is a need to assess utilization studies of benzodiazepines.

Objectives: To assess utilization pattern of benzodiazepine class of drugs at few selected hospitals of an Indian city.

Methods: A prospective observational study design was adopted including patients of either sex, aged more than 18 years and who received benzodiazepine in their prescription during the study period visiting the study site. The required informed consent was obtained prior to the enrollment in the study. A standard data collection form was used to record the required patient information which included demographic details, diagnosis, medication, etc.

Results: Out of 473 patients receiving benzodiazepine in their prescription, majority of the patients were diagnosed with schizophrenia (36.45%) followed by anxiety disorder (21.23%). Among the various benzodiazepines used, clonazepam (52.43%) was the most prescribed drug followed by lorazepam (46.28%) apart from few fixed dose combination drug products.

Conclusions: The study revealed that the usages of benzodiazepine was in accordance to the treatment guidelines. Mostly, the drugs are utilized in psychiatric specialties and the most commonly prescribed drug in the class is Clonazepam.

575 | One-year persistence of potentially inappropriate medications use in older adults: A population-based study in Quebec, Canada

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Background: The use of potentially inappropriate medications (PIMs) is associated with negative health outcomes. Although previous studies have assessed the trend of PIM use over time, none has determined whether PIMs are used continuously in the same individuals.

Objectives: To assess one-year persistence of PIM use and to identify factors associated with such persistence in community-dwelling older adults.

Methods: We conducted a retrospective population-based cohort study of community-dwelling older adults aged ≥66 years in Quebec, Canada, using the Quebec Integrated Chronic Disease Surveillance System. To be included, individuals had to be continuously insured with the public drug plan between April 1st, 2013 and March 31st, 2015. We defined PIMs according to the 2015 Beers Criteria's list of drugs that should be avoided. Individuals who initiated a PIM between April 1st, 2014 and March 31st, 2015 (no PIMs prescription in the previous year) and who had at least one-year follow-up after the first PIM dispensing were retained in the study. Persistence of PIM use at one year was defined as a continuous treatment with any PIM, with no interruption longer than 60 days between prescriptions refills. Similarly, we measured one-year persistence of specific PIM use in subcohorts of individuals who had initiated those specific PIMs. Multivariate robust Poisson regressions were performed to identify factors associated with one-year persistence. Results were reported as rate ratios (RR) with their 95% confidence intervals.

Results: Among the 75 844 older individuals who initiated a PIM, 25.1% (95% CI: 24.8%–25.4%) had a persistent use of at least one PIM over a one-year period. The median time to first PIM discontinuation was 31 days (IQR: 21–92) in non-persistent individuals. The probability of persisting at one-year was higher for those who initiated peripheral alpha-blockers (50.5%), antipsychotics (43.9%), long-duration sulfonylureas (40.2%) and proton pump inhibitors (36.0%). Factors significantly associated with persistence of PIM use included being older (≥86y, RR: 1.82; 1.76–1,89), being a man (1.13; 1.11–1.15), and having a higher number of medications and chronic diseases (ranges 1.06–1.34/1.18–1.62), specifically the presence of Alzheimer disease and related disorders (1.81; 1.74–1.89).

Conclusions: A quarter of older adults initiating a PIM is persistently exposed to at least one PIM the whole following year. There is a need to further explore if persistent use of PIM leads to a higher risk of adverse events than sporadic use.

576 | Changes in schizophrenia documentation in nursing home residents varies by antipsychotic exposure, dementia, and race

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Background: Since the CMS National Partnership to improve dementia care, the inappropriate use of antipsychotics in nursing home (NH) residents has been reportedly decreasing. However, the National Partnership may have contributed to an increase in schizophrenia reporting, perhaps as a means to reclassify inappropriate antipsychotic use as appropriate.

Objectives: The purposes of this work were to examine the effects of the CMS National Partnership on the rate of schizophrenia diagnoses among NH residents given antipsychotics with and without dementia and identify variation in the reporting of schizophrenia between Blacks and non-Blacks. We hypothesized that following the partnership initiative, assessments from NH residents with ADRD would show higher rates of schizophrenia. Furthermore, we hypothesized that Blacks would also experience lower increases in schizophrenia reporting.

Methods: This study used a quasi-experimental difference-in-difference (diff-in-diff) design to test the effect of National Partnership that took effect in March 2012. Using 2011–2015 Minimum Data Set 3.0 resident assessment data, we analyzed the admission assessment for newly admitted NH residents. There were 6 quarters of data prior to and 14 quarters post partnership initiative. Trends in schizophrenia diagnoses for residents with and without Alzheimer's disease and related dementias (ADRD) and according to Black versus non-Black race were compared.

Results: There were over 8.5 million new admission assessments. The overall rate of schizophrenia reported on assessments declined for both ADRD and non-ADRD residents after 2012, though the decline was less for those with ADRD (Δ = 0.056%) compared to those without ADRD (Δ = 0.260%) (Diff-in-diff = 0.00204; $p < 0.001$). Schizophrenia rates also dropped for ADRD and non-ADRD residents after 2012, except for those on an antipsychotic at the time of assessment (Diff-in-diff = 0.01603; $p < 0.001$). They saw a 3.3% increase in reported schizophrenia. Among assessments which reported antipsychotic drug use, the rates of schizophrenia increased slightly after 2012 (Diff-in-diff = 0.024; $p < 0.001$), but the increase was greater for Black residents (6.25%) as compared to non-Blacks.

Conclusions: These findings show that there have been statistically significant changes in the documentation of schizophrenia on MDS assessments. However, changes, direction, and magnitude depend upon the subpopulation under consideration. Those who use antipsychotics and Blacks have seen small but significant increases in diagnostic coding, which call for further investigation.

577 | Treatment patterns among elderly patients diagnosed with diffuse large B-cell lymphoma in the United States

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive Non-Hodgkin Lymphoma (NHL), accounting for a third of all new NHL diagnoses in the United States (US) and generally occurs in elderly with a median age at diagnosis of 70 years. For previously untreated patients, CHOP-like chemotherapy (R-CHOP) is the standard of care. For patients not cured by front-line therapy there is a need for effective subsequent treatment.

Objectives: To describe the treatment patterns of elderly DLBCL patients in the US enrolled in Medicare.

Methods: Patients diagnosed with DLBCL between 2004–2011 were identified from the SEER-Medicare linked database. Patients aged 65 years or older at diagnosis, with no evidence of hospice care prior to diagnosis, and 12 months of continuous enrollment in Medicare Part A and Part B prior to diagnosis were included in the analysis. Chemotherapy, stem cell transplant (SCT), and immunotherapy claims were used to construct lines of therapy after initial diagnosis. The proportion of patients treated in first line (1 L), second line (2 L), and third line (3 L) were reported. The most common regimens for each line of therapy were described.

Results: Of 22,004 DLBCL patients (50% male, median age: 78y) meeting the selection criteria, 52.7% (*N* = 11,603) were treated on or after initial diagnosis. 7,943 patients (76.3% of untreated patients) died without receiving treatment. 3,615 patients were treated in the 2 L setting and 1,121 were treated in 3 L. The most common regimens in the 1 L setting were R-CHOP (58.7%), rituximab (RTX) monotherapy (9.9%), and R-CVP (6.5%). The three most common 2 L regimens were RTX monotherapy (14.1%), R-CHOP (11.3%), and rituximab and bendamustine (R-Benda) (5.9%). In the 3 L setting, the most common regimens were RTX monotherapy (12.4%), R-Benda (7.8%), and SCT (6.4%). There were 219 (1.9%) treated patients that received SCT, with most occurring in a 2 L+ setting (85.4%, *n* = 187).

Conclusions: Among treated elderly DLBCL patients, most are receiving guideline recommended therapies in the 1 L setting. Treatment in the 2 L and 3 L setting is more heterogeneous indicating the difficulty of treating relapsed or refractory (R/R) disease. Recent approvals of chimeric antigen receptor T-cell (CAR-T) therapies will offer new options for R/R disease. Further studies are necessary to understand the most effective regimens in the R/R setting.

578 | Attitudes towards Deprescribing in older adults with limited life expectancy: Two systematic reviews

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Background: Deprescribing of unnecessary medications is particularly relevant in older adults with limited life expectancy, as they have a considerable use of prescription drugs and are generally more susceptible to the potential harms of multiple medications.

Objectives: To explore the attitudes of health care professionals (HCPs), as well as patients and their relatives towards deprescribing in older adults with limited life expectancy by performing two systematic reviews.

Methods: We conducted a systematic literature search from inception to December 2017 using MEDLINE, EMBASE, and CINAHL. Both quantitative and qualitative studies were included if they concerned older people with limited life expectancy, including older people residing in any kind of aged care facility, or were based on representative patient profiles. The studies included in the review of HCPs' attitudes towards deprescribing were analyzed with inspiration from Joanna Briggs Institute's method for synthesis of qualitative data in systematic reviews. Results from the studies concerning the attitudes of older adults and their relatives were obtained by narrative synthesis.

Results: Eight studies were included in the review of HCPs' attitudes towards deprescribing in older adults with limited life expectancy. The studies mainly concerned the views of general practitioners and other physicians. Factors that influenced HCPs' decisions to initiate or suggest deprescribing in this population were related to four overall themes: 1) Patient and relative involvement, 2) The importance of teamwork, 3) HCPs' self-efficacy and skills, and 4) The impact of organizational factors. Six studies were included in the review of the attitudes of older adults and their relatives. A number of facilitators and barriers to the process of deprescribing in older people with limited life expectancy were identified. Facilitators included discussing the deprescribing process with HCPs, experiencing adverse events and weaning off the medications, while barriers included fear of deterioration, acceptance of condition, and lack of current harm.

Conclusions: We have identified multiple and interdependent barriers and facilitators for deprescribing among older adults with limited life expectancy. Initiatives to facilitate deprescribing practices within this population should target several of the possible issues identified.

579 | Potentially inappropriate medications and risk of autonomy loss for activities of daily living in the elderly

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Background: Elderly persons are subject to polypharmacy that may be partly justified but can lead to adverse effects. In this population, explicit criteria were proposed to identify potentially inappropriate medications (PIM) that must be avoided. The prevalence of PIM use was found to be high (40–50%) and the loss of autonomy could be a significant adverse effect associated with PIM.

Objectives: The objectives were i) to estimate the prevalence of PIM use and its evolution over time and ii) to study the relationships between PIM and autonomy loss for Activities of Daily Living (ADL).

Methods: The study was conducted on the *Echantillon Généraliste des Bénéficiaires* (EGB) among people aged 65 and over. ADL-dependency was defined using an algorithm previously developed and validated,

which includes data on reimbursed drugs, medical acts, products and deliveries, chronic diseases, age and sex. PIM were defined based on the Beers 2015 criteria that were considered into two groups: i) PIM + including criteria directly measurable or measurable under conditions that can be identified using EGB data and ii) PIM- including criteria with conditions that are not entirely measurable. The association between PIM and ADL-dependency was analyzed using a delayed entry Cox model with adjustment on the number of drugs used and Charlson's comorbidity index. PIM criteria that were associated with ADL-dependency were determined.

Results: In 2010, 50.5% of elderly subjects had used at least one PIM+ or PIM- and 35.5% at least one PIM+. In 2015, prevalence had decreased by 7%. Most users consumed 1 PIM criterion, 8.5% 2 criteria and 3.5% ≥3 criteria. PIM related to CNS were the most commonly used, especially BZD and BZD-related hypnotics. Proton pump inhibitors (PPI) were also frequently used (21.2%). There was an increased risk of ADL-dependency as soon as a PIM criteria was used. Of the 22 PIM+ criteria, first-generation antihistamines, barbiturates, BZD, BZD-related hypnotics, meprobamate and antipsychotics were significantly associated with ADL-dependency. By adding PIM-criteria, 3 additional criteria were significantly associated with ADL-dependency: digoxin, amiodarone and PPI.

Conclusions: This study showed that PIM are still frequently used in the elderly population and were associated with an increased risk of becoming dependent. It is therefore essential to take into account prescribing recommendations in order to better adapt the treatment in the elderly.

580 | Patterns of antipsychotic use among older adults with late-life psychotic disorders

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Background: There are growing numbers of older adults who are diagnosed with schizophrenia and related forms of late-life psychosis (LLP). Antipsychotics are necessary medications for the majority of individuals with LLP although there are few randomized controlled trials of antipsychotics (APs) for individuals with LLP and this population may be susceptible to AP related side-effects. There is limited information available about the current patterns of AP use among individuals with LLP. Our study examined the patterns of antipsychotic use among older adults with LLP in Ontario, Canada.

Objectives: 1.) To describe AP use among older adults with LLP in Ontario, Canada including types of antipsychotics (typical or atypical antipsychotics), patterns of use (monotherapy, polypharmacy), routes of administration, and dose equivalencies.

Methods: We undertook a cross-sectional study to describe the patterns of AP use among older adults LLP using linked administrative databases at ICES at Queen's University. We identified all adults in the province of Ontario, Canada who met case criteria for LLP using an algorithm for psychotic disorders. Individuals age 66 years or older who met cohort inclusion criteria were included in the study sample. Exposure to AP medications was determined using outpatient prescription medication claims in the 120 days preceding index. AP use was characterized as typical AP or atypical AP as well as whether AP use was monotherapy or polypharmacy. Dosage of AP were recorded for each AP and converted to Olanzapine equivalents. Descriptive statistics were used to summarize AP use within the study sample.

Results: There were 48,354 individuals in the LLP cohort using the sensitive case definition. In the study sample 52% received no AP, 33% received atypical AP monotherapy 6% received typical AP monotherapy and 8% received AP polypharmacy. The respective AP categories in the sensitive cohort definitions were: no AP 28%, atypical AP monotherapy 44%, typical AP monotherapy 44%, and AP polypharmacy 21%. In the sensitive cohort, individuals receiving AP polypharmacy had the highest mean daily (SD) Olanzapine dose equivalents 24.5 mg (22.9 mg), followed by typical AP monotherapy 9.49 mg (15.7 mg), and atypical AP monotherapy 8.1 mg (8.3 mg).

Conclusions: Our large population-based study found variation in the patterns of AP use among older adults with LLP. Some prescribing practices such as high-doses of AP medications and polypharmacy may be associated with adverse events in this population and the outcomes associated with different patterns of AP prescribing require further study.

581 | Risk of major bleeding in elderly users of non-vitamin K antagonist Oral anticoagulants according to advanced age

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Background: Recently, use of non-vitamin K antagonist oral anticoagulants (NOAC) are increasing worldwide. However, evidence on the bleeding risk associated with increasing age among elderly NOAC users have been lacking.

Objectives: We aimed to investigate risk of major bleeding in elderly NOAC users in different age groups.

Methods: We performed a case-crossover study using Korea Insurance Review and Assessment Service-Aged Patient Sample database during January 1, 2016 to December 31, 2016. Aged patients with hemorrhagic events using NOAC were included. Major bleeding events were defined as gastrointestinal, cerebrovascular, or other bleedings. We defined the case period as 1 to 30 days and the control period as 60 to 90 days, respectively, before the date of hemorrhagic event. We categorized aged patients into 3 groups (65–74, 75–84, and 85 or older). Odds Ratios (ORs) with 95% confidence intervals (CIs) were calculated by conditional logistic regression.

Results: A total of 8,042 patient with bleeding were studied, with means age of 75.5 (±6.2) years, of whom 4,601 (57.21%) were female. The number of patients using dabigatran, rivaroxaban, apixaban, and edoxaban was 1,570 (19.5%), 4,758 (59.2%) 1,773 (22.0%), and 685 (8.5%). The OR of bleeding associated with NOAC use was 2.85 (95%, CI 2.50–3.20). The OR of major bleeding in each age groups was 2.86 (95% CI, 2.38–3.42) for 65–74 years, 2.79 (95% CI, 2.32–3.34) for 75–84 years, and 3.19 (95% CI, 2.02–4.96) for 85 years or older.

Conclusions: Major bleeding events needs to be carefully monitored in elderly patients using NOAC, especially in patients aged 85 years or older. Additional factors including diseases and NOAC dose need to be further investigated.

582 | Real-world evidence of statin effectiveness in older adults

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Background: Uncertainty regarding the benefit, if any, of statin use in the elderly persists. This population is poorly represented in trials, and those that are included rarely have the complex constellation of comorbid conditions typically present in patients age 75 and older.

Objectives: Among older patients at elevated cardiovascular risk, estimate the effect of statin initiation on 2-year all-cause mortality.

Methods: Using Medicare fee-for-service data (2007–2013), we identified patients ≥66 years of age at the time of an outpatient visit with 12-months of continuous enrollment, at elevated cardiovascular risk, with no major contraindications to statin initiation and no statin prescription fills in the preceding year. We classified patients with a statin claim in the 14 days after the index visit as exposed (otherwise unexposed) and assessed all-cause mortality over 2-years of follow-up. Level II CPT codes were used to control for differences in low-density lipoprotein (LDL), HbA1C, systolic and diastolic blood pressure at baseline. (We used multiple imputation [*N* = 20] to impute values for patients without a baseline level coded.) Propensity score models were fit within strata of sex and age (≤75, >75 years) to allow covariate effects to vary between these patient subgroups. We estimated relative and absolute effects of statin initiation within these subgroups using standardized mortality ratio weighting (SMRW) with 1% asymmetric trimming.

Results: We identified 646,394 eligible patients, 13% of whom initiated a statin within 14 days of an index visit. Median 2-yr mortality was 8%. Crude estimates indicated implausibly strong effects in some groups and substantial heterogeneity (e.g. RR = 0.55 among women >75; RR = 0.75 in men ≤75). After adjusting for age and sex specific propensity scores, estimates moved towards the null but statin initiation remained protective in all subgroups. Among those ≤75, effectiveness did not differ by sex (RR_{women} = 0.82, 95%CI: 0.76, 0.89; RR_{men} = 0.85, 95%CI: 0.78, 0.93). Among those >75, statin initiation was more beneficial in women (RR_{women} = 0.79, 95%CI: 0.75, 0.83) than men (RR_{men} = 0.87, 95%CI: 0.81, 0.93). Heterogeneity by age was more pronounced on the absolute scale, while the difference by sex among those >75 was more modest (RD_{women} = −1.7% vs RD_{men} = −1.3%).

Conclusions: Among older adults at elevated cardiovascular risk, we found reductions in all-cause mortality consistent with estimates from prior meta-analyses for patients age 66–75. Among those >75 years of age, the estimated treatment effect in the treated also indicates a benefit in a diverse, real-world patient population.

583 | The association between potentially serious alcohol medication interactions and falls in community dwelling older adults: A longitudinal Irish study

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Background: Assessment and management strategies to prevent falls in community-dwelling older adults stress the importance of taking into account patient's medications. However, observational studies have not considered alcohol-medication interactions as a risk factor for falls in community dwelling older adults, despite the high propensity for concurrent use of alcohol with medications among older adults.

Objectives: The aim of this study was to investigate the association between potentially serious alcohol-medication interactions (POSAMINO criteria), hypothesized to increase the risk of falls in older adults, and falls in community dwelling older adults at two and four years follow-up.

Methods: This prospective cohort study included 1457 community dwelling older adults aged ≥65 years who participated in the nationally representative Irish Longitudinal Study on Aging (TILDA), with complete alcohol and regular medication data to allow for the application of the 23 falls-related POSAMINO criteria. Self-reported falls at two and four years follow-up were assessed including any falls (yes/no); injurious falls (yes/no) and the number of falls (count variable).

Results: In total, 357 (24%) and 608 (41.8%) participants reported falling since their baseline interview at 2- and 4-years respectively; 145 (10%) reported an injurious fall at 2-years and 268 (18%) at 4-years. Median (IQR) number of falls was 1 (1–2) at 2-years and 2 (1–3) at 4-years. Exposure to CNS POSAMINO criteria, hypothesized to increase the risk of falls due primarily to increased sedation, was associated with an increased risk of falls (aRR 1.50, 95% CI 1.21 to 1.88) and injurious falls (aRR 1.62, 95% CI: 1.03 to 2.55) at 4-years, after adjusting for established risk factors for falls in community dwelling older adults.

Conclusions: Exposure to potentially serious alcohol-medication interactions involving CNS agents are positively associated with the risk of falls and injurious falls among community-dwelling older adults at four years follow-up. Assessment and management strategies to prevent falls in community-dwelling older adults should consider patients' alcohol consumption alongside their assessment of patient medications, particularly among those receiving CNS agents.

584 | Potentially inappropriate medications among Chinese older adults in community healthcare institutions in Beijing

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Background: Potentially inappropriate medications (PIMs) are prominent prescribing issues in elderly patients worldwide, enhancing the risk of adverse reactions and negative health outcomes. However, little research has focused on the PIMs of Chinese older adults in community healthcare institutions (CHIs).

Objectives: To evaluate the PIMs prevalence and influence factors associated with PIMs in CHIs for the elderly.

Methods: We conducted a retrospective study, deriving data on diagnoses, prescriptions and demographic characteristics of patients aged ≥60 from the electronic health records of 65 CHIs in Beijing, 2014–2017. *Criteria of PIM for Older Adults in China*, including 28 high-risk medications to be avoided, 44 low-risk medications to be used with caution and 28 medications that could cause drug-disease interactions, were applied to evaluate PIMs. Multivariate logistic regression was used to analyze the influence factors of PIMs. Ethics approval was obtained from Peking University Institution Review Board.

Results: 3,283,254 prescriptions were included in total. The percentage of prescriptions with at least one PIM was 27.0% (30.1%, 24.6%, 25.6% and 27.6% from 2014 to 2017, respectively). 991,141 medications were detected resulting in 0.3 PIMs per prescription on average and the distribution of PIMs in our sample was as follows: 17,955 high-risk medications were identified and the most commonly prescribed PIMs were diazepam (47.2%), lorazepam (21.6%) and alprazolam (20.8%); 354,608 low-risk medications were identified and the most commonly prescribed PIMs were clopidogrel (36.1%), estazolam (31.9%) and ibuprofen (17.3%); 618,578 medications that could cause drug-disease interactions were identified and the nonsteroidal anti-inflammatory drugs use for hypertension patients was the most prevalent (94.1%). Age ≥ 90 (OR: 2.027, 95% CI: 1.992–2.062), with commercial medical insurance (OR: 1.189, 95% CI: 1.093–1.293), having ≥5 prescribed medications (OR 10.244, 95% CI 10.136–10.353) and having 4–6 comorbidities (OR: 3.810, 95% CI: 3.787–3.832) were significant predictors for PIMs.

Conclusions: Prescribing of PIMs for older adults is common in CHIs in China, especially for patients who are aged, having more comorbidities and medications, and insured by commercial medical insurance. PIM Criteria can be used as tools to guide clinicians and pharmacists to identify PIMs. More strategies aiming at promoting prescribing practices and quality use of medicines are needed.

585 | Trends in skeletal-related event hospitalization and use of bone targeting agents in older patients with bone metastases from solid tumors in the United States: 1994–2015

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Background: Skeletal-related events (SREs) are associated with bone metastases (BMs) from solid tumors leading to decreased quality of life and increased healthcare resource utilization, particularly hospitalizations. Clinical trials have shown efficacy of bone targeting agents (BTAs) in reducing SRE incidence, but few population-based studies have examined trends in BTA use and SRE-related hospitalization in older pts with BMs.

Objectives: To describe BTA use and assess rates of first SRE-related hospitalization over time (1994–2015) in a population-based cohort of elderly pts with BMs from solid tumors in the US.

Methods: We assembled period prevalent cohorts of pts with BMs in each year 1994–2015 using Medicare 5% (1993–2007) and 20% (2007–2015) sample data. For each yearly cohort, we required age ≥ 66 years at BM index date and continuous Medicare fee-for-service enrollment for 12 months prior. Pts were followed from BM index date to the earliest of death, disenrollment, or 12/31 of the cohort year. During follow-up, we identified pts with first SRE-related hospitalization (spinal cord compression, pathologic fracture, surgery to bone, radiation to bone) and pts treated with BTAs (pamidronate; zoledronic acid [ZA]; denosumab). We described trends in proportions of pts receiving BTAs and rates of first SRE-related hospitalization over years. We evaluated trends in first SRE-related hospitalization rates using a Poisson regression model with splined curve of calendar year after adjusting for baseline characteristics.

Results: Yearly cohorts included 3599–4559 eligible pts in 1994–2007 and 17,774–19,423 in 2008–2015. Proportions receiving BTAs were < 1% in 1994–1995, steadily increased to 18% in 2001, and dramatically increased to 34%–44% in 2003–2015, mainly due to introduction of ZA in 2002 and denosumab in 2010. Overall, crude rates of first SRE-related hospitalization decreased from 19.5 per 100 patient-years in 1994 to 9.2 in 2015. Rates of first SRE-related hospitalization decreased, on average, 3% each year before 2008 and 4.3% per year from 2008 after adjustment for changing patient characteristics.

Conclusions: From 1994–2015, BTA use increased substantially after 2002 among older pts with BMs from solid tumors, although most pts did not receive a BTA within any given calendar year. Rates of first SRE-related hospitalization decreased over the same time period, with a more rapid decrease from 2008 onwards. Further studies are needed to better understand SRE management among pts with BMs in the real-world setting.

586 | Benzodiazepines and risk of autonomy loss for activities of daily living in the elderly

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Background: Benzodiazepines (BZD) are widely used drugs that can lead to important adverse effects such as falls and fractures, behavioral disorders, and a faster cognitive decline. These effects are mainly observed among the elderly in whom BZD can accumulate. In addition to these effects, BZDs could also increase the risk of autonomy loss among the elderly.

Objectives: The objective of this project was to study relationships between BZD and autonomy loss for Activities of Daily Living (ADL) among the elderly.

Methods: The study was conducted on the *Echantillon Généraliste de Bénéficiaires de l'Assurance Maladie* from 2010 to 2015 among people aged 65 and over affiliated to the general scheme of health insurance. ADL-dependency was defined using an algorithm previously developed and validated, which includes information on reimbursed drugs, medical acts, products and deliveries, chronic diseases, age and sex. BZD use profiles were defined as follows: no use, current use-not chronic (<6 months over 12), chronic use-currently discontinued, chronic and current use. BZD were also categorized into anxiolytics/hypnotics and short/long half-life. After a descriptive analysis of BZD use, the analysis of the association between BZD and ADL-dependency was performed among men and women separately, using a delayed entry Cox model and time-dependent variables. Adjustment considered the use of other drugs (anti-dementia drugs, opioid analgesics, other psychotropic medications), the number of drugs used each month, and the Charlson comorbidity index.

Results: Women represented two third of BZD users; anxiolytics were more used than hypnotics and short half-life BZD were twice more used than long half-life BZD. Moreover, most users presented with chronic use. Risk of autonomy loss was increased in BZD users, slightly more in men; this was found for both anxiolytics and hypnotics. Regarding short *versus* long half-life BZD, the association was found mainly for short half-life BZD. For long half-life BZD, it was significant only in women. Current use-not chronic was associated with the highest increase (men: RR = 1.9, 1.6–2.2; women: RR = 1.6, 1.4–1.8).

Conclusions: This study highlighted the association between BZD use and the occurrence of ADL-dependency, for both anxiolytics and hypnotics, whatever the use profile. Risk was especially increased for short-term ongoing use, consistently with what has been shown for trauma or accidents.

587 | Drug use among older people admitted to nursing homes

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Background: Nursing home residents represent a particularly vulnerable population with a high burden of morbidities and an extensive drug use. Drug use patterns should be investigated to promote safe and appropriate treatment.

Objectives: To describe drug use patterns in nursing home residents in relation to time of admission to nursing home.

Methods: In collaboration with 11 Danish municipalities, we constructed a database on all older people admitted to nursing homes from January 1, 2015 to December 31, 2017. Individual level data on time of admission was linked to the Danish health registries to obtain information on morbidity and drug use. We described use of drugs from 24 months before and up to 36 months after admission to nursing homes.

Results: We identified 5279 residents admitted to nursing homes from January 1, 2015 to December 31, 2017. The majority was female (67%) and the median age was 84 (interquartile range [IQR] 77–89). Thirty-eight percent were still alive after three years. At time of admission, cancer (25%), stroke (24%), and dementia (22%) were the dominant diagnoses. The median number of unique drug classes filled within the last six months increased from 6 ([IQR] 3–9) two years before admission to 8 ([IQR] 5–11) by the time of admission. Hereafter, it remained constant throughout the two-year follow-up period. At time of admission, paracetamol was the most frequently used drug (56%), followed by diuretics (37%), agents working on the renin-angiotensin system (31%), opioids (30%), and statins (30%). Prevalent use of preventive medications, e.g. statins and antihypertensive agents, remained fairly unchanged from two years before to two years after admission to nursing home, whereas a pronounced increase was observed for paracetamol, laxatives, anti-infectives, and anti-depressants during the same period. Incident use of new drug classes similarly increased markedly from 20/100 residents per month to 65/100 residents per month during the last 9 months before admission.

This was mainly driven by an increasing proportion of new users of laxatives, analgesics (paracetamol and opioids), and anti-infectives. Additionally, incident use of benzodiazepine derivatives increased more than a 3-fold during this period. After admission, the overall incident rate rapidly declined and leveled off at around 30/100 residents per month.

Conclusions: Incident and prevalent use of drugs increased in relation to time of admission to nursing home. Both use of preventive medication and drugs at high risk of causing adverse side effects are widespread.

588 | Receipt of psychotropic treatment among working-age, long-stay nursing home residents with serious mental illness

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Background: Nursing home care may be inappropriately replacing community-based care and specialty psychiatric long-term care, particularly for working-age adults with serious mental illness (SMI). Contemporary information is scarce about these residents with SMI, including how long they say in the nursing home and what mental health care they receive.

Objectives: To describe clinical characteristics and receipt of psychotropic treatment among working-age, long-stay nursing home residents with SMI within the first 90 days of the nursing home stay.

Methods: We used the national Minimum Data Set (MDS) 3.0 to first identify 62,079 working-age adults (aged 18–64 years) with SMI who were newly admitted to U.S. nursing homes in 2014 and then examined who remained in the nursing home for at least 90 days. MDS 3.0 is a comprehensive assessment of active clinical diagnoses, functioning, medication, and non-pharmacological treatments. It is completed for all residents of all Medicare−/Medicaid-certified nursing facilities throughout the nursing home stay. SMI was broadly defined as an active diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, depression, and/or anxiety disorder. Receipt of psychotropic medication included antidepressants, antianxiety medication, antipsychotics, and hypnotics received at any time in the seven days before the admission assessment and the first 90-day assessment.

Results: Of the newly admitted working-age residents with SMI, 25.9% (n = 16,088) remained in the nursing home for at least 90 days. Nearly one-fifth of these long-stay residents were less than 50 years old. Depression was the most common active psychiatric diagnosis at admission (68.6% of long-stay residents), followed by an anxiety disorder (41.2%) and schizophrenia or other psychotic disorder (33.5%). Comorbid psychiatric diagnoses were documented for 47.7%. Almost all received at least one psychotropic medication at admission (92.9%) and the first 90-day MDS (93.2%), with antidepressants most commonly received (admission: 70.3%; 90 days: 72.7%). Antipsychotics were received by almost half of residents (admission: 45.6%; 90 days: 46.5%). Multiple psychotropic medications were received by slightly more than half of residents (admission: 51.1%; 90 days: 54.1%).

Conclusions: Working-age adults with SMI are long-stay nursing home residents and likely have complex care needs. Additional research on potential unmet need and predictors of functioning is necessary for understanding the quality of life for these adults and their likelihood of returning to the community.

589 | Adverse drug reactions as cause of hospital admissions in older adults in a teaching Hospital in Chile

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Background: The safety of drug prescribing has become a very important topic in geriatric medicine. Adverse drug reactions (ADRs) are common problems causing hospital admissions and higher health care costs. Limited information is available of ADRs as cause of hospital admissions in older adults in Chile.

Objectives: To estimate incidence and determinants of hospital admissions for ADRs in older adults in a medicine unit of a teaching hospital in Chile.

Methods: A prospective cohort study was conducted in a sample of older adults 60 years and older admitted in the medicine unit of a teaching hospital in Chile. Sociodemographic characteristics, clinical and pharmacotherapy profile of was collected by patient interview and medical records. Suspected hospital admission for ADRs were subsequently evaluated by an internal medicine physician and two clinical pharmacists, and causality assessment of each ADR was undertaken to determine whether each suspected reaction was possible, probable or established. The assessment of ADRs causality was performed using the Naranjo algorithm. Drugs were classified according to Anatomical Therapeutic Chemical classification. Determinants of hospital admission for ADRs were identified by using multivariate logistic regressions.

Results: During the study period a total of 350 older adults were admitted at medicine unit. The mean ± SD age was 73.0 ± 8.7 years, 51.1% were women, and 63.1% of patients were using 5 or more medications (mean 6.5 ± 3.6 drugs/patient). The most common comorbidities were hypertension (68.9%) and Type 2 Diabetes Mellitus (36.3%). Twenty eight (8.0%) patients suffered a hospital admission for ADR at medicine unit. Cardiovascular drugs accounted for 28.9% of the cases, followed by alimentary tract and metabolism drugs (23.7%), and nervous system drugs (13.2%). The most common system organ class affected for ADRs was metabolism (8 cases). The drugs most frequently involved were glyburide (6 cases) and hydrochlorothiazide (4 cases). The causality of ADRs detected were established (5.3%), probable (57.9%), and possible (36.8%). Polypharmacy (5+ drugs) was a predictor of hospital admissions for ADR in the sample studied (OR: 3.3; 95%CI 1.3–8.9).

Conclusions: Approximately one in ten hospital admissions of older adults at medicine unit were due to ADRs in the sample studied. Future interventions to prevent ADRs could be focused mainly on cardiovascular and metabolism drugs, and patients with polypharmacy. Better understanding of ADRs could improve safety of care and to target potential interventions to prevent or reduce severity of ADRs among older adults.

590 | The goldilocks of diabetes care: A retrospective evaluation of prescribing practices related to the intensity of glycemic control among the elderly population with type 2 diabetes across Canada

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Background: Diabetes is highly prevalent among older adults. Overall evidence suggests a less intensive approach with heightened attention to safety is recommended in this population. Significant concerns have been raised about the potential over-treatment in older adults.

Objectives: To assess potential over-treatment related to intensity of glycemic control in an elderly primary care population with diabetes across Canada.

Methods: A retrospective population-based cohort study was conducted from 2010–2017, utilizing prescriptions generated within the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database. Patients aged ≥65 years with diabetes defined by the CPCSSN validated case definition with at least one HbA1c measurement were included. The intensity of glycemic control was assessed in two cross-sectional years (2012, 2016). Over-treatment was defined as an index HbA1c (the first recorded HbA1c of the year) of <7% and prescription of any anti-diabetic medication other than metformin within 9 months before and 3 months after the index HbA1c. Secondary outcomes included the proportion of patients with HbA1c <7% and prescription of high-risk hypoglycemic agents (sulfonylureas, insulins, or meglitinides), and the number of medications per patient within HbA1c subcategories (<7%, 7% - <8%, 8% - <9%, and ≥ 9%).

Results: A cohort of 33,864 patients (51.6% male) with a mean age of 76.3 years was identified. The rate of over-treatment was 7.0% in 2012 and 6.9% in 2016 with a p-value of 0.64 (CI -0.32 to 0.52). High-risk hypoglycemic agents accounted for 84.4% and 68.6% of over-treatment medications in 2012 and 2016, respectively. The majority of patients (53.4% (2012) and 56.4% (2016)) were not receiving any anti-diabetic medications. Approximately one-third of the patients with HbA1c ≥ 9% were prescribed no medications (33.6% (2012) and 35.8% (2016)). Metformin-only users made up 19.1% (2012) and 21.5% (2016) of the cohorts.

Conclusions: Although potential over-treatment (too hot) exists in this broad Canadian primary care population, the rate was low with no evidence that it was increasing over time. Of concern, however, is that over 1/3 of patients with poorly controlled diabetes receiving no medications (too cold). Clearly, there is a need for much more individually tailored (just right) personalized diabetes management in Canada.

591 | Use of benzodiazepines and other sedative medications among older patients in Quebec: A population-based study between 2000–2015

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Background: Benzodiazepines and other sedative medications have been associated with an increased risk of falls, cognitive problems and hospitalizations in older individuals. Yet it is difficult to develop interventions to ensure optimal use, since there is little information on the actual use of these medications among older patients in the province of Quebec, Canada.

Objectives: To describe the annual prevalence of use of benzodiazepines and other potentially inappropriate medications prescribed to treat insomnia among older patients in Quebec from 2000 to 2015.

Methods: We conducted a population-based cohort study using data from the Quebec Integrated Chronic Disease Surveillance System. We included all individuals aged 66 years and over who were covered by the public drug insurance plan in each financial year (April 1stto March 31st) from 2000 to 2015. For each year, we evaluated the age-standardized proportion of individuals using benzodiazepines, defined as the presence of at least one claim for one drug of the class in the given year. Similarly, we calculated age-standardized proportions of users for antidepressants (trazodone and tricyclic), quetiapine (up to 25 mg), cyclobenzaprine and hydroxyzine in the same period.

Results: The proportion of individuals with at least one claim of benzodiazepines decreased from 33.43% in 2000 to 25.78% in 2015. An overall decline in the proportion of users was observed for all benzodiazepines with the exception of clonazepam whose proportion increased from 3.22% to 4.24%. Conversely, the proportion of users increased for some potentially inappropriate sedatives, in particular for trazodone (1.15% to 3.12%) and quetiapine (0.07% to 1.88%).

Conclusions: From 2000 to 2015, older adults in Quebec were less likely to be prescribed benzodiazepines but used more trazodone and quetiapine. However, the proportion of individuals using sedative medications remains high. Given the risks associated with these drugs, there is a need to develop interventions to reduce their use.

592 | Polypharmacy among older individuals with chronic obstructive pulmonary disease: Trends between 2000–2015 in Quebec, Canada

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Background: The treatment of chronic obstructive pulmonary disease (COPD) and concomitant diseases requires several medications. Yet there is little data on how the pharmacological burden progressed over time among older individuals with COPD.

Objectives: 1) To describe the proportion of older adults with COPD in Quebec, Canada, that were exposed to polypharmacy (≥10, ≥15 or ≥ 20 medications/year) between 2000 and 2015; 2) To calculate the proportion of individuals receiving specific prescriptions for COPD (short-acting bronchodilators, long-acting bronchodilators, inhaled or oral corticosteroids, antibiotics, anti-smoking agents, phosphodiesterase 4 inhibitors and methylxanthines) during this period.

Methods: We conducted a population-based cohort study with data from the Quebec Integrated Chronic Disease Surveillance System. Individuals aged ≥66 years with COPD, covered by the universal public drug plan and alive for the duration of the year studied (2000 to 2015) were included. We calculated the total number of drugs used at least once by each individual during each of the studied years. We used age-standardized proportions to compare proportions of users between the years studied.

Results: The average number of drugs used increased from 12.0 in 2000 to 14.8 in 2015. The proportion of individuals using ≥10 drugs increased from 62.0% to 74.6%; while it increased from 31.2% to 45.4% for ≥15 drugs; and from 12.3% to 22.4% for ≥20 drugs. The proportion of individuals receiving long-acting bronchodilators increased from 18.7% in 2000 to 69.6% in 2015. For the same period, the use of short-acting bronchodilators decreased from 81.5% to 67.9%, and that of inhaled corticosteroids from 60.6% to 26.0%. The proportion of users of methylxanthines inhibitors decreased from 15.0% to 1.9%.

Conclusions: Older individuals with COPD are increasingly exposed to polypharmacy. Identifying which polypharmacy is beneficial is a priority.

593 | SSRI & SNRI use in adults & elderly

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Background: Antidepressants, and specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are widely used. Their efficacy in the elderly is however debated, and it is believed that this population is overtreated.

Objectives: To determine the development in users of SSRI and SNRI in Sweden (SE), Denmark (DK) and Norway (NO) over time, with focus on elderly users.

Methods: A registers study from 2006–17 in SE, DK and NO identifying adults each calendar year with a least one redeemed prescription. Adults were defined as age of 18+ in DK and age of 20+ in SE and NO. Elderly were defined age of 80+. We collected information for the following drugs: SSRIs (ATC code: N06AB): citalopram (N06AB04), escitalopram (N06AB10), fluoxetine (N06AB03), fluvoxamine (N06AB08), paroxetine (N06AB05) and sertraline (N06AB06); and for SNRIs: duloxetine (N06AX21) and venlafaxine (N06AX16). All numbers are given as users per 1000 inhabitants.

Results: For SSRIs the proportion of elderly users were 2–3 times higher than among adults both in SE and DK, though the proportion of elderly users have decreased since 2010. In NO, the proportion of adult and elderly users were lower and more stable over time. [2017 adults: SE 78, DK 52, NO 44 per 1000. Elderly: SE 169, DK 115, NO 64.2 per 1000]. The most prevalent candidates of SSRIs among elderly users were citalopram and sertraline; They had the same trend as for SSRIs combined, with most users in SE and DK and a high proportion among the elderly users. However, whereas the users of citalopram have been decrease since 2010, the users of sertraline have been increasing SE and DK. [citalopram 2017 adults: SE 24, DK 21, NO 5 per 1000. Elderly: SE 98, DK 67, NO 10 per 1000; Sertraline 2017 adults: SE 32, DK 22, NO 8 per 1000. Elderly: SE 48, DK 34, NO 9 per 1000]. For the third most common candidate, escitalopram there has been an increase in users in NO and SE and higher proportion of elderly users. [2017 adults: SE 15, DK 5, NO 27 per 1000. Elderly: SE 22, DK 11, NO 42 per 1000]. Decreasing proportions of adult and elderly users were observed for paroxetine, fluvoxamine and fluoxetine, being the least prevalent SSRIs [2017 all countries <6 per 1000]. The proportion of SNRIs users of duloxetine and venlafaxine increased in the study period. NO had the lowest proportion of users of duloxetine [2017 adults: SE 7, DK 7, NO 2 per 1000] and venlaflaxine [2017 SE 12, DK 11, NO 8 per 1000]. The proportions of elderly users were lower than among adults.

Conclusions: In general, NO had fewer users of SSRIs and SNRIs than SE and DK. For citalopram and sertralin the proportion of elderly aged 80+ were much higher than in the adult population.

594 | Potentially inappropriate medication users with pre-clinical Alzheimer's disease more susceptible to anticholinergic challenge

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Background: Potentially inappropriate medication (PIM) use may lower cognitive reserve (CR), decreasing the threshold for Alzheimer's disease (AD) symptom expression. Given the high burden of both PIM use and AD in the older adult population, optimizing medication use may delay progression from pre-symptomatic AD (pAD) to AD by augmenting CR.

Objectives: We investigated the association between baseline PIM use and CR among participants with and without pAD in a randomized medication therapy management (MTM) trial.

Methods: We are conducting a randomized trial targeting PIM use through an MTM intervention. The Medication Appropriateness Index for medications in 2015 Beers' criteria (MAI-PIM) quantified PIM use. Cognitive outcomes were quantified using change scores of executive function and immediate recall neuropsychological tests (Trail Making Test B [TMTB] and California Verbal Learning Test [CVLT]), standardized to the population mean. Tests were administered with and without anticholinergic challenge, such that larger change scores between two paradigms corresponded to lower CR (i.e. the participant compensated less for anticholinergic challenge). Participants were stratified by pAD status derived from PET scans. Spearman correlation coefficients (r) were used to assess the relationship between medication appropriateness and CR at enrollment. P-values of <0.05 were considered statistically significant.

Results: Based on 41 participants (mean age 73.1 years [SD 5.7]; 66% female), the median (IQR) MAI-PIM at baseline was 4 (0.5–6.5), and 34.3% met criteria for pAD. 21.5% of reported medications (n = 120) were present in the Beers' criteria. The most common PIMs were anticholinergics, non-steroidal anti-inflammatory drugs, and proton pump inhibitors (31.7%, 25.8%, and 18.3% respectively). Those with pAD had larger change scores for executive function and immediate recall (mean [SD] TMTB -0.34 [1.2]; 0.08 [1.1] and CVLT 9.0 [6.8]; 3.3 [7.4] for pAD and non-pAD respectively). Higher MAI-PIM scores were correlated with larger change scores (r = 0.27 [p = 0.087] and r = 0.33 [p = 0.036] for TMTB and CVLT).

Conclusions: Among community-dwelling non-demented older adults, anticholinergic challenge resulted in larger observed differences in cognitive test scores both among participants with evidence of pAD and among participants taking more PIMs. These results support the hypothesized relationship between CR and medication appropriateness, highlighting the potential significance of medication management therapy as a tool to delay progression to symptomatic AD.

595 | Computer support and collaboration in the older Person's medication use

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Background: Interprofessional collaboration has become a concept to improve patients care and safety. An increased focus on collaboration between different professions and the patient itself is important for optimizing safe medication use.

Objectives: To study if the use of a web-based computer support system for patients and healthcare professionals can facilitate the discovery and identifying of potential adverse drug reactions in an early phase and thereby contribute to a safer drug treatment.

Methods: A prospective crossover design was conducted including 50 patients, aged 75–95 year, living in their own homes. Information was obtained from patients monitoring of potential symptoms by a web-based computer support system for one year. The first half part of the study period, the patients register freely, while during the second half, they were suggested symptoms. The symptoms were based on prodromal symptoms to conditions most frequently causing hospitalisations. The VM signaled when registration of symptoms was made on three occasions under 21 days. The patient received a "call" to contact their nurse for assessment of the symptoms. After screening the nurse determined whether these symptoms warranted a doctor's visit, a medical examination or a consultation with the nurse.

Results: Preliminary results based on to date, 27 completely monitored patients, totally 367 (39%) registrations for men and 583 (61%) for women. The average of symptoms recorded by men was 9,5, range (1–34) and 17,0 range (2–93) for women. Under the period of spontaneous registration, the mean value for men and women was 9,5 (1–34) and 11 (1–44) respectively and under the period of predefined symptoms 1,3 (1–5) and 5,1 (0–49). Average number of symptoms at each registration for men was 1,9 range (1,0-3,7) and 2,1 range (1,0-3,8) for women. Symptoms mostly reported by patients was; tiredness, pain, symptoms from the GI-tract, breathlessness and instability. A total of 72 signals were provided, from these, about ten medication reviews were generated. Fifteen ordinary physician visits were performed and about 25 nurse contacts were conducted under the monitoring period.

Conclusions: We have evaluated a method of a patient-based monitoring process, by uptake of the patient's directly described symptoms by a vigilance module adapted in a web-based computer support system. A first source signal from the patients for further evaluation and thereby facilitate the discovery and identifying of potential adverse drug reactions in an early phase and thereby contributing to a safer drug treatment.

596 | Translation, cultural adaptation, and psychometric properties of the Danish version of the revised Patients' attitudes towards Deprescribing questionnaire

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Background: The revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire is a 22-item instrument capturing older patients' beliefs and attitudes towards deprescribing.

Objectives: To translate and culturally adapt the English version of the rPATD questionnaire into Danish and subsequently validate the Danish version in a cohort of nursing home residents.

Methods: The rPATD questionnaire was translated and culturally adapted according to recognized guidelines. Following this, the pre-final questionnaire was pilot tested through semi-structured interviews with 11 nursing home residents and ultimately adjusted into a final version. The validation of this final version was carried out among nursing home residents recruited from nursing homes within the Region of Southern Denmark.

Results: The rPATD questionnaire was successfully translated into Danish, and the subsequent pilot test showed that the Danish version was acceptable by the nursing home residents. A total of 159 participants were included in the validation (median age of 82 years; 39% males). More than half of the participants believed that they took a large number of medications (63%; *n* = 100), and 27% (*n* = 43) felt that they took one or more medications which they no longer needed. Overall, 44% (*n* = 70) of the participants would like to try stopping one of their medications to see how they would feel without it, and 37% (*n* = 59) would like their physician to reduce the dose of one or more of their medications. Further, the majority of the participants were willing to stop taking one or more of their regular medications if their physician said it was possible (86%; *n* = 137). Despite this, 93% (*n* = 148) of the participants reported not having troubles taking their daily medications, and 73% (*n* = 116) did not consider their medications a burden to them. The psychometric testing will be conducted during the spring.

Conclusions: We have successfully translated and culturally adapted the rPATD questionnaire into Danish. The current results from the field test suggest that Danish nursing home residents believe their use of medication is extensive and that they are open towards deprescribing. Pending psychometric testing, the Danish version of the rPATD questionnaire can be used in future studies.

597 | Potentially inappropriate medication use in older adults in Quebec, Canada: A population-based cohort study

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Background: The use of potentially inappropriate medication (PIMs) in the older population remains common. Yet their use is associated with negative health outcomes and significant cost for health care organizations. Few population-based data exist on PIM use and associated factors according to the 2015 Beers Criteria in community-dwelling older people.

Objectives: To assess the prevalence of potentially inappropriate medication (PIM) use and identify associated factors in a large cohort of community-dwelling older adults aged ≥66 years insured with a universal health care system in Quebec, Canada.

Methods: A population-based cohort study was conducted using the Quebec Integrated Chronic Disease Surveillance System (QICDSS) database. The QICDSS includes data on drug claims for community-dwelling older adults aged ≥65 years with chronic diseases or at risk of developing them who are insured by the public drug plan (90% of older people). Individuals aged ≥66 years continuously insured by the public drug plan between April 1st, 2014 and March 31st, 2016 were included. PIMs were defined using the American Geriatrics Society 2015 version of the Beers Criteria. The proportion of individuals who had at least one claim for a PIM between April 1st, 2015 and March 31st, 2016 was calculated. Descriptive statistics were performed to describe patient characteristics and PIM use. We conducted multivariate robust Poisson regression analyses to explore factors associated with PIM use and calculated rate ratios (RR) and 95% confidence intervals.

Results: A total of 1,105,295 individuals were included (mean age: 74.9 [SD 7.0] years, women: 56.4%). Of these, 48.3% (95% CI: 48.2–48.4%) were prescribed at least one PIM. The most prevalent PIMs were benzodiazepines (25.7%), proton-pump inhibitors (21.3%), antipsychotics (5.6%), antidepressants (5.0%) and long-duration sulfonylureas (3.3%). Factors associated with PIM exposure included being a woman (RR: 1.20; 95% CI: 1.20–1.21), increased number of medications and having a high number of chronic diseases, especially mental disorders (1.50; 1.49–1.51).

Conclusions: Almost one out of two community-dwelling older adults in Quebec use a least one PIM. From a public health perspective, it is imperative to reduce the use of PIMs, by limiting their prescription and by promoting their deprescribing, which necessitates not only the active involvement of prescribers, but also patients.

598 | Identification of potential drug-related problems and drug-related risk factors in home-dwelling older adults

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Background: Complex combination of medicines, associated to the decline of physic and cognitive functions entails older adults an increased risk of adverse drug events. In home-dwelling adults, 4%–53% of the prescriptions are inappropriate and are associated with an increased risk of hospital admission and emergency department visits. Taking in account that medications errors remain a leading public health issue among the elderly, identifying Drug-related problems (DRPs) and DRPs- risk factors in home-dwelling older patients would help to find assertive strategies to decreased DRPs in these population.

Objectives: Systematically review the most frequent DRPs and DRPs-risk factors in home-dwelling older adults.

Methods: A MEDLINE-PubMED scientific database search with the combination of terms drug-related problems, elderly, older and medication-related problems was performed. Studies that analyses DRPs in people living in the community without residing in assisted living facilities or long-term care facilities, publish in January 2001 through December 2018 were included.

Results: After a critical selection, 15 studies were systematically reviewed, 6 in community pharmacies, 6 in primary care, 2 home medication review notes and 1 outpatients departments of a hospital. Despite diverged in design all studies report and classified DRPs. The number of DRPs identified per article range from [131; 11419] performed 24392 DRPs. Major DRPs observed are related with drug selection (20. 2%) followed by compliance (12.2%) and dose selection (9.4%). Drug use process problems were also observed in 7.4% of the patients. 8.6% DRPs results in problems of treatment safety. The main DRPs-risk factors pointed out in the included articles were related with the number of drugs and the number of health care providers visited. According with the included studies both risk factors are associated with compliance, drug selection and drug interaction problems.

Conclusions: The high prevalence of DRPs in home-dwelling older adults clearly demonstrated the need of interventions to improve medicines use in this population. Funding: Project MedElderly [SAICT-POL/23585/2016], supported by FCT/MCTES, Portugal 2020 and Centro 2020; Project APIMedOlder [PTDC/MED-FAR/31598/2017], supported by POCI, in its FEDER/FNR component POCI-01-0145-FEDER-031598, and the FCT, in its state budget component (OE). Thanks are due for the financial support to Institute for Biomedicine - iBiMED (UID/BIM/04501/2013 and POCI-01-0145-FEDER-007628).

599 | Drug burden of polypharmacy and anticholinergic/sedative drugs and physical/cognitive/mental related outcomes of the community-dwelling elderly people: The Kawasaki well-being project

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Background: Drug burden due to polypharmacy and anticholinergic drugs is associated with reduction in physical and cognitive functions, posing significant problems in elderly population.

Objectives: To assess drug burden and its association with patient outcomes in the community-dwelling independent elderly.

Methods: The cross-sectional survey was conducted from March to December 2017 on the community-dwelling elderly in an urban area of Kawasaki City, as a part of The Kawasaki Well-being Project. Inclusion criteria were independent, aged 85 to 89 years, participating in The Kawasaki Well-being Project. Data on drugs and physical/cognitive/mental outcomes were collected with self-administrated questionnaires and interview, as well as physical exams. We investigated the associations between drug burden and physical/cognitive/mental outcomes. Drug burden was measured using the number of medications (polypharmacy) and Drug Burden Index (DBI) based on the use of anticholinergic and sedative drugs. Multivariate regression analysis was performed on the outcome measures including Activity of Daily Living (ADL), Instrumental Activity of Daily Living (IADL), Mini Mental State Exam (MMSE), Japanese-version CHS (J-CHS), and EQ 5D5L.

Results: A total of 389 subjects were analyzed, the mean age of the study population was 86 years, 48% were male and most had 5 diseases or more. Polypharmacy of five concomitant drugs or more was found in 243 people (62%) and exposure to the drugs accounting for DBI in 142 people (36.5%). We found that this population was physically healthy, and had high quality of life. After adjustment with sex, age, education levels, the number of diseases, smoking status, and alcohol drinking, the number of the drugs was significantly associated with J-CHS (p = 0.003) and EQ 5D5L (p = 0.001). The DBI score was significantly associated with EQ 5D5L (p = 0.01).

Conclusions: The study participants were healthier than general elderly population. It was suggested that polypharmacy and anticholinergic burden may affect frailty and QOL in the elderly. Because of cross-sectional nature of the study, causal relationship cannot be established. Further research is warranted to investigate the long-term effects of polypharmacy and anticholinergic/sedative drugs on elderly people.

600 | Prescription pattern for geriatrics a case study of Jos University teaching hospital Nigeria

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Background: There is a high rate of polypharmacy and prevalence of potentially inappropriate medication (PIM) use among the elderly, affecting over 30% of this group of patients.

Objectives: To describe the prescription pattern and inappropriate medication use in elderly Nigerian out-patients.

Methods: This was a descriptive retrospective study of 350 elderly patients aged 65 years and above who attended the general, medical, eye and surgical out-patient clinics of a Nigerian tertiary teaching hospital for a period of one year. The WHO prescribing indicators were used for the drug utilization while the Beers Criteria 2015 was used to screen for potentially inappropriate medications.

Results: Drugs prescribed were 1378, giving an average of 3.94 ± 1.97/patient out of which antihypertensives accounted for 26.06%, analgesics 13.58%, multivitamins/food supplements were 8.24%. Study identified 131 patients with at least one potentially inappropriate medication, rate being 37.43%, classes of drugs inappropriately used include nonsteroidal anti-inflammatory, cardiovascular and muscle relaxant drugs.

Conclusions: The drug utilization pattern among elderly outpatients of this tertiary hospital were not optimal and 37.43% inappropriate prescribing occurred which constitute a major problem in management of the elderly. Healthcare providers therefore need to be trained/retrained for proper handling of geriatrics.

601 | Use of cardiovascular drugs among older people in Greece consuming more than five drugs daily

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Background: Polypharmacy is common among older people in Greece, with cardiovascular drugs being the most frequently used category of medications in this group of patients.

Objectives: The aim of this study was to explore the use of cardiovascular drugs in older patients (> 65 years) receiving five or more than five drugs daily in the community of Thessaloniki, Greece.

Methods: The sample was collected using the new Electronic Health Records that have been applied in pharmacy stores during the last years in Greece. All prescriptions dispensed during one month in a pharmacy store of western Thessaloniki were used. Prescriptions concerning patients older than 65 years were collected for the study. Medications were coded by the Anatomic Therapeutic Chemical classification. The statistical package SPSS was used for statistical analysis.

Results: Polypharmacy (≥5 medications daily) was observed in 55% of patients older than 65 years (mean age 77 years, range 65–99), of whom 42% were male and 58% female. Cardiovascular drugs were used by 86% of these patients. The most commonly used categories of cardiovascular drugs were: diuretics (75%), AT1 inhibitors (66%), calcium chanel blockers (53%), beta blockers (46%), ACE inhibitors (18%), vasodilators (11%). 74% of patients used a combination of cardiovascular drugs.

Conclusions: One out of two people older than 65 years used five or more medications daily. The majority of older patients using ≥5 medications daily (almost 9 out of 10) used cardiovascular drugs, with 74% of them using a combination of cardiovascular drugs.

602 | Effect of adverse drug reactions on length of stay in older adults in a teaching Hospital in Chile

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Background: Aging is associated with a variety of physiological changes affecting the pharmacokinetics and pharmacodynamics, which may increase the potential for drug toxicity and Adverse Drug Reactions (ADRs). The effect of ADRs on length of stay (LOS) in older adults has been insufficient described.

Objectives: To determine the incidence of ADRs and its effect on the LOS among hospitalized older adults in an Internal Medicine Department.

Methods: A prospective cohort study was conducted in a sample of hospitalized older adults 60 years and older admitted in the internal medicine department of a teaching hospital in Chile. Sociodemographic characteristics, clinical and pharmacotherapy profile were collected by patient interviews and medical records. A clinical pharmacist joined in clinical rounds and each suspected ADR detected was analyzed by an internal medicine physician and two clinical pharmacists. Causality assessment of each ADR was undertaken to determine whether each suspected reaction was possible, probable or established. The assessment of ADRs causality was performed using the Naranjo algorithm. The effect of ADRs on LOS was determined using multivariate Cox regression model.

Results: A total of 229 patients were included, the mean age was 72.9 ± 8.7 years, and 57.6% (132) were women. The 33.2% of older adults suffered at least one ADR. A total of 112 ADR were detected in 76 patients. The causality of ADRs detected were established (4.5%), probable (55.4%), and possible (39.3%). Inpatient older adults with ADRs spent a mean of 2 more days hospitalized in the internal medicine department than those without ADRs (8.2 ± 5.0 vs 6.2 ± 4.2; $p < 0.005$). LOS was statistically higher in older adults with ADRs versus those without ADRs (HR 1.47; 95%CI 1.10–1.96) controlling by Charlson comorbidity index, sex, age, number of drug taken and previous ADR.

Conclusions: One on three older adult patients suffer at least one ADR in the Internal Medicine Department, increasing significantly the mean LOS in 2 days. There is a potential to optimize the use of hospital beds and patient safety preventing ADR in older adults.

603 | Usefulness of a new clinical pharmacology service in a Single Center to optimize drug therapy in the elderly in Colombia

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Background: In the elderly, the polypharmacy and inappropriate use of drugs is worsedue to the co-morbidities that lead to more prescriptions, frequently exceeding >10 drugs per patient. This excessive formulation of drugsincreases at least twice the risk of adverse events and is a marker ofincreased mortality.

Objectives: To implement a clinical pharmacology service in a developing country wecharacterized the pharmacological risk of a population of 3734 individualsin order to promote the rational use of drugs and the reduction of excessivemedicine consumption in the patients with highest pharmacological risk.

Methods: A scale of pharmacological risk with 4 categories was built. The highest risk (Group 4) commonly includes women older than 65 years, with acreatinine clearance <50 ml/min and receiving at least 10 drugs. Pharmacologist reviewed the medical records of group 4 patients. Additionally, Beers and STOPP criteriawere assessed and major and moderate drug interactions werechecked. With the

previous analysis an optimization plan was set to remove inappropriate drugs. The program began in mid-November 2017 and is currently ongoingat the IPS Universitaria in Medellín, Colombia.

Results: The target population comprised 3734 patients. After stratification,770 subjects were allocated to Group 4 (baseline). Group 3(moderate risk) included 2141 patients, Group 2 (low risk) 389subjects and Group 1 (minimal risk) 434 patients. The most frequently deprescribed drugs (reason) were: protonpump inhibitors (no indication), aspirin (no indication), trazodone (ineffective), albuterol (no indication), furosemide (noindication as first line for hypertension), sertraline (no indication). The baseline features of G4: median of age (range min to max) 79 (21–104), women (69%),median of drugs per patient (range min to max) 12 (11–24),number of patients with risk reduction (G4 to G3) 93 (13%),number of drugs deprescribed by clinical pharmacologist 895, estimated savings related to deprescribed drugs (U$) 113.502 per year, median of drug interactions found (range min to max) 7 (0–45).

Conclusions: A drug optimization program was succesfully implemented in an ambulatory healthcare setting in Colombia. After 10 months of intervention, 13% ofthe patients from Group 4 were reclassified to Group 3, mainly by the deprescription of drugs without indication. The impact of the program onquality of life, hospital admissions and incidence of adverse drug reaction will be assessed after 1 year.

604 | Physicians' knowledge of appropriate prescribing for the elderly - a survey among family and internal medicine physicians in Nigeria

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Background: Drug treatment of elderly patients is associated with potential adverse drug reactions (ADRs). Prescription and use of inappropriate medications have been identified as being responsible for the ADRs in many cases. Several tools/criteria such as the Beers criteria have been developed to screen for inappropriate prescribing in elderly patients. There is dearth of information about the knowledge of Nigerian physicians regarding appropriate prescribing for the elderly.

Objectives: The primary objective of this study was to assess the knowledge of Nigerian physicians working in Family Medicine and Internal Medicine about appropriate prescribing of medications for the elderly.

Methods: The study was a cross-sectional questionnaire-based study conducted among physicians working in four tertiary healthcare facilities located in two contiguous regions in Nigeria. The questionnaire apart from the bio-demographic details included ten clinical vignettes which assessed the knowledge of respondents about medicine use in the elderly with a total score of 10 marks. A score of less than 5 was taken as poor knowledge. Descriptive analysis and Chi square were used to obtain the general characteristics of the study participants and determine the level of significance of groups of categorical variables respectively.

Results: One hundred and five (105)physicians working in Family and Internal Medicine departments of four Nigerian tertiary healthcare facilities returned completed questionnaires. Twenty percent of respondents knew about Beers criteria while 15.6% were familiar with the STOPP criteria. Majority (83; 84.7%) of the respondents were confident of their ability to prescribe rationally for elderly patients. The mean knowledge score was 5.3 ± 2.0 with 32 (30.5%), 41 (39%) and 32 (30.5%) having low, average and good scores respectively. The association between the knowledge score, duration of practice and seniority was statistically significant (p = .004 and.012 respectively. The strength of this association is further confirmed by the Odds Ratios (OR) of 3.6 and 3 respectively.

Conclusions: The knowledge of Nigerian doctors on appropriate prescribing for the elderly was good. This is despite their poor familiarity with the screening tools for inappropriate medications.

605 | Cost-effectiveness of adjuvant whole breast irradiation

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Background: Combining External Beam Whole Breast Irradiation (EBWBI) with endocrine therapy remains a recommended alternative to endocrine therapy alone for elderly women with Estrogen Positive (ER+) Early Stage Breast Cancer (ESBC), post-breast conserving surgery (BCS). Although EBWBI in adjunct with endocrine therapy results in superior loco-regional tumor recurrence outcomes, metastatic and survival outcomes for both strategies have been shown to be similar. EBWBI is expensive and physically inconvenient for the elderly. EBWBI is associated with increased toxicities among which cardiotoxity is the most concerning. An earlier cost-effectiveness study found the combination of EBWBI with endocrine therapy more cost-effective than endocrine therapy alone, however the study failed to consider cardiotoxicity of EBWBI and the life expectancy of elderly patients.

Objectives: To estimate the lifetime cost-effectiveness of including EBWBI in the adjuvant regimen for elderly ER+ ESBC women, post-BCS, considering radiation-induced cardiotoxicity.

Methods: Using Markov model, Incremental Cost-Effectiveness Ratio (ICER) due to EWBI was estimated from payers' perspective. In the model, the cohort became tumor-free post-BCS, and could either remain tumor-free, or experience ipsilateral tumor recurrence,

metastasis or both before death, over their remaining lifetime. Some patients in the cohort may develop coronary heart disease at any living stage. The progression of each patient in the model depends on the adjuvant strategy received. Cost data, transitional probabilities and health state utilities data were all derived from the literature. The Net Monetary Benefits (NMB) were also estimated. Costs in Dollars were adjusted by cumulative inflation rate and future costs were discounted. Quality Adjusted Life Years (QALYs) were used as unit of effectiveness. Future QALYs were discounted. Deterministic and probabilistic sensitivity analyses were conducted.

Results: Endocrine therapy alone resulted in average lifetime cost and effectiveness of $28478.94 and 15.50 QALYs respectively. EBWBI plus endocrine therapy resulted in average lifetime cost and effectiveness of $40061.72 and 33.76 QALYs respectively. The NMB from endocrine therapy alone was $746585.55 while EBWBI plus endocrine therapy had a NMB of $1648104.65. With the Willingness to Pay (WTP) of being $50,000, EBWBI plus endocrine therapy had higher probability of being cost-effective (0.926).

Conclusions: Including EBWBI in the adjuvant regimen for elderly ER+ ESBC women post-BCS appeared to be more cost-effective than omitting it even when cardiotoxicity of radiation is considered.

606 | Impact of drug insurance type (private/public) on the cost of drugs of Quebecers

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Background: In the province of Quebec, residents are either insured by the public drug insurance (RPAM) or a private drug insurance. Drug cost in Quebec has three components: molecule's price, wholesaler margin of profit and pharmacist's fee. The first two components are regulated by the RPAM and are the same for publicly and privately insured patients. The third component is fixed (between CAD$8.40 and CAD$9.00) and regulated by the RPAM for publicly insured patients while it is determined freely by the pharmacy owner for privately insured patients. Although with methodological limitations, four studies reported higher drug cost for privately than publicly insured patients.

Objectives: This study aimed to compare the drug cost of Quebec residents covered with private drug insurance to those covered by the RPAM.

Methods: We used a sample of patients selected from reMed, a drug claims database of Quebecers insured by the RPAM and private drug insurances. We matched 3766 pairs of prescriptions bought by 1386 patients between January 1st 2015 and September 14th 2017. Each pair of filled prescriptions had the same drug, dose and formulation (i.e. DIN), same quantity dispensed, were dispensed in the same pharmacy and had to be bought twice within three months by the same patient: once while the patient was insured by the RPAM and once while he/she was insured by a private drug insurance. The difference in drug cost for each prescription before and after the drug insurance change was analyzed with Student's t-test for paired samples.

Results: 65.2% of the patients in our sample were between 40 and 65 years old and 59.2% were covered by a private drug insurance before changing to the RPAM and 59.1% contributed to 2 prescriptions or more to the analysis. We observed that privately insured patients had to pay more for their medications (CAD$46.50) than publicly insured patients (CAD$38.96): mean difference = CAD$7.54; (95% CI 7.03–8.05) representing a difference of 25.7%. At the provincial level, we estimated that this difference in cost could represent an annual excess cost of about CAD$971 million (based on an estimated 128 800 00 prescriptions bought annually by Quebecers covered by private drug insurances).

Conclusions: This study showed that, on average, drug cost is substantially higher for privately insured Quebecers. Knowing that adherence is affected by drug cost, these results will be useful to help public health authorities to make informed decisions about drug insurance policies.

607 | Mind the gap: A comparison of encounter location and medical costs during the one-month periods immediately before and after a short gap in United States Medicaid healthcare coverage

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Background: Patients may experience short (7–60 days) gaps in Medicaid coverage due to a variety of societal, lifestyle, and employment reasons. During these gaps it is difficult for these individuals to easily find alternate sources of coverage or access health services.

Objectives: This study aimed to understand if the types of admission and healthcare costs of patients differed between the one-month periods immediately before and after a short gap in Medicaid enrolment. A GSK funded study.

Methods: IBM Watson Health Medicaid data was used. Gaps in enrolment were evaluated for each patient enrolled during 2010–2017, and the first gap between 7–60 days was used. The one-month periods of continuous enrolment immediately before and after the gap were evaluated. Age and gender were determined one month before the gap. The location of encounters during these periods were determined. Costs analyses were determined for patients with Fee-for-Service plans only, and costs were inflation-adjusted to 2017 US dollars.

Results: 30.8% of Medicaid patients (7,292,231) had a gap of at least one day, and of these 2,208,752 (30.3%) had an eligible gap. The mean gap length was 27.8 (SD 10.6) days. The mean age was 17.2 (14.6) years, and 58.6% were female. Patients were more likely to have an ER visit (7.8% vs 7.1%, p = < 0.0001), an inpatient encounter (3.6% vs 2.9%, p = < 0.0001), and/or require home help (2.3% vs 2.1%, p = < 0.0001) after the gap than before. Overall, more diagnosis codes

were recorded after the gap (mean 7.4 (SD 32.3) vs 7.1 (SD 30.3), p = <0.0001).

1,489,021 (67.4%) of gap patients had eligible cost data. The mean (SD) total medical costs were higher after return to coverage ($368.31 (6,002.4) versus $196.13 (2,841.3), p = < 0.0001). Procedure costs were also significantly increased after their return to coverage, ($362.31 (5,965.7) versus $193.52 (2,829.6), p = < 0.0001). There was no difference in medication cost.

Conclusions: Healthcare costs and resource utilization were found to increase once patients were able to return to coverage. This may reflect the patients' inability to seek care during the gap, and so they require more care once they return to coverage.

This has implications for pharmacoepidemiology studies as, if a study period starts immediately after a gap, then the observation will start with an unrepresentative high cost (and potentially high 'risk') period. This work highlights a unique patient subset enrolled in Medicaid coverage that may require careful consideration when designing pharmacoepidemiology studies.

608 | Utilization patterns, expenditures, and estimated savings associated with analog or human insulin products in the Medicare part D program

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Background: High cost insulin analogs (e.g. glargine) are frequently used to treat patients with type 2 diabetes in the US. Recent evidence shows that switching older adults with type 2 diabetes from analog to lower cost human insulin (e.g. NPH or human premixed 70/30) is not associated with worsened glycemic control or increased risk of hypoglycemia and may result in cost savings for payors and patients.

Objectives: To describe utilization patterns and expenditures for analog and human insulins separately in the Medicare Part D program and to estimate potential savings under 3 counterfactual scenarios between 2012 and 2016.

Methods: We used the Medicare Part D Spending Dashboard, which summarizes data available the Part D Prescription Drug Event (PDE) data to tabulate volume (where 1 dosage unit = 1 ml = 100 IU insulin) and expenditures for human or analog insulin products from 2012 to 2016. We included all standard strength insulin formulations except inhaled insulin. To estimate potential savings and informed by literature, we considered 3 counterfactual scenarios: 1) optimistic, where utilization in Part D was 70% human and 30% analog, 2) moderate, where utilization was 50% human and 50% analog and 3) pessimistic, where the overall proportion represented by analogs was 10% less than observed each calendar year. We report gross and net expenditures for the observed and counterfactual scenarios, after accounting for a class-specific 25% rebate. We inflated all dollars to 2016 using the CPI-U.

Results: Our sample included 8 human and 19 analog insulin products. The number of beneficiaries increased from 4.1 million in 2012 to 5.2 million in 2016. Similarly, the volume of insulin dispensed increased from 389 million units to 486 million units. The mean units dispensed/beneficiary was 94.8 (range 92.8 to 96.1). The proportion of insulin dispensed as analogs increased from 78% in 2012 to 83.6% in 2016. Gross expenditures for all insulin products increased from $4.9 billion in 2012 to $11.9 billion in 2016, a cumulative total of $43.7 billion. The estimated 5-year savings under optimistic, moderate, and pessimistic counterfactual scenarios, inclusive of rebates, would have been $11.6 billion, $7.2 billion and $2.2 billion, respectively.

Conclusions: Most insulins dispensed in the US Medicare drug benefit program were for analog products. Where it may be clinically appropriate, increased utilization of comparable human insulin products may result in substantial savings for Medicare.

609 | Depression treatment, healthcare expenditures, and depression severity in patients with depression using patient health questionnaire-9 scores to assess depression severity

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Background: Depression is a prevalent mental health condition associated with significant economic burden and morbidity. Severity of depressive symptoms is an important factor when determining appropriate treatment for depression. Though the Patient Health Questionnaire-9 (PHQ-9) is a validated tool used to assist clinicians in assessing depression severity, these scores are often unavailable in administrative claims databases.

Objectives: To characterize treatment for depression and healthcare expenditures by depression severity among patients administered the PHQ-9.

Methods: Adult patients with PHQ-9 score between 1/1/2011 and 9/30/2016 were identified using MarketScan Claims and Electronic Medical Records Database (CED). The first PHQ-9 was the index date; 12 months continuous enrollment before and after the index date was required. Depression severity, assessed via PHQ-9 scores, was categorized as minimal (<5), mild (5–9), moderate (10–14), or severe (>14). Depression treatment and all-cause healthcare expenditures during follow-up were assessed and stratified by pre-existing mental health (MH) diagnoses.

Results: 11,066 patients met inclusion criteria; mean patient age was 66 years and 56% of patients were female. 11% of patients had PHQ-9 scores indicating depression (4% mild, 4% moderate, and 3% severe). Patients with a pre-existing MH diagnosis (19%) reported more severe depression compared to those without a pre-existing MH diagnosis (MH: 6% mild, 7% moderate, 6% severe; no MH: 3% mild, 3% moderate 3% severe; $p < 0.001$ for all). Antidepressant treatment was more

common in patients with severe depression during follow-up; those with a pre-existing MH diagnosis had the highest rates of treatment (MH: 56% minimal, 76% mild, 83% moderate, 82% severe; no MH: 14% minimal, 48% mild, 62% moderate, 76% severe; $p < 0.001$ for all). Mean all-cause expenditures were similar in patients with mild ($14,983), moderate ($15,403), and severe depression ($15,046); expenditures for each group were significantly higher than expenditures in patients with minimal depression ($11,161; $p < 0.001$ for all).

Conclusions: Though 7% patients had severe or moderate depression, a significant proportion received no antidepressant therapy which may represent unmet need. Further research is needed to understand barriers for depression treatment and the impact on healthcare costs.

610 | Cost effectiveness analysis of rivaroxaban compared to warfarin and aspirin for stroke prevention atrial fibrillation in the Indonesian healthcare setting

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Background: Main drugs used in the prevention of stroke among atrial fibrillation (AF) patients are antiplatelets (aspirin) and oral anticoagulants (OAC). OAC therapy can be difficult to administer due to drug and food interactions, adds the burden of required blood monitoring, narrow therapeutic window, and requirements for dose titration. Rivaroxaban is a single-dose oral anticoagulant which does not require blood monitoring, dose titration or has dietary interactions. Phase III clinical data from the ROCKET trial have recently been reported the non-inferiority of rivaroxaban over warfarin for the prevention of strokes in AF patients.

Objectives: To develop an economic model evaluating the clinical and cost-effectiveness of rivaroxaban for the prevention of stroke in non-valvular AF patients in the Indonesian health care settings.

Methods: This economic evaluation study with cost-effectiveness analysis included patients diagnosed with non-valvular atrial fibrillation in several hospitals in Indonesia during the period of 2012–2013. The perspective of the study was the health care perspective. The intervention was rivaroxaban, compared to warfarin. Markov model was used, comprised of health and treatment states describing the management and consequences of AF. The main analysis was based on data from the phase III trials. Three months was used as cycle length. The time horizon was set at patients' lifetime (20 years). Costs and outcomes were discounted at a 3% annual rate. Subgroup analysis and extensive sensitivity analysis was conducted.

Results: Willingness to pay (WTP) threshold in Indonesia was set as IDR 133,375,000 per quality-adjusted life year (QALY). Base case rivaroxaban vs warfarin has ICER of IDR 141,835,063 per QALY at the current cost of rivaroxaban IDR 23,500 and ICER of 130,214,687 per QALY at the proposed cost of rivaroxaban IDR 22,000. One-way sensitivity analysis showed that the key drivers of cost-effectiveness were the utility decrement applied to stable warfarin patients, discontinuation/subsequent discontinuation rates for rivaroxaban, and discontinuation/subsequent discontinuation rates for warfarin. The probabilistic sensitivity analysis suggested that rivaroxaban was cost-effective compared to warfarin in about 45% of cases at the WTP per QALY.

Conclusions: Rivaroxaban with the proposed price of IDR 22,000 was more cost-effective when compared to warfarin.

611 | Accuracy of budget impact estimations of new oncology drugs in the Netherlands

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Background: Innovations in oncology has resulted in an increased number of treatment options for cancer patients. The growing expenditures for expensive medicines is considered as a major challenge to healthcare systems. For governments or other payers, high prices, *off-label* potential and increasing number of oncology approvals and label extensions cause a substantial financial risk. When deciding on reimbursement of an expensive drug, the pharmaceutical company and/or payer usually quantify the expected costs known as Budget Impact (BI). Accurate BI estimates are important as they are used in reimbursement decisions. BI estimates can thus directly affect patient access to new potentially life-saving oncology drugs.

Objectives: To assess the accuracy of BI estimates of new oncology drugs in the Netherlands.

Methods: We selected products for which Marketing Authorization was granted by the European Medicines Agency between 1-1-2000 and 1–10-2015. Of these, products belonging to the L01 (antineoplastic agents) ATC-category for which a reimbursement dossier was published by the National Health Care Institute (ZIN), were included. From the dossiers, we extracted the estimated (est) annual BI per product. These estimates are the annual BI for the 3-year period after the publication of a dossier. Data on observed (obs) BI were provided by FarmInform. This population-level data comprises of monthly volumes of all prescription drugs that was multiplied by the official list price at the time of prescription in the Netherlands. We used the final year of the 3-year period to compare to the observed BI. Prediction accuracy was calculated as net difference (est - obs), absolute difference (|est - obs|), relative difference (obs / est; range = [0, ∞]) and symmetric relative difference (e ^|Ln (obs/est)|, range = [1, ∞]).

Results: We included 22 products that had a total estimated and observed BI of € 572 million (M) and € 380 M, respectively. The absolute- and net difference was € 404 M and € -191 M, respectively. The mean and median net difference in BI was € -8.7 M and € -2.9 M, respectively. For the absolute difference, these figures were € 18.4 M (mean) and € 6.0 M (median). The relative difference was 1.07 (mean) and 0.64 (median). The mean and median symmetric relative difference was 8.62 and 2.15, respectively.

Conclusions: The median symmetric relative difference of 2.15 implies that >50% of estimations were off by more than a factor 2. On the 22 novel oncology products, € 191 million less than estimated was actually spent. We think that these large deviations warrant further development of independent BI prediction models based on sound methods and tools.

612 | The impact of cost-related medication nonadherence on out-of -pocket costs and productivity among cancer survivors

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Background: A large body of evidence shows that nonadherence to medication may lead to worse health outcomes, and further reduces patients' productivity and increase total medical costs. Despite the heavy economic burden among patients with cancer, the impact of cost-related medication nonadherence on patients' productivity and personal financial burden remains unclear.

Objectives: To estimate the impact of cost-related medication nonadherence on productivity and out-of-pocket costs among patients with cancer.

Methods: A retrospective, pooled cross-sectional study was conducted using data from the National Health Interview Survey (NHIS), 2011–2017. Cost-related medication nonadherence was identified if the respondent answered a "yes" to any of the following NHIS survey prompts: "skipped medication doses to save money in past 12 months", "took less medication to save money in past 12 months" or "delayed refilling prescription to save money in past 12 months". An ordered logistic regression was used to determine the impact of cost-related medication nonadherence on patients' out-of-pocket costs (less than $2,000, $2,000-4,999, $5,000 or more). A negative binomial regression was implemented to estimate the impact on productivity, which was measured as productivity loss by using the lost workdays per year. In addition, demographics, income, health status and insurance related information were controlled in these two regressions.

Results: A total of 6,734 and 18,027 patients were identified out of 705,669 respondents for nonadherence on productivity and out-of-pocket-costs, respectively. The results showed that the cost-related medication nonadherence could increase out-of-pocket costs by 84% [OR = 1.84, (95% CI: 1.65 to 2.05, P = 0.000)] and productivity loss by 24% [IRR = 1.24, (95% CI: 1.03 to 1.49, P = 0.023)] among patients with cancer.

Conclusions: Cost-related medication nonadherence may lead to a decrease in productivity and a higher financial burden for patients with cancer, suggesting strategies and interventions are needed to further enhance cancer patients' affordability and adherence.

613 | Opportunity costs of receiving palliative chemotherapy for metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background: The median overall survival (OS) of mPDAC is less than 1 year. Factors that contribute to quality of life during treatment are critical to study. One key measure, time spent obtaining clinical services, is understudied.

Objectives: We compared cumulative outpatient time with OS among patients (pts) with mPDAC receiving palliative chemotherapy.

Methods: We conducted a retrospective analysis using 4 patient-level time measures calculated from the medical records of pts with mPDAC receiving FOLFIRINOX, gemcitabine, or gemcitabine + nab-paclitaxel within the University of Pennsylvania Health System between 1/1/2011 and 1/15/2019. These measures included total number of days with at least one visit (encounter days), total visit time (time between leaving and returning home on each visit day, using geocoded coordinates of each pt's home address), care time (time spent with providers, receiving cancer treatment, or undergoing imaging studies), and non-care time (difference between total visit time and care time). We provided descriptive statistics on cumulative time measures and compared each measure to overall survival time.

Results: 365 pts were identified (median age 65 years, 52% male, 78% white, 62% received gemcitabine + nab-paclitaxel, 79% deceased, and median OS 231 days (IQR, 110–438)). On average, pts had 22 (IQR, 10–41) calendar days with at least one outpatient visit, accounting for nearly 10% of their total days survived. Per visit, median visit time was 4.6 hours, of which greater than 50% of time was accounted for by non-care time including wait and commute time.

Conclusions: Pts receiving palliative chemotherapy for mPDAC spend 10% of their OS time on outpatient healthcare. More than half of this time is spent commuting and waiting for care, with a median of 2.5 hours of non-care time per encounter. These data highlight the need to optimize outpatient healthcare efficiency.

614 | Healthcare resource use and economic burden of respiratory illness among extremely preterm infants in the Netherlands

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Background: Improvements in neonatal care have led to increased survival of extremely preterm infants along with associated increases in healthcare resource utilization (HRU). Respiratory illness is a key driver of hospitalization and costs for this population. Characterizing clinical burden is critical to develop strategies to improve outcomes and reduce HRU.

Objectives: This study assessed HRU in terms of bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) of preterm infants born in the Netherlands.

Methods: A retrospective analysis of the PHARMO Database Network was conducted on infants with a birth record in the Netherlands Perinatal Registry and data in the Out-patient Pharmacy and Hospitalization Database. Infants born at 24–37 weeks gestational age (wGA) from 1999–2015 without congenital malformations were selected. Prevalence of BPD and CLD was determined by diagnostic codes, hospital admissions and a medication-based algorithm; HRU and costs were stratified by those complications. This abstract focuses on extremely preterm (<28 wGA) infants.

Results: Of 101,329 infants born, 7,328 were preterm, and168 extremely preterm infants (52% female) were included. Of those, 40% and 29% had BPD and/or CLD, respectively. Mean (SD) costs of the birth hospitalization for extremely preterm infants were €126,350 (€101,900). In the period up to 1- and 2-year corrected age (CA), total costs for HRU, including hospitalisations and medication, were €10,500/PY and €6,700/PY, respectively. Costs and HRU were higher for infants with BPD or CLD than for those without either. Mean (SD) costs for birth hospitalization were: €163,850 (127,000) and €101,150 (71,350) for infants with or without BPD, respectively; €166,700 (125,750) and €101,800 (75,050) for infants with or without CLD. Readmission rates at 1 year CA were also higher for infants with respiratory illnesses: 1.30 and 1.05 per person-year for infants with or without BPD, respectively; 1.34 and 0.86 per person-year for those with or without CLD. At 1 year CA, 50% of extremely preterm infants received pulmonary medications: inhaled bronchodilators (36%), diuretics (20%), inhaled steroids (18%), and systemic corticosteroids (5%).

Conclusions: Among preterm infants born in the Netherlands, extreme prematurity was associated with high rates of BPD and CLD and accompanying increased costs and HRU. These findings underscore the need for new interventions to reduce the burden of respiratory illness in this vulnerable population.

615 | Healthcare costs and resource utilization associated with select severe adverse events in patients with metastatic urothelial cancer treated with first-line systemic therapies

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Background: Prior studies reported substantial economic burden due to metastatic urothelial cancer (mUC), but limited information on costs and healthcare resource utilization (HRU) related to severe adverse events (SAEs) is available for this population.

Objectives: To estimate incremental healthcare costs and HRU associated with select SAEs among patients (pts) with mUC treated with first-line (1 L) systemic therapy.

Methods: Adults treated with 1 L chemotherapy or immuno-oncology therapy (IO) (first therapy administration defined index) between 1/2012–9/2017, ≥1 UC diagnosis code, and continuous enrollment for ≥6 months pre- and ≥ 3 months post-index date were identified using IQVIA™ Real-World Data Adjudicated Claims - US database. Pts with incident SAEs (febrile neutropenia [FN], dehydration, acute kidney injury [AKI], sepsis, colitis, hepatitis, adrenal insufficiency, and pneumonitis) during the 1 L treatment period (up to earliest of treatment switch, discontinuation, end of continuous enrollment, or end of data availability) were identified using inpatient claims. Per pt per month (PPPM) incremental cost differences (CDs) and HRU rate ratios (RR) comparing pts with and without the select SAEs were calculated using multivariate linear regression and Poisson regression, respectively, to adjust for baseline differences.

Results: Of 2,031 pts, 94% were treated with chemotherapy and 6% with IO. The median age of pts was 62 years and 34% were female. The adjusted mean PPPM CD between pts with and without SAEs was $6,130 ($p < 0.01$). The greatest CDs were observed for pneumonitis ($20,242; $p < 0.01$), sepsis ($9,490; $p < 0.01$), and AKI ($8,843; $p < 0.01$). Significant CDs were also observed for colitis ($7,202; $p < 0.01$), dehydration ($7,125; $p < 0.01$), and FN ($4,231; $p < 0.01$). HRU burden was greater in pts with SAEs than in pts without SAEs (hospitalization RR = 7.82 [$p < 0.01$], emergency room RR = 1.64 [$p < 0.01$], outpatient visits RR = 1.05 [$p < 0.01$]). Pts with the following SAEs had a higher rate of hospitalization compared to pts without the SAE: AKI (RR = 4.83; $p < 0.01$), dehydration (RR = 4.72; $p < 0.01$), sepsis (RR = 4.49; $p < 0.01$), pneumonitis (RR = 4.43; $p < 0.01$), colitis (RR = 3.45; $p < 0.01$), FN (RR = 3.17; $p < 0.01$), and hepatitis (RR = 2.21; $p < 0.01$).

Conclusions: SAEs occurring during 1 L therapy for mUC can result in significant burden to pts, families, and healthcare systems. Appropriate selection of therapies based on future validated biomarkers,

patient education, and early AE diagnosis may reduce the impact of SAEs on healthcare costs and HRU.

616 | An analysis of the effectiveness outcomes of economic studies evaluating ophthalmic drugs: A systematic review

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Background: Poor consistency has been observed between the clinical outcomes assessed in trials to support the marketing approval of new drugs and the clinical outcomes subsequently used in cost-effectiveness studies to support decision-making processes.

Objectives: To characterize the type of clinical outcomes (primary or secondary) considered as effectiveness measures of economic studies of ophthalmic drugs.

Methods: Cost-effectiveness studies evaluating ophthalmic drugs were identified through a systematic search conducted in Pubmed and Embase from its inception until November 2018. Cost-utility, cost–benefit and cost minimization analysis were excluded. Therapeutic area (according to "Preferred Term (PT) of MedDRA dictionary, type of economic study (trial- or model-based), effectiveness measures and sources of effectiveness were extracted. Study design, primary and secondary outcomes were extracted from the sources of effectiveness.

Results: Twenty-eight cost-effectiveness studies were included. Most cost-effectiveness studies (n = 18; 64.2%) retrieved their effectiveness measures from experimental sources, while five (17.9%) retrieved from observational sources and five (17.9%) from other type of data sources. Seven (25%) cost-effectiveness studies used data from a primary outcome of a clinical study as an effectiveness measure, six (21.4%) used data from both primary and secondary outcomes and five (17.9%) used data from secondary outcomes. It was not possible to identify the outcomes used as effectiveness measures in ten (35.7%) cost-effectiveness studies.

Conclusions: A considerable number of cost-effectiveness studies in ophthalmology used effectiveness measures not defined as primary outcomes in clinical studies. Cost-effectiveness studies should include data from relevant clinical outcomes in order to properly assess the economic value of drugs.

617 | Economic evaluation of bevacizumab added to chemotherapy for metastatic colorectal cancer (mCRC) in Indonesia

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Background: Studies of metastatic colorectal cancer (mCRC) should be performed to evaluate the use of bevacizumab in mCRC patients and provide scientific evidence for policy maker. Currently, bevacizumab is available in the National Formulary and is included in the national health insurance benefit package.

Objectives: The aim of this study is to review the cost-effectiveness of adding bevacizumab to the chemotherapy regimen for mCRC patients in Indonesia.

Methods: The Economic evaluation used methods of cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and budget impact analysis (BIA) analysis included patients diagnosed with mCRC in several hospitals in Indonesia during the period of 2009–2017. The perspective of the study was the societal perspective. The intervention was bevacizumab added to chemotherapy, compared to chemotherapy alone. CEA applied real-world data approach measuring the clinical outcome of progression-free survival and overall survival. CUA used modeling-based economic evaluation was used in this study to calculate the lifetime cost, lifetime outcome, and ICER (incremental cost-effectiveness ratio) values of both interventions. The pharmacoeconomic analysis uses a cost-utility analysis method which compares the cost with QALY (quality-adjusted life-year) outcome. BIA estimated additional budget to provide therapy for all mCRC patients in Indonesia.

Results: The addition of bevacizumab to the chemotherapy regimen for the treatment of mCRC patients resulted in a longer 1-month PFS clinical outcome and a 2 month longer OS. Adding bevacizumab to chemotherapy in mCRC patients resulted in better clinical outcome (longer PFS and OS), with the ICER of IDR 531.527.028 per year PFS and IDR 1.012.060.452 per year OS. Adding Bevacizumab to chemotherapy in mCRC patients was not cost-effective, with the ICERs from healthcare perspective were IDR 653.336.010 per QALY and IDR 354.719.903 per QALY if using secondary data approach and real-world data approach, respectively. Meanwhile, the ICERs from a societal perspective were IDR 668.091.070 per QALY and IDR 385.393.873 per QALY using secondary data approach and real-world data approach, respectively. Adding bevacizumab to chemotherapy in mCRC patients would require an additional budget of IDR 514.855.919.662 for 6,110 mCRC patients for duration therapy of 1,5 years.

Conclusions: The addition of bevacizumab on the current standard of care for metastatic colorectal cancer patients was not a cost-effective treatment.

618 | How different regulatory systems recognize and reward pharmaceutical innovation - a comparative analysis of intelectual property (IP) protection, marketing authorization and pricing/reimbursement systems with a focus on oncology

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Background: Innovation is recognized in different ways among the various organizations regulating the development and commercialization of medicines; leading to differences in requirements and incentive structures.

Objectives: We aim at reviewing and comparing definitions, incentives and rewards to innovation among decision-making bodies in the US and Europe (EU, Belgium, France, Germany, Netherlands, Sweden and UK).

Methods: Methods: Review of the published literature through Medline and gray sources (guidelines, legislation and official communications, and decisions) illustrated with a case study in oncology.

Results: The definition of innovation varies significantly across stakeholders. The establishment of a New Chemical Entity by patenting an invention is followed by the registration of a pharmaceutical product that may or may not be assigned a new ATC class, depending on novelty of chemical class and pharmacological properties. Then, regulators assess the degree of innovation more comprehensively to consider early access (FDA, EMA). Finally, HTA bodies consider the value of that innovation in terms of patient, caregiver and/or societal benefit in order to determine premium pricing and coverage. Criteria for differentiation varies across countries (formulation, mechanism of action, mode of administration, etc.). Premium pricing for a patent-protected innovative product requires therapeutic advantage in terms of safety, efficacy (HAS/France), quality (IQWIG-GBA/Germany), morbidity and quality of life (CRM/Belgium), or cost (TLV/Sweden and NICE/England and Wales) and demonstrated additional clinical benefit over existing therapies. Other criteria such as unmet need or disease severity have been considered though rarely and the value of incremental innovation or patients/carers' convenience have been insufficient to justify premium pricing by themselves.

Conclusions: Patent protection, marketing authorization and pricing/reimbursement systems serve different purposes so the thresholds to define "innovativeness" escalate with each step and so do geographical disparities. IP protection follows international conventions. Incentives for innovation are rather consistent across regulators; entailing mainly expedited procedures and less burdensome evidence requirements. Conversely, priorities for pricing/reimbursement to recognize and reward innovation do not align.

619 | Opioid use, healthcare expenditures, and pain severity in osteoarthritis patients using patient reported pain scores to assess pain severity

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Background: Over 30 million adults in the U.S. have osteoarthritis (OA) and the economic burden of OA-related pain is substantial. Opioid use is prevalent OA patients to manage OA-related pain. Though treatment guidelines for management of chronic pain recommend against using opioids to manage mild pain or as a first line therapy to manage chronic pain, opioids may still be used to manage mild pain or as a first line therapy in OA patients.

Objectives: To describe the prevalence of opioid use and healthcare expenditures in OA patients by patient reported pain severity.

Methods: Adult OA patients with valid pain scores at OA diagnosis were identified between 1/1/2002 and 9/30/2016 in the MarketScan Claims and Electronic Medical Records Database (CED). Date of pain score was the index date; 12 months continuous enrollment before and after the index date was required. Patients with baseline opioid use or joint replacement during the observation period were excluded. Four pain severity cohorts, based on score at diagnosis, were used: none (0), mild (1–3), moderate (4–6), severe (> 6). Opioid use and healthcare expenditures were measured during follow-up and compared by pain severity.

Results: 3,984 OA patients met the patient selection criteria; mean patient age was 66 years and 58% were women. 65% of patients had pain at diagnosis (15% mild, 26% moderate, 24% severe). Strong opioid use was more prevalent in patients with mild (27%), moderate (28%), and severe pain (36%) relative to patients without pain (18%, $p < 0.001$ for all); prevalence of strong opioid use was similar in patients with mild and moderate pain ($p = 0.59$). Mean healthcare expenditures in patients with moderate ($14,106) or mild ($12,235) were not significantly higher than patients with no reported pain ($14,342). Patients with severe pain had significantly higher mean expenditures ($16,796) than patients with no pain; $p = 0.04$) and patients with mild pain ($p < 0.01$).

Conclusions: Though highest rates of strong opioid use were observed in patients with severe pain, strong opioid use was also prevalent in patients with mild pain. Further research is necessary to assess whether use of strong opioids is consistent with treatment guidelines for patients with mild OA-related pain.

620 | Analysis of the price difference rate between essential and non-essential medicines in China

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Background: China launched the current health care reform in 2009 to address the issue of access to appropriate medicines for 1.3 billion people. The new editions of the National Essential Medicines List (NEML) have been launched since June 1, 2015, with the aim of providing essential medicines to all.

Objectives: The purpose of this study was to analyze the price of essential and non-essential medicines in the market, to review the impact of essential drug policies on drug pricing, and to provide recommendations for policy makers.

Methods: In this study, 21 dynamic monitoring and data collections were conducted for drug retail distributors (n = 62) and hospital pharmacies (n = 61) in China's provinces (n = 27) between 2014 and 2017, and drugs (n = 5379) From different manufacturers (n = 2806) to assess the impact of the essential drug policy on drug pricing. Define the "Price Difference Rate (PDR)" as "(retail price-ex-factory price) / ex-factory price x 100%". Descriptive analysis, chi-square test, case analysis are used in this study.

Results: 1. The medicines with PDR of less than or equal to 0.25 accounts for 59.1% of the total, 18.2% is PDR of greater than 0.25 and less than or equal to 0.5, 11.7% is PDR of greater than 0.5 and less than or equal to 1, and 9.3% is PDR of greater than 1 and less than or equal to 3, PDR of more than 3 accounted for 1.7%; 2. Among the drugs with PDR of more than 5, 82.12% were domestically produced, 75.93% belonged to the NEML, Rx accounted for 99.74%, and only 19.91% were sold in hospital pharmacy; 3. The top three PDR medicines are Ganmao Granule (PDR = 1685.52%, Chinese patent drug, cold medicine), Ofloxacin Glucose Injection (PDR = 1667.66%, antibiotic), Yuanhu Anodyne((PDR = 1221.86%, OTC, Chinese patent drug). 4. Drugs with PDR of less than 1 are classified into three categories. Rename the drug with PDR of 0.25 or less for A, PDR is greater than 0.25 and less than or equal to 0.5 for B, and the others for C: ①Drugs in NEML of A(68.07%), is lower than B(66.73%) and C(63.79%) significantly (chi-square = 66.279,p = 0.000); ②Western drugs of A(73.17%) is over B(55.20%) and C(61.57%) with statistically significant difference (chi-square = 1014.425,p = 0.000); ③Injection in A was 28.41%, which was significantly higher than 13.60% in B and 19.63% in C (chi-square = 1163.150, p = 0.000); ④2.9% of A was OTC, is lower than B(5.06%) and C(5.52%) significantly (chi-square = 131.148, p = 0.000).

Conclusions: The coverage of the types of essential drugs is still not broad enough, the price of drugs is floating and unstable during circulation, and the price of national essential drugs needs to be strictly controlled.

621 | The cost of hospitalization and length of stay due to hypoglycemia in patients with diabetes mellitus: A cross-sectional study

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Background: hypoglycemia in patients with diabetes mellitus is a frequent and costly adverse drug event. There have been no studies in the Middle East countries that estimate the hospitalization cost and length of stay due to hypoglycemia in patients with DM.

Objectives: to estimate hospitalization cost and length of stay due to hypoglycemia, and to identify determinants of variation in hospitalization cost and length of stay among patients with diabetes mellitus.

Methods: a cross-sectional study was conducted in Jordan using inpatients records of two private hospitals for patients with diabetes mellitus, who have been hospitalized due to hypoglycaemia between January 2009 and May 2017. All hospitalization costs were inflated to costs in 2017. Hospitalization cost was estimated from patients perspective in Jordanian dinars (JOD). Multiple linear regression analysis was used to identify predictors of hypoglycemia hospitalization cost and length of stay.

Results: a total of 126 patients with diabetes mellitus were hospitalized due to hypoglycemia. The mean patients age was 64.2 (SD = 19.6) years old, of which half were male. The median length of hospital stay was two days (IQR = 2 days). The median cost of hospitalization for hypoglycemia was 163.2 JOD ($230.1) (IQR = 216.3 JOD, $305.0). Patients who had a family history of diabetes mellitus had higher hospitalization cost and longer length of stay (0.306 and 0.275, $p < 0.05$). Male patients and patients who were without smoking history had longer length of stay (0.394 and 0.456, $p < 0.01$).

Conclusions: hospitalization due to hypoglycaemia among patients with diabetes mellitus represents a substantial economic burden within hospital settings. Healthcare professionals should give more attention to this adverse drug event to decrease the burden of its associated cost.

622 | The devil you should know: Adjustment for confounding bias is rare in observational economic evaluations in cardiology

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Background: Similar to comparative effectiveness studies, observational economic evaluations (i.e., economic evaluations based solely on observational data) are prone to confounding bias. However, prior studies have shown that adjusting for confounding is poorly done if

done at all in observational economic evaluations. In 2013, Kreif et al. published a checklist aimed at improving the quality of confounding bias adjustment in these studies. In the same year, Husereau et al. published the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement that identified what items should be reported in all economic evaluations. We hypothesized that these publications improved the methodological quality of observational economic evaluations.

Objectives: Our primary objective was to investigate whether and how confounding is accounted for in observational economic evaluations in Cardiology. Our secondary objective was to assess adherence to the CHEERS Statement in selected publications.

Methods: We performed a systematic review of PubMed, Embase, Cochrane Library, Web of Science and PsycInfo databases using a set of Medical Subject Headings (MeSH) and keywords covering topics in "Observational Economic Evaluations in Health" and "Cardiovascular Diseases". Any study published between January 1st 2013 and December 31st 2017 answering our search criteria was eligible for inclusion; no other exclusion criterion was imposed. We screened all eligible reports to identify which confounding adjustment method, if any, was used. We also assessed which items of the CHEERS Statement were reported.

Results: A total of 8,771 unique citations were screened, with 43 manuscripts selected for full text extraction. Out of the first 10 studies fully reviewed, only 3 (30%) adjusted for confounding bias; 1 study used covariate matching, 1 study used propensity score matching and 1 study used multivariate regressions. Secondary results indicate that, on average, studies reported 16 (range 13–19) out of the 21 relevant items identified in the CHEERS Statement.

Conclusions: Despite previous efforts, our interim results indicate that confounding bias is poorly controlled for in observational economic evaluations. Such results support continued educational efforts aimed at improving researchers' knowledge and skills regarding confounding bias and methods aimed at addressing this issue. Revising the CHEERS Statement to better account for observational economic evaluations (e.g., adding items specific to confounding bias) may improve the methodological quality of future publications.

623 | Incidence and treatment-related economic burden of HPV-related cervical, vulvar, vaginal, and anal cancers in the US

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Background: Human papillomavirus (HPV) infection is the most common sexually transmitted infection in the US. Persistent infection with high-risk types can progress to cancer.

Objectives: To estimate the incidence and direct medical costs of cervical, vaginal, vulvar, and anal cancers attributable to high-risk types targeted by the 9-valent (9v) HPV vaccine in US.

Methods: Cervical, vaginal, vulvar, and anal cancer cases were identified from the SEER (Surveillance, Epidemiology, End Results) cancer registry. Included patients were newly diagnosed at age 9 and above in the year of 2015. Cancer histology was limited to squamous cell carcinomas. Incident cases were estimated by using age/gender/site-specific SEER incidence rates and published US population data. Since only a proportion of these cancers are attributable to HPV, Published estimates of the proportion of each cancer site attributable to the 9vHPV vaccine-types were further applied to estimate incident cases attributable to these types.

Results: The 2015 annualized incidence rate per 100,000 person-years of cervical, vaginal, vulvar, anal (female), and anal (male) cases was 5.85, 0.29, 1.42, 1.78, and 0.95, respectively. The economic burden of cervical, vaginal, vulvar, anal (female), and anal (male) cancer was $671 million, $50 million, $88 million, $129 million, and $71 million, respectively. Cervical cancer treatment costs accounted for 63% of the overall treatment costs of the 4 types of cancers. The economic burden of these cancers attributed to the 9vHPV vaccine types was over $1.0 billion.

Conclusions: Cancers attributable to 9vHPV vaccine types inflict substantial health and economic burden on society. The estimate of economic burden is conservative, as it does not include costs of prevalent infection (other than newly diagnosed cases), costs associated with screening and treatment of pre-cancers, indirect costs such as productivity losses due to cancer morbidity and mortality, and the burden of other HPV-related cancers (e.g., penile, oropharyngeal). Screening/HPV vaccination can help reduce the burden of these HPV-related cancers.

624 | Cost analysis of hepatitis C treatments in Saudi Arabia

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Background: Hepatitis C is a costly disease that requires economic allocation of resources towards medication selection and purchases to avoid huge budget impacts. The Ministry of Health in Saudi Arabia stated that 1,327 new cases of Hepatitis C were identified in 2015 with an incidence rate of 4.21 per 100,000 populations. A blood testing and screening suggest a prevalence rate of 0.4%–1.1% of the total population.

Objectives: To analyze the cost of anti-hepatitis C medications prescribed at a tertiary hospital in Saudi Arabia by achieving the following objectives: estimating the total cost of hepatitis C treatment for each patient and determining the incident rate based on the hospital data.

Methods: A retrospective data retrieved from Electronic medical records (EHR) for all adult patients attended the Hepatology

outpatient clinic at a tertiary hospital during the period of (Jun 2015-Dec 2017) with positive hepatitis C test and treated with the following medication: Harvoni (ledipasvir-sofosbuvir), Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabruvir), Daklinza (daclatasvir) with Sovaldi (sofosbuvir) or Zepatier (grazoprevir-elbasvir). Micro-costing bottom up approach used to determine the direct medical costs of the disease from the perspective of the hospital. An excel worksheet was created for data entry. Study was approved by the institutional review board (IRB) with reference no (17/0045).

Results: A total of 89 patients with a positive serology of hepatitis C were identified. The mean age of the patients were 61 years. The genotype 4 is most dominant (60%) followed by genotype 1 (17%). Patient presented with other comorbidities include hypertension and other cardiovascular disease 49%, Diabetes Miletus (23%) and thyroid disorder (9%). A 12 weeks course of antiviral agents used to treat hepatitis C was: Harvoni 57%, Viekira Pak 21%, Daklinza with Sovaldi 15% or Zepatier 7%. Most common reported side effect were fatigue, heartburn and shortness of breath mostly seen with Harvoni treated patients. Complication of the disease includes cirrhosis 47%, fibrosis 27% and cancer 6%. 67% of patient treated with Harvoni has end up with cirrhosis while 69% of patient treated with Daklinza has fibrosis. Viekira Pak was associated with less disease complication cases. The estimated cost associated with treating one patient was around 179,380 Saudi Riyals ($ 47,835).

Conclusions: Hepatitis C has a huge impact on the health budget specifically when associated with the disease complications. Although the treatment is expensive, but rational use of this medication together with early intervention will result in cost reduction.

625 | Assessment of incidence and severity of drug related problems in patients with chronic diseases and pharmacist intervention in net cost savings

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Background: Patients suffering from hypertension and diabetes with comorbidities receive poly pharmacy and likely experience drug related problems, that may negatively affect therapeutic outcomes and treatment costs. Many global studies have suggested the positive influence of pharmacist intervention in improved health outcomes and net cost savings.

Objectives: To assess the prevalence and severity of drug related problems (DRP) in patients with chronic disorders and influence of pharmacist intervention in minimizing the DRP and net cost savings.

Methods: Cross sectional intervention study design.

Results: During the study period, a total of 1210 houses were visited and health status of 4327 people were assessed in urban Suryapet, Telengana State, India. Among them, 304 (7.02%) individuals (Male: 63%, Females: 37%) were found suffering from chronic diseases. Among them, 223 (75%) patients were suffering from cardiovascular and 81 (25%) patients were suffering from endocrine disorders. As per Cipole's classification, a total of 141 Drug Related Problems were identified among the prescriptions received by the patients. Drug interactions were 93 (66%), adverse drug reactions 26 (18.4%), Failure to receive drugs 11(7.8%), sub-therapeutic dosage 5(3.5%), over dosage 4 (2.8%) and Drug use without indication 2(1.4%). The net cost of DRP was calculated using direct and indirect medical costs. it was found that, a sum of Indian Rupees 26,200/− (USD 400) can be saved if timely interventions are made in the above 141 DRPs.

Conclusions: Pharmacist intervention through pharmaceutical care can minimize drug related problems and improve health outcomes and reduce health care expenditures. <!--EndFragment-- > .

626 | Possible channeling bias in the evaluation of cardiovascular risk of triptans: The importance of comparator selection in observational research

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Background: In observational research, comparator choice can directly affect the validity of study results, clinical interpretation, and implications. Triptans, widely prescribed acute migraine medications, have vasoconstriction properties and, therefore, triptan labels contain a contraindication for ischemic heart conditions.

Objectives: To explore the potential of channeling bias in the evaluation of adverse cardiovascular (CV) outcomes among migraine patients initiating triptans and alternative active comparators.

Methods: We conducted a retrospective, new-user cohort study using the MarketScan Database (2004–2016) to evaluate the risk of myocardial infarction (MI) and stroke among treated and untreated patients with acute migraine and nonmigraine controls. To assess the impact of comparator choice, migraine patients initiating triptan treatment were compared to those initiating opiates or prescription nonsteroidal anti-inflammatory drugs (NSAIDs). We used propensity score methods and Cox-proportional hazard regression to estimate adjusted hazard ratios (aHRs) with 2-sided 95% confidence intervals.

Results: 455,776 patients (mean age ± SD: 37.62 ± 12.31 years) initiated triptan treatment. These patients were younger, had fewer comorbidities, concomitant medications, CV risk factors, and hospital visits compared to untreated migraine patients (n = 1,240,116) or those initiating prescription NSAIDs (n = 325,419) or opiates (n = 52,793). Consistent with current knowledge, patients with migraine were found to be at an increased risk for stroke compared to nonmigraine patients (aHR = 2.16, 2.08–2.23), but not for MI (aHR = 0.96, 0.91–1.02). Inconsistent with existing evidence, the aHRs for MI and stroke of patients initiating triptans were 0.52 (0.29–0.92) and 0.47 (0.35–0.63), respectively, compared to patients initiating opiates, and 0.92 (0.44–1.90) and 0.39 (0.27–0.55), respectively, compared to patients initiating NSAIDs.

Conclusions: Given the CV warnings included in current triptan labeling, the finding of 'protective' effects of triptans for MI and stroke compared to alternative treatments suggest channeling of migraine patients at high CV risk away from triptans and towards alternative treatments. Such channeling may pose substantial challenges in using triptans as comparators for novel migraine treatments in future observational post-marketing CV risk studies.

627 | Cohort study of the relative incidence of major cardiovascular events among patients initiating prucalopride versus a matched comparator cohort in a multinational study: Study design and comparability of cohorts

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Background: Given prior safety experience with other 5-HT4 agonists, an observational cohort study was conducted to evaluate the cardiovascular (CV) safety of prucalopride in support of approval of prucalopride for chronic constipation (CC) in the United States.

Objectives: To describe methods and resulting comparability of cohorts in a multi-database, multinational study of prucalopride and polyethylene glycol 3350 (PEG) initiators treated for CC, following a harmonized protocol; assess the performance of propensity score (PS) stratification and trimming to obtain comparable study cohorts; and report study design decisions undertaken when comparability could not be achieved.

Methods: In this observational, population-based cohort study (EUPAS9200) conducted in 5 data sources from 3 European member states, prucalopride initiators were matched on age, sex, and index date to PEG initiators (1:5 ratio). Data sources included the Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN), and the Information Services Division (ISD) of Scotland in the United Kingdom; the Swedish National Registers (SNR) in Sweden; and the German Pharmacoepidemiological Research Database (GePaRD) in Germany. Study exposures, CV risk factors, and other covariates were identified from health care utilization codes harmonized across databases. CV outcomes were identified using database-specific algorithms based on diagnosis codes. PS in each database was estimated using logistic regression, with prucalopride versus PEG as the outcome and including clinically relevant variables associated with major adverse CV events, which were the primary Post-authorisation Safety Study (PASS) endpoint.

Results: 12,030 prucalopride initiators and 59,985 PEG initiators were identified. After matching and trimming, cohorts from the UK and Sweden were well balanced for CV risk factors and cancer. Matching on 2 additional variables (recent hospitalization, prescriber type) was needed in Sweden. However, in Germany, PEG initiators remained older and sicker than prucalopride initiators. Prevalence of these characteristics also differed from those in the UK and Sweden.

Conclusions: Matching, trimming, and PS stratification yielded comparable cohorts in 4 of 5 data sources. Use of these methods could not achieve balance for key covariates within the German cohort, likely due to reimbursement differences in Germany. Consequently, the pooled PASS analyses included only data from the UK and Sweden.

628 | Confounding effect of smoking on the association between fluoroquinolone and risk of aortic aneurysm

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Background: Several epidemiologic studies have reported an approximately 2-fold increased risk of aortic aneurysm associated with fluoroquinolone use. However, none of these studies collected information on smoking status, which is an important confounder and could potentially explain away the observed increased risk in these studies.

Objectives: To conduct a series of quantitative bias analyses to evaluate the impact of unmeasured smoking on the association between fluoroquinolone use and aortic aneurysm risk.

Methods: We applied three common approaches previously published - the E-value approach, the rule-out approach and the array approach, to evaluate the potential confounding effect of smoking. The E-value represents the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure (RR_{EC}) and disease outcome (RR_{CD}) to fully explain away an apparent exposure-disease association (APR). The rule-out approach is similar to the E-value approach but provides a more precise estimation of RR_{EC} and RR_{CD} based on a prior assumption on the marginal prevalence of confounder (P_C) and exposure (P_E). The array approach is mathematically similar to the rule-out approach but estimates the "true" exposure-disease association based on APR, RR_{CD} and the prevalence of confounder in the exposure group (P_{C0}) and non-exposure group (P_{C1}).

Results: For an APR of 2, the E-value is 3.41, suggesting that smoking needs to be associated with both aortic aneurysm and fluoroquinolone with a minimal magnitude of 3.41 (when RR_{EC} equals RR_{CD}) to fully explain a 2-fold increase of the observed risk. The array approach found that if smoking increases the risk of aortic aneurysm by at least 7-fold (high estimate in literature), the smoking prevalence in fluoroquinolone users needs to be at least 45%, assuming a smoking rate

of 15% in the reference group to drive an APR from 2 to null. An in-house simulation based on a wide range of P_C - P_E combinations using the rule-out approach found that the required RR_{EC} and RR_{CD} by rule-out approach were always larger than the E-value (3.41, when RR_{EC} equals RR_{CD}).

Conclusions: It would require strong associations between smoking and both aortic aneurysm and fluoroquinolone use to explain away the observed association between fluoroquinolone and aortic aneurysm. Therefore, it is unlikely that smoking alone would explain the observed association.

629 | Antidepressant medication, suicidal behavior and violent crime in a cohort of Danish patients with affective disorders

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Background: Initiation of antidepressant medication may increase the risk of self-harm and aggressive behavior the weeks after start due to alleviated psychomotor inhibition preceding the improvement of mood.

Objectives: To examine the association between initiation of antidepressant medication and subsequent suicidal behavior and violent crime in relation to time since initiation.

Methods: A cohort of 95 794 patients with a first-time hospital contact for an affective disorder in the Danish National Patient Registry (DNPR) were followed for purchase of antidepressant medication, suicide, suicide attempts and conviction for violent crime in the Danish Prescription Registry, Cause of Death Registry, DNPR and the National Crime Register between 1997 through 2015. Associations between antidepressant medication and outcomes were analyzed using Cox proportional hazard regression for the first 28 days, 28 to 365 days and more than 365 days after initiation. Hazard ratios were adjusted for sociodemographic and clinical variables.

Results: During follow-up, 73.7% (*n* = 70 577) of patients initiated antidepressant medication, 0.8%(*n* = 798) committed suicide and 6.2%(*n* = 6101) attempted, while 3.4%(*n* = 3226) were convicted a violent crime. Patients, who initiated antidepressant medication had the same rates of suicide (adjusted hazard ratio 0.86 (0.58 to 1.20), as patients with no use of antidepressant medication the first 28 days and the following 28–365 days, while there was a slightly higher risk after 365 days. Patients who started antidepressant medication had higher rates of attempted suicide but not the first 28 days of treatment. Antidepressant medication was not associated with violent crime.

Conclusions: Initiation of antidepressants was not associated with suicidal behaviour or violent crime, when confounding by indication was reduced by restricting analyses to patients with affective disorders assumed to be more homogenous with regard to psychatric comorbidity.

630 | Use of external comparators for health technology assessment submissions - an analysis of HTA accelerator

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Background: For rare diseases and cancers a high demand exists for faster access to novel therapies. Patient populations are often limited in size, making randomized control trials impractical. The number of approvals through facilitated regulatory pathways supported by single-arm trial (SAT) data is increasing. Absence of direct comparators poses HTA assessment challenges. External comparators may provide supporting contextual evidence, however for HTA assessment no formal guidance exists. The aim of this study was to characterize HTA submissions regarding use of external comparators and submission success.

Objectives: Quantify and characterize HTA submissions, with a focus on SATs and external comparators.

Methods: A retrospective descriptive study using a database of publicly available information on HTA submissions (HTA Accelerator) which covers submissions globally across all therapies 1996–2018 from 100+ agencies in 32 countries. Submissions were selected based on inclusion of external comparator data. Descriptive statistics summarized submission characteristics and outcomes, qualitative analyses explored feedback on acceptability of evidence and methodology.

Results: In 16 countries, 165 SAT submissions were identified; 61%(*n* = 100) for oncology indications. Submissions originated most frequently from France 25%(*n* = 41) and UK 18%(*n* = 30). The frequency increased annually (n = 1 in 2011; *n* = 49 in 2017). External comparators were used in 47%(*n* = 78) of submissions, most often from prior RCT(45%, *n* = 35) and observational studies(32%, *n* = 25). A positive or positive with restrictions outcome was received for 68%(*n* = 53) submissions with external comparators vs 55%(n = 35) without. For submissions with positive outcomes the increased uncertainty of evidence compared to a direct comparator was acceptable if the evidence was sufficiently strong and aligned with patient values. For submissions with negative outcomes the low quality of external comparator evidence and/or use of inappropriate methodology was highlighted.

Conclusions: This study showed use of external comparator data in HTA submissions based on SAT has increased over time. Use of such data is associated with higher submission success. The qualitative analysis of HTA feedback suggested that it is important to consider external comparator data in a strategic way and to consider why and how the comparator is selected and incorporated into the analysis. A limitation of this study was that not all the data within submission

packages were publicly available, so the frequency of use of external comparators may be underestimated.

631 | Assessment of channeling among initiators of suvorexant compared to other insomnia drugs

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Background: Channeling bias is a selection bias which may occur when a newly marketed drug and an established drug, with similar indications, are prescribed to patients with different prognostic characteristics.

Objectives: To assess potential channeling of newly marketed suvorexant compared to other FDA approved insomnia medications (zolpidem, temazepam, ramelteon, and low dose doxepin) on important baseline prognostic factors.

Methods: A new user cohort study was conducted using the Optum Research Database with patients initiating the insomnia drugs between January 01, 2015 to September 30, 2017. A look-back period of 12 months prior to the index date was used to describe baseline characteristics using ICD and NCD codes. Baseline characteristics were summarized using descriptive statistics. Between-group differences in baseline characteristics were compared using absolute standardized differences (ASD) with an ASD $\geq$ 10% representing a meaningful difference. The ability to balance important prognostic factors was examined using propensity score (PS) matching and inverse probability of treatment weighting (IPTW).

Results: The analysis included a total of 24,450 suvorexant, 438,756 zolpidem, 116,549 temazepam, 9,104 ramelteon, and 1,322 doxepin new users. Compared with zolpidem, suvorexant users were generally older (mean [SD] =65.0 [14.7] vs 56.3 [15.5] years, 59% vs 32% $\geq$65 years, ASD = 57.8%); included a greater proportion of females (65% vs. 48%, ASD = 15%); with a higher percentage of comorbidities, most notably ASD $\geq$ 25% for depression, diabetes, musculoskeletal pain, arthritis, anxiety, hypothyroidism, hyperlipidemia, urinary problems, and prior insomnia drug use (57% vs 6%, ASD = 134%). Baseline characteristics for new users of suvorexant were more similar to ramelteon and low dose doxepin. PS matching and IPTW allowed us to achieve reasonable balance (ASD <10%) in important prognostic variables.

Conclusions: Channeling of suvorexant to patients with different prognostic characteristics was observed, most notably in comparison with zolpidem. In this analysis, PS matching and IPTW allowed us to achieve reasonable balance in important measured covariates. The observed channeling and ability to achieve balance in measured covariates is an important consideration for future comparative effectiveness and safety studies of suvorexant and other sleep hypnotics.

632 | Lurking Berkson's bias in pharmacoepidemiology: Tales of colliders

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Background: Pharmacoepidemiology has made enormous strides in the last decade due to adoption of causal modeling and new methods in biostatistics, allowing for novel discoveries and associations among exposures and outcomes of life-threatening diseases. However, when exploring new avenues of association context is often lost, which can introduce spurious associations between pairs of variables when one is conditioned (by design or analysis) on a common effect of a pair of variables. This is due to selection bias, and is often referred to as collider bias, or Berkson's bias.

Objectives: The objective of this study was to explore possible collider biases in data from a survey used to identify self-reported HPV vaccine uptake, as well as attitudes about the vaccine among 18–26 year old women.

Methods: A survey including questions about health, vaccine attitudes, demographics and HPV vaccine series initiation and completion was distributed to women age 18–26 in Utah. 327 surveys were included in the analysis.

Directed acyclic graphs (DAGs) were used to identify potential sets of variables that can become correlated (d-connected) after adjusting on a potential collider. Generalized linear models were used to test relationships between variables. The structural model considered was whether attitudes about vaccines (e.g., vaccines are a good way to protect public health) and age commonly cause vaccine initiation and would become d-connected after conditioning on initiation.

Results: There was a significant relationship between belief that vaccines are a good way to protect the public health and vaccine initiation (p = 0.00367) as well as age and initiation (p = 0.00237). Furthermore, there was no relationship between age and belief vaccines are good for public health in the overall cohort (p = 0.281). However, after restricting analysis to the subset of participants who had initiated the vaccine series, age and belief about vaccines for public health became significantly associated (p = 0.0402). This would imply vaccine initiation is a potential collider or introduces collider-stratification bias, i.e., age is not independent of vaccine belief given vaccine initiation.

Conclusions: Recognizing the significance of context in pharmacoepidemiology is vital. Conditioning on a collider can lead to seemingly paradoxical findings that can have an enormous impact on how we view and design research in the healthcare setting. Without recognizing this, precious resources can be allocated in the wrong direction due to spurious associations among otherwise independent variables, creating delays in true discoveries, treatment and cures where time is of the essence.

633 | Analytic and design approaches to unmeasured confounding by body mass index

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Background: Body mass index (BMI), often an important confounder, is unavailable in insurance claims data and its accurate prediction is difficult. There is increasing interest in internal validation via linkage to electronic health records (EHR) systems to augment claims data.

Objectives: To describe confounding of the association of NSAIDs initiation and venous thromboembolism (VTE) by BMI in a cohort study of U.S. women, and explore approaches to control confounding by mimicking a claims data analyses with BMI data available from an internal EHR validation study.

Methods: We identified new use of NSAIDs (exclusive of aspirin and coxibs) and incident VTE (deep vein thrombosis or pulmonary embolism) among 39,876 participants of the Women's Health Study (WHS) followed from 1993–2011 with annual questionnaires. We defined NSAID initiation as the first reported use for ≥4 days of the past month and counted only VTE events confirmed by an endpoint committee. We designed as-treated analyses comparing NSAIDs initiation with non-initiation (NIC) and acetaminophen initation (AIC) comparators. The unit of analysis was the questionnaire. At-risk follow-up periods began on the questionnaire date. Follow-up was censored on the earliest of the first reported treatment change or 5 years after each eligible index date. Propensity scores incorporating age, BMI, comorbidities, concurrent medication use, and interaction with calendar time were estimated and implemented by standardized morbidity ratio weighting. We estimated hazard ratios (HR) with 95% confidence intervals (CI) using Cox proportional hazard models with a robust variance. We describe confounding by BMI in the NIC and AIC analyses and examine the performance of multiple imputation (MI) of BMI using 10% and 50% internal validation samples under scenarios of missing completely at random (MCAR) and 1.5 and 3.0-fold increased probabilities of missingness for normal BMI values (18.5- < 25 kg/m^2).

Results: HRs (95% CI) for NIC and AIC analyses were, crude: HR_{NIC} = 1.33 (1.06, 1.66) and HR_{AIC} = 1.03 (0.65, 1.65), and fully adjusted: HR_{NIC} = 1.29 (1.03, 1.62) and HR_{AIC} = 0.87 (0.53, 1.44). Adjusted HRs changed +5% (HR_{NIC} = 1.36) and + 2% (HR_{AIC} = 0.89) with omission of BMI. Prediction models for BMI yielded R^2 = 0.15. Fully adjusted HRs from MI ranged 1.28–1.31.

Conclusions: MI approaches show potential for confounding control with internal validation data despite suboptimal prediction, but resampling is needed to describe the sampling distributions. Availability of BMI, an important confounder, had less impact on the treatment estimate than use of an active comparator.

634 | Multiple risk factor control and risk of cardiovascular events and mortality in people with type 2 diabetes in the UK

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Background: Control of multiple cardiovascular risk factors among people with type 2 diabetes (T2DM) improves outcomes in trial settings but whether this relationship between simultaneous achievement of risk factor targets and cardiovascular (CVD) risk exists in routine clinical practice is not well established.

Objectives: Our aim was to describe the association between control of five key modifiable risk factors and risk of CVD in people with type 2 diabetes in contemporary clinical practice.

Methods: We used electronic health records from the Clinical Practice Research Datalink (CPRD) in England and SCI-Diabetes in Scotland, to identify people with T2DM during years 2006–2015. Patient profiles for HbA1c (≥7.0% /53 mmol/mol), systolic blood pressure (>140 mmHg), total cholesterol (>4 mmol/L), triglyceride (>1.7 mmol/L), and current smoking status were determined at the index date for study entry. Missing data on risk factors were multiply imputed. Cox models estimated adjusted hazard ratios (HRs) for incident or recurrent major CVD events (fatal or non-fatal coronary heart disease or stroke) associated with the number of risk factors above thresholds. Risk estimates were meta-analyzed across the 2 databases.

Results: During the study period, 27,900 (27.4%) of 101,749 T2DM patients in CPRD and 101,362 (30.6%) of 330,892 T2DM patients in SCI-Diabetes experienced one or more CVD events. CVD risk increased for each additional risk factor above recommended targets. Compared to all risk factors at target, those with 5 risk factors above target had pooled adjusted HRs of 1.40 (95% CI 1.33–1.47) for overall CVD events, 1.25 (1.18–1.32) for non-fatal CHD, 2.30 (2.02–2.63) for non-fatal stroke, 1.46 (1.31–1.63) for heart failure hospitalization, 1.43 (1.35–1.52) for CVD morality, 1.84 (1.60–2.11) for CHD mortality and 1.80 (1.33–2.43) for stroke mortality. In patients defined as at low risk for CVD (no history of CVD or CKD-stages 4/5), the association with risk factor control was greater, with a two-fold increase in risk for total CVD events (HR 1.96; 95% CI 1.82–2.12) and CVD mortality (HR 2.27; 95% CI 1.85–2.79) with 5 risk factors above targets compared to all risk factors at target. In those defined as at high risk of CVD, overall there was a weak association with the number of risk factors above target and risk of CVD events.

Conclusions: Every additional risk factor above recommended targets increased cardiovascular event risk. There is considerable scope to improve CVD risk factor control in people with T2DM, especially those at low risk of CVD.

635 | Evaluation of confounding by smoking and obesity in a study of pancreatic and thyroid cancer incidences in patients treated with exenatide, an administrative healthcare database investigation supplemented with medical records

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Background: Residual confounding by unmeasured or poorly captured factors, such as smoking and obesity, is an important concern in studies using administrative healthcare databases. Sensitivity analyses to estimate the extent of confounding required to fully explain the observed findings are necessary.

Objectives: To estimate the impact of confounding by smoking and obesity on the observed findings of exenatide use and pancreatic and thyroid cancers using information abstracted from medical records.

Methods: We applied the rule-out approach presented by Schneeweiss to explore the extent to which residual confounding could explain the observed findings relating to exenatide use and pancreatic and thyroid cancers in a propensity-score matched cohort study of patients with diabetes. We abstracted information on smoking and obesity from medical records within a subset of patients included in a nested case–control study. We projected a wide range of magnitudes of association between smoking or obesity and each cancer ($RR_{\text{confounder-disease (CD)}}$) and between exenatide and smoking or obesity ($OR_{\text{exposure-confounder (EC)}}$) based on the information abstracted from medical records and the literature. The impact of confounding by smoking and obesity were quantified to demonstrate how strong the OR_{EC} and RR_{CD} must be to fully explain the observed findings (the apparent relative risk [ARR]).

Results: The originally observed findings of ARR from the claims-based cohort study were 0.76 (95% confidence interval [CI]: 0.47–1.21) for exenatide use and pancreatic cancer and 1.46 (95% CI: 0.98–2.19) for exenatide use and thyroid cancer. From the medical records, the observed prevalence of smoking was 21% and obesity 75%; the observed OR_{EC} was 0.26 for exenatide and smoking and 2.65 for exenatide and obesity. In the literature the observed RR_{CD} was 1.7 for smoking and pancreatic cancer and 2.08 for obesity and pancreatic cancer; RR_{CD} was 0.75 for smoking and thyroid cancer and 1.50 for obesity and thyroid cancer. The analyses show that the OR_{EC} and RR_{CD} for smoking or obesity would have to be much stronger than the observed OR_{EC} and RR_{CD} in order to fully explain the observed ARR between exenatide use and pancreatic and thyroid cancers.

Conclusions: It is unlikely that residual confounding by smoking or obesity alone explains the original findings between exenatide use and pancreatic and thyroid cancers.

636 | Using different look back periods to calculate the Charlson comorbidity index (CCI) in NVAF patients treated with oral anticoagulants (OACs)

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Background: The definition of look back windows can influence the estimated prevalence of chronic conditions.

Objectives: We investigated how different look back periods influenced estimates of the prevalence of comorbidities included in and estimates of the Charlson Comorbidity Index (CCI) in non-valvular atrial fibrillation (NVAF) patients receiving oral anticoagulants (OACs).

Methods: Adults with NVAF in the UK newly initiating warfarin, apixaban or rivaroxaban (index date) between 2012 and 2017 were identified from linked primary (Clinical Practice Research Datalink) and secondary care (Hospital Episode Statistics) data. The look back period used for identifying comorbidities was defined as ever (all available data), 3 years and 1 year prior to index date. CCI scores were estimated using previously published methods and described using number and proportions.

Results: A total of 15,860 patients were identified, which included 56.6% warfarin, 17.1% apixaban and 26.3% rivaroxaban users. The prevalence of all comorbidities was higher when using the ever look back period compared to 1 and 3-year periods. The largest differences were observed for renal disease, where the prevalence increased from 12.1% to 18.5% and 28.8% for a 1-year, 3-year and ever look back period for all treatment groups. The second largest difference was for malignancies, which increased from 4.8% to 7.7% and 17.0%, respectively. Using a 1-year look back period, 44.1% of users had a CCI score greater than 0; the equivalent estimates were 53.5% using a 3-year lookback and 65.9% using an ever look back period.

Conclusions: These data emphasize the importance of considering all available data when constructing look back windows to estimate the prevalence of chronic conditions, and highlights the high prevalence of renal disease in NVAF patients initiating treatment. Further research is needed to determine the impact of varying look backs on

consequent ability to control for confounding in comparative studies of treatment effectiveness and safety.

637 | Missing the trees for the forest plots: Where subgroups fall short

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Background: Interest in precision medicine and application of randomized trials to external populations are topics of increasing interest. Subgroup analyses, forest plots, and outcome models examining marginal interaction have been used to indicate if drugs perform better or worse in some patients, but many are reluctant to draw conclusions from them due to concerns regarding chance findings. Less attention has been paid to causal relationships that render marginal estimates of effect measure modification (EMM) from subgroup analyses misleading.

Objectives: Evaluate potential for bias in estimates of treatment effect modification by subgroups related to study eligibility.

Methods: We posited a source population described by two independent binary variables: M and N. Individuals with at least one of M or *N* = 1 were eligible for a randomized controlled trial of treatment X on risk of outcome event Y (risk = 0.10 when X = 0). In the base population, M caused EMM of X while N did not: in patients with M = 0, X doubled risk of Y, while in patients with M = 1, X tripled risk of Y. We varied prevalence of M and N in the source population between 25%, 50%, and 75%. M and N were used as stratification variables for crude subgroup analyses and calculation of the ratio of risk ratios (RRR) between the strata. We also conducted regression analyses including terms for X, M, N, and interaction terms for both M and N.

Results: Distortion in M and N's modification of X's treatment effect was consistent and calculable. Subgroup estimates of the M interaction term were unbiased with a RRR of 1.5 comparing stratum M = 1 to M = 0 regardless of M or N prevalence. While N did not modify the effect of X in the source population, analyses of EMM by N comparing stratum N = 1 to *N* = 0 indicated RRRs of 0.75, 0.83, and 0.92 when the prevalence of M in the source population was 25%, 50%, and 75% respectively; the prevalence of N was irrelevant. This problem persisted with risk differences, if M and N both caused EMM, and if M and N were associated with increased sampling probability rather than inclusion criteria. Multivariable regression, however, generally produced accurate estimates of EMM by M and N.

Conclusions: If M is a modifier, requiring M or N for study eligibility distorts estimates of EMM by N: stratum N = 0 all have M = 1 while stratum N = 1 inherits the source population's distribution of M. Associations between modifiers and trial selection can result in misleading estimates of treatment effect heterogeneity. Investigators should be wary of using simple forest plots and instead take into account multiple variables when evaluating potential effect heterogeneity, even when treatment has been randomized.

638 | Post-surgery infection and subsequent mortality among hip fracture surgery patients: Different methods for dealing with time-varying confounding in a Danish population based cohort study, 2004–2016

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Background: Complications and comorbidities affecting mortality, such as heart diseases and infections, are common after hip fracture surgery. Thus, when estimating the causal effect of infection on subsequent mortality, adjustment for baseline confounders alone may be insufficient.

Objectives: We compared different methods of handling time-varying exposure and confounding when estimating the effect of having a post-surgery hospital-treated infection on 1-year mortality in hip fracture patients.

Methods: In this nationwide cohort study using data from Danish registries, we included patients aged ≥65 years with a first-time hip fracture surgery in 2004–2016. Patients were classified as exposed after they had a record of a hospital-treated infection within 1-year after the surgery. With infection as a time-varying exposure, we calculated adjusted hazard ratios (aHR) for 1-year mortality with 95% confidence intervals (CI) using 1) Cox regression with baseline confounders only, 2) Cox regression with time-varying confounders, and 3) marginal structural models (MSM). Among the confounders were comorbidities and medications at baseline and during follow-up as time-dependent covariates.

Results: We included 81,704 patients with hip fracture surgery of whom 22,023 (27%) had a hospital-treated infection within 1 year after the surgery, including pneumonia (9,327 patients, 11%). The crude mortality rates per 100 person years among patients with and without infections were 69 and 29, respectively. The corresponding estimates for patients with and without pneumonia were 111 and 31. The aHRs for mortality for any infection (yes vs. no) were 2.71 (CI 2.64–2.79) when adjusting for baseline variables only, 2.55 (CI 2.48–2.63) after additionally adjusting for time-varying confounders, and 2.44 (CI 2.36–2.52) when using MSM. For pneumonia (yes vs. no), the aHRs corresponding to the three approaches were 3.51 (CI 3.39–3.63), 3.20 (CI 3.09–3.31), and 3.33 (CI 3.19–3.47), respectively.

Conclusions: Having a hospital-treated infection, particularly pneumonia, yielded an increased risk of 1-year mortality after hip fracture surgery. The aHRs were attenuated when accounting for time-varying confounding, supporting the notion that adjustment for baseline confounders alone may yield a biased estimate of the causal effect of infection on mortality in this setting.

639 | Indication bias in the study of comparative effectiveness of direct oral anticoagulants in the prevention of stroke

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Background: Oral anticoagulants are indicated for the prevention of stroke in patients with atrial fibrillation. Observational studies comparing the effectiveness of individual OACs have poorly documented and controlled for sources of indication bias.

Objectives: To assess the preventive effect of individual DOACs on stroke as compared to VKAs according to the type of atrial fibrillation.

Methods: From two national registries, patients with previous history of atrial fibrillation and with or without a first-ever incident stroke were selected. Atrial fibrillation was confirmed with an EKG as non-valvular (NVAF) and stratified according to (i) type of NVAF ([paroxysmal and persistent] or permanent) and (ii) incident (<1 year) or prevalent NVAF (1–5 years; >5 years). Stroke and non-stroke patients were matched on index date, age and gender. VKAs and dabigatran, rivaroxaban or apixaban use before index date and association with stroke was studied in different NVAF strata using multivariable conditional logistic models, controlled for clinically significant confounding factors (liver or renal impairment, cardiovascular history, other risk factors).

Results: 2586 stroke cases with NVAF history were matched to 4810 randomly selected non-stroke patients with NVAF history. An inverted U-shape association for the duration of the NVAF and stroke was observed (OR = 0.53 95%CI[0.45–0.62] for incident NVAF, OR = 1 for mid-duration prevalent NVAF and OR = 0.58 95%CI[0.51–0.67] for long-term prevalent NVAF; the OR for permanent NVAF and stoke as compared to paroxysmal and persistent NVAF was 2.35 95%CI[2.02–2.73]). Sources of indication bias occurred as VKAs and each individual DOAC displayed very different patterns of use according to the type and history of atrial fibrillation. In incident NVAF, dabigatran, rivaroxaban and apixaban had an overall OR for stroke of respectively 0.53 95%CI[0.24–1.13], 0.61 95%CI[0.36–1.02] and 0.32 95%CI[0.17–0.60] when compared to VKAs while they were respectively 0.54 95%CI[0.33–0.89], 0.78 95%CI[0.54–1.13] and 1.13 95%CI[0.64–1.98] in mi-duration prevalent NVAF (or similar ORs in long-term prevalent NVAF). No difference between these NOACs compared to VKAs was observed in permanent vs paroxysmal and persistent AF (all point OR in the vicinity of 0.6 in both strata).

Conclusions: Studies concluding on a relative beneficial effect of some individual NVAF as compared to others without stratifying for indication should be interpreted with caution particularly in view of the observed U-shape risk relation/effect modification for history of AF.

640 | Challenges in conducting a multinational European study of severe hypersensitivity reactions among recipients of intravenous iron

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Background: Severe hypersensitivity reactions (SHRs) in intravenous (IV) iron treatment are a known but rare, and therefore poorly characterized, safety concern. A regulatory-mandated postauthorization safety study (PASS) with multiple sponsors will assess the risk of SHRs in IV iron users in Europe. A multidatabase study approach is required to evaluate this rare safety outcome. Results will be available in 2020.

Objectives: To describe cohort attrition of IV iron users and challenges encountered in conducting this PASS.

Methods: Cohorts of new and prevalent adult IV iron users with at least 12 months of available information were identified from seven data sources in five countries: Denmark (national and regional registers), France (SNDS), Germany (GePaRD, QiN, DIMDI-DaTraV), the Netherlands (PHARMO), and Sweden (national registers). The algorithms used to identify SHRs rely both on diagnostic codes and markers of SHRs

(e.g., symptoms and treatments). A cohort of IV penicillin users was identified, where feasible, to assess the performance of the algorithm. Code lists for the algorithm and covariates were harmonized across data sources. Validation of cases through source record review is planned in Denmark and the Netherlands. Indirect external validation of the SHR algorithm will be conducted in the Oldenburg University Hospital in Germany. Data source-specific analyses and pooled analysis of aggregate data will follow a common protocol.

Results: Heterogeneity in the data available across data sources was addressed through collaborative work across all research centers. Drug exposure is captured through prescription, dispensing, or administration records from hospital or outpatient settings, thus requiring tailored definitions of "time at risk" windows. As of January 2019, based on data from three data sources after cohort attrition, approximately 180,000 IV iron users with a first use, 102,000 IV iron users with a second use, and 80,000 IV iron users with a third or subsequent use were eligible for the study. The IV iron cohort sizes vary greatly across data sources and countries. Data for all IV iron types are not captured in any single data source.

Conclusions: Initial data suggest sizeable numbers of IV iron users. However, the informativeness of results for individual drugs will depend on the relative use of each IV iron subtype and the frequency of SHRs. Understanding the commonalities and differences of the data available in the collaborating centers and standardizing data definitions are critical to conducting a multidatabase study.

641 | Bias reduction with multiple imputation of lab results from a limited internal sample

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Background: Trials suggest that GLP1 receptor analogues (GLP), a class of injectable antidiabetics, may increase retinopathy risk. Assessing drug safety in MarketScan data offers opportunities to examine this signal but presents challenges due to the lack of clinical detail. Lab results, e.g. Hemoglobin A1c (HbA1c), which may improve confounding control, are only available for a fraction of enrollees.

Objectives: To evaluate if multiple imputation (MI) of lab results in an internal validation study could further balance cohorts for diabetes severity when assessing whether GLP increases diabetic retinopathy (DR) risk compared with long acting insulin (LAI), a drug usually reserved for more severe diabetes.

Methods: Using MarketScan data 2007–2015, we identified GLP and LAI new-users who were < 65 years of age. We excluded patients with a history of blindness, low vision, or retinopathy therapy. We defined DR as having a claim for photocoagulation, intravitreal injection, or vitrectomy plus ≥1 DR or diabetes diagnosis code on the same day. We identified baseline lab values (HbA1c, GFR, HDL, LDL, triglycerides) in the 30 days prior to the index date. GFR was based on serum creatinine and MDRD formula (not including race) for those with GFR = 0 (14% of values). We set implausible lab values to missing. We then used MI using fully conditional specification regression in arbitrary missing pattern to impute lab values. We used propensity scores (PS) to evaluate the balance of measured and imputed confounders. We estimated adjusted hazard ratios (aHR) and 95% CI using inverse probability treatment weighted Cox proportional hazards models censoring for treatment changes.

Results: Lab values were available for ~6% of GLP (1896/31599) and LAI (3643/60723). Before MI, HbA1c level was 7.6% in GLP and 8.4% in LAI. The imputed mean HbA1c levels were virtually identical. After PS weighting, HbA1c level was 7.6% for both GLP and LAI. The crude rates of DR/1,000 person-years were 10 in GLP and 29 in LAI over a median duration of 0.64 and 0.58 years, respectively. Comparing GLP to LAI, the crude HR was 0.34 (0.30–0.39), the aHR ignoring lab values was 0.46 (0.40–0.53). After adjustment for imputed lab measures, the aHR was 0.55 (0.45–0.67).

Conclusions: Using MI to leverage lab data on a fraction of the cohort moved the aHR towards the null. Residual confounding is likely as balance of imputed value does not achieve full confounding control, since the imputed values do not capture the full risk associated with HbA1c. Identifying comparator drug classes used for similar disease severity, may still be the most robust approach to implicitly control for diabetes severity.

642 | Comparison of new user definitions in multi-specialty EMR data

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Background: New user designs are typically preferred in pharmacoepidemiology to avoid bias.

Objectives: The optimal implementation of a new user design in electronic medical record (EMR) data, where the concept of 'enrollment' does not exist, has not been well studied.

Methods: We used data from PCORnet, a large U.S. comparative effectiveness research network consisting of multiple EMR data sources, to compare various new user definitions, with rheumatoid arthritis (RA) as an exemplar use case. The first prescription appearing in the data for RA medications of interest (methotrexate [MTX], a biologic, or targeted therapy [i.e. tofacitinib]) was identified in the EMR prescribing data and defined as the index date. Five new user definitions with varying requirements for the type of prior EMR data needed to construct a 'baseline' period were evaluated. New user definitions tested included 0) no requirement for any prior data; 1) >6 m from first medical inpatient or outpatient medical encounter of any type; 2) >6 months from first prescription for any medication; 3) > 6 months from first medical encounter for RA (ICD9:714.*; ICD10:M05.*, M06.*); 4) >6 months

from first prescription for any RA therapy (biologics, targeted therapy, or conventional DMARD including HCQ, SSZ, LEF). The rate of hospitalized infection according to new user definition was examined.

Results: A total of 6621 RA patients initiated one of 9 unique DMARDS, biologics or targeted medications. Mean (SD) age was 55(16) years, 78% women, 43% MTX, 38% TNFi biologics; 19% non-TNFi therapy, 38% oral glucocorticoids. The distribution of time from the first medical encounter to the index date for the first RA medication was a median (IQR) of 1428 (590,2704) days for definition 1, appreciably longer than for definition 4 (median 1178 days; IQR: 581–2068). The proportion of patients that would be classified as new users across the five definitions was: 100% (base case, 1st Rx is index date with no prior data required), 83% (>6 m from first visit), 57% (>6 m from first Rx of any type), 71% (>6 m from first RA visit), and 29% (>6 m from first RA drug), respectively. The overall rate of serious infections in the first 6 months after initiation was 2.8/100 patient years; ongoing work is evaluating how infection rates vary across the 5 new user definitions.

Conclusions: A range of tradeoffs exist in how to best apply new user definitions to multi-specialty EMR data. These design features can misclassify new medication use and result in high variability in sample size, patient characteristics, and outcomes. More rigorous and specific definitions are likely preferred for most pharmacoepidemiology studies to avoid bias.

643 | A simple method to find applicable lengths of washout periods for identifying new users in pharmacoepidemiologic study

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Background: New-user design can exempt from potential selection bias and therefore serves as standard approach in pharmacoepidemiologic study. However, appropriate lengths for washout period to identify new users vary among studies.

Objectives: We proposed a method to test the rate of prevalent users to find applicable lengths of washout period for identifying new users of medications.

Methods: We used Longitudinal Health Insurance Database which included a random sample of 1 million Taiwanese population from 2003 to 2013.We included four study cohorts with patients receiving antidiabetic, antihypertensive, lipid lowering agents and antipsychotics, respectively, during study period. We assumed those without a record of specific cohort medications for 10 years washout period were incident users. We adopted different lengths of washout period from 0 to 10 years and examined corresponding rate of residual prevalent users we included. We defined 10% or less as acceptable rate for residual prevalent users.

Results: We included 60343, 185067, 73715, and 55602 users of antidiabetic, antihypertensive, lipid lowering agents and antipsychotics, respectively. We identified 6009, 16573, 11288, 17545 incident users of antidiabetic, antihypertensive, lipid lowering agents and antipsychotics, respectively, by 10 years washout period. While 1-year washout period was implemented, we included 4.6%, 12%, 13.8%, and 44.2% residual prevalent users of antidiabetic, antihypertensive, lipid lowering agents and antipsychotics. We found it required 0.94, 1.5, 1.8 and 5.7 years washout periods to include less than 10% of prevalent users in the antidiabetic, antihypertensive, lipid lowering agents and antipsychotic cohorts, respectively.

Conclusions: The findings indicated the applicable lengths of washout period various in medications. We suggest investigators to use this simple method and trade-off between simple size and validity issues, to find applicable lengths of washout period while designing a pharmacoepidemiologic study.

644 | Impact of non-adjustment for smoking status during pregnancy and pre-pregnancy obesity on the association between gestational antidepressant use and risk of low birth weight infants

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Background: Use of antidepressants during pregnancy has been associated with increased risk of low birth weight in claim database studies. However, such results may be confounded by maternal smoking status during pregnancy and pre-pregnancy obesity for which no information is generally available in administrative databases.

Objectives: To estimate the degree of bias introduced by the non-adjustment for smoking status during pregnancy and pre-pregnancy obesity in the association between gestational antidepressant use and the risk of low birth weight infants.

Methods: We identified a subgroup of women from the Quebec Pregnancy Cohort (QPC) who had delivered a singleton live birth, and answered a self-administered questionnaire on family history and lifestyles during pregnancy. We linked the questionnaire data to the QPC data using the unique personal identifiers. We first estimated the association between antidepressant use during pregnancy and the risk of low birth weight infant without adjusting for smoking and pre-pregnancy obesity. We then calculated the association while adjusting for smoking and maternal pre-pregnancy weight. We finally calculated the percent bias induced by the lack of information on smoking and pre-pregnancy obesity in the QPC estimates using Schneeweiss' method.

Results: Among 3,192 participants, 460 (14.4%) used antidepressants during pregnancy. Antidepressant users were more likely to be smokers (47.1% vs. 33.3%), and had higher prevalence of pre-pregnancy obesity (14.2% vs. 10.8%) than non-users. Overall, the crude estimate for the association between antidepressant use during

pregnancy and the risk of low birth weight was 1.74 (95%CI 1.5–2.0; $p < 0.01$). Adjusting for smoking status resulted in an estimate of 1.18 ($p > 0.05$), and for maternal pre-pregnancy weight, 1.00 ($p > 0.05$). The percent bias introduced by the non-adjustment for smoking and maternal pre-pregnancy obesity using only the QPC data was 6.24%, which did not change the direction of the effect.

Conclusions: Lack of adjustment for smoking and maternal pre-pregnancy obesity led to a small overestimation (6.24%) of the association between gestational antidepressant use and the risk of low birth weight infants, but the direction of the association was unaffected. Given that studies performed on cohorts such as the QPC usually adjust for proxies of missing data, such as physician visits, hospitalizations, of maternal comorbidities, the percent bias is expected to be even lower, which is reassuring.

645 | Case validation of cutaneous lymphoma to minimize protopathic bias

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Background: Protopathic bias (PB) occurs when a drug is prescribed for initial signs/symptoms of an outcome not yet diagnosed, reflecting a reversal of cause and effect. PB may be of particular concern when studying outcomes with long latencies, such as cancer. It is commonly controlled by including a time lag in sensitivity analyses. In a multi-country study on the association of topical tacrolimus and pimecrolimus with cutaneous lymphoma (CL), PB was a concern because CL may present symptoms resembling atopic dermatitis and therefore may be treated with the study medication.

Objectives: To evaluate the potential for PB by acquiring further information on the medical history of CL cases, specifically to assess whether treatment with the study medications was initiated for symptoms that were compatible with early manifestations of CL.

Methods: In Sweden, researchers reviewed hospital medical records of CL cases identified through the Swedish national cancer registry. In the United Kingdom, researchers from the Clinical Practice Research Datalink (CPRD) sent questionnaires to general practitioners (GPs) with CL cases. Information extracted included date of CL diagnosis; date of start of symptoms; location and extent of CL; biopsy results; and skin conditions such as psoriasis or atopic dermatitis, including location, extent, and date of onset.

Results: In total, 29 (CPRD) and 73 (Sweden) potential CL cases were identified. In CPRD, GP questionnaires were sent for all 29 potential cases identified, and 19 have been returned to date. One did not provide additional information. Diagnosis was confirmed in 13 cases, and date of CL diagnosis was identified earlier by GPs than by case screening algorithm in four cases. Six cases had a prior history of skin condition on the same location as CL, one did not, and six did not provide enough information. In Sweden, it was possible to request information for 65 potential cases. To date, 48 medical records have been received.

Conclusions: Based on reviewed cases, the additional clinical information modified the outcome diagnoses or the date of symptoms initiation in half of the patients. Nearly half of the confirmed cases were previously diagnosed with benign skin conditions that share signs and symptoms with CL. Reverse causation could then introduce bias in the study results.

646 | Unmeasured confounders may cause underestimation of anti-osteoporotic drug effects in postmenopausal women with osteoporosis in Taiwan

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Background: Previous pharmacoepidemiologic studies showed controversial results while evaluating effectiveness of anti-osteoporotic drugs, possibly because unmeasured confounders were not considered in some studies.

Objectives: The study aimed to evaluate confounders that were not available in the claims data but measureable in a validation dataset for the studies assessing anti-osteoporotic drugs.

Methods: We analyzed Taiwan's National Health Interview Survey (NHIS) 2005 and 2009 for the study, which included 30,680 and 30,528 random sample of Taiwanese population respectively. We identified a cohort of postmenopausal women over 55 years old diagnosed with osteoporosis and a history of fracture. We classified patients into treatment of anti-osteoporotic drugs and non-treatment group. We included factors that may associate with healthier behaviors or recurrence of fracture, such as patients' age (65+ vs 55–65), body mass index (BMI), education level (junior high school and above or not), exercises (within two weeks or not), smoking, alcohol, betel nut and job status. Adjusted odds ratios and 95% confidence intervals (CI) derived from multivariate modified Poisson regression were used to evaluate the differences between treatment vs non-treatment group.

Results: We identified a total of 1592 postmenopausal women over 55 years old with osteoporosis and fracture, and 52% of them were treatment group. The mean age and BMI were 67.63 (SD 8.94) and 24.35 (SD 3.75) respectively. We found treatment group was older (adjusted odds ratio 1.09; 95% CI 1.07–1.11), had higher BMI (1.04; 1.01–1.08), had lower education level (1.38; 1.01–1.89), without exercises (1.21; 0.95–1.56) and more alcohol intakes (1.20; 0.86–1.69) compared to non-treatment group. We found the rates of smoking

(3.0%) and betel nut (1.3%) were low in the study population, and there was no difference between treatment and non-treatment group.
Conclusions: The finding indicated the treatment group of anti-osteoporotic drugs had higher baseline risk of recurrence of fracture compared to non-treatment group. We may underestimate the effects of drugs if the unmeasured confounders were not considered or unmeasurable while using claims databases for pharmacoepidemiologic studies.

647 | Misclassification of case–control studies in PubMed

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Background: Authors' accurate use of terminology about epidemiological methods is important for clearly communicating about research to readers. Users of the medical literature rely on such information to guide them in their use of evidence to support patient care. However, historical changes in the meanings of epidemiologic terms could undermine these goals. For example, the term "retrospective" has historically been used to refer to a case–control study design. More recently, however, the term has come into wide usage as a description of a study's data source.
Objectives: Using a corpus of human immunodeficiency virus (HIV) studies, we evaluated the association between use of the term *retrospective* in a study's title/abstract and the likelihood that it would be indexed as a case–control study in PubMed.
Methods: We conducted a cohort study of PubMed research articles that were indexed with the MeSH term *HIV* between 1992 and 2017. We identified observational studies using a validated search filter for observational studies from the National Institute for Health and Care Excellence (NICE). The exposure of interest was the presence of the term *retrospective* in the title and/or abstract of an article, and the outcome was the PubMed Medical Subject Heading (MeSH) term for case–control studies. We estimated risk ratios (RRs) and 95% confidence intervals for the association between the exposure and the outcome overall and by year.
Results: A total of 88,771 studies met the eligibility criteria during the study period. The number of studies per year ranged from 2667 (3.0%) in 1992 and 3997 (4.5%) in 2010. The RR for the association between the term *retrospective* and the MeSH term for case control studies was 29.2 (27.8, 30.7), and 26.4 (25.1, 27.8) when controlling for year. By year, the association was strongest in the first year (RR 72.4, 95% CI 46.0, 113.9), but then declined substantially in each subsequent year, stabilizing at a magnitude below 40% by 1998. The magnitude was lowest in 2005 (RR 21.1, 95% CI 16.1, 27.7).
Conclusions: Use of the term retrospective is strongly associated with the MeSH term for case–control studies. This association initially decreased but has remained stable from 2005 onward. This suggests potential bias in study classification if use of the term *retrospective* is now more commonly associated with data source than with study design. In ongoing research, we are examining the association between true study design and classification as a case–control study, as well as examining use of the term *retrospective*.

648 | Gender and authorship in pharmacoepidemiology: Studying the authorship patterns of Canadian network for observational drug effect studies research

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Background: The Canadian Network for Observational Drug Effect Studies (CNODES) studies the benefits and risks of post-market drugs using de-identified population-based administrative healthcare data. Its Knowledge Translation (KT) Team is evaluating the efforts to mobilize this research for accountability, demonstrating value, and learning. Acknowledging the gender gap in authorship across academia, the CNODES KT Team looked at the relationship between gender and authorship, both in their own articles and the broader pharmacoepidemiology literature.
Objectives: To investigate gender patterns in authorship of both CNODES articles and the body of literature that cites them.
Methods: CNODES articles published between 2012 and 2017 were identified in SciVal; all articles that had cited the CNODES articles were extracted using Scopus' citation tracking tools. Scopus author IDs for each author were used to extract their full name from the Scopus application programming interface (API). A web service (www.genderapi.com) was used to estimate the gender of both the CNODES authors and the citing authors. The service provides an estimated gender and a probability of being correct; all probabilities <80% were converted to "indeterminate". Once the data were extracted, cross tabulations and visualizations were created, and testing was performed using chi-square tests.
Results: The 28 CNODES articles (2012–2017) were written by 106 authors with many appearing multiple times (266 total authorships). The web service estimated 46 female, 54 male, and 8 indeterminate gender authors for the CNODES articles; total authorship credits were estimated as 84 female, 161 male, and 21 indeterminate. These authorship patterns roughly matched the gender balance in the citing literature, with 774 female, 1817 male, and 73 indeterminate (32% vs. 29% female, p-value = 0.399). Six of the 28 CNODES articles had no female authors, but there was no noticeable pattern in authorship position (e.g. first, second, last, etc.) for either the CNODES articles or the citing literature.
Conclusions: The female authorship rate in the CNODES-cited pharmacoepidemiology literature was 29%; CNODES publications had a similar rate. Further work is needed to determine barriers and facilitators to women's inclusion in project teams and publications, as well as work towards interventions to remove modifiable barriers.

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649 | Performance of genetic risk scores as an instrumental variable in pharmacoepidemiology

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Background: Genetic risk scores (GRS) has been used as an instrumental variable (IV) to control for unmeasured confounding in Mendelian randomization studies. However, little is known if the genetic marker (GM) acts as confounding and that marker simultaneously used for calculating the GRS.

Objectives: We aimed to assess methodological issues of the GRS as an IV in realistic pharmacoepidemiologic settings.

Methods: We simulated data in several scenarios with varying strength of the IV (GRS), little violation of the basic IV assumptions (e.g. GM directly affects the outcome), and GM acts as confounding. In each scenario, the number of replications was 1000 times with 100000 observations. All variables were time-invariant, exposure effect was homogeneous, and in the standard situation, the GRS satisfied its basic assumptions (e.g. independence from pleiotropy). The GMs were simulated using the uniform distribution on the interval from 0.05 to 0.95 and the effect of the markers was generated using the lognormal distribution with mean zero and standard deviation one. We constructed the GRS using a weighted sum of allelic count where the weights being given by regression coefficients in the same data. The true exposure effect for all scenarios was $\beta = 1$. Two-stage linear IV models were applied to estimate the exposures effects on the outcome. Confidence intervals (CI) were estimated in a non-parametric way using 2.5 and 97.5 percentiles of the 1000 estimates.

Results: In standard situation (i.e. perfect IV), the exposure effects were similar with the true value ($\beta = 1$), 1.00 [95% CI: 0.99–1.01]. However, when a marker acts as a measured confounder and that marker also used for calculating the IV (GRS), the effect estimate was shifted away from the true value, 1.18 [1.16–1.19] and the bias was increased with the strength of the confounding. Furthermore, when a GM violates its basic assumption (e.g. GM directly affects the outcome), the effect estimate was highly biased 1.34 [1.32–1.36]. When we removed those GM that acts as confounding or has small association with confounders, the IV estimate was similar to the true value.

Conclusions: Our study suggests that the exposure effects from the IV analysis using GRS as an IV can be valid when the estimates are reported from perfect IV models. We recommend not to use those genetic markers that act as confounders or slightly violates the basic IV (GRS) assumptions.

650 | Outcome classification methodology and heterogeneity of association between BMI and COPD in the UK biobank cohort

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Background: Phenome-wide association studies (PheWAS) to assess phenome-wide correlates of specific exposures often use readily available outcome definitions (e.g. through ICD10 codes) in lieu of more complex disease definitions that require additional methodological and analytic considerations. However, these crude disease definitions may be vulnerable to measurement bias.

Objectives: This GSK-funded study evaluated how the association of a well-measured risk factor with disease phenotype varies by phenotyping methodology. To explore this question, we assessed the association between body mass index (BMI) and chronic obstructive pulmonary disease (COPD) using three definitions of COPD cases; and, how this association is modified by smoking status. While smoking status is a stronger risk factor for COPD, we selected BMI as our primary exposure given its limited vulnerability to reporting bias (compared to self-reported smoking) and low BMI's well-established association with COPD.

Methods: We used data from 502,616 UK Biobank participants to evaluate BMI and smoking measures from baseline data collection against three COPD case definitions: 1) "raw" defined as forced expiratory volume in one second (FEV1) over forced vital capacity (FVC) < 0.7; 2) "best" defined as FEV1/FVC < 0.7 controlling for the quality of the blow; 3) "ICD10" defined as having a record of a COPD-related ICD10 code (J440, J441, J449) in Health Episodes Statistics (HES) records. We used multiple logistic regression models to calculate ORs and 95% CIs per 5 kg/m^2 increase in BMI on the odds of COPD for each COPD definition, stratified by smoking status, adjusting for sex and age.

Results: Our results indicate heterogeneity in the strength and direction of association across all COPD definitions and smoking status strata. Among never smokers, the odds of COPD per 5 kg/m^2 increase in BMI were 0.78 (0.77, 0.79) for "raw", 0.75 (0.74, 0.76) for "best", and 1.54 (1.47,1.61) for "ICD10". Among previous smokers, ORs were 0.82 (0.81, 0.83) for "raw", 0.83 (0.82,0.84) for "best", and 1.42 (1.38, 1.46) for "ICD10". Finally, for current smokers, ORs were 0.66 (0.64, 0.67) for "raw", 0.64 (0.62, 0.66) for "best", and 1.02 (0.99, 1.06) for "ICD10".

Conclusions: This example shows that readily available homogenous disease traits in lieu of more complex disease definitions can lead to substantial heterogeneity in association estimates. Particularly, the common practice of using disease-related ICD10 codes from HES to derive disease phenotypes in the UK Biobank could be biased towards more severe cases given the hospital source population.

651 | Outcome definition influences the relationship between genetic polymorphisms of ERCC1, ERCC2, SLC22A2 and cisplatin nephrotoxicity in adult testicular cancer patients

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Background: Although previous research identified putative genetic polymorphisms associated with cisplatin nephrotoxicity, varying outcome definitions potentially contributed to the variability in effect size and direction of this relationship.

Objectives: To validate the use of already associated genetic variants to predict cisplatin nephrotoxicity and to determine if different cisplatin nephrotoxicity definitions contributed to the variability in effect size and direction of already published associations between these genetic polymorphisms and cisplatin nephrotoxicity.

Methods: We selected variants that have been significantly associated with cisplatin-induced nephrotoxicity in more than one published study (*SLC22A2* rs316019; *ERCC1* rs11615 and rs3212986; *ERCC2* rs1799793 and rs13181) and performed a replication study to confirm associations between genetic polymorphisms and cisplatin nephrotoxicity using various outcome definitions. We included 282 germ cell testicular cancer patients treated with cisplatin from 2009 to 2014, aged >17 years recruited by the Canadian Pharmacogenomics Network for Drug Safety. Nephrotoxicity was defined in four grading tools: (1) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for acute kidney injury (AKI) or CTCAE-AKI; (2) adjusted cisplatin-induced AKI; (3) elevation of serum creatinine; and (4) reduction in the estimated glomerular filtration rate (eGFR). Logistic and multiple regression was used to calculate the effect sizes.

Results: Significant relationships were only found when using the CTCAE v4.03 definition: heterozygous carriers of the *ERCC1* rs3212986 variant had a protective effect from cisplatin nephrotoxicity (OR_{adj} 0.24; 95% CI:0.08–0.70; p = 0.009) while carrying the *SLC22A2* rs316019 polymorphism was associated with a higher risk of cisplatin nephrotoxicity (OR_{adj} 5.06; 95%CI:1.69–15.16; p = 0.004). No significant associations were identified using the other three nephrotoxicity definitions.

Conclusions: Our study showed that different case definitions lead to variability in the genetic risk ascertainment of cisplatin nephrotoxicity. Therefore, consensus on a set of clinically relevant outcome definitions that all such studies should follow is needed.

652 | Uptake of the Ontario naloxone program for pharmacies

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Background: Naloxone is a life-saving antidote for opioid overdose. Increased access to take-home naloxone has been endorsed for regions with an ongoing opioid crisis. In June 2016, the Ontario government implemented the Naloxone Program for Pharmacies (ONPP) to enhance free access to naloxone.

Objectives: We examined the uptake of the ONPP and characterized individuals receiving and pharmacies dispensing naloxone kits.

Methods: We conducted a population-based study of all Ontario residents who received a naloxone kit between July 1, 2016 and March 31, 2018. This involved 1) a cross-sectional analysis of monthly rates of naloxone kits dispensed, individuals accessing naloxone and pharmacies dispensing naloxone; 2) a descriptive analysis of all individuals and pharmacies who accessed and dispensed naloxone, respectively. In each analysis, we stratified individuals according to their opioid exposure as follows: current prescription opioid agonist therapy (OAT) recipient, current prescription opioid recipients, past opioid exposure, and no/unknown opioid exposure.

Results: Over the study period, the rate of naloxone kits dispensed increased from 1.9 to 54.3 kits per 100,000 Ontario residents. By March 2018, 2,729 community pharmacies dispensed 91,069 naloxone kits to 67,910 unique individuals. Naloxone uptake differed between exposure groups, which were highest among OAT recipients (40.7%), and low among current prescription opioid recipients (1.6%) and individuals with past opioid exposure (1.0%). Naloxone dispensing was highly clustered within pharmacies, with one-third (33.7%) of kits being dispensed by 1.0% of naloxone-dispensing pharmacies.

Conclusions: The ONPP led to substantial uptake of naloxone in Ontario; however, access is concentrated among a small proportion of pharmacies and is low among high-risk prescription opioid recipients.

653 | Opioid prescription patterns among patients diagnosed with rheumatoid arthritis in United States

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Background: Rheumatoid Arthritis (RA) is a chronic disease associated with chronic pain. Patients often seek medical consultation not only to treat RA but also to manage pain. Literature shows that about 40% of RA patients receive opioids.

Objectives: To assess opioid prescription patterns among RA patients.

Methods: This retrospective cohort study was conducted among all US adults (≥18 years) using IBM® MarketScan® Research database (2012–2017). The study includes eligible patients with continuous enrolment for at least 2 years, minimum of 2 RA diagnoses ≥30 days apart and at least one opioid prescription (cohort A). We cannot verify if opioids were filled for RA pain from the data, but we excluded patients with history of malignancies and other inflammatory conditions to narrow the scope of the population. Patients were followed for 2 years after index date (date of 1st opioid prescription post RA diagnosis) to assess opioid treatment patterns. We also analyzed a subset of RA patients that had targeted therapy prior to index date (cohort B). Opioids were grouped as: strong (fentanyl, hydrocodone, hydromorphine, morphine, oxycodone, oxymorphone, propoxyphene) and weak (codeine, tramadol, tapentadol). The study estimated sequence and switches of opioids and developed sankey charts and sunburst plots to describe patterns in both cohorts. This study was funded by GSK.

Results: About 36% of all RA patients receive an opioid prescription. The study identified 62,131 and 15,452 patients in cohort A and B respectively. Demographic distribution and opioid patterns were consistent in both cohorts. Both cohorts were mostly female (78–79%) with mean ages of 57(±13) and 55(±12) years respectively. Among those with any opioid prescribed, most received at least one strong opioid (A: 83%, B: 84%) over the follow-up period. Mean (±SD) number of opioid prescription fills over 2 years was 10(±12) [strong: 7(±11); weak: 3(±6)] in cohort A and 8(±10) [strong: 6(±9); weak: 2(±4)] in cohort B. On assessing lines of opioid prescriptions, the most commonly prescribed opioid was hydrocodone followed by tramadol and oxycodone in both cohorts. Among those who switch to a new opioid (42–44%); hydrocodone, tramadol and oxycodone remain choice of opioid. Analysis of treatment sequence show that 13–15% switch ≥3 times over 2 years.

Conclusions: Most RA patients that receive opioids get multiple prescriptions within 2 years of follow up. Over 40% of patients switch opioids. Additionally, over 80% receive a strong opioid prescription. The study concludes that irrespective of the cause, there is high burden of pain among RA patients.

654 | Opioid prescribing and health outcomes in Indiana, USA before and after release of Centers for Disease Control and prevention opioid prescribing guidelines

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Background: From the opioid epidemic in the U.S., one of the most significant strategies to mitigate misuse is the release of CDC's guideline for prescribing opioids for chronic pain in March 2016. However, there has been debate regarding its impact on patients.

Objectives: To compare opioid prescribing and health outcomes before and after the release of the CDC guidelines.

Methods: This is a retrospective cohort study of patients whose data are contained within the Indiana Network for Patient Care (INPC) data. INPC is a health information exchange data from Indiana's health systems covering approximately 70% of Indiana's population. Inclusion criteria was opioid naive patients (age ≥ 18) who received the first opioid prescription (index) within study period with no history of opioid prescription in the previous year. Exclusion criteria was cancer, hospice care, and terminally ill patients. The outcomes include number of day supply, dose in morphine milligram equivalent (MME), recipient of opioid and benzodiazepine within 1 month, use of short and long acting opioids within 1 year, and diagnoses of opioid abuse, dependence, and overdose. These outcomes were compared between before and after the guideline was released using t-test or Wilcoxon rank sum for continuous variables and Chi-square for categorical variables. Data for patients with index date in 2014 and 2017 was used as the period before and after the guideline release, respectively. The follow-up was 1 year after the index. All statistical analyses were performed using SAS 9.4 and p value<0.05 was considered statistically significant.

Results: A total of 127,421 and 34,090 opioid prescriptions were identified for 50,053 and 19,213 patients in 2014 and 2017 respectively. After the guideline release, the median number of day supply for each prescription decreased (7 [range 1, 120] vs 5 [range 1, 90], $p < 0.0001$), but the median MME did not differ significantly (5 [range 0.19, 240] for both years). Patients receiving opioid and benzodiazepine increased (4.0% vs 9.5%, $p < 0.0001$) and patients using both short and long acting opioids decreased (4.5% vs 1.5%, $p < 0.0001$). Patients with opioid abuse diagnoses decreased from 0.08% to 0.03% ($p = 0.0366$), dependence diagnoses decreased form 0.17% to 0.08% ($p = 0.0087$), and those with overdose decreased from 0.03% to 0 ($p = 0.0165$).

Conclusions: Opioid prescribing and adverse health outcomes related to opioids generally decreased after the release of the guideline but further research should be conducted to include patients in other years and account for temporal changes.

655 | Assessing the impact of opioid prescribing guidelines for dentists in Ontario, Canada

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Background: New dental opioid prescribing guidelines were introduced in November 2015 in Ontario, Canada. The document suggested using opioids as a third or fourth line of therapy for acute dental pain and recommended limits on prescription quantity when opioids are warranted.
Objectives: As dentists are the second largest group of opioid prescribers in this province, we sought to examine the impact of these guidelines on their prescribing patterns.
Methods: We conducted a population-based, cross-sectional study of Ontarians who received a prescription opioid from a dentist between July 1, 2012 and September 30, 2017. We calculated the rate of individuals dispensed prescription opioids per 100,000 population, and the population exposure to opioids (volume) in total morphine milligram equivalents (MME) per 100,000 population, monthly over the study period. We used interventional autoregressive integrated moving average (ARIMA) models to examine the impact of the dental opioid prescribing guidelines on prescribing patterns.
Results: The rate of individuals that were dispensed prescription opioids from a dentist remained stable over the study period (range from 161 to 140 individuals per 100,000 population between July 2012 and September 2017), and was not significantly impacted by the release of the dental opioid prescribing guidelines (p = 0.10). Although, the release of the guidelines were associated with a significant decrease in the volume of opioids dispensed to dental patients (p = 0.01), which reduced by 23.2% between November 2015 and September 2017 (from 20.7 MME to 15.9 MME per 100,000 population, respectively).
Conclusions: Changes in the volume of opioids prescribed by dentists, even in the absence of reductions in the population-adjusted rate of opioid prescribing, suggest that dental opioid prescribing guidelines can lead to important practice change. Future studies should examine consistency of practice between dentists, and whether opioid exposure among dental patients is leading to long-term use.

656 | A comparison of opioid-involved fatalities captured in the National Poison Data System and in death certificate literal text data

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Background: The ongoing epidemic of opioid-related deaths necessitates timely and detailed surveillance data. The National Poison Data System (NPDS) collects near real-time, drug-specific information from exposure calls to US poison control centers (PCCs). However, NPDS captures only a fraction of opioid-involved fatalities, and whether the proportion of deaths captured varies across time, drug, and other factors is unknown. Previous studies comparing PCC death data to National Vital Statistics System-Mortality (NVSS-M) data were limited by lack of drug specificity in International Classification of Diseases codes. The recently-developed Drug-Involved Mortality (DIM) database now allows identification of specific opioid moieties involved in death.
Objectives: To describe and compare the number and characteristics of opioid-involved deaths captured in NPDS and US death certificates, across commonly prescribed opioids and over time.
Methods: NPDS, which collects data on calls to US PCCs, and DIM, which combines information from literal text of US death certificates and NVSS-M, were queried for opioid-involved deaths from 2010–2015. Characteristics of the two case-series were compared.
Results: DIM contained 154,016 opioid-involved deaths, and NPDS contained 2,524 fatal opioid exposures, a ratio of 61:1. The number of opioid-involved deaths remained stable in NPDS but increased in DIM. On average, deaths involving opioids with higher mean potency per unit (as measured by morphine milligram equivalents) among dispensed prescriptions were more likely to be captured in DIM relative to NPDS, as compared to those with a lower mean potency per unit. Notably, the increase in fentanyl-related deaths seen in DIM since 2013 was not observed in NPDS. Proportion of female decedents was higher in NPDS relative to DIM, as was proportion of suicide cases. Mean and median ages were slightly higher in NPDS compared to DIM. The majority of cases in DIM (65.4%) did not include route of exposure, whereas >90% of cases in NPDS specified route.
Conclusions: NPDS and DIM are useful resources for examining trends in opioid-involved deaths, but there are important differences between them. While NPDS captures more information on route of exposures, it captures a small fraction of opioid-involved deaths, and caution is warranted in making inferences about mortality trends and comparisons across opioids using this data source. Of particular note, the sharp increase in fentanyl-involved deaths observed in DIM was not seen in NPDS, possibly due to illicit fentanyl's high potency and rapidly fatal effects.

657 | Persistent opioid prescribing after minor surgery in Trinetx

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Background: There is concern about persistent opioid prescribing after surgery, with recent data indicating that ~6% of US patients are affected.
Objectives: To assess persistent opioid prescribing after minor surgery in TriNetX, a federated research network that provides statistical summaries of de-identified patient data. Differences by age, sex, and history of mental health disorders were explored.
Methods: Opioid-naïve patients aged ≥18 years who underwent minor surgery (i.e. varicose vein removal, laparoscopic cholecystectomy, laparoscopic appendectomy, hemorrhoidectomy, thyroidectomy, transurethral prostate surgery, parathyroidectomy or carpal

tunnel release) were analyzed in TriNetX "Analytics" (TriNetX, Cambridge, MA), which contains electronic medical record data of ~38 M US patients (analysis 8-Feb-2019). Patients had to have their first opioid prescription record (VA code CN101) in the perioperative period between 1 month before and 2 weeks after surgery. Persistent opioid prescribing was defined as at least one opioid prescription between 90 and 180 days after surgery, a time at which patients are expected to have recovered from minor surgery. Patients with an anesthesia procedure code during 180 days after surgery were excluded as to minimize inclusion of patients with potential postoperative opioid prescribing because of other procedures or diagnoses.

Results: 122,793 patients met the eligibility criteria. The mean age was 51 years (SD 18). About 61% were women, 74% were white and 9% African-American. Persistent opioid prescribing after minor surgery occurred in 4.8% of the patients (range: 2.5% for parathyroidectomy to 9.2% for varicose vein removal). It was similar in men and women (odds ratio [OR] 1.00, 95% confidence interval [CI] 0.95 to 1.06) but increased with higher age (OR 40–64-year-olds vs. 18–39-year-olds 1.48, 95% CI 1.38 to 1.58; OR 65-year-olds and above vs. 18–39-year-olds 1.74, 95% CI 1.62 to 1.86). In a joint analysis of sex and age, men aged 18–39 years had the lowest risk (referent) and men aged 65+ years the highest risk (OR 2.79, 95% CI 2.48 to 3.14). Higher risk was also seen in patients with a preoperative diagnosis of mood disorders (ICD-10 codes F30-F39; OR 2.08, 95% 1.93 to 2.25) and mental and behavioral disorders due to psychoactive substance use (ICD-10 codes F10-F19; OR 1.74, 95% CI 1.61 to 1.89).

Conclusions: This analysis based on electronic medical record data indicates that persistent opioid prescribing after minor surgery occurs in ~5% of patients, and lays bare sex and age differences and higher risk among patients with mental health disorders. These results are in line with previous data.

658 | Differences in opioid prescriptions among age categories of older adults

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Background: Pain is increasingly treated with opioids, especially in older adults. This increase is seen not only in the United States, but also in Europe. There is evidence that the potential harms of opioid therapy disproportionality affect older adults and little is known about differences in opioid use within the older adult population.

Objectives: The aim of this study is to provide information on trends of frequency and nature of opioid prescriptions for older adults of different age categories, in a primary care setting.

Methods: Data (2005–2017) were derived from routine electronic health records of general practices participating in Nivel Primary Care Database. All opioid prescriptions with ATC-code N02A were selected, with the exception of codeine. Diagnoses were recorded using ICPC-classification. Older adults were categorized in three age categories (65–74, 75–84 and 85 years and older). Descriptive analyses were used to describe the trend of opioid prescriptions to older adults in different age categories for specific opioids and the nature of opioid prescriptions described with diagnoses registered with the prescribed opioids and duration of the opioid prescriptions.

Results: There is an increase in the proportion of older adults who received at least one opioid between 2005 and 2017 (170% increase for 65–74 year olds, 167% for 75–84 year olds and 263%for patients aged 85 years or older). Patients in the oldest age category are more likely to be prescribed an opioid compared to the other age categories, especially when it comes to strong opioids (128,9 patients per 1.000 registered patients compared to 52.5 (65–74 years) and 84.4 (75–84 years) per 1.000 in 2017). Opioids, both strong and weak are mostly prescribed for musculoskeletal diagnoses in all age categories. Yet there are differences in other diagnoses patients in the three different age categories get a prescription for. Over half of the older adults received two or more opioid prescriptions and more than 30% of the older adults used strong opioids chronically.

Conclusions: Opioid use in older adults changes with increasing age in frequency and nature. The high risks associated with opioid use in older adults, stresses the importance to monitor patients individually throughout the treatment.

659 | Risk factors for new and persistent chronic opioid use after hip fracture surgery: A Danish nationwide cohort study from 2005 to 2016

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Background: Opioids are commonly prescribed for acute pain treatment in hip fracture (HF) patients. However, 80% of patients taking opioids will experience an adverse effect and some patients might develop a chronic use of opioids after surgery.

Objectives: The aim was to examined several patient- and surgery related risk factors for new and persistent chronic opioid use after HF surgery.

Methods: Using Danish nationwide health registries, we identified all HF surgery patients ≥65 years of age (n = 69,456). Among opioid naïve patients before surgery, we defined new chronic opioid use as at least two dispensing of opioid within 1 year after surgery. Persistent chronic opioid use was defined as at least one dispensing of opioids 6 months before and two dispensing within 1 year after surgery. We calculated adjusted odds ratios (aOR) with 95% confidence intervals

to explore following risk factors: age, sex, surgical indications, preoperative medications, and comorbidities defined through Charlson Comorbidity Index (CCI low, medium and high) and a number of individual comorbidities.

Results: A total of 9% patients were new users, whereas 13% were persistent users. The aORs for being a new user were 1.39 (1.28–1.50) and 1.23 (1.15–1.32) for age groups 65–74 and 75–84 years, (ref = 85+) 1.09 (1.02–1.16) for female (ref = male), 1.02 (0.96–1.09) and 0.93 (0.86–1.02) for medium and high CCI (ref = low, no known comorbidity), 1.20 (1.12–1.29) and 1.53 (1.38–1.70) for overweight and obese patients (ref = normal body mass index), and 1.26 (1.15–1.37) for preoperative use of NSAID. The aORs for being a persistent user were 1.45 (1.35–1.55) and 1.25 (1.18–1.33) for age groups 65–74 and 75–84 years, 1.83 (1.72–1.95) for female, 1.59 (1.50–1.69) and 2.07 (1.93–2.22) for medium and high CCI, 1.19 (1.10–1.1.29) and 1.35 (1.23–1.48) for underweight and obese patients, and 1.75 (1.63–1.88) for preoperative use of NSAID. There was no association between other potential risk factors and chronic opioid use.

Conclusions: We identified several risk factors associated with new and persistent chronic opioid use, including high age, female sex, comorbidity and preoperative NSAID use. This is clinically relevant in order to identify and develop more effective and targeted preventive intervention strategies to reduce opioid use and thereby the associated adverse events among elderly patients.

660 | Prescription opioid use and dose trajectories before diagnosis of opioid use disorder or overdose among US adults

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Background: With increasing efforts to scrutinize opioid prescribing, little is known about how prescription opioid patterns preceding opioid use disorder (OUD) or overdose have been changed.

Objectives: To determine prescribed opioid fills and dose trajectories in the year before an OUD or overdose diagnosis among US adults.

Methods: This retrospective cohort study used 2005–2016 Truven MarketScan Commercial Claims data to construct a cohort of individuals aged 18 to 64 years with incident OUD or overdose following 12 months of health plan enrollment preceding the diagnosis. We measured prevalence of opioid prescription fills and trajectories of opioid morphine equivalent dose (MED) prescribed in the year before OUD or overdose.

Results: Of 218,690 adults with incident OUD or overdose, 34.0% were aged 18 to 30 years, 46.9% were females, and 85.1% were metropolitan residents. Over one-third of 199,617 adults with incident OUD and 20,417 with incident opioid-related overdose filled no opioid prescription in the year before the diagnosis. In both OUD and overdose cohorts who filled opioid prescriptions, 5 distinct prescribed daily dose trajectories preceding diagnosis emerged: consistent low dose (less than 3 mg MED, 34.4% for OUD and 44.4% for overdose); consistent moderate dose (20 mg MED, 27.5% and 8.8%); consistent high dose (150 mg MED, 14.6% and 14.3%); escalating dose (from less than 3 to 20 mg MED, 14.1% and 10.4%); and de-escalting dose (from 20 to less than 3 mg MED, 9.4% and 22.1%). Overall, over two-thirds of patients with OUD or overdose with prescription opioids were prescribed a mean daily dose below 90 mg MED before diagnosis.

Conclusions: In US commercially insured adults with incident OUD or overdose, absence of opioid prescription fills in the year before diagnosis was prevalent, and the majority received prescription opioid doses below the recommended risk threshold of 90 mg MED. Current programs flagging high-risk patients from their prescription opioid use may be ineffective at identifying patients with OUD or overdose.

661 | Trends in opioid use among commercially insured pregnant women with severe maternal morbidity in the United States, 2007–2015

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Background: Severe maternal morbidity (SMM), or life-threatening complications during delivery, affects more than 50,000 pregnant women in the United States annually- its incidence more than doubling over the past two decades. Little research has evaluated the association between prenatal exposure to high risk medications, such as opioids, and SMM.

Objectives: To compare and contrast the prevalence and patterns of opioid use in a cohort of pregnant women with and without SMM.

Methods: This retrospective study used a 10% random sample of commercially insured enrollees in the IQVIA™ PharMetrics Plus adjudicated claims database. We identified all women (12–55 years of age) with completed pregnancies from 2007–2015, having continuous medical and prescription drug coverage for three months prior to the date of conception through three months post-delivery. We then identified pregnancies with SMM using an algorithm developed by the Centers for Disease Control and Prevention. Opioid exposure during pregnancy was defined as having at least one claim for an opioid product at any period during pregnancy; exposure during each prenatal and postnatal period was also estimated separately. Chi-square tests were employed to test for differences in opioid exposure.

Results: Among 154,200 pregnant women in our sample, 2,004 (1.3%) had SMM. Prevalence of opioid exposure increased in pregnancies with SMM from 8.2% in 2007 to 14.0% in 2015 ($p < 0.01$). The reverse was seen for pregnancies without SMM, with prevalence of opioid use decreasing from 10.7% in 2007 to 8.3% in 2015 ($p < 0.01$). The prevalence of opioid exposure at any time during pregnancy and in each period was significantly higher (all p-values <0.01) for pregnancies with SMM as compared to those without: any time during pregnancy (14.5% vs 9.8%); three months prior to conception (9.5% vs 7.3%); 1st trimester (6.3% vs 4.2%); 2nd trimester (5.9% vs 3.7%); 3rd trimester

(6.3% vs 4.3%) and three months post-delivery (62.1% vs 45.7%). Among pregnant women who were exposed to at least one opioid during pregnancy, a significantly higher proportion were dispensed ≥3 opioids in the SMM group compared to those without SMM (20.7% vs 16.2%, p < 0.01).

Conclusions: This study provides evidence that opioid exposure in pregnancies with SMM has increased in the past decade and is more common in pregnant women with SMM compared to pregnant women without SMM. Further research should be undertaken to establish the potentially causal relationship between high risk medication use, including of opioids, and increased trends in SMM nationally.

662 | Concomitant use of Z-drugs with prescribed opioid agents and the risk of overdose: A cohort study

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Background: Mortality from opioid-related overdose continues to increase in the US, with prescription opioids involved in at least 30% of all overdoses in 2017. Z-drugs are central nervous depressants and, although generally perceived as safe, may increase the risk of overdose when prescribed with opioids.

Objectives: To determine the rate of overdose among patients using opioids and z-drugs as compared to patients using opioids alone.

Methods: We conducted a cohort study using the MarketScan research databases 2004–2015. Patient episodes with concomitant exposure to z-drugs (zolpidem, zopiclone, zaleplon) and prescription opioids ('exposed') were 1:1 matched to patient episodes with exposure to prescription opioids alone ('reference') based on type of opioid (generic), morphine equivalents, calendar year, and hospitalization within the last 30 days of the qualifying prescription. Patients with cancer or palliative care were excluded. Primary outcome was defined as opioid and/or psychotropic-related overdose within 30 days of index date, using an intention-to-treat approach. Hazard Ratios (HR) and 95% CI were estimated from cox proportional hazard regression models with fine stratification on the propensity score (including 65 variables) to control for confounding. Sensitivity analyses were performed to test the robustness of the findings, including extending the follow-up time to 90 days, and employing a stricter outcome definition (i.e., requiring respiratory failure code).

Results: The cohort comprised 750,819 exposed and 750,819 reference episodes. The mean age was 50 years and 41% were male. Most characteristics were well balanced, except for number of generics, clinical diagnoses, and depressive comorbidity, which were more common among patients with concomitant z-drugs. There were 787 overdose events among the exposed (13 per 1,000 person-years) versus 365 events among the reference group (6 per 1,000 person-years), for an unadjusted HR of 2.13 (95% CI: 1.88–2.41). With fine stratification on the PS, the HR attenuated to 1.74 (1.55–1.96). Results of sensitivity analyses were consistent: 90 days follow-up period (HR = 1.50, 1.39–1.62) and stricter outcome definition (HR = 1.43, 1.13–1.79).

Conclusions: Among patients receiving prescription opioids, after controlling for characteristics of the opioid use and other confounders, concomitant treatment with z-drugs was associated with a substantial increase in the risk of overdose. Caution is required when prescribing these agents to patients on opioid therapy and interventions to improve rational prescription are needed.

663 | Direct and indirect effects of medication assisted therapy on nonfatal opioid overdose among patients with opioid use disorder within prescriber networks

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Background: Medication Assisted therapy (MAT) is approved for the treatment of OUD (buprenorphine/naloxone, methadone, naltrexone). Patients prescribed MAT may influence each other's health outcomes due to shared prescribers and prescriptions. In the presence of dissemination (or spillover), four effects are: *direct* (effect on patients prescribed MAT themselves compared to those not prescribed, at a fixed MAT coverage); *indirect* (effect on patients not prescribed MAT, but sharing a network with patients prescribed MAT, comparing two coverage levels); *total* (direct and indirect); *overall* (comparing two coverage levels).

Objectives: To assess these causal effects of MAT on nonfatal opioid overdose (OOD) among patients with diagnosed OUD within prescriber networks in the U.S.

Methods: This was a retrospective cohort study using an administrative database (Optum Clinformatics® Data Mart; Optum Insight, Eden Prairie, MN). Patients (> = 18 years) with OUD diagnosis between 2010 and 2015 were identified and did not have OUD, OOD or MAT during the previous year. Within 60 days of OUD diagnosis (index period), patients were considered exposed to MAT if they had > = 1 prescription. Patients were grouped into prescriber networks by their main prescriber (determined by prescribing patterns), coverage of MAT for network was calculated, and networks >3 patients were included. We used an inverse probability weighted approach to quantify these effects of MAT during the index period on nonfatal OOD.

Results: A total of 18,353 patients in 2,278 networks were included, 11% had MAT prescriptions; 2% had nonfatal OOD during follow-up; 54% were female; mean age was 53 years; and mean Charlson Comorbidity Index (CCI) was 1.37. Among networks with no MAT prescribing, the unadjusted cumulative incidence of OOD was 2% (95% confidence interval (CI): 0.016, 0.021). Adjusting for age, gender, CCI, number of opioid dispensing and clustering by network with a random intercept, the high coverage (87.5%) networks had 9% reduction in the total (CI: −0.17, −0.01) and an 8% reduction in the overall effect estimates (CI: −0.14, −0.01) compared to medium coverage (50%). The direct (8%) and indirect (1%) estimates were protective but not significant (CI = −0.18,0.02; CI = −0.11, 0.09, respectively).

Conclusions: Among patients prescribed MAT in higher coverage networks, there were 9 per 100 patients fewer cases of nonfatal OOD than among patients not prescribed MAT in medium coverage networks. Increasing MAT coverage within the prescriber practices could offer additional benefit among OUD patients.

664 | Dual trajectories of opioid and benzodiazepine use and risk of opioid overdose among US Medicare beneficiaries

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Background: Despite clinical guidelines and US Food and Drug Administration black-box warnings cautioning against concurrent opioid and BZD use (hereafter OPI-BZD use), the number of patients with OPI-BZD use increased by 41% between 2002 and 2014. OPI-BZD use increases the risk of overdose and other adverse outcomes, especially among older adults. Little is known about the patterns of concurrent OPI-BZD use most associated with opioid overdose risk.

Objectives: To examine the association between OPI-BZD dose and duration trajectories and subsequent opioid overdose among Medicare beneficiaries.

Methods: This nested case–control study included 412,930 fee-for-service Medicare beneficiaries who newly initiated prescription opioids (OPIs) from 2011–2015. Cases (n = 346) were identified as having a diagnosis of opioid overdose from inpatient or emergency department claims within the year after initiating OPIs. We identified 1,524 controls (up to 1:10 ratio) matched by the propensity score including age, gender, calendar year of OPI initiation, Elixhauser comorbidity index, and the corresponding index date (i.e., matched case's overdose date ±30 days) for each case. We used a machine learning approach, specifically, bi-kmeans clustering modeling, to identify distinct OPI-BZD dose and duration trajectories, based on average daily morphine milligram equivalent (MME) for OPIs and standardized daily dose for BZDs, within 90 days preceding the opioid overdose episode or the corresponding index date. We used multivariable logistic regressions to estimate odds ratios (OR) of opioid overdose risk across trajectories, adjusting for socio-demographics and health status factors (e.g., mental health disorders) selected by the least absolute shrinkage and selection operator (LASSO).

Results: Among 1,870 beneficiaries (mean age ± SD = 56.3 ± 15.4, female = 41.4%, white = 78.3%), 4 distinct trajectories were identified (1 trajectory with minimal or no OPI-BZD use, and 3 OPI-BZD trajectories with different doses). Compared to beneficiaries with minimal or no OPI-BZD use (34.1% of the cohort), the overdose risk varied by trajectory: consistent low-dose OPI-BZD use (58.7%; OR = 2.00, 95%CI = 1.38–2.90); consistent low-dose OPI use and extremely high-dose BZD use (3.3%; OR = 5.76, 95%CI = 2.51–13.21); and consistent high-dose OPI-BZD use (3.9%; OR = 11.45, 95%CI = 5.57–23.54).

Conclusions: Among Medicare fee-for-service beneficiaries, opioid overdose odds varied substantially across OPI-BZD use trajectories, with individuals having consistent high-dose OPI-BZD use having more than 10 times overdose odds.

665 | Concomitant use of opioids or psychotropic medications among skeletal muscle relaxant users in the United States: A cross-sectional study

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Background: Skeletal muscle relaxants (SMR), a group of medications indicated for acute and painful musculoskeletal conditions, are commonly co-prescribed with opioids and psychotropic medications for the treatment of pain and other comorbidities.

Objectives: To estimate the prevalence of SMR and concomitant opioid or psychotropic medication use among commercially insured adults in the US.

Methods: A cross-sectional study was conducted using the IBM MarketScan Commercial Claims Database. For each year from 2006 to 2015, we calculated proportions of SMR users with concomitant use of opioids, antidepressants, anticonvulsants, benzodiazepines, or other sedatives and hypnotics, where concomitant use was defined as total overlap in days' supply of SMRs and the medication class of interest for more than 14 days. The results were stratified by age group and gender.

Results: We identified 6.7 million unique beneficiaries with SMR fills during the study period. Overall, proportions of SMR users with concomitant medication use were 21.8% for opioids, 19.9% for antidepressants, 10.4% for anticonvulsants, 6.0% for benzodiazepines, and 5.5% for other sedatives and hypnotics. From 2006 to 2015, concomitant use of anticonvulsants increased by 59.5%. The increasing utilization of opioids peaked around 2011 and declined slightly thereafter. In comparison, changes in the use of other medication classes were

small. Females had greater concomitant psychotropic medication use, but similar concomitant opioid use compared to males. For all medication classes, concomitant use increased with age.

Conclusions: Concomitant use of opioids and psychotropic medications was common among SMR users. Given the overlapping adverse event profiles, future studies should examine the risk of potential harms associated with the use of these psychoactive medication combinations.

666 | Predictors of long-term opioid use in HIV patients who initiated antiretroviral therapy

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Background: Pain management is important for quality of life in patients with HIV. However, pain management via opioids may have an inappropriate risk/benefit ratio. Little is known about risk factors associated with long-term (LT) opioid use in this population.

Objectives: To identify the predictors of LT opioid use in HIV patients who initiated standard combination anti-retroviral therapy (cART).

Methods: Using Medicaid data (2002–2009) from Kentucky (KY), Maryland (MD), North Carolina (NC), and Washington (WA), we conducted a retrospective cohort study to examine LT opioid use in HIV patients initiating cART. LT opioid use was defined as 90 days of continuous use, accepting <32 days gap over a six-month period. We excluded any patients who filled a prescription of ART or opioid during the washout period defined as the six-months prior to initiating cART. Potential predictors of LT opioid use (demographic characteristics, comorbidities, specific medications, and polypharmacy based on number of medications used, excluding cART) were measured during the washout period and identified using logistic regression with backward selection, and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were estimated.

Results: LT opioid use occurred among 1,192/13,003 (9.2%) eligible patients. Strong predictors of LT opioid use were metastatic solid tumors (aOR = 2.51; 95% CI = 1.15–5.47), substance use disorders excluding alcohol and tobacco use (1.78; 1.53–2.07), hepatitis C infection (1.67; 1.41–1.98), pain-related disorders [back pain (1.47; 1.14–1.88), neuropathic pain (1.57; 1.27–1.94), and unclassified pain (1.50; 1.07–2.12)], chronic obstructive pulmonary disease (1.22; 1.01–1.47), benzodiazepine use (1.48; 1.21–1.82), non-opioid analgesics (1.38; 1.19–1.59), antidepressant use (1.30; 1.14–1.49), and polypharmacy (1.89; 1.55–2.32). Patient factors associated with lower odds of LT opioid use were cardiovascular disease (0.69; 0.54–0.89), younger age (0.98; 0.97–0.98), male sex (0.88; 0.77–0.99), and black vs. white race (0.66; 0.56–0.78).

Conclusions: Comorbidities and polypharmacy were important predictors of LT opioid use in HIV patients initiating cART. Further studies should evaluate patient outcomes associated with prescribing LT opioids in this population.

667 | Patterns of opioid use among patients with cancer-related pain diagnoses

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Background: Efforts to curb the opioid overdose crisis are sweeping and may impact the prescribing of controlled substances in unintended ways. Anecdotal reports suggest patients with cancer-related pain bear a disportionate burden as scrutiny of opioid utilization intensifies, but this population's patterns of opioid use remain understudied.

Objectives: To examine patterns of opioid use among patients with cancer pain diagnoses.

Methods: A retrospective cohort study of 18 to 64 years old cancer patients identified in IQVIA™ PharMetrics Plus (1/1/2007–12/312015). Patients with cancer pain diagnoses (ICD-9 code 3383) were compared to those without cancer pain diagnosis. Individuals were required for continuous enrollment of insurance plans for 12 months pre- and 24 months post-index date of cancer diagnosis. Prevalent opioid use was defined as any use post-index. Incident opioid users were individuals with opioid use post-index but no use pre-index. Morphine equivalent daily dose (MEDD) was calculated as (Quantity x Strength x Conversion Factor)/Total Days Supplied. Descriptive analyses examined prevalence, incidence, duration of use, and MEDD. As well, adjusted logistic regression compared opioid use in those with and without cancer pain.

Results: Our sample included 34,979 individuals, 648 (1.9%) with and 34,331 (98.1%) without cancer pain. Of these, 38.3% were males, with mean and median age of 54 and 55 years. Overall, 8,856 (25.3%) patients used opioids during follow-up, and 272 (3.1%) were new users. Prevalent opioid use in patients with and without diagnoses of cancer pain were 42.0% and 25.0%, respectively. In addition, 1.9% and 2.0% of patients with and without cancer pain were new users. Mean (median) duration of opioid use 24 months post-index were 345 (230) days and 21 (120) days for patients with and without cancer pain. Mean (median) MEDD among individuals with and without cancer pain were 58.6 mg (30.1 mg), and 25.7 mg (12.2 mg), respectively. Adjusting for other clinical, demographic, and prescription factors, patients with diagnoses of cancer pain had 2.3 times (95% CI = 1.7–3.1) the odds of using opioids compared to patients without cancer pain.

Conclusions: Despite higher likelihood of opioid use, over half of patients with cancer pain diagnoses had no opioid use during follow-up. Overall, cancer patients with cancer-related pain were more than two times likely to receive an opioid and had double MEDD than those without cancer pain. Optimal treatment of cancer pain are difficult to define. More research to examine the impact of increasingly restrictive opioid policies on patients requiring pain management is needed.

668 | Opioid overdose in patients treated with extended-release naltrexone: Postmarketing data from 2006 to 2018

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Background: Opioid overdose rates are rising in the United States. Patients with opioid use disorder (OUD) treated with monthly naltrexone extended-release injectable suspension (XR-NTX), a μ-opioid receptor antagonist, may be vulnerable to opioid overdose if they attempt to override the blockade, miss a dose, or discontinue XR-NTX. Clinical trials of patients treated with XR-NTX have not demonstrated an increase in overdose susceptibility compared with treatment-as-usual, placebo, or buprenorphine-naloxone.

Objectives: To assess postmarketing rates of reported fatal and non-fatal opioid overdose, and all-cause overdose, during and after treatment with XR-NTX.

Methods: Case data from postmarketing adverse event reports received from 2006 to 2018 for patients treated with XR-NTX (for any indication) were manually reviewed for reported opioid overdose cases; identified cases were adjudicated by ≥2 reviewers. Assessable cases were categorized by overdose type and timing of the event from the last dose of XR-NTX (latency): ≤28 days (on-treatment), 29–56 days, and > 56 days.

Results: An estimated 495,602 patients were treated with XR-NTX (for any indication) from 2006 to 2018. We identified 161 cases in which opioids were specifically stated as the cause of overdose; 41% (66/161) of cases contained adequate information to assess latency of event from last dose of XR-NTX. For the 66 assessable cases, opioid overdose rates were similar for each latency category. For the assessable cases of opioid overdose, the reporting rates (per 10,000 patients) were 0.54 (0.24, fatal), 0.34 (0.16, fatal), and 0.44 (0.40 fatal) for ≤28 days, 29–56 days, and > 56 days from last dose of XR-NTX, respectively. For 63 cases with sufficient information, the median latency for events occurring ≤28 days from last XR-NTX dose was 18 days (range: 1 to 28 days); for 29–56 days was 43 days (range: 29 to 56 days); and for >56 days was 76.5 days (range: 60 to 145 days). For the 131 assessable cases of all-cause overdose, the reporting rates (per 10,000 patients) were 1.11 (0.46, fatal), 0.67 (0.38, fatal), and 0.87 (0.71, fatal) for ≤28 days, 29–56 days, and > 56 days from last does of XR-NTX, respectively.

Conclusions: Based on assessment of 12 years of postmarketing overdose data, the rates of fatal and non-fatal opioid overdose and all-cause overdose during or after treatment with XR-NTX were < 1/1000. As the incidence of opioid overdose in the United States continues to rise, further research is needed to better understand the risk of overdose in patients receiving or discontinuing medication for opioid use disorder. Analysis was funded by Alkermes, Inc.

669 | Recent changes in the prevalence of rapid tapering of opioid doses in Ontario, Canada

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Background: There is emerging concern that opioid doses are being rapidly tapered to quickly conform with new opioid guidelines and changing policies. This practice is concerning as it may lead to patients to rapidly entering withdrawal, and potentially seeking opioids from illicit sources.

Objectives: To investigate the prevalence of rapid opioid tapering in Ontario, Canada.

Methods: We conducted a cross-sectional study among patients receiving high-dose (≥ 200 MME for at least 30 days) opioids from January 2014 to December 2017. We measured the proportion of recipients who experienced a drop in their dose of ≥50% that was sustained for at least 30 days. We also explored the proportion of recipients who had their opioids abruptly discontinued.

Results: Overall, 38.3% of individuals who met our eligibility criteria were rapidly tapered during the study period. The annual prevalence of rapid tapering was stable between 2014 (16.2%) and 2016 (16.3%), before increasing to 20.2% in 2017. The monthly prevalence of rapid tapering ranged between 1.8% and 2.3% prior to November 2016 at which point it increased, reaching a high of 3.4% in March 2017. A similar trend was observed in the annual prevalence of abrupt opioid discontinuation (range 5.9 to 6.1% from 2014 to 2016; rising to 7.4% in 2017).

Conclusions: Recent policy changes and updated guidelines may have led to a small increase in the rate of rapid dose tapering and abrupt opioid discontinuation. The implications of this increase should be studied for potentially serious adverse effects on patients.

670 | Association of new opioid continuation with surgical specialty and type in the United States

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Background: The consequences of opioids—including post-surgical prescriptions—remain a critical public health issue.

Objectives: To determine how procedure type and subspecialty group influence new opioid use after procedures.

Methods: Design and setting: Retrospective cohort study using IBM MarketScan Commercial Claims and Encounters data from January 2011 to December 2015 of adult individuals who had only one procedure on a given day and filled at least one opioid prescription in the perioperative period, from 30 days before to 2 weeks after the procedure. A multivariable logistic regression model was used to determine the difference in new opioid continuation among type of procedure and subspecialty. Exposure: The preassigned MarketScan service categories were used to define two types of procedures: (1) "operating room (OR) procedures" were those prespecified as "major" procedures or occurring in the operating room, and (2) "non-OR procedures" were procedures prespecified as "minor", "other", or not occurring in the operating room. For each invasive procedure claim, the surgical subspecialty was identified using the provider type associated with the claim. For a comparison group of individuals not exposed to procedures, we identified a 10% sample of patients aged 18 to 64 who did not undergo a procedure in the study periodOutcome: New opioid continuation defined priori as receipt of prescription opioids between 90–180 days after the procedure.

Results: Among 912,882 individuals, new opioid continuation was higher for non-OR compared to OR procedures (13.1% versus 9.2%; aOR 1.61; 95% CI 1.59–1.64) and higher for subspecialties including colorectal surgery (aOR 1.35; 95% CI 1.26–1.43) and cardiovascular surgery (aOR 1.30; 95% CI 1.12–1.50) compared to urology as a referent.

Conclusions: Opioids prescriptions associated with non-operating room surgical exposures appear to confer higher risk regarding conversion to new long-term opioid use.

671 | Opioid and concomitant benzodiazepine outpatient prescription claims among women with pregnancies in 2014

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Background: Opioid exposure during pregnancy has been associated with adverse neonatal and infant outcomes; some evidence suggests that concomitant use of benzodiazepines may increase these risks.

Objectives: To document the proportion of women who filled any opioid prescription, as well as those who filled both an opioid and a benzodiazepine prescription, during pregnancy.

Methods: We used data from the 2013–2015 IBM MarketScan Commercial Database for this analysis. We included women aged 15–44 years with private health insurance and prescription drug coverage. Pregnancies were identified using pregnancy-related diagnosis or procedure codes indicating a live birth or pregnancy loss. We included pregnancies with an estimated date of last menstrual period (LMP) or date of delivery/end of pregnancy in 2014 (i.e., at least one day of pregnancy in 2014). We then restricted to pregnancies with continuous enrollment from 90 days before LMP to 90 days after the end of pregnancy or that were missing only one month of enrollment during that time period. To capture any prescriptions filled during pregnancy (defined as LMP to seven days before date of delivery/end of pregnancy to exclude delivery-related dispensations), we searched outpatient pharmacy prescription claims for opioid- and benzodiazepine-containing medications using National Drug Codes.

Results: Among the 482,917 pregnancies that met our inclusion criteria, 9.7% of women filled at least one prescription for an opioid from an outpatient pharmacy during pregnancy. The most common types of opioids dispensed during pregnancy were hydrocodone (5.0% of all pregnancies), codeine (3.3%) and oxycodone (1.8%). Opioid claims varied by time period during pregnancy, with 5.1% filling in their first trimester, 3.7% in second, and 4.1% in third (excluding the week before delivery/end of pregnancy). Among women who filled a prescription for an opioid during pregnancy, 7.8% also filled a prescription for a benzodiazepine-containing medication during pregnancy, with the most frequent combination of medications being hydrocodone and alprazolam (2.4%).

Conclusions: In this dataset, nearly 1 in 10 women filled a prescription for an opioid from an outpatient pharmacy during pregnancy; among these women, about 8% also filled a prescription for a benzodiazepine. Because prenatal use of opioids poses recognized fetal and infant risks with additional safety concerns around concomitant use of benzodiazepines, more work is needed to understand opioid prescribing patterns and outcomes to promote guideline-concordant prescribing during pregnancy.

672 | How many elderly in Norway are persistent opioid users? -a comparison of two approaches to define persistent opioid use

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Background: Traditional methods for identifying persistent opioid use provide limited information on the longitudinal course of use. Group based trajectory modeling (GBTM) may overcome some of these limitations.

Objectives: Aim 1: Defining persistent opioid use and comparing the results from two approaches; 1) two traditional definitions using amount dispensed and distribution of dispensing; 2) GBTM Aim 2: Use GBTM in a persistent opioid use population to look at the trajectories of use.

Methods: We used data from the Norwegian Prescription Database (NorPD) from 2013–2014 of dispensed opioid use among persons 65 years or older. We included only persons receiving at least two prescriptions within 365 days. We defined persistent opioid use to capture continuous high-dose users over one year (strict), or to capture persistent use of lower doses allowing for at least one quarter of the year without dispensing (wide). The results were compared to GBTM with three groups. The model used oral morphine equivalents and investigated changes in amount from the first 30 days of use in 2013 in the following 11 periods of 30 days. The overlap between the clinical definitions and the GBTM was used to compare the approaches. In addition, GBTM was applied on the strict definition population to discover any additional useful information about the usage patterns.

Results: There are 104,411 elderly with more than one prescription of opioids. By the strict definition 4.7% of the opioid users were persistent users and by the wide definition 28.3%. Using GBTM, 6.1% of patients had an increasing use of opioids and 40.2% had a stabile use. The overlap between the strict definition and GBTM was poor. Only 26% of the increased use GBTM group and 8% of the steady use group was also part of the strict definition. The overlap for the wide definition was better, 87% of the increased use GBTM group and 52% of the stabile use group was included in both. These two GBTM groups covered almost all persons in the strict/wide definitions. In the non-overlapping part of the GBTM groups, the average doses dispensed were too low to be captured by the clinical definitions, indicating low doses or intermittent use. Finally the GBTM grouping of patients in the strict definition showed that 14.2% had a strong increasing use, 18.3% had a mildly increasing use and the rest had use throughout the 360 days without any increases.

Conclusions: Using GBTM in NorPD does not identify persistent opioid users well enough. Our GBTM model had high specificity but low sensitivity. However GBTM can provide interesting results when used in conjunction with other approaches.

673 | Regional examination of increased buprenorphine in the US (2008–2017)

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Background: The opioid epidemic in the United States continues to be a problem with no clear solution. Recent advances in the medical field have offered prescription medications such as buprenorphine to treat opioid dependence.

Objectives: The purpose of this study was to identify trends in buprenorphine prescriptions across states and U.S. territories.

Methods: Data were extracted from the U.S. Drug Enforcement Administration's Automation of Reports and Consolidated Orders System (ARCOS) for 2008–2017. Each state was analyzed for buprenorphine prescription in milligrams per 100,000 persons.

Results: The average percent increase across all states and territories from 2008–2017 was 304%. North Carolina and Arkansas saw the greatest percentage increase in buprenorphine prescription per 100,000 at 785% and 701%, respectively. Maine and Utah had the lowest percentage increase with 105% and 116%, respectively. In general, the midwest had the greatest overall percentage increase in buprenorphine prescription over the decade, however, the northeast region has consistently shown the highest prescriptions per 100 K throughout the ten-year span.

Conclusions: All states and territories across the United States had increased buprenorphine prescription over the last decade from 2008–2017. Further investigation into the causal factors underlying these pronounced elevations are ongoing.

674 | Incidence and persistence of opioid use after surgery among opioid-Naïve adults in a large commercial US health plan

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Background: Postsurgical opioid use has been well characterized in the US, but less is understood about the incidence and persistence of opioid Rx among insured opioid-naïve pts across surgical specialties.

Objectives: To investigate the incidence/persistence of opioid use after surgery among opioid-naïve adults in a large US commercial health plan and provide insights on postsurgical opioid overuse for pts, payers, and providers.

Methods: Using the HealthCore Integrated Research Database, we conducted a retrospective claims study of pts aged ≥18 y who underwent primary surgical procedures between 4/1/2015 and 3/31/2016. Eligible pts had 1 surgery during the index period, no opioid Rx filled 1–6 mo before index surgery, inpatient stay ≤30 d, ≤2 cancer diagnoses, and complete medical/Rx claims during 6 mo before and after index surgery. Opioid use was tracked in 3 time periods: *perisurgical* (opioid medical claim/Rx between 1 mo presurgery & 2 wk postsurgery), *continued* (perisurgical opioid & ≥1 opioid Rx filled between 3 wk & 3 mo postsurgery), and *persistent* use (perisurgical opioid & ≥1 opioid Rx filled 4–6 mo postsurgery).

Results: Of 778,479 screened pts, 387,186 were eligible. Mean (SD) age was 54 (16) y and 54% were women. Among surgeries with >100 pts (n = 384,976), 198,257 (52%) pts had perisurgical opioid use. Among these, 22,291 (11%) pts had continued and 14,355 (7%) had persistent opioid use. Incidence of perisurgical opioid Rx initiation was higher (82%) among pts undergoing musculoskeletal vs nonmusculoskeletal (44%) surgery. Incidence varied by specialty (range, 10–92%) but was ≥75% for high-volume surgeries (eg, cholecystectomy, 89%; arthroscopic rotator cuff, 89%; inguinal hernia, 88%; cesarean, 79%). A gradated decrease was seen in opioid Rx from perisurgical to continued to persistent use following high-volume musculoskeletal procedures, with the highest rates of persistent use for knee replacement (16%), cervical fusion (14%), and lumbar decompression (10%). In contrast, a steep drop-off in opioid Rx use from perisurgical to continued use was observed for high-volume nonmusculoskeletal surgeries followed by similar levels of continued vs persistent use (eg, cholecystectomy, 5–6%; inguinal hernia repair, 5%; cesarean delivery, 4–5%).

Conclusions: ~200,000 (52%) opioid-naïve surgery pts initiated postsurgical opioids in a large commercial US health plan, of whom 7% had persistent use. Patterning of opioid Rx duration varied by specialty/procedure. These data highlight procedures that may benefit most by adoption of opioid-reducing multimodal pain-management protocols.

675 | Incidence of chronic opioid use in seniors

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Background: Chronic opioid use in non-cancer patients is a well-known predictor of opioid-related harms. Data on opioid use in vulnerable populations, such as seniors, are scarce.

Objectives: i) To estimate the incidence of chronic opioid use in seniors (age ≥ 65); ii) To compare the characteristics of chronic and non-chronic opioid users.

Methods: A cohort study was conducted using the Quebec administrative claims (RAMQ) databases. We selected a random sample of non-cancer outpatients aged ≥65 initiating an opioid (index date) between 01 January 2014 and 31 December 2016. Patients were followed for 12 months after index date. The standard definition for chronic opioid use adopted was 90 consecutive or 120 cumulative days with an active opioid prescription during the 12-month follow-up. Demographic characteristics, medical history, comorbidity, and opioid treatments were compared in the chronic and non-chronic opioid users.

Results: The cohort included 34,779 elderly opioid-initiators, of whom 1601 (4.6%) transitioned to chronic use (mean [SD] duration of use was 241.8 [87.4] days vs 13.2 [17.3] days in non-chronic users). The mean daily dose in morphine equivalent (MME/day) [SD] was however lower in chronic than in non-chronic users (29.2 [28.1] vs 32.9 [21.0]). Chronic users were more likely (71.2%) than non-chronic users (60%) to be female (11% diff. 95%CI: 9–14%). Over a quarter (27.8%) of chronic users were ≥ 85 years of age vs 12.0% in non-chronic users (16% diff. [14–18%]). In the year prior to index date almost half of chronic users (46.4%) had a diagnosis associated with chronic pain (arthritis, spinal stenosis, fibromyalgia, neuropathy, etc.) vs 32.0% in non-chronic users (14% diff. [12–17%]). One-fifth (20%) of chronic users had a psychiatric comorbidity (mood disorder, schizophrenia, anxiety, etc.) vs 10% in non-chronic users (10% diff. [8–12%]) and, 10.6% of chronic users had dementia vs 4.1% in non-chronic users (6% diff. [5–8%]). Of chronic users, 22.5% started opioid therapy with a long-acting opioid vs 1.4% of non-chronic users (21% diff. [19–23%]) and transdermal fentanyl at initial prescription was more frequent in chronic (7.3%) than non-chronic (0.3%) users (7% diff. [6–8%]). Almost a quarter of chronic users (24.1%) had an initial opioid prescription ≥30 days vs 3.8% in non-chronic users (20% diff. [18–23%]).

Conclusions: Female sex, age ≥ 85, chronic pain, mental health issues, dementia, initial prescription of ≥1 month and long-acting opioids were more common in chronic opioid users. A better understanding of these factors may inform targeted interventions and policies to reduce opioid use in seniors.

676 | Trends in the acquisition and distribution of opioid drugs among ten contiguous states

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Background: The opioid epidemic has garnered nationwide attention in recent years as a public health crisis and national emergency, with an estimated 130 Americans dying each day from an opioid overdose. West Virginia, Ohio, New York, and Pennsylvania have been particularly impacted.

Objectives: This study seeks to examine the pattern of acquisition/distribution between 2007 and 2017 for 19 different opioid medications across 10 contiguous states (PA, NY, NJ, DE, MD, WV, OH, MI, IN, KY) in the eastern and midwestern USA.

Methods: Drug weights were obtained from the US Automated Reports of Consolidated Orders System (October, 2018), a comprehensive publicly available resource from the Drug Enforcement

Administration. Total drug weight acquired/distributed is reported each quarter year, and these values were converted to oral morphine equivalents to facilitate comparison among drugs.

Results: Over the studied period, there has been a general downward trend in legal acquisition/distribution of common opiates such as fentanyl and oxycodone. For example, in Pennsylvania, oxycodone usage declined by 22.7% between 2012 and 2017. Similarly, New York and Ohio oxycodone usage between 2012 and 2017 declined by 31.8% and 20.3% respectively. Oxycodone usage declined notably in West Virginia, decreasing by 44.9% between 2012 and 2017.

Conclusions: With a better understanding of patterns of use and how that may affect adjacent states, public policy may be shaped to best mitigate the worst outcomes of the opioid epidemic locally and nationwide.

677 | Oversight of extended release/long acting (ER/LA) opioids by the U.S. Food and Drug Administration: A narrative review

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Background: Extended release and long acting (ER/LA) opioids are powerful pain relievers with a high potential for non-medical use. Since 2012, they have been subject to a U.S. Food and Drug Administration (FDA)-mandated Risk Evaluation and Mitigation Strategy (REMS), including voluntary prescriber continuing education (CE), to "reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse."

Objectives: To evaluate FDA and sponsor assessments of the REMS, including whether and how well such assessments allowed the effectiveness of the REMS to be appraised.

Methods: We conducted a narrative review of 5,963 pages of FDA documents obtained through a Freedom of Information Act (FOIA) request, including annual, manufacturer-submitted, REMS assessments from 2012 through 2017 and FDA reviews of these assessments.

Results: Based on a preliminary review of the documents obtained, the REMS assessments included enrollment targets, compliance audits, prescriber and pharmacist surveys, and safety and prescribing surveillance. The REMS's primary goal was to train 60% of ER/LA prescribers (192,000/320,000) within four years; 46% of this target number (88,316/192,000) were trained within four years from REMS initiation. Audits of REMS programs indicated close adherence to FDA guidelines for the design of CE, non-representative surveys of self-selected populations suggested modestly greater ER/LA knowledge among CE completers than non-completers and most claims-based surveillance indicated declining ER/LA use. Despite this, the effect of the REMS on prescribing or safety outcomes could not be ascertained because claims-based analyses lacked adequate controls and were not linked, on a prescriber-level, to CE completion. Although the FDA requested studies tracking prescribing and safety as a function of CE training, as of the 60-month report (2017), these had not been performed. In its 2017 review, the FDA concluded it was impossible to determine if the REMS was successfully impacting prescribing or patient safety.

Conclusions: Five years after initiation, the FDA and ER/LA sponsors could not determine whether the ER/LA REMS reduced inappropriate prescribing or improved patient outcomes. Alternative observational study designs would have allowed for stronger causal inference.

678 | Antidiabetic medication, level of glycaemic control, and risk of fracture in patients with type 2 diabetes mellitus: A nested case–control study

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Background: Patients with diabetes mellitus type 2 (DM2) have an increased risk of fracture. However, the effect of antidiabetic medication in association with glycaemic control on the risk of fracture is not well understood.

Objectives: To evaluate the association between use of antidiabetic medication, level of glycaemic control, and risk of low-trauma fractures in patients with incident DM2.

Methods: We conducted a nested case–control analysis with patients registered within the UK-based Clinical Practice Research Datalink who had an incident diagnosis of DM2 from 1995–2017. Cases were patients with a low-trauma fracture after the DM diagnosis. We excluded patients with diagnosed osteoporosis, cancer, HIV, and alcoholism. We matched four controls to each case by age, sex, general practice, fracture date, DM type and DM duration. Exposure of interest was any prescription for an antidiabetic drug (metformin, DPP4-inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, sulfonylureas). We assessed glycaemic control as the average HbA1c level during the last three years before the fracture. We conducted conditional logistic regression analyses, and adjusted for covariates including body mass index, smoking, and previous fractures.

Results: We identified 8122 cases (31.6% males) and 32470 matched controls. Current use (last prescription ≤60 days before the fracture) and past use (last prescription >60 days before the fracture) of glitazones (pioglitazone and rosiglitazone) was significantly associated with an increased risk of fracture compared to non-use of glitazones. Long-term use of glitazones also led to an increased risk of fracture (1–9 prescriptions aOR 1.22, CI 95% 1.10–1.34; 10–19 prescriptions

aOR 1.39, CI 95% 1.22–1.59; ≥20 prescriptions aOR 1.41, CI 95% 1.27–1.55) compared to non-use. Both associations were independent of HbA1c levels. In contrast, we found a statistically significant decreased risk of fracture in current users of metformin with good to moderate HbA1c levels of 6.5–7.5% (aOR 0.88, CI 95% 0.80–0.96) and 7.5–8.5% (aOR 0.79, CI 95% 0.68–0.91) compared to non-users of metformin. However, patients with HbA1c levels <6.5% (aOR 0.90, CI 95% 0.80–1.01) or > 8.5% (aOR 0.86, CI 95% 0.71–1.04) had no altered risk of fracture compared to non-users. We observed no statistically significant association between the use of other antidiabetic medication, HbA1c level, and the risk of fracture.

Conclusions: The effect of glycaemic control on the risk of low-trauma fracture differs between metformin and glitazone users.

679 | Risk of hand osteoarthritis in new users of hormone replacement therapy: A nested case–control analysis

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Background: The increase in hand osteoarthritis (OA) incidence in postmenopausal women and the presence of estrogen receptors in cartilage suggest that hormone replacement therapy (HRT) could help to prevent the development of OA. Small cross-sectional studies investigating the association between HRT and hand OA yielded conflicting results.

Objectives: To estimate the risk of hand osteoarthritis (OA) in new users of hormone replacement therapy (HRT).

Methods: We conducted a nested case–control study using data from the UK based Clinical Practice Research Datalink (1998–2017). In an inception cohort of women entering at age 45, we matched patients with hand OA during follow-up (cases) to OA-free controls (1:4, risk-set sampling) on age and calendar date (index date). We applied multivariable conditional logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) of hand OA in association with new HRT use when compared to non-use, overall, stratified by timing of HRT use (current or past use) and in patients with recorded menopause only. In women with recorded menopause, we calculated separate ORs subdivided by time between menopause and HT initiation (current users) and by time between HT cessation and the index date (past users) when compared to non-users.

Results: Among 3440 cases and 13,760 controls (mean age 50.9 years), we observed an overall adjusted OR (aOR) of hand OA of 1.32 (95% CI 1.17–1.48) in HRT users compared to non-users which attenuated to 0.98 (95% CI 0.85–1.14) in patients with recorded menopause. In all analyses, compared to non-use, current HRT use was associated with lower and past use with higher aORs of hand OA than overall HRT use. Among women with recorded menopause, the proportion of hand osteoarthritis diagnoses decreased with time after menopause. A maximum proportion of 18.4% of women (158 of 860 cases) had hand osteoarthritis recorded within ≤1 year after recorded menopause. Furthermore, in patients with recorded menopause, we observed a non-significantly decreased aOR of hand OA in current users if HRT was initiated within 90 days before/after recorded menopause (0.72, 95% CI 0.55–0.96), aORs increasing with later HRT initiation. Furthermore, among past users, compared to non-users, the aOR of hand OA was non-significantly increased (1.25, 95% CI 0.86–1.81) if HRT was stopped ≤1 year before the index date, aORs approximated the null with increasing duration between HT cessation and the index date.

Conclusions: HRT was associated with a decreased risk of hand OA if initiated around menopause and the risk of hand OA increased shortly after HRT cessation.

680 | Association between fluoroquinolone use and Achilles tendon pathology: Active comparator new user investigation

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Background: Fluoroquinolones are broad-spectrum antibiotics that have an affinity for connective tissue, which may result in a negative impact to collagen fibrils. Previous case series have suggested a potential association with increased risk of Achilles tendon pathology.

Objectives: Further investigate the association between fluoroquinolone use and Achilles pathology using an active comparator new user study design in a large population of commercially-insured individuals.

Methods: The MarketScan Commercial Claims and Encounters database was used to assess Achilles pathology among fluoroquinolone initiators from 2000–2014. Two comparator groups were used: sulfonamide and amoxicillin initiators, both antibiotics with similar indications for treatment. Oral fluoroquinolone, sulfonamide, and amoxicillin initiators aged 13–64 years were identified using a 180-day washout period and followed until discontinuation (with a 60-day grace period), end of continuous enrollment, or switching treatments. Achilles pathology included ruptures and tendinopathies, which were identified by ICD-9 or CPT code following a 180-day washout period. Cox proportional hazard models were used to estimate adjusted hazard ratios (adjHR) and 95% confidence intervals (CI) after standardizing the cohort by age, sex, baseline comorbidities, and indications using inverse probability of treatment weighting (IPTW).

Results: There were 14,735,795 fluoroquinolone, 7,287,896 sulfonamide initiators, and 22,927,124 amoxicillin initiators. Fluoroquinolone initiators were slightly older, more likely to be female, and

had more baseline comorbidities. There were 12,802 Achilles pathologies among fluoroquinolone initiators (45.7 per 10,000 person-years), 4,170 Achilles pathologies among sulfonamide initiators (35.0 per 10,000 person-years), and 8,596 Achilles pathologies among amoxicillin initiators (60.2 per 10,000 person-years). After IPTW, fluoroquinolone initiators were 12% more likely than sulfonamide initiators (adjHR = 1.12, 95% CI 1.08, 1.15) and 26% more likely than amoxicillin initiators (adjHR = 1.26, 95% CI 1.23, 1.30) to have an Achilles pathology during or immediately following antibiotic use.

Conclusions: An increased risk of Achilles pathology was observed among fluoroquinolone initiators compared to sulfonamide and amoxicillin initiators, but the increase in risk was attenuated when compared to sulfonamide initiators. These findings highlight the importance of selecting an appropriate comparator group and carefully considering unmeasured confounders.

681 | Dose-dependent effects of gabapentin and pregabalin on the day of surgery in total hip and knee arthroplasties

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Background: Gabapentinoids (GBPs), gabapentin and pregabalin, are commonly prescribed drugs within perioperative multimodal analgesia protocols. Despite widespread use in a wide range of doses, little is known regarding the optimal dose which reduces opioid consumption with minimal risks.

Objectives: To assess dose-dependent effects of GBPs on pulmonary complications and opioid consumption following total hip or total knee arthroplasty (THA/TKA).

Methods: Using the Premier Database of more than 500 US hospitals, including information on patient demographics, hospital characteristics, patient-specific date-stamped billing logs, and ICD-9 codes, we identified adults who underwent elective primary THA/TKA between 2009 and 2014. The exposure was receipt of a GBP (gabapentin or pregabalin) on the day of surgery. Gabapentin dose was categorized into five groups: none, 1–350, 351–700, 701–1050, and > 1050 mg per day. Pregabalin dose was categorized into four groups: none, 1–110, 111–250, and > 251 mg per day. The outcomes were measures of postoperative complications: receipt of naloxone after the day of surgery, non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), and opioid consumption (measured using parenteral morphine equivalents) on the day of surgery and the day before discharge. We used multilevel regression models to examine associations between the categorized exposures and the outcomes.

Results: Among 863,139 patients undergoing THA/TKA, overall, 11.5% received gabapentin and 10.7% received pregabalin. Prevalence of naloxone use, NIV, and IMV was 0.6%, 2.5%, and 0.5% respectively. GBP receipt at any dose on the day of surgery was associated with increased odds of each postoperative pulmonary complication. Compared with lower doses, the highest dose of gabapentin (>1050 mg) was associated with greater odds of naloxone use (OR, 2.90; 95% CI, 2.49–3.88), NIV (OR, 1.58; 95% CI, 1.44–1.72), and IMV (OR, 1.58; 95% CI, 1.29–1.93). Similarly, the highest dose of pregabalin (>250 mg) was associated with greater odds of naloxone use after surgery (OR, 2.17; 95% CI, 1.61–2.93), NIV (OR, 1.52; 95% CI, 1.27–1.82), and IMV (OR, 1.68; 95% CI, 1.15–2.46). We found no clinically meaningful association between exposure to either gabapentin or pregabalin and opioid consumption.

Conclusions: Exposure to GBPs at any dose on the day of surgery was associated with increased odds of postoperative naloxone use, NIV, and IMV, and the effects were generally greater at higher doses. In contrast, there were no clinically meaningful differences with respect to opioid consumption.

682 | Sodium-glucose cotransporter 2 inhibitors and risk of fractures: Analysis of the FDA adverse event reporting system database

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Background: The CANVAS trial showed that canagliflozin, a sodium-glucose cotransporter 2 inhibitors (SGLT2i), may increase the risk of bone fracture. However, a recent large cohort study suggested no increased risk of fractures for canagliflozin, the recent EMPA-REG OUTCOME and DECLARE-TIMI 58 trials showed no increased risk for other SGLT2i. The effect of SGLT2i on fractures remained uncertain.

Objectives: To assess the association between SGLT2i and fractures using FDA Adverse Event Reporting System (FAERS) database.

Methods: By running a query on AERSMINE (an open access web data mining tool of FAERS) from 2013 Q2 to 2018 Q1, we obtained the fractures cases related to SGLT2i (dapagliflozin,canagliflozin, empagliflozin) and comparator drugs. The fractures events were identified by MedDRA v21.0. We conducted two mutually exclusive comparisons: 1) compared SGLT2i to all other glucose lowering drugs (GLDs) excluding insulins; 2) compared SGLT2i to dipeptidylpeptidase-4 inhibitors (DPP4i) as both classes are new

second-line treatment for diabetes with similar reporting rates and DPP4i are not associated with increased risk for fracture. Additionally, we stratified analyses on individual SGLT2i and age groups (25–65 years,≥65 years). In each comparison, we calculated proportional rate ratio (PRR) and 95% CI using 2 × 2 tables by SAS 9.4. A signal is defined as PRR >2.

Results: A total of 295 SGLT2i associated fractures cases were identified, 153 cases for canagliflozin, 93 cases for dapagliflozin, 50 cases for empagliflozin. Compared to all other antidiabetic drugs excluding insulins, the PRR for SGLT2i, canagliflozin, dapagliflozin and empagliflozin was 0.67(0.60–0.76), 0.60(0.51–0.71) 0.86(0.70–1.06) and 0.62(0.47–0.81), respectively. In the analyses stratified by age group, the PRR for 25–65 years, >65 years was 0.70(0.58–0.85) and 0.80(0.65–0.97) respectively. Compared to DPP4i, the PRR for SGLT2i, canagliflozin, dapagliflozin and empagliflozin was 0.46(0.40–0.54), 0.44(0.37–0.53), 0.54(0.42–0.69) and 0.43(0.31–0.60), respectively.

Conclusions: Our analysis based on FAERS database indicated that there was no significant association between SGLT2i and fractures. However, this study is limited by reporting bias, lack of denominator data, and FAERS cannot be used to assess the incidence. Thus, further studies are warranted to assess the potential fractures risk associated with SGLT2i.

683 | Assessing the incidence of osteosarcoma among teriparatide users via linkage of data from Medicare part D and multiple state cancer registries in the USA

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Background: Teriparatide, approved for treatment of osteoporosis in adults, caused a dose-dependent increase in the incidence of osteosarcoma (OS) in rats during preclinical testing. This study is 1 of 5 OS surveillance studies initiated since initial drug approval in 2002 to evaluate a potential increased risk of OS with teriparatide treatment.

Objectives: To estimate the incidence rate ratio (IRR) of OS among patients aged 65 years or older treated with teriparatide versus a cohort of matched comparators. The secondary objective was to describe characteristics and similarities of each cohort.

Methods: All state cancer registries in the United States (US) were invited to participate in this population-based comparative cohort study. Exposure details for each teriparatide user and up to 4 comparators matched on age, sex, 3-digit zip code, date of prescription fill and number of unique therapeutic classes of medications dispensed were identified via Medicare Part D prescription claims. Demographic and clinical characteristics were assessed on a subset using Medicare Parts A, B, and D. Outcomes were identified via linkage with participating state cancer registries through Medicare's trusted third party. Patients were followed to date of OS diagnosis, death, or end of study.

Results: Among patients, 153,316 in the teriparatide cohort and 613,247 in the comparator cohort were linked to 811 OS cases from 26 participating state cancer registries (covering 68% of US cases aged 65+ diagnosed 2007–2014). Cohorts were predominantly female (91%); 59% were aged 75+ on the index date. Corticosteroid use was higher in the teriparatide versus comparator cohort in the baseline (39% vs. 31%) and follow-up periods (45% vs. 36%). History of fracture was higher in the teriparatide cohort compared to the comparator cohort (23% vs. 8%). The cohorts were well balanced on known OS risk factors and the Charlson comorbidity index. Mean duration of treatment with teriparatide was 10 months. No cases of OS were observed in the teriparatide cohort and the rate in the comparator cohort was consistent with the background rate among adults aged 65+. (To protect patient privacy, non-zero cell counts <11 cannot be disclosed for Medicare). The IRR was 0.0 (95% CI, 0.0 to 3.2).

Conclusions: The incidence of OS among teriparatide-treated patients aged 65 years or older in the US ranges from 0 to 3.2 times the incidence of OS in US patients aged 65 years or older treated with other medications. Given the low incidence of OS, this range of effect is inconsistent with a large absolute increase in risk for OS.

684 | Risk of fall injuries with concomitant use of beta-blockers and CYP2D6 inhibitors

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Background: Fall injury is a common public health problem that increases with an aging population and so does the use of beta-blockers with risk of adverse effects such as drop in blood pressure, dizziness and syncope leading to an increased risk of fall injury. Several beta-blockers including the most frequently used beta-blocker metoprolol are metabolized through CYP2D6; inhibited metabolism results in increased concentrations in blood and may thus increase the risk of adverse effects.

Objectives: To investigate if the initiation of beta-blockers associates with increased risk of fall injury. Further, to investigate if concomitant use of a drug that inhibits CYP2D6 increases the risk of fall injury in patients with newly initiated treatment of CYP2D6-metabolized beta-blockers.

Methods: Design: This is a national, registry-based case-crossover study covering all adults in Sweden. Setting: We have retrieved all cases of hospital-admitted first-time occurring fall injuries in adults 2006–2013 from the National Patient Register with linked data

about dispensed drugs from the Swedish Prescribed Drug Register. Exposures: The exposure to newly initiated treatment with beta-blockers (7838 cases) in the case period, the 14 days preceding the occurrence of fall injury, was compared to a previous control period of equal length. CYP2D6-inhibitor use was considered if dispensations occurred within the 91 days preceding the index date (in a similar way for the control period) as in Sweden, one prescription covers the treatment up to a maximum length of three months. We did separate analyses with the strongest CYP2D6-inhibitors to explore a potentially larger impact on risk of fall-related injuries. Main outcome measures: All hospitalized first fall-related injuries classified according to ICD-10, codes W00-W19. Statistical analysis: The case-crossover design can be thought of as a matched case–control study where the case serves as its own control. Conditional logistic regression was applied to calculate odds ratios (OR) with 95% confidence interval (CI).

Results: For beta-blockers (all types), the OR of fall injury was 1.02 (95% CI 0.97–1.07) without concomitant use of CYP2D6-inhibitors while with concomitant use of CYP2D6-inhibitors the OR was 1.03 (95% CI 0.93–1.14). Restriction to use of strong CYP2D6-inhibitors resulted in an increased risk (OR 2.13; 95% CI 1.38–3.22).

Conclusions: The risk of fall-related injuries related to beta-blocker use was not affected by overall CYP2D6-inhibitor use. However, the risk of fall injury was increased for beta-blockers when strong CYP2D6-inhibiting drugs were used at the same time.

685 | Evaluation of myalgia related adverse event reports attributed to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors within the FDA adverse events reporting system (FAERS)

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Background: The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of cholesterol-lowering medications that provide significant reductions in lipids but at a large cost relative to statins. There has been concern about the effect of PCSK9 inhibitors on the muscles as a side effect as seen in most lipid-lowering agents. However, no study has analyzed spontaneous reports of myalgia related adverse events with this drug class.

Objectives: The objective of this study is to describe and evaluate the myalgia related spontaneous adverse event reports attributed to PCSK9 inhibitors.

Methods: The published FAERS database quarterly files starting from the third quarter of 2015 till the third quarter of 2018 were queried for reports listing myalgia related adverse events mainly fibromyalgia and all types of muscle pain and stiffness attributed to two drugs in PCSK9 inhibitors (Alirocumab; Evolocumab) as the primary suspected drug with event dates from 2015 to 2018. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for each drug which is calculated like risk ratio and odds ratio, respectively using a two-by-two contingency table as the framework for analysis.

Results: Among 1,910,439 FAERS reports between July 2015 and September 2018, there were 47,069 myalgia related adverse events reports. Of which 3035 (6%) mentioned PCSK9 inhibitors as the primary suspected drugs: 827 (1.75%) mentioned alirocumab, while 2208 (4.69%) mentioned evolocumab. The PRR and ROR for the mentioned drugs was: alirocumab (PRR: 6.166, 95%CI: 5.78–6.57, ROR: 7.07, 95%CI: 6.56–7.62), evolocumab (PRR: 4.11, 95%CI: 3.95–4.28, ROR: 4.45, 95%CI: 4.25–4.65).

Conclusions: The study showed a statistically significant result. Among PCSK9 inhibitors, alirocumab exposure was associated with the highest frequency of reported myalgia related adverse effects than evolocumab. Although FAERS is subjected to significant limitations, the results suggest that PCSK9 inhibitors are associated with a higher risk of myalgia related adverse events as statin agents.

686 | Association between SGLT-2 inhibitors and lower extremity amputation among patients with type 2 diabetes: A systematic review

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Background: SGLT2 inhibitors (SGLT2i) are a commonly prescribed treatment for type 2 diabetes. Although they reduce the risk of major cardiovascular events and all-cause mortality compared with many alternatives, some evidence suggests they are associated with an elevated risk of lower limb amputation.

Objectives: To comprehensively synthesize evidence regarding whether SGLT2i therapy is associated with increased risk of lower limb amputation and other serious cardiovascular events as compared with other antihyperglycemic agents (AHAs).

Methods: We conducted a systematic review based on searches of PubMed, EMBASE, Scopus, and CENTRAL. We included randomized controlled trials and cohort studies, case control, or self-controlled studies assessing the safety outcomes of interest in adults with type 2 diabetes taking SGLT2i. The primary outcome was risk of lower limb amputation. Secondary outcomes included peripheral arterial disease, peripheral vascular disease, venous ulcerations, and diabetic foot infections.

Results: Preliminary searches have yielded six retrospective cohort studies including a total 451,801 SGLT2i patients and 2,856,950 users of other AHAs. Two studies examined the risk for canagliflozin alone against other AHAs, while four examined the risk for the entire SGLT2i class. One study comparing amputation risk for SGLT2i against all non-SGLT2i AHAs found a statistically significant increased risk of amputation (adjusted hazard ratio (aHR) = 1.99, 95% confidence interval [CI] = 1.12–3.51), while two studies found no difference. One study found a statistically significant decreased risk of amputation (aHR = 0.74, CI 0.57, 0.96) for use of SGLT2i vs. sulfonylureas. None of three studies comparing amputation risk of SGLT2i against DPP-4 inhibitors found a statistically significant difference in amputation risk (aHR range 0.88–1.50), nor did the study comparing risks in users of GLP-1 receptor agonists (aHR = 1.41). Four of the six studies examined prescribing data among commercially insured adults only, and all studies used propensity score-matched cohorts to compare risks across treatment groups. The studies were of fair to good methodological quality. Incorporation of randomized studies, and meta-analysis, are forthcoming.

Conclusions: This ongoing systematic review revealed considerable heterogeneity in the results of six retrospective cohort studies examining the association between SGLT2i and lower extremity amputation. The magnitude and direction of risk difference varied by study and by drug class comparator.

687 | Risk of tendinopahty associated with fluoroquinolones: A systematic review and meta-analysis

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Background: Tendinopathy is a known adverse reaction associated to fluorquinolones, but a meta-analysis was not yet published.

Objectives: This study aims to investigate the risk of tendinopathy associated with fluoroquinolones.

Methods: A literature search was conducted to identify observational studies evaluating the risk of tendinopathy associated with fluoroquinolones. The outcomes assessed were the risk of Achilles tendon rupture (ATR), risk of Achilles tendinitis (AT) and risk of any tendon disorders (ATD). A meta-analysis was performed by pooling odds ratios (ORs) with their 95% confidence intervals (CIs). Results were stratified according to age, type of fluoroquinolone and corticosteroid use.

Results: Thirteen studies were included. Fluoroquinolones were associated with an increased risk ATR [OR 2.24 (95% CI 1.70–2.94); I^2 = 82.9%], AT [OR 3.95 (95% CI 3.11–5.01); I^2 = 0%] and ATD [OR 1.99 (95% CI 1.35–2.93); I^2 = 89.5%]. Patients aged ≥60 years old presented an increased risk of ATR and AT. Patients aged <60 years presented an increased risk of ATD. Ofloxacin (OR 2.84; 95%CI 1.31–6.19) and norfloxacin (OR 3.02; 95%CI 1.32–6.93) are associated with an increased risk of ATR. Risk of ATR is superior among patients simultaneously using fluoroquinolones and corticosteroids (OR 16.04; 95%CI 6.28–41.00) when compared those using only fluoroquinolones (OR 2.31; 95%CI 0.82–6.51).

Conclusions: The results of this meta-analysis confirm the risk of tendinopathy associated with fluoroquinolones. Older age and concomitant use of corticosteroids seems to be additional risk factors for tendinopathy.

688 | Results of a long-term postmarketing case series of adult osteosarcoma and teriparatide in the United States

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Background: The Osteosarcoma Surveillance Study was initiated at the time of approval of Forteo in the United States (US) to monitor for a potential association between teriparatide (an osteoporosis treatment) and osteosarcoma (OS). OS occurs at a background incidence rate of approximately 2.5 cases per million per year in US adults aged 40 years or older.

Objectives: To provide final study results, including descriptive characteristics of adult patients with OS.

Methods: Incident cases of OS diagnosed between January 1, 2003, and December 31, 2016, were identified through participating cancer registries in the US. Information on prior exposure to medications and possible risk factors was obtained via self-report (or proxy-report) telephone interview. Exposure information was verified through medical record abstraction for a sample of patients. A standardized incidence ratio was estimated to compare the observed to expected number of OS cases with a prior history of teriparatide treatment. The expected number of exposed OS cases was the product of the background incidence rate of OS standardized to the age and sex distribution of teriparatide-treated patients, the person-years at risk following first exposure to teriparatide, and the percentage of cases that were interviewed.

Results: Interviews were completed for 24% (1,173) of patients diagnosed with OS between 2003 and 2016; three reports of teriparatide use prior to diagnosis were identified. Based on the background incidence rate, the expected number of OS cases among patients treated with teriparatide was 4.17. Given the three observed cases, the standardized incidence ratio was 0.72 (90% CI, 0.20–1.86). Demographic characteristics were similar for interviewed and noninterviewed patients, and agreement was 92% or higher between self-reported and chart-recorded osteoporosis medication exposure information. Mean age of interviewed patients

was 61 years, 53% were male, and 84% were white. The prevalence of known risk factors for development of OS among the OS cohort was 19% for history of radiation and 4% for history of Paget's disease of bone.

Conclusions: This study found that the incidence of OS associated with teriparatide use during the 15-year surveillance period was no different than that which would be expected based on the background incidence rate of OS.

689 | Statin use and muscular problems: A cross-sectional analysis of the ELSA-Brasil musculoskeletal cohort

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Background: The efficacy and relative safety of statins is well stablished but they have been associated with muscular problems, ranging from pain and weakness to rhabdomyolysis.

Objectives: To investigate the association of statin use and muscular pain and weakness, according to type, intensity and duration of use and the modification of this association by hypothyroidism, altered liver function and use of drugs known to interact with statins in a heterogeneous sample of Brazilian adults.

Methods: We conducted a cross-sectional study using baseline data from ELSA-Brasil Musculoskeletal cohort, an ancillary study of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Those providing data on statin use and pain and/or weakness, and without rheumatoid arthritis and lupus, were included. Pain was defined as pain, discomfort or stiffness in the last seven days in the lower back or hips/thighs. Five-times sit-to-stand (FTSTS) and handgrip tests were used as proxy of muscle weakness (i.e. greater times in FTSTS and lower grip strength). Statin users were identified by self-reported statin use in the last two weeks. Associations were tested through logistic (pain) and linear (muscle weakness) regressions. Multivariate models were adjusted for age, sex, education, body mass index (BMI), physical activity, pain in other sites and analgesic/anti-inflammatory use. Multinomial models (univariate and adjusted for age, sex and BMI) tested the modification effects of hypothyroidism, altered liver function and drugs that interact with statins. Muscle weakness variables were dichotomized for multinomial analysis, using the first and last quintiles of distributions of handgrip and FTSTS tests, respectively, as cut-offs.

Results: The sample comprised 2843 participants (55.9 +/− 8.9 years; 52.5% women; 21.0% current statin users). After adjustments, associations were only observed for statin use and pain in the hips/thighs among those using the drug for <1 year [OR 2.26; IC 95% 1.35–3.79] and between atorvastatin use and longer times in the FTSTS test, 0.5 (0.44–1.33) seconds more compared to non-users. There were indication that hypothyroidism and altered liver function modify the relationship between statin use and pain in the hips/thighs.

Conclusions: Our study provides evidence for differential effects of the type and duration of statin use in the occurrence of muscular problems. Additionally, findings on the increased chance of adverse events among individuals with certain comorbidities may indicate the need for considering individualized risk–benefit evaluations to guide clinical decision-making.

690 | Concomitant opioid and benzodiazepine or Z-drug use: Analysis of the Food and Drug Administration's adverse event reporting system

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Background: While adverse consequences of the opioid epidemic has captured the public's attention there is less awareness of a possible contributing role of hypnotics. The concomitant dispensing of opioids and benzodiazepine along with evidence of increased risks for difficult breathing and death led the FDA to issue their strongest *Boxed Warnings* in 2016. Investigations of other adverse events occurring with concomitant use of opioids and Z-drugs are scarce.

Objectives: To investigate the association of concomitant use of opioids and benzodiazepines or Z-drugs with five serious adverse events using spontaneous adverse-event reports.

Methods: Data from the United States Food and Drug Administration's Adverse Event Reporting System (FAERS) from 1969 through third quarter 2018 were utilized. Preferred Terms according to MedDRA were used to identify reports related to drug abuse, death, completed suicide, cardiac arrest, and overdose. Benzodiazepines included chlordiazepoxide, alprazolam, diazepam, clonazepam, and lorazepam. Z-drugs included zaleplon, zolpidem, zopliclone, and eszopiclone. Opioids included oxycodone, hydrocodone, and fentanyl. The selected drugs were included, regardless of route of administration, if they were noted to be suspect in the case report. Associations between drugs and events were measured by Empirical Bayes Geometric Mean (EBGM) and the corresponding lower bound of the 90% confidence interval (EB05). EB05 $\geq$ 2 were considered significant signals.

Results: For opioid-only, EBGMs ranged from 3.84 [EB05 = 3.81] for death to 12.59 [12.44] for drug abuse. In contrast, concurrent benzodiazepine or Z-drugs and opioid EBGMs were 7.72 [7.56] for death, 12.87 [12.37] for overdose, 22.04 [21.16] for cardiac arrest, 22.05 [21.35] for drug abuse, and 37.42 [35.88] for completed suicide. With the exception of completed suicide, concomitant benzodiazepine and opioid had stronger signals (EBGM

ranged from 7.84 [7.68] for death to 36.01 [34.43] for completed suicide) for each outcome relative to concomitant Z-drugs and opioid (EBGM ranged from 6.59 [6.21] for death to 52.32 [47.56] for completed suicide).

Conclusions: Concomitant use of benzodiazepines or Z-drugs and opioids are more strongly associated with five serious adverse events compared to opioid use alone. Health care professionals must be judicious in co-prescribing opioids with benzodiazepines or Z-drugs, especially in patients at risk of suicide.

691 | Benzodiazepines, opioids, & mortality in hemodialysis patients

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Background: In the general population, benzodiazepine-related mortality is a growing public health concern especially in light of the opioid epidemic; mortality risk is elevated when benzodiazepines are combined with medications that affect the central nervous system. Patients initiating hemodialysis (HD) are 3-times as likely to be prescribed opioids and have an excess burden of conditions that are indications for benzodiazepines. Yet, among HD patients, the burden of benzodiazepine prescribing, and the mortality risk associated with benzodiazepines among those with and without opioid co-prescribing are unclear.

Objectives: To describe benzodiazepine prescribing, opioid co-prescribing and subsequent mortality risk among HD patients.

Methods: A cohort study of adults initiating HD (1/2013–12/2014) was assembled linking the national registry of HD patients to Medicare claims through the United States Renal Data System. We identified risk factors (registry- and claims-based) for incident benzodiazepine prescribing and quantified the association between benzodiazepines (time-varying) using adjusted Cox proportional hazards models. We tested for effect modification by time-varying opioids.

Results: Of the 120,123 HD patients, 26.3% had at least one prescription for a benzodiazepine between 2013 and 2014. However, within 6 months of HD initiation, 21% of white and only 12% of non-white patients had a prescription for benzodiazepine; after adjustment, white patients were 1.66-fold (95% CI: 1.62–1.71) more likely to have a prescription for benzodiazepine. Furthermore, prior use of opioids (HR = 2.06, 95% CI 2.00–2.13), sedatives (HR = 1.86, 95% CI 1.80–1.92), and antipsychotics (HR = 2.21, 95% CI 2.13–2.30) were all independently associated with initiation of benzodiazepines. HD patients with a benzodiazepine prescription were at 1.49-fold (95% CI 1.41–1.57) greater risk of mortality. This mortality risk differed by opioid prescriptions (p for interaction<0.001): among those with opioids, benzodiazepines were associated with a 1.80-fold (95% CI 1.62–1.99) increased risk of mortality, while among those without opioids it was associated with a 1.34-fold (95% CI 1.26–1.43) increased risk. Inferences were similar in a sensitivity analysis using an ITT approach with propensity score adjustment.

Conclusions: Patients initiating HD, and particularly white patients, are often prescribed benzodiazepines, which increased risk of mortality by 1.5-fold. This risk is elevated in patients who are also prescribed opioids. This high-risk co-prescribing should be recognized by physicians caring for this vulnerable population.

692 | Comparative safety of medications for insomnia and risk of suicide attempt in the Department of Veterans Affairs

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Background: Guidelines for the treatment of adult insomnia recognize that trazodone and other off-label medications are commonly prescribed despite poor evidence. The Department of Veterans Health Affairs (VA) fills high volumes of inexpensive, over-the-counter sedating antihistamines and older antidepressants in addition to benzodiazepines and zolpidem. Yet little is known about the comparative safety of these agents with regard to suicidal behavior.

Objectives: To assess the comparative effectiveness of the safety of medications routinely used to treat insomnia in VA.

Methods: Design: Comparative safety using propensity score-matched samples. Data and Setting: Electronic medical records from the US Department of Veterans Health Affairs (VA) Corporate Data Warehouse. Subjects: VA patients without any history of suicidal ideation or behavior 12 months prior to first exposure. Exposures: VA formularies and data were used to identify prescriptions for insomnia. Agents accounting for at least 1% of total insomnia fill volume were < 200 mg trazodone, hydroxyzine, diphenhydramine, zolpidem, lorazepam, diazepam and temazepam. Exposure was defined as an incident monotherapy exposure preceded by 12-months without any insomnia medications. Subjects with insomnia polypharmacy or cross-overs in the 12 months following first exposure were excluded. Outcomes: Suicide attempts within 12 months of first exposure.

Results: 348,449 subjects met criteria and three well-balanced cohorts by drug class matched to zolpidem were created. After adjusting for days' supply, mental health history and, pain and central nervous system medication history, hazard ratios (compared to zolpidem) were as follows: (<200 mg) trazodone (HR = 1.61, 95% CI: 1.07–2.43); sedating antihistamines (HR = 1.37, 95% CI: 0.90–2.07) and benzodiazepines (HR = 1.31, 95% CI: 0.85–2.08).

Conclusions: Compared to zolpidem, hazard of suicide attempt was 61% higher with trazodone (<200 mg). No significant differences in

suicide attempt risk were identified between benzodiazepines or sedating antihistamines and zolpidem, respectively. These findings provide the first comparative effectiveness evidence against the use of trazodone for insomnia.

693 | Assessing the risk of depression associated with 5A-reductase inhibitor use: A population-based retrospective cohort study in Korea

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Background: 5α-reductase inhibitors (5ARI) are one of the most prescribed treatments for benign prostatic hyperplasia (BPH). Recently, several cases of depression after administration of 5ARI have been reported from the Korea Adverse Event Reporting System (KAERS).

Objectives: To compare the association between use of 5ARI or α-blocker (AB) as a treatment for benign prostatic hyperplasia (BPH) and the risk of depression.

Methods: We performed a retrospective cohort study using the Health Insurance Review and Assessment Service (HIRA) claim data from 2011 to 2017. New patients diagnosed with BPH and who take treatments that contain either a 5ARI or an AB (i.e. alfuzosin, tamsulosin, terazosin, silodosin, doxazosin; comparator group) between July 1, 2013 and June 30, 2015 were included. Patients with mental illness(i.e. depression, self-harm) in the 2 years prior to first exposure(5ARI or AB) were excluded. The primary outcome was depression (defined by ICD-10: F32–34, F38, F412, F432 and related drugs), and the secondary outcome was an anxiety disorder (ICD-10: F40–41). To adjust for confounding we used logistic regression to implement 1:1 propensity score (PS) matching of patients initiating 5ARI to those initiating AB. To compare the risk of depression associated with 5-ARI use compared to AB use we used cox proportional hazard models.

Results: We identified 1,461 5ARI and 18,650 AB patients. Balance in baseline characteristics between the treatment groups was achieved within PS matched pairs (1,461 pairs). Compared with the AB medication group, the 5ARI group significantly had lower depression (HR: 0.69, 95% CI: 0.51–0.92). However, we could not statistically find clinically relevant differences after PS matching (HR: 0.91, 95% CI: 0.61–1.36). Similar results were observed when evaluating the risk of anxiety.

Conclusions: The risk of depression or anxiety associated with 5ARI use was not meaningfully different from use of AB. We suggest that medical officials perform appropriate medication treatment for BPH patients by considering treatment benefit rather than depression risk.

694 | Switching from methadone syrup to capsule and all-cause mortality risk

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Background: In France, various interventions have targeted methadone to increase its accessibility and safety. They included the possibility to switch to a capsule form after treatment stabilization under syrup since 2008, and the extension of capsule maximum prescription from 14 to 28 days since October 2014. This led to an increasing use of methadone. However, growth in methadone misuse resulting in fatal cases have also been observed over the last years, and the potential role of switching from syrup to capsule in the occurrence of these events has been questioned.

Objectives: To assess the risk of all-cause mortality associated with switching from methadone syrup to capsule.

Methods: This study was carried out over a total period extending from January 1st, 2008 to December 31st, 2015, using the nationwide French Health Insurance database. A case-time-control design was used to take into account time trends estimated from a time-control group. Cases and time-controls had to meet the following eligibility criteria: (i) age 16 years or over, (ii) affiliated to the General Scheme of the French Health Insurance from 2008/01/01 to 2015/12/31, (iii) at least one reimbursement of methadone between 2009/01/01 and 2015/12/31. The exposure of interest was the switch from methadone syrup to capsule. All events of death that occurred between 2009/10/01 and 2015/12/31 were considered for the outcome of interest. Each case was matched on sex, age +/− 1 year, and coverage by supplementary state health insurance coverage (CMU-c) at index date to one randomly selected time-control. A risk window of 60 days prior to the event was retained for the main analysis. It was separated

from the three 60-days control windows considered by a 30-days wash-out period. Patients were included only when date(s) of switch could be ascertained for all time periods of interest. The association between switch from methadone syrup to capsule and the risk of death was analyzed using a conditional logistic regression model.

Results: 5,310 subjects (77.8% men; median age 44 years, IQR: 36–51; 36.2% covered with CMU-c) were included in the main analysis (2,650 cases and 2,650 time-controls). Of these, 204 cases and 126 time-controls appeared discordant for exposure between the risk and control windows. The analysis found no association between death and switch from methadone syrup to capsule in the 60 preceding days (OR IC95%: 1.31; 0,80–2.16). Sensitivity analyses provided consistent results.

Conclusions: Switching from methadone syrup to capsule was not associated with an increased risk of death in methadone users, although a short-term risk increase cannot be fully eliminated.

695 | Impact of the extension of maximum prescription duration of methadone capsule on all-cause mortality

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Background: Case reports of misuse or death related to methadone use have increased in France over the last years, while several interventions have been set up to improve methadone accessibility and safety, including the possibility to switch to a capsule form after treatment stabilization under syrup, and the extension of capsule maximum prescription duration.

Objectives: To analyze the impact on mortality of the extension of maximum prescription duration of methadone capsule form.

Methods: An Interrupted Time Series analysis was performed over a total period extending from January 1st, 2009 to December 31st, 2016, using the nationwide French Health Insurance database. The studied intervention was the extension of maximum duration of prescription of methadone capsule from 14 to 28 days, which is permitted since mid-October 2014. The studied population consisted of all subjects with at least one reimbursement of methadone capsule between 01/01/09 and 12/31/16, aged 16 or older and affiliated to the General Scheme of French Health Insurance. The time series was constituted of the measured number of deaths per 100,000 methadone capsule users, estimated on a monthly basis. The intervention impact was estimated considering i) the change in the monthly number of deaths consecutive to the intervention; ii) the change in the slope of the studied time series consecutive to the intervention. Firstly, the series was decomposed using a moving-average model and seasonal adjustment was performed. The series was then analyzed using a segmented linear regression model. The date of intervention was considered to be November 1st 2014 in the model. To observe a possible anticipation or delay in the intervention effect, sensitivity analyses considered different intervention dates (10/01/14, 11/01/14 and 01/01/15).

Results: The monthly number of users of methadone capsule increased steadily over the study period, from 4,229 in January 2009 to 29,912 in December 2016. The monthly number of deaths per 100,000 users varied from 0 (March 2009) to 95.6 (July 2009); most measures were comprised between 25 and 75/100,000. No significant impact of the intervention was found neither on the monthly number of deaths (− 5/100,000) nor in its trend (pre-intervention slope: 0.04 (−0.15; 0.23); post-intervention: −0.4 (−1.2; 0.4). Sensitivity analyses provided consistent results.

Conclusions: The extension of the maximum duration of prescription of methadone capsule to 28 days, which was accompanied by a huge increase in the number of methadone capsule users, did not appeared associated with an increase in mortality among methadone capsule users.

696 | Trend analysis of amphetamine-class overdose deaths in Kentucky

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Background: In 2016, for the first time, amphetamine was listed among the top 15 most commonly detected substances among U.S. drug overdose decedents, with methamphetamine listed as fourth. From 2011 to 2016, the rate of methamphetamine-involved overdose deaths in the U.S. more than tripled.

Objectives: The purpose of this study was to analyze how increases in amphetamine-salt prescriptions dispensed is related to amphetamine-class involved drug overdose deaths in Kentucky, and to examine if amphetamine-class overdose deaths cluster geographically.

Methods: Data from the Kentucky Drug Overdose Fatality Surveillance System, years 2016–2018, was analyzed to identify decedents that tested positive for methamphetamine or amphetamine in their post-mortem toxicology testing. Prescription drug monitoring program

data was analyzed to calculate the number of amphetamine-salt prescriptions dispensed to Kentucky residents. These measures were calculated at the quarter level. A negative-binomial regression was used to estimate the effect the number of amphetamine-salt prescriptions dispensed in each quarter has on the count of amphetamine-class overdose deaths. Additionally, counts of amphetamine-class overdoses by county were aggregated for the entire study period and a Moran's I analysis was performed to determine if amphetamine-class overdose deaths are clustered geographically.

Results: Preliminary data from 2018 overdose fatality surveillance indicate sustained increases in amphetamine-class overdose mortality, as counts of overdose deaths per quarter increased 97% from Q1/2016 to Q3/2018. The count of amphetamine-salt prescriptions dispensed to Kentucky residents was significantly associated with the count of amphetamine-class overdose deaths (p = 0.01), with every 1,000 additional prescriptions dispensed associated with a 3% increase in amphetamine class-involved overdose mortality. Geographically, the Moran's I test resulted in a z-statistic of 0.28 with a p-value of 0.001, indicating that similar rates of amphetamine-class overdose deaths cluster spatially.

Conclusions: Amphetamine class-involved overdose deaths have increased substantially over time in Kentucky. This increase is positively associated with the number of amphetamine-salt prescriptions that were dispensed in the same quarter. Moreover, high rates of amphetamine class-involved overdose deaths are clustered geographically. This finding provides insight into areas that can be targeted for public heath interventions to reduce amphetamine-class overdose morbidity and mortality.

697 | Predictors of justice system involvement in antipsychotic users in Manitoba, Canada

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Background: Mental illness increases the risk of criminality and victimization. Antipsychotic medications reduce criminality, but less is known about the effect of antipsychotic use on victimization.
Objectives: To describe characteristics of antipsychotic users who had justice system involvement and to identify risk factors for justice system involvement as accused or victim.
Methods: We used administrative databases at the Manitoba Centre for Health Policy (MCHP) to create a cohort of incident antipsychotic users in Manitoba, Canada from 2002–2015. We linked prescription records to population registry, hospital abstracts and medical services databases to obtain descriptive statistics. We used justice databases to identify antipsychotic users with justice system involvement after incident antipsychotic use, categorized as accused or victim. We used multivariable logistic regression to identify predictors of justice system involvement, adjusting for age, sex, socioeconomic status, incident antipsychotic and baseline diagnoses. Analyses were conducted with SAS® software.
Results: There were 76 459 incident antipsychotic users from 2002 to 2015; 5.3% were subsequently accused of a crime and 3.5% were victims. Only 40.2% of accused and 33.7% of victims filled an antipsychotic prescription in the 6 months prior to a justice incident. Common baseline diagnoses were mood/anxiety disorder (65.0%), dementia (21.2%), substance use disorder (16.9%), psychotic disorder (15.5%), ADHD (12.0%) and personality disorder (5.6%). Females were 52.6% less likely to be accused of a crime (adjusted OR 0.48, 95%CI 0.42, 0.53) but 78.3% more likely to be the victim (aOR 1.78, 95%CI 1.54, 2.06) versus males. Predictors of being accused included having a baseline diagnosis of ADHD (aOR 1.2, 95%CI 1.0, 1.3) mood/anxiety disorder (aOR 1.5, 95%CI 1.3, 1.6), personality disorder (aOR 1.5, 95%CI 1.3, 1.8), substance use disorder (aOR 1.2, 95%CI 1.1, 1.4), or suicide attempt (1.4, 95%CI 1.1, 1.8). ADHD, mood/anxiety disorder and personality disorder were associated with being a victim of a crime (aOR 1.3 [95%CI 1.1, 1.5], 1.2 [95%CI 1.0, 1.4], and 1.5 [95%CI 1.2, 1.9], respectively).
Conclusions: Our preliminary results suggest individuals with mental illness diagnoses remain at elevated risk of criminality and victimization despite antipsychotic use. Efforts to improve antipsychotic persistence may mitigate risk in this population, but further research is warranted. **Disclaimer** Results and conclusions are those of the authors; no official endorsement by Manitoba Health, Seniors and Healthy Living or MCHP is intended or should be inferred.

698 | Does aspirin use increase the risk of age-related macular degeneration: A population-based comparative cohort study

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Background: In elderly people with cardiovascular diseases, aspirin is the medication prescribed for prevention of secondary events. Its well-known side effect was bleeding, whether in gastrointestinal or ocular fields. However, its effect on AMD occurrence is inconclusive and conflicting from previous studies. To compare those people taking aspirin to those who do not is not fair because those two groups are not comparable. Aspirin users are prone to have more underlying diseases, especially cardiovascular diseases. Confounding by indication bias is a major concern when aspirin users are compared to non-aspirin users. Clopidogrel is a drug often used in patients similar to aspirin users, especially when patients were intolerant to aspirin. It is an alternative medication for aspirin users and is indicated with acute coronary syndrome, recent myocardial infarction, recent stroke, or coronary artery diseases.

Therefore, to investigate the risk of AMD for aspirin use in this study, we used clopidogrel to compare the estimated risk of AMD for these two groups.

Objectives: To estimate the risk of age-related macular degeneration (AMD) among aspirin users compared with clopidogrel.

Methods: Method: We conducted a population-based retrospective comparative cohort study using Taiwan's Longitudinal Health Insurance Database (LHID), which was randomly selected from the National Health Insurance Research Database (NHIRD). We included patients more than 45 years-old who initiated aspirin during 2001–2010 and they all tracked to 2013. The comparison groups are patients who were prescribed clopidogrel.

Main Outcome:The outcome of interest was AMD defined by ICD-9-CM code of 362.50–52 or 362.57. We used multivariate Cox regression modeling and propensity score (PS) matching to balance the characteristics of patients between groups to estimate the hazard ratio.

Results: After applying the methods, we had 109,534 aspirin users and 3,619 clopidogrel users. Male gender (51.12%) was predominate over females (48.88%) in the aspirin-user group. Our results showed no significant different risk of AMD between aspirin and clopidogrel users, while the multivariate Cox model showed HR was 1.13 (95% CI, 0.97–1.32) and the PS model showed HR was 1.09 (95% CI, 0.54–2.17). The incidence of aspirin users developing AMD was 8.18 per person-year, while the incidence of clopidogrel users was 10.07 per person-year.

Conclusions: Patients with long-term use of aspirin did not have higher risks in developing AMD compared to clopidogrel users.

699 | The association between treatment with montelukast and migraine - a symmetry analysis

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Background: Leukotriene receptor antagonists (LTRA) are used to treat asthma and rhinitis. Headache has been reported as a very common adverse event, and a few pharmacovigilance reportings identified migraine as suspected adverse event of LTRA. However, the association has not been established in controlled designs. On the contrary, LTRA have been tested as a potential migraine treatment but failed in a single randomized controlled trial.

Objectives: To assess whether treatment with the only approved LTRA in Denmark, montelukast, was associated with the initiation of triptans.

Methods: A prescription sequence symmetry analysis was employed on all Danish residents aged ≥18 years with at least one filled prescription of the montelukast (ATC R03DC03) from 2000–2016, who also filled their first ever prescription for triptans (ATC N02CC) within an interval of 180 days before or after the montelukast initiation. We calculated the crude sequence ratio (SR) and corresponding 95% confidence intervals (95%CI). The SR is the ratio between subjects with montelukast prescribed before sumatriptan and subjects with montelukast prescribed after triptans, which is a valid estimate of the incidence rate ratio.

Results: During the study period, 440 persons were identified initiating triptans within 180 days before and after their initial montelukast prescription. Of those, 352 (80.0%) were females, and 280 (63.6%) had a Charlson Comorbidity Index of 0 corresponding to a low comorbidity burden. Of the incident users of montelukast and triptans, 209 initiated montelukast before and 231 initiated montelukast after triptan treatment, yielding a crude SR of 0.90 (95%CI 0.75–1.10). The SR of females and males were 0.92 (95%CI 0.75–1.14), and 0.83 (95%CI 0.56–1.29), respectively. Neither therapeutic indications of asthma (short- and long-acting inhalation treatment without recorded prescriptions of systemic antihistamines or nasal topical anti-allergic treatment) SR 0.72 (95%CI 0.48–1.15) nor therapeutic indications allergic rhinitis (recorded prescriptions of systemic antihistamines or nasal topical anti-allergic treatment or both without short- and long-term inhalation treatment) SR 0.79 (95%CI 0.53–1.21) were associated with a modified risk of triptan initiation. Post-hoc analyses with time-windows of 30- and 90 days showed similar SRs (1.22 [95%CI 0.76–2.11] and 0.96 [95%CI 0.74–1.26] respectively).

Conclusions: We did not find any association between initiation of montelukast and onset of migraine (initiation of triptans), neither in patients with suspected asthma or patients with suspected allergic rhinitis without asthma.

700 | Excess of all-cause mortality associated with benzodiazepine use: A cohort study

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Background: At the moment benzodiazepine are steered at for overuse in the opioid-epidemic context, better understanding how their patterns of use could be associated to the risk of death appears essential. Although previous studies included large populations and yielded precise estimates, the key issue concerns the influence of the definition used for assessing benzodiazepine use on the results and conclusions.

Objectives: To investigate the association of chronic use of benzodiazepines with all-cause mortality.

Methods: A cohort of non-prevalent benzodiazepine users aged ≥65 years at beginning of follow-up was identified using a French national health care insurance system claims database (Echantillon Généraliste de Bénéficiaires, EGB), between 2010 and 2015. *Chronic use* was defined as a cumulated use of at least six months over the previous 12 months on the basis of a monthly assessment of benzodiazepine use status during the whole follow-up. Adjusted Hazard ratios (aHR) for

all-cause mortality over a six-year follow-up, estimated using Cox regression model with patterns of benzodiazepine use and confounders as time-dependent covariates.

Results: 54,958 met the inclusion criteria: mean age at inclusion 76 years, 53% female. Exposure to benzodiazepines represented 7.7% of the cumulative time of follow-up for the whole cohort. 6,314 benzodiazepine chronic users represented overall 6.1% of the cohort follow-up time. aHR decreased with age for all patterns of benzodiazepine use. At age 65, aHR for all-cause mortality were 2.26 (1.96–2.61) for benzodiazepine *short-term use*, 3.86 (3.04–4.90) for benzodiazepine *chronic use - discontinued*, and 3.05 (2.17–4.29) for benzodiazepine *chronic use - ongoing*, respectively at age 80, 1.62 (1.48–1.79); 2.00 (1.82–2.19) and 1.13 (1.02–1.26).

Conclusions: These findings confirm the existence of an excess risk of mortality associated with the use of benzodiazepines, and provide pattern-specific and age-specific estimates for this association: age < 80, short-term use, or chronic use (≥6 months over one year) recently interrupted. If the latter were likely to be driven by an indication bias, the associations found for ongoing chronic use and, to a lesser extent, for short-term use conversely support a potential causal hypothesis. Consequently, these findings provide further evidence to support the recommendation that benzodiazepines should be used with caution in the young elderly in whom they are often considered well tolerated, even after the initiation period.

701 | Spontaneous parasomnia adverse event reports associated with benzodiazepines and Z-drugs

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Background: While prescriptions for benzodiazepines plateaued over the past 20 years, new prescriptions for Z-drugs skyrocketed. Through consistent case reports and case-series, it is known that Z-drugs are associated with parasomnias, but epidemiological investigations of these adverse events are scarce. As benzodiazepines were the primary drug class used for sleep prior to the introduction of Z-drugs, a direct comparison of Z-drugs with benzodiazepines is warranted.

Objectives: To assess the association of parasomnia adverse event reports with benzodiazepines and with Z-drugs.

Methods: Data from the United States Food and Drug Administration's Adverse Event Reporting System (FAERS) from 1969 through third quarter 2018 were utilized. Preferred Terms according to MedDRA were used to identify reports of somnambulism (includes sleep-walking and sleep-driving), sleep-related eating disorders, sleep terror (includes night terror), and nightmare. Benzodiazepine drugs included chlordiazepoxide, alprazolam, diazepam, clonazepam, and lorazepam. Z-drugs included zaleplon, zolpidem, zopliclone, and eszopiclone. The selected drugs were included, regardless of route of administration, if they were noted to be suspect in the case report. Associations between drugs and events were measured by Empirical Bayes Geometric Mean (EBGM) and the corresponding lower bound of the 90% confidence interval (EB05). EB05 ≥ 2 were considered significant signals.

Results: From 1969-2018Q3, there were over 123,000 complaints related to benzodiazepines and over 45,000 complaints related to Z-drugs. Of these, 746 benzodiazepine complaints and 2600 Z-drug complaints were parasomnias. EBGM's were substantially higher for Z-drugs than for benzodiazepines for all four adverse event categories. For benzodiazepines, EBGM's ranged from 1.68 for sleep-related eating disorder to 2.57 for somnambulism, with only somnambulism providing a statistically significant signal (EB05 = 2.2). In contrast, for the Z-drugs, EBGM and corresponding EB05 values were elevated for sleep terrors (3.71, 2.59), nightmares (5.52, 5.06), somnambulism (85.13, 81.22), and sleep related eating disorder (95.72, 83.99).

Conclusions: Our analyses of the FAERS database revealed that Z-drugs are strongly associated with four types of parasomnias including three for which there was no signal on benzodiazepines.

702 | Risk of death associated with the use of antipsychotic drugs among Parkinson's disease with psychosis

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Background: The use of antipsychotics is associated with increased mortality in the general population and patients with certain diseases, but whether this risk extends to patients with Parkinson's with Psychosis (PDP), particularly for typical/conventional and atypical antipsychotics (TAP and AAP), has not been well known.

Objectives: To estimate the association between new use of antipsychotic medications and mortality.

Methods: PDP patients ≥65 years old were identified from the CMS Medicare data (2012–2015) to create three cohorts: new users of TAP, of AAP, and untreated. For treated patients, index date was the date of the first TAP or AAP exposure after the first PDP diagnosis in the study period. For untreated PDP, index date was the date of the first PDP diagnosis. Patients were censored at earliest of loss to follow-up, death, end of enrollment, end of study period, end of treatment, or switch from AAP to TAP or vice versa, wherever appropriate. Untreated patients should not have any exposure to antipsychotics during the study period. Age-standardized mortality rates were estimated based on US Census 2000. Three separate pairwise matched cohorts were generated by using propensity score matching to adjust for confounding. All-cause deaths were compared for each matched pair using Cox proportional hazards models, if

proportionality assumptions were held. Otherwise, Poisson regression was used. Sensitivity analyses including adjustment of residual confounding for time since the first PDP were performed.

Results: Of 33,415 elderly people in the study cohort, 818 initiated a TAP, 4,793 an AAP, and 27,804 were untreated of any AP. Age-standardized mortality rates per person-year were 0.68 (95% CI: 0.47–0.90), 0.29 (95% CI: 0.28–0.30) and 0.21 (95% CI: 0.19–0.24) among TAP, AAP and untreated, respectively. New use of TAP vs AAP was associated with an increased risk of death (HR = 1.74, 95% CI: 1.31–2.31). New use of TAP vs untreated was associated with an increased risk of death (IRR = 2.16, 95% CI: 1.70–2.72). In contrast, new use of AAP compared to untreated, was associated with a decreased risk of death (HR = 0.56, 95% CI: 0.51–0.62). Results were confirmed in sensitivity analyses.

Conclusions: Our finding confirmed that among elderly PDP patients, the risk of death associated with TAP is greater than the risk of death associated with AAP. Interestingly, with the same study design to minimize the immortal bias while comparing with untreated PDP, the study found that new TAP use increased mortality risk, but not AAP. Further research may need to confirm our new finding by using non-active comparator.

703 | Association of macular disease with use of pentosan polysulfate sodium

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Background: Recently a unique pigmentary maculopathy in the setting of chronic exposure to pentosan polysulfate sodium (PPS), a treatment for interstitial cystitis (IC) was described. These patients all had macular pigmentary changes that were ascribed to dry macular degeneration or pattern dystrophy. Herein, we assess the risk of macular disease in PPS users.

Objectives: To determine if an association between PPS use and macular disease exists.

Methods: A retrospective, matched cohort study using data from a large national US medical claims database was performed. The exposure cohort consisted of all patients prescribed PPS from 2002–2016. The index date was the date when the patient first filled a prescription for PPS, and patients were required to have at least 2 years prior to and 5 years after the index date for inclusion. Controls were matched 5:1 for age, gender, race, insurance plan eligibility start/end date and were assigned the same index date their exposed match. Another analysis required 7 years of follow up. Exclusion occurred for being <18 years old and any dry macular degeneration (dAMD) or drusen diagnosis prior to the index date. Two primary outcomes were identified. The first was defined as a new International Classification of Disease (ICD-9/10) diagnosis code for a hereditary or secondary pigmentary retinopathy (maculopathy) with the secondary outcome also including a new diagnosis of dAMD or drusen (maculopathy+AMD). Multivariate logistic regression analyses were performed controlling for demographic and systemic health variables. Subanalysis was also performed comparing only IC patients.

Results: 3012 and 1604 PPS users were compared to 15060 and 8017 at 5 and 7 years respectively. At 5- and 7-year follow-up, 9(0.3%) and 10 (0.6%) PPS patient had a maculopathy outcome, compared to 32(0.2%) and 25(0.3%) control patients respectively. There were 103(3.4%) and 87(5.4%) PPS patients with maculopathy+AMD compared to 440(2.9%) and 328(4.1%) control patients at 5 and 7 years, respectively. At 5-years, multivariate analysis showed no significant associations ($p > 0.13$). However, at 7 years PPS users had a significantly increased odds of having Maculoapthy+AMD (OR = 1.41, 95% CI: 1.09–1.83, $P = 0.009$), but not maculopathy (OR = 1.87, 95% CI: 0.87–3.99, $P = 0.11$). IC subanalysis showed increased odds at 5 years (OR = 2.91, 95% CI: 1.15–7.36, $P = 0.02$), but not at 7(OR = 1.46, 95% CI: 0.66–3.24, $P = 0.35$) for the maculopathy outcome.

Conclusions: PPS exposure was associated with a new diagnosis of macular disease. These results corroborate findings of the initial case series that suggest an association between PPS exposure and a novel maculopathy.

704 | Stuttering and methylphenidate

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Background: Methylphenidate (MPH) is a piperidine derivative structurally and pharmacologically similar to amphetamine. MPH is indicated for Attention Deficit Hyperactivity Disorder (ADHD) over 6 years of age. Stuttering affects about 5% of all children, especially boys. Several studies demonstrate a higher prevalence of stuttering in ADHD. The studies concerning the combination stuttering with methylphenidate are contradictory: MPH sometimes suitable for treating stuttering, on the other hand stuttering associated with the use of MPH.

Objectives: To investigate the association between methylphenidate and stuttering.

Methods: Data from Vigibase, the WHO pharmacovigilance database including more than 18 million reports of Individual Case Safety Reports (ICSRs) sent by national pharmacovigilance systems were used for this disproportionality analysis. We analyzed reports in the database that were coded with the MedDRA Preferred Term “dysphemia” and with the Lower Level Terms (LLT) “stutter” and “stuttering”. Association between exposure to MPH and occurrence of the adverse drug reaction was estimated by a disproportionality analyze. For this analyze, the Proportional Reporting Ratio (PRR) and the Reporting Odds Ratio (ROR) were calculated. The 95% Confidence Intervals (CIs) were calculated using the Woolf Method. All analyses were performed using SAS 9.4 Software.

Results: Among the 18 446 691 ICSRs registered in Vigibase, 2 975 were dysphemia cases of which 46 reports were associated with MPH treatment. Most of them were observed in males (n = 33), mean age was 13.52 years +/− 13.12. For the PT "dysphemia", the PRR and ROR were as following: PRR = 7.3 (95% CI: 5.4–9.7) and ROR = 7.3 (95% CI: 5.4–9.8). With the LLT "stuttering", 584 cases were registered in the database. We identified 17 cases with MPH with the mean age of 13.28 +/− 9.75 years and 67% male. The PRR and ROR were respectively 13.9 (95% CI: 8.6–22.5) and 13.9 (95% CI: 8.6–22.5).
Conclusions: Our data have to be considered as a pharmacovigilance signal. The mechanisms inducing stuttering are not completely known. An increased dopamine activity has been associated with stuttering. MPH increases dopamine release. So, further pharmacovigilance surveys and clinical studies are needed to conclude about MPH and stuttering.

705 | Use of B2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson's disease

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Background: A recent high-impact study showed that use of the β2-adrenoreceptor (β2AR) agonist salbutamol was associated with a dose-dependent decreased risk of PD in both an epidemiological and biochemical setting. Consistently, chronic use of β2-adrenoreceptor (β2AR) antagonists, e.g. propranolol, was reported to be associated with an increased risk of PD in the epidemiological substudy.
Objectives: To further investigate the association between β2AR agonist and antagonist use and risk of idiopathic Parkinson's disease (iPD).
Methods: We used the nationwide Danish healthcare registries to conduct a case–control study of incident cases of iPD between 2000 and 2011. Comparing the use of β2AR agonists among iPD cases to that among disease-free population controls (matched 1:4), we obtained odds ratios (ORs) associating use of β2AR agonists and antagonists with iPD, using conditional logistic regression and adjusting for potential confounders.
Results: We identified 2790 iPD cases matched to 11,160 population controls. Long-term β2AR agonist use was associated with reduced risk of PD (adjusted OR 0.57; 95% CI 0.40–0.82). However, short-term β2AR agonist use showed a comparable association (OR 0.64; 95% CI 0.42–0.98) and a formal test for risk reduction per year of exposure was negative (p_{trend} = 0.97). We additionally found protective association with other markers of smoking, i.e. chronic obstructive pulmonary disease diagnosis (OR 0.61), long-term use of inhaled corticosteroids (OR 0.46), and inhaled anticholinergics (OR 0.33). Finally, strengths of associations were consistent regardless of timing of use relative to date of diagnosis. Regarding β2AR antagonist use, increased risks were only observed for propranolol and metoprolol and associations were markedly stronger for short-term than long-term use.
Conclusions: We confirmed an association between β2AR agonist and antagonist use with reduced and increased PD risk, respectively. However, our data indicate the association of β2AR agonists to be indirectly mediated by smoking, which is known to be associated with reduced risk of PD. The association of β2AR antagonists indicates reverse causation, with PD symptoms triggering their prescription, rather than β2AR antagonists causing PD. Thus, current epidemiological data does not support a causal link between β2AR agonists and antagonists and PD risk.

706 | Association of the inhaled corticosteroids and the risk of cataract requiring surgery in adults with asthma: A population-based study in South Korea

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Background: In asthmatic patients, inhaled corticosteroids (ICS) are usually recommended globally as well as in Korea, but the relationship with cataracts is not clear yet. As the number of prescription for ICS and cataract operations increases every year, studies on the relationship between the use of ICS and the occurrence of cataract are needed.
Objectives: The study aimed to examine the association between the use of ICS or ICS/Long-acting beta-adrenoceptor agonist (LABA) and the incidence of cataract requiring surgery among the asthmatic patients aged 40–99 in Korea.
Methods: We conducted a population-based retrospective cohort study using the Health Insurance Review & Assessment database from Jan 2013 to Dec 2016. Newly diagnosed asthmatic patients between Jan 2014 to Dec 2015 with no history of cataract diagnosis and surgery were identified. The study outcome was the cataract surgery. It was followed-up until the time of the outcome of interest or the end of the study, whichever comes first. After applying propensity-score matching, we compared the risk of cataracts by using Cox proportional hazards model.
Results: Among 1,025,857 asthmatic patients who were initiated asthmatic medication, 146,499 (14.28%) were on ICS or ICS/LABA and most of patients were prescribed oral corticosteroids (1,025,192; 99.9%). The number of patients who had cataract operations were

2,266 (1.55%) in ICS users and 11,280 (1.28%) in non-users. We found no statistically significant association between the use of ICS and the cataract requiring surgery during the entire follow-up period (Hazard Ratio (HR): 0.957; 95% CI:0.897–1.021). Similarly, in the subgroup analyses, there were no significant differences in the results by gender, prescription of oral corticosteroids, and comorbidity.
Conclusions: The study did not support the relationship between ICS or ICS/LABA medication to adult asthmatic patients and the occurrence of cataract that led to surgery comparatively within a short period of time.

707 | A safety signal of somnambulism with the use of antipsychotics: A pharmacovigilance disproportionality analysis

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Background: Antipsychotics are widely used in psychiatry, particularly in schizophrenia bipolar disorders.
Objectives: This study aimed at investigating the risk of somnambulism adverse drug reaction (ADR) associated to their use.
Methods: Individual case safety reports (ICSRs) collected in VigiBase®, and related to antipsychotics (Anatomical Therapeutic Chemical (ATC) classification N05A) and Preferred terms (PT) "Somnambulism" of the MedDRA classification were analyzed. A descriptive analysis was performed according to median age, gender, seriousness, drug and indication. Disproportionality analyses were performed using information component (IC) in comparison to full database. A signal was considered if the lower limit of 95% credibility interval (LL 95%CI) was positive.
Results: A total of 450 ICSRs of somnambulism were identified for antipsychotics; median age of patients was 47 years (interquartile range: 36–58), and 39% were men. Only one antipsychotic was involved in most cases (94%); 40% were serious and 14% resulted in hospitalization or hospitalization prolongation. Quetiapine was involved in 51% of ICSRs, olanzapine in 12%, and aripiprazole in 10%. The indication was informed in 68% of ICSRs; the main represented were bipolar disorders (26%), depression (11%), and schizophrenia (14%). ADR co-reported with somnambulism concerned mostly somnolence (10%), insomnia (10%), and weight increased (9%). Signals of disproportionate reporting were found for 10 antipsychotics including quetiapine (IC 3.39, LL CI95% 3.20), asenapine (IC 3.17, LL CI95% 2.49), ziprasidone (IC 2.68, LL CI95% 2.09), lurasidone (IC 2.43, LL CI95% 1.45), olanzapine (IC 1.57, LL CI95% 1.16), pimavanserin (IC 2.08, LL CI95% 1.15), aripiprazole (IC 1.43, LL CI95% 0.98), lithium (IC 1.04, LL CI95% 0.22), brexpiprazole (IC 1.63, LL CI95% 0.10), and tiotixene (IC 2.09, LL CI95% 0.04), yet not for risperidone (*n* = 14, IC -0.98, LL CI95% -1.83), clozapine (*n* = 13, IC -1.56 LL CI95% -2.45) or haloperidol (*n* = 6, IC -1.85, LL CI95% -0.47).
Conclusions: This study found signals of disproportionate reporting of somnambulism for major antipsychotics including quetiapine, olanzapine and aripiprazole, yet not for risperidone, clozapine or haloperidol. All signals concerned atypical antipsychotics (expected lithium) and none classical antipsychotics. The absence of signal with classical antipsychotics will have to be further investigated through *ad-hoc* and more robust studies.

708 | Abstract Withdrawn

709 | Spontaneous reporting of rare events associated with atypical antipsychotics using the FDA adverse event reporting system

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Background: Atypical antipsychotic drugs (APD) have chiefly replaced typical antipsychotics (TA) as first line drugs for the management of schizophrenia and related disorders. Although APD cause less extrapyramidal side-effects than TA, further identification of their safety profile is required. Few case reports and studies have reported an association between APD and cardiomyopathy, hypothermia and priapism. However, to the best of our knowledge, no study has collectively examined the safety profile of all FDA approved APD with very rare adverse events (AEs), particularly cardiomyopathy, priapism and hypothermia.
Objectives: To assess the association of APD with spontaneous reporting of cardiomyopathy, priapism and hypothermia in the FDA Adverse Event Reporting System (FAERS).
Methods: Reports from 1989 to 2018 in FAERS of all single ingredient, FDA approved APD, regardless of the route of administration were included in the analysis. Identified APD were aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, brexpiprazole and cariprazine. AEs of interest included cardiomyopathy, hypothermia, and priapism. Reports were restricted to instances where the drug was noted as suspect in the case report. Associations between drugs and events were measured by Empirical Bayes Geometric Mean and the lower bound of the 90%

confidence interval (EB05). A signal was defined as drug-AE pair having an EB05 $\geq$ 2. All analyses were performed using DrugLogic-QSCAN®.
Results: There were 386,029 reports included in the analysis. Risperidone (20.9%), clozapine (19.5%) and quetiapine (19%) were the most reported APD, while brexpiprazole (1.8%), iloperidone (0.2%), cariprazine (0.18%) were the least reported. There was disproportionate reporting of cardiomyopathy with clozapine and olanzapine (EB05 = 6.95 and 2.2, respectively). Similarly, olanzapine, risperidone, quetiapine, aripiprazole and clozapine were associated with higher reporting of hypothermia (EB05 = 7.4, 7.1, 2.8, 2.7, and 2.6 respectively). Last, all APD were associated with disproportionate reporting of priapism except for lurasidone, asenapine, brexpiprazole and cariprazine.
Conclusions: APD are associated with disproportionate higher reporting of cardiomyopathy, hypothermia and priapism. Although the results do not indicate causality, they should raise awareness among physicians to monitor for these potentially life-threatening AE, particularly with certain APD. Further studies are needed to validate these findings.

710 | Disproportionality analysis of emotional and mood disturbances with statins using the Food and Drug Administration adverse event reporting system

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Background: Statin drugs are prescribed to treat patients with hypercholesterolemia. Their popularity has been tempered by various side effects. Case and anecdotal reports note the possibility of an increase in emotional and mood disturbances (i.e. anger and irritability) as more patients are exposed to statins. Few studies have reported an association between statin use and these types of adverse events. To the best of our knowledge, no study has investigated these types of disturbances and statins with a spontaneous reporting database.
Objectives: The objective of this study was to conduct a disproportionality analysis among U.S. marketed statins for the Medical Dictionary for Regulatory Activities High Level Terms (MedDRA HLT) Emotional and Mood Disturbances NEC. This HLT includes the Preferred Terms (PTs) anger, irritability, emotional distress, among others. The FDA Adverse Event Reporting System (FAERS) was used for analyses.
Methods: All FAERS data from 1969 to 2018 (3rd Q) was used. Oral formulation, single active ingredient statins were included (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin). The association of the HLT Emotional and Mood Disturbances NEC to the individual statins was evaluated using the Empirical Bayes Geometric Mean (EBGM) and the lower bound of the 90% confidence interval (EB05). A signal was defined as drug-event pair having an EB05 $\geq$ 2. The secondary analysis signal threshold was the combination of Proportional Reporting Ratio (PRR) $\geq$2, $N \geq 3$, and $Chi^2 \geq 4$. The DrugLogic-QSCAN® platform was used for all analyses.
Results: Atorvastatin was associated with the greatest number of overall case reports for any adverse event (N = 291705), while pitavastatin was the lowest (N = 4661). None of the statins achieved an EB05 of $\geq$2: simvastatin (0.72), atorvastatin (0.65), pravastatin (0.56), lovastatin (0.55), rosuvastatin (0.55), fluvastatin (0.39), pitavastatin (0.33). Similarly, none of the statins reached the signal threshold for the secondary analysis. All PRR values were below 1.0.
Conclusions: In our analyses, none of the FDA approved and U.S. marketed statins were associated with disproportional reporting for the HLT Emotional and Mood Disturbances NEC. In fact, all seven statins were reported at a lower frequency than expected, compared to the entire FAERS database. The values suggest a possible protective effect. However, due to well-known underreporting associated with spontaneous reporting databases, caution is warranted. Further studies are required to confirm these findings.

711 | Impulse control disorders associated with dopamine agonists in patients with prolactinomas: A literature review

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Background: Dopamine agonists (DAs) have been associated with impulse control disorders (ICDs). Previous studies evaluating the epidemiology of ICDs have generally been limited to patients with Parkinson's disease (PD) and the prevalence and characteristics of DA-associated ICDs are relatively unknown in patients with prolactinomas.
Objectives: We conducted a literature review of epidemiologic studies evaluating the DA-associated risk of ICDs among patients with prolactinomas, with a focus on cabergoline and bromocriptine.
Methods: Keywords were searched on PubMed and EMBASE for English-language articles published through January 2019. We included epidemiologic studies that are designed to investigate the association between any types of ICD and either cabergoline or bromocriptine. Following PRISMA guideline, two independent reviewers screened, adjudicated, and extracted data. Any discrepancies were resolved through discussion and a third reviewer if needed.
Results: Of the potential 621 articles, 1 randomized control trial (RCT), 2 observational studies and 12 case reports/series were eligible for inclusion in this review. According to the RCT and observational studies, the

incidence of ICDs ranged from 3% to 25% in prolactinoma patients receiving cabergoline or bromocriptine. In the RCT of 38 patients and an observational study of 25 patients who received cabergoline, hypersexuality was the only type of ICDs reported. Furthermore, hypersexuality, followed by pathological gambling and excessive shopping, was the most predominant ICDs in the larger observational study among 77 patients received either cabergoline or bromocriptine. Twelve case reports/series on a total of 22 prolactinoma patients with DA-associated ICDs were identified. Manifestations include hypersexuality (n = 13), pathological gambling (n = 10), excessive shopping (n = 1) and compulsive eating (n = 1), indicating some patients experienced multiple ICDs. These ICDs were usually reversible after a decrease or cessation of dopamine agonists. Interestingly, all instances of hypersexuality occurred in men with wide age (16–78 years) and drug dose range (0.07–1 mg/day for cabergoline and 0.07–15 mg/day for bromocriptine).

Conclusions: The results of our review indicate that prolactinoma patients may develop ICDs, especially hypersexuality, as side effects of bromocriptine or cabergoline treatment. However, the available evidence remains largely anecdotal and insufficient to draw conclusions about the causality and factors associated with the increased ICD risk.

712 | Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population

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Background: Previous overseas studies and case reports have suggested that anticonvulsants be associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). However, evidence for the risks is scarce in Japan.

Objectives: To investigate the risk of SJS/TEN in patients newly-treated with anticonvulsants in Japan.

Methods: We conducted a 1:4 matched case–control study using 2005–2017 claims data from the JMDC Inc. SJS/TEN cases were identified using a claims-based algorithm developed from the electronic medical records in a Japanese university hospital in a previous study (sensitivity 76.9%, specificity 99.0%). This algorithm consisted of the following three domains: 1) clinical course for SJS/TEN; 2) medical encounters for mucocutaneous lesions from SJS/TEN; and 3) item to exclude differential diagnosis of paraneoplastic pemphigus. SJS/TEN-free controls were matched to cases on age, sex, and index date (date of diagnosis) by risk-set sampling. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for SJS/TEN associated with each suspected anticonvulsant use (90 days prior to the index date) versus anticonvulsant non-use. We calculated cumulative incidences of SJS/TEN for new users of 33 anticonvulsants. Causality between anticonvulsants and SJS/TEN in each exposed case was assessed using the algorithm of drug causality for epidermal necrolysis (ALDEN) score.

Results: The case–control study included 49 SJS/TEN cases (20 male and 29 female) and 196 controls. Mean age at index date for cases and controls combined was 42.5 years. There were increased odds of SJS/TEN in the new users of lamotrigine (OR 21.14, 95% CI 3.59-∞) and carbamazepine (OR 21.14, 95% CI 3.59-∞). The ALDEN score was more than probable for 100% of cases exposed to lamotrigine or carbamazepine. Cumulative incidences of SJS/TEN were 87.0/100,000 new users for lamotrigine, and 48.4/100,000 new users for carbamazepine. We found no significant elevated odds in the users of other anticonvulsants.

Conclusions: Exposure to lamotrigine and carbamazepine was associated with an increased risk of SJS/TEN.

713 | Risk of extrapyramidal syndromes associated with antipsychotic polypharmacy: A retrospective study based on spontaneous reporting system databases

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Background: Extrapyramidal syndromes (EPS) are adverse events associated with use of antipsychotics. Antipsychotic polypharmacy is common in clinical practice although supporting evidence is limited. Many reports suggest an association between each antipsychotic drug and EPS; however, the risk of EPS associated with their polypharmacy has not been fully evaluated.

Objectives: The purpose of this study is to examine the association of antipsychotic polypharmacy on EPS using US and Japanese spontaneous reporting system databases.

Methods: We analyzed reports of EPS between 2004–2017 in the FDA Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report database (JADER), and calculated the reporting odds ratio (ROR) of antipsychotic polypharmacy associated with EPS. Antipsychotic polypharmacy was defined as use of more than one antipsychotic.

Results: For EPS, the RORs of antipsychotics were 6.33 (95% CI 6.20–6.46) in FAERS, and 18.18 (16.90–19.55) in JADER, respectively. The ROR of a multiple antipsychotic (FAERS: ROR 7.01, 95% CI 6.72–7.32, JADER: 15.27, 13.86–16.82) was higher than that of a single antipsychotic (FAERS: 5.88, 5.74–6.01, JADER: 12.08, 11.17–13.07).

Conclusions: Antipsychotics were significantly associated with EPS, and the profile was stronger in antipsychotic polypharmacy. That suggests the possibility of an increased risk of EPS with increasing number of antipsychotics. Further investigation is needed to confirm these findings.

714 | Risk of suicide attempt and the use of antidepressants in Taiwan

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Background: Use of antidepressants to reduce risk of suicide in patients with major depression remained controversial. It warrants cautions on possible confounding by indications in the comparisons between antidepressant users and non-users from previous studies.
Objectives: To compare the risk of suicidal attempts between patients with depression persisted to antidepressants vs non-persisted patients.
Methods: We analyzed Taiwan's National Health Insurance Research Database (NHIRD) between Jan 1, 2003 and Dec 31, 2010. We included patients newly received antidepressants for 90+ days from two or more antidepressant prescription and diagnosed with depression. We considered persisted patients as those continuously used antidepressants after index date, which was defined as 90 days after drug initiation, otherwise non-persisted patients were defined as those who discontinued antidepressants after index date. We followed patients until discontinuation of the antidepressant or occurrence of suicide and suicidal attempts. We performed Cox's proportional hazards models with adjustment for patients' age, sex and psychiatric conditions and medications to evaluate the risk of suicide attempts between antidepressants persisted and non-persisted patients.
Results: We identified a total of 5238 patients in the study; with a mean age of 50.9 (SD 16.8) and 35.1% were male. We found 4172 were persisted patients and 1066 were non-persisted. The incidence rates of suicide attempts were 3.9 per 100,000 person-years and 6.9 per 100,000 person-years in persisted and non-persisted patients, respectively. We found the risk of suicide attempts were lower in persisted patients (adjusted hazard ratio, 0.79; 95% CI, 0.35 to 1.8) compared to non-persisted patients; however no statistical significance.
Conclusions: This population based study indicated that the risk of suicide attempts tended to be lower in antidepressant persisted patients compared to non-persisted patients. It warrants future investigations to include larger sample size to confirm the findings.

715 | Comparative risk of mortality among individual antipsychotics in patients with dementia

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Background: Antipsychotic medications are commonly used for behavioral and psychological symptoms of dementia (BPSD); however the US FDA warned an increased mortality risk of antipsychotics in elderly patients. Understanding different mortality risk profiles among antipsychotics helps to avoid unintended outcomes.
Objectives: To compare the mortality risk between individual antipsychotics in patients with BPSD.
Methods: We conducted a retrospective cohort study using the Taiwan's National Health Insurance Research Database (NHIRD) from 2003–2013. Study population consisted of patients aged 65+ years who diagnosed with BPSD newly receiving antipsychotic medications. The outcome of interest was all cause of mortality. We performed intent-to-treat analysis and followed patients until they died or 180 days after antipsychotics initiation. Quetiapine was selected as reference group for comparison because it was most commonly used antipsychotic. We performed Cox proportional hazards models with adjustments of covariates such as age, sex to compare the mortality risk between antipsychotic users.
Results: We identified a cohort of 41,932 patients with a mean age of 81.1 years (SD 7.04) and 47.49% female. Quetiapine (38.4%) was the most frequently used antipsychotics, followed by haloperidol (16.5%) and Risperidone (16.0%). The overall mortality rate was 0.84 cases per person-year among all antipsychotic groups. We found the mortality risk were higher in haloperidol (adjusted hazard ratio, 1.78; 95% CI, 1.70–1.85) and risperidone (1.23; 1.17–1.29) compared with quetiapine users. Olanzapine (1.07; 0.91–1.25) posed similar risk compared with quetiapine. We found patients receiving amisulpride (0.86; CI 0.69–1.08) and aripiprazole (0.64; 0.49–0.84) had lower risk of mortality compared to quetiapine users.
Conclusions: The finding warrants caution on increased mortality risk in patients receiving haloperidol and risperidone. Amisulpride and aripiprazole may provide more favorable risk profiles in mortality that could be considered for patients with BPSD.

716 | Oral antidiabetes drugs and risk of stroke

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Background: Diabetes is a known risk factor for stroke. Publications have reported increased risk of stroke in users of sulfonylureas, with little consideration for indication comorbidities, coprescriptions or type of stroke (ischemic or hemorrhagic).
Objectives: To explore the association between type of oral antidiabetes treatment used and the risk of stroke in patients with diabetes.
Methods: From two national registries, patients with diabetes were identified, excluding patients treated with insulin or other injectable

antidiabetes treatments. Incident stroke was defined as: (i) a first-ever; (ii) fatal or non-fatal; (iii) ischemic stroke or haemorrhagic stroke; (iv) documented by CT scan or MRI; (v) irrespective of symptom duration. Stroke cases were matched to non-stroke patients (referents) on age, gender, index date (date of stroke diagnosis for cases and date of recruitment for non-cases) and history of atrial fibrillation (AF). All treatments received in the previous 12 months before stroke or index date were considered (most documented from medical records). The associations between each OAD used and the risk of stroke were assessed with multivariable conditional logistic models. Potentially cofounding risk factors considered in the model were: antiplatelet agents and anticoagulants use, history of cardiovascular diseases, hyperlipidemia, renal impairment, liver disease.

Results: The prevalence of diabetes was 22% in stroke registry and 19% in AF registry (adjusted odds ratio (OR) for diabetes and incident stroke: 1.25 with a 95% confidence interval (CI) of [1.05–1.49], with similar OR for ischemic and hemorrhagic stroke). Among them, 362 stroke cases with diabetes were identified in the registries, matched to 362 randomly selected non-stroke patients with diabetes. The adjusted OR for the use of metformin only was OR = 0.90;95%CI [0.56–1.43], for of the use of sulfonylurea only OR = 0.89;95%CI [0.49–1.64], for of the use of glinide only OR = 1.65;95%CI = [0.71–3.80], for of the use of DPP-4 only OR = 0.78;95%CI [0.32–1.90]. Similar results were found when each OAD was used in combination with any other OAD. Analyses restricted to ischemic stroke provided similar results.

Conclusions: No significant difference in the risk of stroke was observed for each individual OAD used in isolation or in combination with other OAD in patients with diabetes.

717 | Trazodone use and risk of dementia: A population-based cohort study

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Background: In vitro and animal studies have suggested that trazodone, a licensed antidepressant, may protect against dementia. However, no studies have been conducted to assess the effect of trazodone on dementia in humans.

Objectives: We conducted an electronic health records study to assess the association between trazodone use and the risk of developing dementia in clinical practice.

Methods: We used The Health Improvement Network (THIN) primary health care data to identify patients aged ≥50 years who received at least two consecutive prescriptions for an antidepressant between January 2000 and January 2017. We compared the risk of dementia among patients who were prescribed trazodone to that of patients with similar baseline characteristics prescribed other antidepressants, using a Cox regression model with 1:5 propensity score matching. Patients prescribed trazodone who met the inclusion criteria (n = 4,716; 59.2% female) were older (mean age 70.9 ± 13.1 versus 65.6 ± 11.4 years) and were more likely than those prescribed other antidepressants (n = 420,280; 59.7% female) to have cerebrovascular disease and use anxiolytic or antipsychotic drugs. After propensity score matching, 4,596 users of trazadone and 22,980 users of other antidepressants were analyzed.

Results: The median time to dementia diagnosis for people prescribed trazodone was 1.8 years (interquartile range [IQR] = 0.5–5.0 years). Incidence of dementia among patients taking trazodone was higher than in matched users of other antidepressants (1.8 versus 1.1 per 100 person-years), with a hazard ratio (HR) of 1.80 (95% confidence interval [CI] 1.56–2.09; $p < 0.001$). When we restricted the control group to users of mirtazapine only in a sensitivity analysis, the findings were very similar to the results of the main analysis. Whilst the incidence of dementia among patients taking trazodone was higher than that in patients taking other antidepressants, the risk differences were closer to zero with increasing duration of treatment, suggesting that people in the prodromal stage of dementia might be more likely to be prescribed trazodone.

Conclusions: We found no association between trazodone use and a reduced risk of dementia compared with other antidepressants. These results suggest that the clinical use of trazodone is not associated with a reduced risk of dementia.

718 | Risk of bullous pemphigoid after initiating dipeptidyl peptidase 4-inhibitor versus 2nd generation sulfonylurea: Multi-database cohort study

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Background: Dipeptidyl peptidase 4-inhibitors (DPP4i) have been linked to bullous pemphigoid. Yet this risk has not been well-established in population-based studies.

Objectives: To compare the risk of bullous pemphigoid in diabetes patients initiating DPP4i versus second generation sulfonylurea.

Methods: We conducted a 1:1 propensity-score matched cohort study of adults aged ≥40 years with type 2 diabetes mellitus who were newly treated with DPP4i or second generation sulfonylurea using 2006–2016 data from two large commercial insurers' databases (Optum Clinformatics™ Datamart and Truven MarketScan) and Medicare. We calculated the incidence rate of bullous pemphigoid identified using diagnosis codes. Hazard ratios (HRs) and 95% confidence intervals (CIs) associated with DPP4i versus sulfonylurea were estimated for middle-age (40–64 years) and older patients (≥65 years) in each database. The inverse-variance fixed-effects meta-analysis was used to pool the results from the three databases.

Results: The analysis included 173,279 propensity-score matched pairs in Optum database (mean age, 61 years; median follow-up, 120 days), 353,580 pairs in Truven database (58 years; 129 days), and 308,170 pairs in Medicare (74 years; 149 days). Initiation of DPP4i compared with sulfonylurea was not associated with bullous

pemphigoid in middle-age patients (incidence rates per 1000 person-years for DPP4i versus sulfonylurea: 0.09 versus 0.14; pooled HR, 0.62; 95% CI, 0.37–1.04). However, DPP4i initiation was associated with an increased risk in older patients (incidence rates, 0.95 versus 0.62; pooled HR, 1.55; 95% CI, 1.30–1.84). The results were consistent across the databases.

Conclusions: These results suggest an increased risk of bullous pemphigoid after initiating DPP4i compared with sulfonylurea in older adults with type 2 diabetes mellitus.

719 | Risk of acute kidney injury and chronic kidney disease following aciclovir and valaciclovir therapy

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Background: Aciclovir and valaciclovir are the most commonly prescribed nucleoside analogues for the treatment of herpes simplex virus infections in Denmark. Use of these drugs has been associated with crystalluria and renal failure. Most studies investigated the association between intravenous use of thesedrugs and acute kidney injury (AKI), but data on oral use and chronic kidney disease (CKD) is sparse.

Objectives: To assess the potential association between use of val−/aciclovir and AKI and CKD.

Methods: The study population consisted of all adults residing on the island of Funen, Denmark (population size: 490,000) at some time during 2000 to 2016, who had at least one creatinine measurement recorded. We defined CKD and AKI according to Kidney Disease Improving Global Outcome (KDIGO) definitions and used Danish health register data combined with data from the Funen Laboratory Cohort (FLaC). To assess the association between val−/aciclovir and AKI a self-controlled case series (SCCS) analysis was undertaken to estimate incidence rate ratios (IRR), these were estimated in 10-day intervals up to 180 days after start of exposure. IRRs were calculated using conditional Poisson regression. We conducted a nested case−control study to assess the association between val−/aciclovir and CKD. We used risk-set sampling and sampled up to 10 sex- and age-matched controls per case. Conditional logistic regression was used to estimate odds ratios (OR).

Results: Assessing the risk of AKI, a total of 69,734 individuals redeemed one or more prescriptions of val−/aciclovir in the study period. Of these, 6635 had AKI and were included in the SCCS-analysis. The crude IRR of AKI during the risk period (prescription duration and 14-days washout period) was 2.12 (95% CI: 1.67–2.70), and the age-adjusted IRR was 2.02 (95% CI: 1.59–2.57). Maximum IRR was observed during ongoing exposure and fell to baseline after 40 days after initiation. Assessing the risk of CKD, 1752 cases (10.4%) and 10,496 controls (10.0%) were exposed to val−/aciclovir. Use of val−/aciclovir was not associated with CKD (adjusted OR: 0.97 95% CI: 0.91–1.03), nor was chronic use (>35 DDD: 0.81 95% CI: 0.54–1.20). We did not observe dose−response patterns related to the cumulative dose.

Conclusions: An increased IRR of AKI was observed during current exposure to val−/aciclovir. However, since one may expect a diagnostic delay this could be due to protopathic bias. We found no association between exposure to val−/aciclovir and CKD.

720 | Fluoroquinolone adverse drug events: Results of an active surveillance project

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Background: Use of fluoroquinolones has been associated with increased risk of rare but serious adverse drug events (ADEs). The Food and Drug Administration has released several warnings recommending use of alternative antibiotics when feasible.

Objectives: The purpose of this active surveillance project was to evaluate risks of rare, serious ADEs in outpatient Veterans treated with fluoroquinolones versus common alternatives (amoxicillin/amoxicillin-clavulanate and azithromycin).

Methods: This was a retrospective cohort analysis of Veterans with new outpatient prescriptions for oral levofloxacin, ciprofloxacin or moxifloxacin (Group 1), amoxicillin or amoxicillin/clavulanate (Group 2), or azithromycin (Group 3) between 6/1/2008 and 5/31/2018. Patients could have multiple prescriptions ≥30 days apart. Primary outcomes were hospitalization or ED visit due to acute myocardial infarction (AMI), ventricular arrhythmia, aortic aneurysm/dissection, Achilles tendon rupture/tendinitis, or peripheral neuropathy over the 30 days following release of the prescription, and 30-day all-cause mortality. Secondary outcomes were outpatient visits for these diagnoses. Propensity score matching adjusted for potential treatment selection bias. Cox proportional hazards models assessed the association between fluoroquinolones and ADEs versus the other antibiotics.

Results: After propensity score matching for baseline demographics, comorbidities, antibiotic indication, and concomitant medications, there were 795,709 well matched outpatients in Groups 1 and 2 and 551,269 in Groups 1 and 3. Based on preliminary results, patients in Group 1 had a greater risk for aortic aneurysm/dissection compared with Group 2 (HR = 1.74; 95% CI 1.27–2.40) or Group 3 (HR = 2.17; 95% CI 1.41–3.34). Patients in Group 1 also had a greater risk for AMI versus Group 2 (HR = 1.52; 95% CI 1.35–1.71) or Group 3 (HR = 1.41; 95% CI 1.22–1.62) and a greater risk for 30-day all-cause mortality versus patients in Group 2 (HR = 2.28; 95% CI 2.19–2.37) or Group 3 (HR = 2.02; 95% CI 1.93–2.12). There was no significant difference in the risk of ventricular arrhythmia between Group 1 and Groups 2 (HR = 1.12; 95% CI 0.85–1.48) or 3 (HR = 1.33; 95% CI 0.92–1.90). Results were similar in secondary analyses.

Conclusions: We identified a possible signal of an increased risk of aortic aneurysm/dissection, AMI, and all-cause mortality with fluoroquinolone use versus amoxicillin/amoxicillin-clavulanate and azithromycin in Veterans. Our findings warrant further investigation in a formal research study with adjustment for additional confounders.

721 | Under-reporting of adverse drug reaction: pharmacovigilance awareness and challenges among resident doctors

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Background: Adverse drug reaction (ADR) reporting is the keystone of pharmacovigilance (PV) and one of the fundamental roles of any healthcare provider. However, under-reporting is recognized as the main cause of poor ADR detection worldwide.
Objectives: To evaluate resident doctors' knowledge and attitude regarding pharmacovigilance and adverse drug reaction reporting system in Alexandria, Egypt.
Methods: A Cross sectional, questionnaire based study conducted to identify the main reasons behind the under-reporting of ADR behaviour among resident doctors. The study was conducted in Alexandria University Hospitals, Egypt. A total number of 304 resident were included. Reporting responsibilities and mechanisms were evaluated and data analysis was conducted using TIBCO Statistica software.
Results: The Majority of the respondents 85.6% never reported any adverse drug event and almost half of them (49%) never heard about the PV reporting centers. Lack of time and poor knowledge about the ADR reporting process were the main reason (75%) behind under-reporting. Other factors associated with under-reporting were fear of appearing unreasonable (35%), believing that only safe drugs allowed in market (42%), indifference (26%) and uncertainty (I'm not sure which drug responsible for this adverse reaction) (36%). General attitude of the respondents about ADR reporting was as follows: ADR reporting should be compulsory (16.27%), doctors should be paid when reporting an ADE (68.5%), prescriber and reporter identity should be concealed (61.42%).
Conclusions: While pharmacovigilance perception and attitude showed a strong influence in ADR reporting, our study found that personal factors appear to play a huge role as well. Regular training sessions and closer relationships with the PV centers could be useful to improve ADR reporting rates. Making ADR reporting guidelines, booklets or posters can also increase the awareness of PV among healthcare professions.

722 | Calcium Channel blocker induced lymphedema among breast cancer patients: A nested case control study

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Background: Lymphedema is a common complication subsequent to breast cancer treatment. Research has shown varying effects of antihypertensive agents, including calcium channel blockers, on lymphedema development.
Objectives: To assess the risk of lymphedema associated with use of calcium channel blockers among breast cancer patients.
Methods: A nested case–control study of adult female breast cancer patients receiving an antihypertensive agent was conducted. The nest comprised patients of breast cancer female patients exposed to antihypertensive agents using administrative claims data between 2007 and 2015. Cases were patients with 1 or more medical claims with a primary or secondary diagnosis for lymphedema or procedure claim for lymphedema treatment and 180 days of continuous enrollment prior to event date. Up to 5 controls from the nest were matched to cases based on nest entry date (180 days), age (5 years), number of hypertensive drug classes, Charlson comorbidity score, thiazide exposure, and insurance type in the 180 days prior to nest entry. Exposure to calcium channel blockers and covariates were identified in the 180 day exposure period prior to event date or imputed event date for controls Conditional logistic regression was used to assess exposure among cases and controls. All statistical analysis was conducted using SAS version 9.3, Cary, N.C.
Results: A total of 717 cases and 1681 matched controls were identified. After matching on baseline characteristics mastectomy (7.8% vs 4.8% p = 0.0039), exposure to radiation therapy (27.1% vs 21.7% p = 0.0046), taxane-based chemotherapy (11.7%vs 7.4% p = 0.0007), anthracycline-based chemotherapy (6.0% vs 3.6%), calcium-channel blocker use (28.3% vs 23.3% p = 0.0087), and Charlson Comorbidity Index (19.8% vs 12.7% p < 0.0001,score of 4 or above. Were all higher in cases during the 180 days prior to the event date. After regression adjustment for cancer treatment, antihypertensive use and Charlson Comorbidity Index during the 180 days prior to event, calcium channel blockers were significantly associated with and increased risk of lymphedema (odds ratio: 1.320 95% confidence interval 1.003–1.737).
Conclusions: Calcium channel blocker use was significantly associated with lymphedema development in breast cancer patients compared to no use of calcium channel blockers.

723 | Incidence of depression and anemia among users of hormonal treatments for endometriosis - final results from the VIPOS study

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Background: Endometriosis is a chronic, gynecological condition characterized by pain and impaired fertility. Dienogest (DNG) 2 mg (Visanne) was approved for endometriosis treatment in 2010. The VIPOS study was part of the post-authorization safety and risk minimization commitment and was designed to assess the safety of DNG 2 mg in comparison to other hormonal treatments for endometriosis with a special focus on clinically relevant depression and anemia.

Objectives: To investigate the incidence of first-time occurrence or worsening of clinically relevant depression and anemia associated with endometriosis-related bleeding.

Methods: Large, prospective, controlled, non-interventional cohort study with active surveillance in six European countries (Germany, Poland, Hungary, Switzerland, Russia and Ukraine). Women with a new hormonal therapy for endometriosis were enrolled by gynecologists and specialized centers between 2010 and mid-2016. Information was collected via self-administered questionnaires at study entry and during follow-up until October 2018. Follow-up questions included information on current health status and further use of endometriosis treatment. All self-reported clinical outcomes of interest were validated by health care professionals.

Results: A total of 27,840 were included into the study, 11.7% of them users of DNG, 12.5% users of other approved endometriosis drugs (OAED) and 75.8% users of hormonal treatments not approved but frequently used for endometriosis treatment (NAED). The last interim analysis in May 2018 was based on 73,512 women years of observation. Overall, 103 depression cases occurred, thereof 12 in DNG users, 2 in OAED users, 52 in NAED users and 37 in Ex-users (women who stopped their endometriosis treatment more than 3 months before). In total, there were 146 anemia cases: 15 in DNG users, 11 in OAED users, 73 in NAED users and 47 in Ex-users. For both depression and anemia, we observed differences between the participating countries.

Conclusions: The VIPOS study will be the largest non-interventional cohort study investigating the risk profile of hormonal endometriosis treatment conducted to date. The final results will be presented at ICPE.

724 | The role of dose escalation in new users of lamotrigine inducing Stevens-Johnson syndrome/toxic epidermal necrolysis: Results from the German registry

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Background: Lamotrigine is known to have a high risk for Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). SJS/TEN are severity variants of a rare but life-threatening disease with common pathogenesis and etiology. It has been suggested that slow dose escalation of lamotrigine, as recommended by the manufacturer, can prevent SJS/TEN.

Objectives: To determine the impact of dose escalation in new users of lamotrigine on development of SJS/TEN.

Methods: The population-based German Registry on severe skin reactions ascertains all hospitalized SJS/TEN-cases in Germany since 1990. 103 SJS/TEN-cases with exposure to lamotrigine were identified between 1992 and 2018 in the Registry. 88 cases were validated as definite, 7 as probable and 8 as possible. We only considered probable and definite cases with recent exposure to lamotrigine in patients ≥12 yrs (n = 86) for this analysis and thus excluded 5 cases with long-term use and 4 children <12 yrs. Causality assessment was performed with a specific algorithm.

Results: 50/86 cases with SJS, 28 with SJS/TEN-overlap and 8 with TEN were analyzed. The median age was 43 yrs (12–91 yrs). Women (67.4%) were more often affected than men. 73 patients (85%) were diagnosed with epilepsy. 24 (27.9%) patients developed SJS/TEN while hospitalized; 23 (26.7%) reported a recent infection. Lamotrigine was considered to be the "very probable" cause in 67 (77.9%) cases, "probable" in 17 (19.8%) and "possible" in 2 (2.3%) cases. Comedication in the relevant time period with highly suspected and suspected drugs to induce SJS/TEN was 5.8% (5/86) and 15.1% (13/86) respectively. The mean number of concomitantly used drugs was 7 (0–59), for antiepileptic comedication 1 (0–7). The most common treatment indication was epilepsy/seizure (87.2%), followed by psychiatric disorders (10.5%). Mean time latency from beginning of lamotrigine use to reaction onset was 23.5 days. We evaluated the dosing regimen for 75 patients with complete medication and dosing history considering the initial dose and dose escalation. In 10 cases, a lower initial dose compared to *lege artis* dosing led to a prolonged time to onset of the reaction (29.9 vs 21.8 d). In particular, 2 patients developed SJS/TEN despite a very low dose of 5 mg/d for 4 weeks.

Conclusions: No relevant differences in terms of reaction severity and overall outcome could be observed with respect to the dosage regimen. However, time to onset was longer when the starting dose was low. These results suggest that the applied dosage regimen is not the decisive factor for triggering SJS/TEN.

725 | Cutaneous allergy as potential long-term effect of hormonal intrauterine systems

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Background: As part of the research aimed at real-world performance, we are exploring new sources of evidence as well as new approaches to predictive device evaluation. Implantable/insertable devices (*e.g.*, intrauterine system - IUS) may result in foreign body responses involving allergic/immune mechanisms. Our previous analysis (ICPE 2018) showed that the likelihood of allergic/inflammatory skin conditions may be increased among inpatient women with IUS removals *vs*. insertions.

Objectives: In this project, we used a claims database to explore the risk of cutaneous allergic conditions among outpatient women.

Methods: We used the Truven Health Analytics MarketScan database to review all outpatient claims from women (aged 15–44) with continuous enrollment from 2008 to 2014. We constructed a cohort with any claim for IUS in 2009, as the populations exposed to either

levonorgestrel-(LNG) IUS or copper-IUS for contraception. As controls, we used a random sample of age-matched women with no IUS use as well as a group with any oral contraceptive use (OC). Cutaneous allergic conditions (Atopic Dermatitis, Eczema, Allergic Urticaria and other Urticaria) were defined per ICD9 codes. After comparing conditions in the baseline year (2008) to 5 years post insertion (2010–2014), we estimated the odds ratios (OR) and confidence intervals (CI) for having cutaneous allergic conditions, controlling for covariates (age, geographic region, urban), other conditions (*e.g.*, diabetes, obesity, smoking, asthma), and presence of allergic conditions at baseline.

Results: Of 8,013,682 eligible women (per 2009), 2.3% had outpatient claims for IUS use. The study cohort was comprised of 10,632 women with 5-year enrollment and either copper-IUS (*N* = 1,454) or LNG-IUS (*N* = 9,169) inserted in 2009. Women using no IUS (*N* = 21,246) and women using OC (*N* = 20,758) formed two comparison groups. Baseline characteristics of all study groups and controls were similar. Logistic regressions showed that, after controlling for baseline characteristics and potential confounders, claims for cutaneous allergic conditions were more frequent among LNG-IUS (but not copper-IUS) users compared to non-IUS users: OR = 1.111 [95% CI: 1.039; 1.187]. No significant difference for cutaneous allergy was found for women using LNG-IUS *vs.* OC.

Conclusions: Hormonal IUSs may slightly increase risk of cutaneous allergy, as shown by the analysis of out-patient women exposed to different contraceptives. Claims data can be suggested as a potential source of pre-existing data that can support evaluation of real-world performance of medical products.

726 | Population-level impact of low-dose aspirin on the prevention of cardiovascular disease, colorectal cancer and safety outcomes in Europe: A micro-simulation model

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Background: Evidence indicates that low-dose aspirin is effective in preventing cardiovascular disease (CVD) and colorectal cancer (CRC), but also increases the bleeding risk. Understanding the population-level impact of low-dose aspirin use is important for informed decision-making.

Objectives: The study aims at simulating the population-level impact of regular low-dose (75–150 mg/day) aspirin use on CVD (myocardial infarction and ischemic stroke), CRC and major bleeding among individuals eligible for primary or secondary CVD prevention in the UK. This abstract summarizes the methodological approach followed.

Methods: Individual-level state transition modeling based on a discrete-step multi-state model (micro-simulation) is used to model the impact of regular low-dose aspirin use on CRC, CVD, and safety events: gastrointestinal bleeding (GI), intracranial hemorrhage (ICH), and symptomatic peptic ulcers (sPU). Individual event histories are simulated for a hypothetical cohort of 1 million adults aged 50–59 and 60–69 years each who are eligible for aspirin use for primary or secondary CVD prevention. Each age cohort is simulated twice with and without low-dose aspirin regular usage. Model parameters are informed based on published scientific literature. Monte Carlo simulation is used to reflect the uncertainty in the input parameters. Multiple scenarios are investigated. The model is developed mimicking the UK epidemiology and prevention guidelines.

Results: The model allows for the simulation of the incidence of study outcomes in cohorts of low-dose aspirin users and non-users, stratified by age and type of CVD prevention. Baseline analysis of 50–59 year old subjects not using low-dose aspirin indicates $596x10^3$ CVD events, $41x10^3$ CRC events, $59x10^3$ GI bleeding events, $11x10^3$ ICH events, and $21x10^3$ sPU events for 1 million subjects with an average follow-up time of 17.6 years.

Conclusions: Modeling through simulation is increasingly used to inform public health and regulatory decision-making. This micro-simulation model constitutes a novel approach to further elucidate the expected benefits as well as risks of low-dose aspirin at the population level.

727 | Safety of dietary supplements use among cancer patients: A systematic review of clinical trials

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Background: Dietary supplements (DS) are commonly taken by cancer patients, but safety of DS use among cancer patients remains unclear.

Objectives: To review the literature regarding safety of DS use among cancer patients systematically.

Methods: A systematic literature search was conducted using PubMed, Clinicaltrial.gov, International Pharmaceutical Abstracts and Alt HealthWatch databases from their inception through October 2018. The included literature was limited to clinical trials published in English, with interventions including DS products in the market, and including outcome measures related to safety endpoints of DS use. Evidence was reviewed by two researchers independently.

Results: Sixty-five studies met inclusion criteria and were included in the review. Use of DS was examined among patients with multiple or unspecified (18), breast (10), colorectal (9), gastrointestinal (GI) and esophageal (7), prostate (6), liver (3), pancreas (3), leukemia (3), head and neck (3), lung (1), skin (1), and thyroid (1) cancer. Botanical DS (12), vitamins (8) and probiotics and synbiotics (7) were the top 3

types of DS evaluated in these trials. While most of studied DS were found to be safe among breast cancer patients, magnesium oxide and alpha lipoic acid products were associated with higher incidence of diarrhea, nausea, and GI related adverse events (AEs). Among patients with colorectal, pancreas, and thoracic esophageal cancer, those using probiotics or synbiotics had significantly lower incidence of infection compared to the control group (n = 6). While most of the trials found vitamin D or vitamin E was safe and tolerable, two studies showed that high doses of vitamin D_3 (10000 IU/d) and vitamin E (3200 mg/d) were associated with more AEs. Use of omega-3 fatty acids supplements had mixed results among different types of cancer patients, with 1 study showing its association with reduction of AEs but other 5 studies showing insignificant results. Among 19 trials including different cancer patients undergoing chemotherapy, most (n = 17) of studied DS (e.g., vitamins, botanical, omega-3 fatty acid) were found to be safe.

Conclusions: While most types of DS appeared safe, this systematic review found limited evidence in the safety of DS use among cancer patients. Cancer patients and their healthcare providers should monitor potential sides effects associated with DS use and its marginal benefits on patient's health conditions carefully. More research using large-scale, rigorous clinical trials is needed to examine the safety of DS use among cancer patients.

728 | Population based estimates of community based adverse drug reactions (ADRs) in the Kingdom of Saudi Arabia

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Background: Adverse drug reactions (ADRs) represent important preventable causes of mortality, morbidity, hospitalization and increased healthcare costs. Traditionally, ADRs are studied in a clinical setting, but it is also important to estimate rates of ADRs in the community.

Objectives: The current study aimed to estimate population-based rates of ADRs in the community in the Kingdom of Saudi Arabia (KSA).

Methods: Nationwide cross-sectional survey was conducted via registered pharmacists at community pharmacies across the 13 regions of KSA. This study used a weighted national sample of KSA community members presenting to community pharmacies for advice or to make a purchase. The data were collected on an electronic online platform and included questions about participants' demographics, health characteristics, experience with ADRs within the last 12 months and assess their knowledge about Saudi Food and Drug Authority reporting system. Descriptive analysis for ADR rates, sample demographics, clinical characteristics, and ADR patterns was conducted. The survey package was used to develop weighted rates with 95% confidence intervals (CI).

Results: Data collection was conducted between June and August 2018. Data from 5,228 surveys were analyzed. After weighting, the national annual rate of ADRs was estimated to be 28.00% (95% CI 26.10% -30.00%). The following chronic diseases were statistically significantly associated with ADR status: high blood pressure, high cholesterol, diabetes, chronic lung disease-asthma and emphysema, kidney disease, and gastrointestinal diseases. The most common ADRs symptoms reported were gastrointestinal disorders, and these were experienced by over 60% of women experiencing ADRs and over 50% of men experiencing ADRs in the last year. General disorders and administration site conditions were also relatively high, with over 18% of men and over 21% of women experiencing ADRs over the last year reporting these symptoms. The largest group of medications reported causing ADRs (38%) fell in many disparate classes. The largest classes reported for causing ADRs were Nonsteroidal antiinflammatory drugs (NSAIDS) (11%), anti-bacterial medications (10%), antihypertensive medications (9%), and oral hypoglycemics (9%).

Conclusions: The results of this population-based estimates of community-based ADRs nationally in KSA showed that more than one-quarter of the population had experienced ADR in the last 12 months. Future study is needed to better understand why these rates are higher in some regions than others, and what is needed to prevent high rates in the subgroup populations.

729 | Mortality due to adverse drug reactions: An analysis of an international pharmacovigilance database

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Background: Adverse drug reactions (ADRs) are a leading cause of death. ADRs are the fourth commonest cause of death after heart diseases, cancers and stroke.

Objectives: The aim of this study was to evaluate the mortality related to ADRs spontaneous reported, in an international pharmacovigilance database and compare the data between areas.

Methods: An extraction of Vigibase, which contains World Health Organization individual case safety reports (ICSRs), was performed. We included, in our study, all reports registered until the December 31, 2018 with the preferred term (PT) “death”. Demographic characteristics of reported cases were evaluated. Geographic variations were also assessed.

Results: Of the 18,446,691 ICSRs reported to Vigibase, 378,025 were death cases. Mean age was 62 +/− 20.2 years with a sex ratio male/female of 1.07. The majority of patients was over 65 years old (31%), across age groups 45–64 (17%), 18–44 (7.6%) and under 18 years (2.3%). Most reports came from America (84%) and from Europe (11%). The most suspected drugs were: fentanyl

(*n* = 16,574), oxycodone (*n* = 15,868), morphine (*n* = 13,976), oxycodone/paracetamol (*n* = 12,537), hydromorphone (n = 12,439). In Europe, the first incriminated drugs were: darbepoietin alfa (*n* = 2,329), clozapine (n = 1,609), warfarin (n = 1,462), leuprorelin (*n* = 924) and zoledronic acid (*n* = 681). The results of Oceania were similar to those of Europe, including clozapine in the first place. The mortality of the pediatric population under two years old represented 1% of the worldwide data and, also, in Europe. In France, in this population, the data showed high prevalence (3%) corresponding to data observed in Africa, particularity in South Africa (3.1%).

Conclusions: ADRs are an important cause of mortality. In our study, the main drug class involved was opioids. This study showed heterogeneity between the different areas. Analysis by age group indicated a relation between the PT "death" and increasing age. Comparing the developing countries, France has the highest percentage of mortality in children under two years old. Some drugs require a reassessment of their benefit/risk ratio.

730 | Evaluation of ethnic differences in incidence of severe cutaneous adverse reactions in east Asians

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Background: Functional genetic polymorphism which affects drug responses is one of important intrinsic factors causing ethnic differences. For example, allopurinol-related severe cutaneous adverse reactions (SCARs) are known to be associated with HLA-B*58:01, of which allele frequency (AF) is largely different among East Asians. However, evidence on ethnic differences in SCARs and relevance of genetic factors among East Asians are still limited.

Objectives: To evaluate ethnic differences in incidence of SCARs and relevance of genetic factors in East Asians.

Methods: We conducted retrospective cohort studies using claims databases in Taiwan, Korea, and Japan; the Health and Welfare Database (HWD) in Taiwan, the Health Insurance Review and Assessment Service (HIRA) database in Korea, and the Japan Medical Data Center (JMDC) claims database in Japan. We selected allopurinol as a target drug, and phenytoin or carbamazepine as a control drug because the differences in AFs of those functional genetic factors of phenytoin or carbamazepine for SCARs are little or much smaller than allopurinol among East Asians. The outcome was the first hospital admission for SCARs including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms during the follow-up period. Crude incidence rates (IRs) of SCARs in allopurinol new users were calculated and compared with those in phenytoin or carbamazepine new users. Crude incidence rate ratios (IRRs) of SCARs were used for evaluation of ethnic difference to cancel out the potential regional differences in diagnostic criteria, and compared with authentic values of AFs.

Results: Crude IRs (95% confidence intervals: CIs) of SCARs in allopurinol users were 2.57 (2.37–2.79), 2.31 (2.30–2.31), and 2.00 (1.24–3.21) per 1000 person years in Taiwan, Korea, and Japan, respectively. The crude IRRs (95%CIs) comparing to phenytoin were 0.63 (0.56–0.72), 0.34 (0.29–0.40), and 0.037 (0.016–0.083), and the IRRs comparing to carbamazepine were 1.22 (1.01–1.47), 0.82 (0.59–0.61), and 0.16 (0.087–0.29) in Taiwan, Korea, and Japan, respectively.

Conclusions: The order of crude IRRs of SCARs, Taiwan > Korea > Japan, was in accordance with the order of the AFs of HLA-B*58:01, 0.101, 0.061, and 0.004 in Taiwan, Korea, and Japan, respectively. Our results suggest that ethnic differences in functional genetic factors might contribute to those for SCAR development among East Asians. Further studies are also needed to evaluate contribution of other non-genetic factors to the ethnic differences.

731 | Medication related hospital admissions to a tertiary care teaching hospital: A prospective cross sectional study

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Background: Increasing availability and usage of medicines can cause medication related problems (MRP) leading to hospitalization and often affecting morbidity and mortality rates.

Objectives: To determine the incidence, nature, and risk factors associated with medication related admissions and their severity and preventability.

Methods: A prospective cross sectional study design was adapted. All those patients admitted due to MRP to the departments of emergency, medicine, pediatrics and dermatology were enrolled over a period of six months. Hepler and Strand's classification of MRP was adopted. All the required data were collected and analyzed using standard descriptive analysis and the risk factors were assessed by using Chi Square test.

Results: of the 500 patients followed, 197 (39%) patients were admitted to the study site due to medication related problems. Males predominance was observed [*n* = 105 (53%)]. Majority of patients' were presented with diabetes [*n* = 97 (49%)] and hypertension [*n* = 77

(39%)] as prevalent comorbid conditions. The most common type of MRP was failure to receive the drugs [*n* = 119 (60%)] followed by adverse drug reactions [*n* = 58 (29%)]. Metformin with glimepiride [*n* = 24 (9%)] followed by insulin [*n* = 18 (7%)] were most commonly implicated drugs. Majority [*n* = 102 (51%)] of these patients had a hospital stay of 3–5 days. The severity of MRPs was observed to be moderate [*n* = 189 (96%)] followed by severe [*n* = 8 (4%)]. Majority [*n* = 167 (85%)] of MRPs were preventable. Polypharmacy, non-adherence, comorbidities were found to risk factors.

Conclusions: The incidence of Medication related hospital admission was high due to polypharmacy, non-adherence, and comorbidities. While, majority of these problems were deemed to be preventable, appropriate use of medications can reduce the medication related hospital admissions.

732 | Frozen in time; contemporizing generic labels

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Background: In April 2018, the FDA commissioner noted that for generic drugs specifically, safety information may not be necessarily up to date. Generic drug labels may get "frozen in time" if the Innovator withdraws from the market leaving only the generic applicants to submit label updates. A key component of optimal product use is adequate and up to date label content that provides the essential information necessary for the safe and effective use of the drug as per relevant available data. Pfizer acquired a number of generic sterile injectables licensed in multiple markets worldwide following an acquisition of a generic company in 2015.

Objectives: To develop a consistent approach and process to contemporize the safety sections of owned sterile injectable labels by use of a core safety document.

Methods: A project team was assembled to create or update an internal document containing Core Safety Information (CSI) and to harmonize safety content of labels, which were dependent on a CSI. Label comparisons to identify differences among the labels and prepare a CSI and accompanying justification document based on safety information in the different local labels were prepared. The relevant information was then integrated into local labels if missing. Redundant and/or repetitive information and concepts, and descriptions of likely routine practice of medicine were not included in the CSI. Standard agreed upon language across products was utilized for concepts such as Driving & use of machines, *Clostridium difficile* diarrhea (for anti-infectives), and Hypersensitivity. Justification data sources included published medical literature and in some circumstances the Pfizer safety database. A Pfizer safety database review was conducted for ADRs that met predefined statistical criteria applied to World Health Organization's safety database.

Results: A total of 29 CSIs were reviewed and 255 updates were incorporated into Contraindications, Warnings and Precautions, Overdose, Drug interactions, Pregnancy and lactation or ADR sections.

Conclusions: A consistent process for the development and maintenance of CSIs for generic products to ensure contemporary labeling is possible.

733 | Prospective cohort study of adverse drug reactions on all admissions to internal medicine: Prevalence, incidence and risk factors

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Background: Adverse drug reactions (ADRs) constitute major clinical burden of public health concern. Intensive adverse drug reactions monitoring in hospitals, though advocated are rare.

Objectives: This study aimed at the intensive monitoring of medical patients for ADRs to assess prevalence, incidence, risk factors and fatality of ADRs leading to hospital admission or occurring in the hospital.

Methods: Prospective cohort observational study on adult patients admitted to the six medical wards of a tertiary institution over a 12 month period. Each patient was assessed for ADRs throughout admission. Patient's demographics, all drugs administered one month prior to admission, on admission and prescribed on discharge were recorded. Statistical analysis included independent T-test, Chi-square test, 95% confidence interval, $p = 0.05$ was taken as significant.

Results: One thousand two hundred and eighty patients admitted to the medical wards were enrolled in the study. Sixty-six patients (5.2%) had adverse drug reactions, which was the cause of admission in 46 (3.6%) while 19 (1.6%) developed ADRs during admission. Seventy ADRs occurred in these 66 patients and involved 43 drugs. NSAIDs (23.3%), antibiotics (20.9%), antituberculosis drugs, glucose lowering drugs and herbal remedies 6.9% each were the most common. Monthly income ($p < 0.001$), and alcohol use ($p = 0.042$) significantly impacted on the occurrence of ADRs. Risk factors for ADR were alcohol use ($\chi^2 = 4.148$, p = 0.042) in patients, polypharmacy, self-medication and cognitive impairment in the elderly. Patients with ADRs stayed longer on admission, 15 days versus 12 days ($p = 0.029$) and though not significantly were more likely to be older 49.3 versus 49.2 years (F = 0,003, $p = 0.956$), females 5.8% versus males 4.8% ($\chi^2 = 0.512$, $p = 0.474$), ingested more medications prior to admission and on admission (4.2 versus 3.8; F = 0.486, $p = 0.486$, 95% CI -1.296 to 0.516 and 7.2 versus 6.8; F = 0.327, $p = 0.567$, 95% CI -1.364 to 0.549) but were discharged with fewer medicines (3.9 versus 5.1; F = 0.145, $p = 0.703$, 95% CI -0.012 to 2.481). Most ADRs were GIT

complications 27/70 (38.6%), cutaneous 14/70 (20.0%), neurological 17/70 (24.3%). Most reactions (71.2%) were adduced to known pharmacological properties of the drugs. Most, 79% patients with ADR fully recovered, 13% died while 7% had prolonged hospital stay.

Conclusions: ADRs involved prescription drugs, and self-medication in this study. Alcohol use was a major risk. Efforts to curtail the menace should include health education and prohibition of sales of prescription drugs without proper prescription.

734 | Real world data Pharmacoepidemiological study on the prevalence of potential drug–drug interactions in Thessaloniki, Greece

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Background: Drug–drug interactions may lead to severe clinical outcomes concerning patients' health, thus posing a serious threat to various fields of Public Health. The above phenomenon is worsened when the number of interactions is risen.

Objectives: The goals of this study are to determine the prevalence of potential drug–drug interactions (pDDIs) among patients of community pharmacies, to shed light on the factors responsible for the growth of this problem and to estimate the probability of major clinical outcomes.

Methods: Data of 24.200 e-prescriptions (2012–2017) were anonymously obtained from community pharmacies of Thessaloniki, the second biggest city of Greece, including gender, age, number of doctors visited, administered medicines and the purchase date. We chose by chance 1.000 patients per year, who were taking 2 or more drugs simultaneously for more than 3 months. For this purpose, the raw data were processed and filtered with specific criteria using R programming language, excluding drugs administered for less than 3 months and nonprescription medicines and patients taking only 1 drug. The first 1.000 patients from each year were isolated and by listing their medicines on the online Drug Interaction Checker of the F.D.A., pDDIs were categorized depending on their clinical significance as major and moderate. The results were analyzed statistically with the IBM SPSS Statistics v.15.0 program using descriptive statistics, chi-square and odds ratios (ORs).

Results: 1307 major pDDIs (185 unique) were found between 17.4% of the patients. Analyses about the APIs, that are most frequently causing major pDDIs, showed that statins are responsible for their occurrence on 8.23% of the patients (6.98% due to simvastatin). Studying pDDIs' clinical outcomes, 8.18% of the patients had increased risk of suffering from major myopathy. Furthermore, while a pDDI occurred in only 5.6% of the patients taking 2–3 drugs, this percentage rose to 16.1% for 4–6 drugs and to 42.5% for more than 7 drugs (p = 0.000). Lastly, age over than 65 years old and number of prescribing doctors greater than 4 proved to be risk factors for the occurrence of pDDIs, both for men (OR 1.642, 95% CI: 1.3–2.1, p = 0.000) and for women (OR 1.943, 95% CI: 1.1–3.6, p = 0.02).

Conclusions: The percentage of patients with at least one major pDDI, compared to that of other developed Western countries like Switzerland (pDDIs between less than 2% of the population), is really high, which needs to be under severe analysis from the Ministry of Health. Additionally, polypharmacy proved to result in increased possibility of emergence for major pDDIs.

735 | Patient exposure during pre-market trials and relationship with post-market safety outcomes

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Background: Drug exposure substantially increases after approval allowing for identification of new risks. The relationship between patient exposure in pre-market clinical trials and post-approval safety label changes is not well understood.

Objectives: To characterize pre-market exposure for New Molecular Entity (NME) and Original Therapeutic Biologic (OTB) and its relationship to post-market safety outcomes.

Methods: We evaluated pre-market exposure and regulatory characteristics for NMEs and OTBs approved by FDA between 10/1/02 and 12/31/14 using publicly available FDA documents. We recorded the number of patients in the clinical development program included in the FDA- defined safety population and the number exposed for 6 months (6 M) and 12 months (12 M). Descriptive statistics were used to describe the safety population, and 6 M and 12 M for products intended for long term use. Post-market safety outcomes sere defined as a safety-related withdrawal or safety-related update to the *Boxed Warning*, *Contraindications*, *Warnings and Precautions*, *Adverse Reactions* or *Drug Interactions* sections of the label. We evaluated the relationship of defined quartiles of the safety population to regulatory pathways and post-market safety outcomes using chi square/Fisher's exact tests. Continuous variables were analyzed using Wilcoxon test.

Results: 339 products (278 NMEs, 61 OTBs) were included in our study. The median size of the safety population was 947 with no change over time. NMEs had more pre-market exposure than OTBs (median: 1057 vs 880, p = 0.04). 111 (33%) were orphan products. The median exposure was lower in orphan compared to non-orphan products (524 vs 1806, p < 0.001). The median size of the safety population was significantly smaller for fast track designation (599 vs 1396, p < 0.001), priority review (612 vs 1662, p < 0.001), and accelerated approval (505 vs 1148, p < 0.001). Expedited programs were associated with a smaller safety population size for non-orphan, but not for orphan products. 236 products were intended for long term use; data was available for 6 M in 176

and 12 M in 169 products. 127 (72%) met the ICH guidelines for 6 M (≥300 participants) and 127 (75%) of the drugs met the ICH guidelines for 12 M patient exposure (≥ 100 participants). The quartiles that had larger safety population size were more likely to have post-market safety outcomes ($p < 0.001$).

Conclusions: Orphan drugs and expedited programs are associated with varying pre-market exposures. The median size of pre-market exposure has not changed over time. Larger safety population size was associated with an increase in post-market safety outcomes.

736 | Adverse drug reactions on female fertility: A study in VigiBase

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Background: Few studies have investigated drug effects on female fertility.

Objectives: We conducted a descriptive study investigating adverse drug reactions (ADRs) on female fertility reported in VigiBase®.

Methods: Vigibase® is an international Pharmacovigilance database created in 1960 and holding over 16 million of ADRs. All reports of ADRs on female fertility registered on VigiBase® between 1967 and December 2017 were analyzed. Female infertility reports were identified using the MedDRA specific terms: "infertility" and "female infertility".

Results: Among the 16,074,663 safety reports registered in VigiBase®, 1,806 ADRs (0.1‰) on female fertility were reported from 1967 to December 2017 in VigiBase®. Notifications increased over time since 2008. Patients are mostly between 20 and 40 years old, a period corresponding to a desire of maternity. ATC classes of drugs involved in female infertility were "genitourinary system and sex hormones" ($n = 928$ cases, 51.4%), "antineoplastic agents and immunomodulating agents" ($n = 359$, 19.9%) and "nervous system" ($n = 146$, 8.1%). The most cited "suspected" drugs were levonorgestrel (25.9%), medroxyprogestérone (8.5%), étonogestrel (5.8%), éthinylestradiol (5.1%), diéthylstilbestrol (3.4%), etanercept (2.5%), vaccine HPV (2.1%), adalimumab (2.0%) and drospirenone (1.6%).

Conclusions: This study found some drugs already known to impair female fertility, like alkylating agents and diéthylstilbestrol. More interesting, the present work described signals for drugs not known to induce this ADR.

737 | The characteristics of drug information inquiries in an Ethiopian University hospital: A two year prospective observational study

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Background: The types of drug-related information request from patients and health professionals, the extent of inquiry and capability of existing drug information centers are seldom studied in Ethiopia.

Objectives: This study aimed to identify the types and characteristics of drug information inquiry at Gondar University specialized Hospital (GUSH), Northwest Ethiopia.

Methods: A prospective observational study was employed from January, 2016 to December, 2017 at Drug Information Center (DIC) of GUSH. The drug information query was collected by distributing the drug information queries in different hospital units through 2 batches of graduating undergraduate pharmacy students. Descriptive statistics were used to describe, characterize and classify drug related queries. Binary logistic regression was employed to identify predictor variables to the type of drug related queries submitted to drug information center.

Results: A total of 781 drug related queries were collected and 697 were included in the final analysis. Near to half (45.3%) of queries comes from the pharmacists followed by general practitioner medical doctors (11.3%) and nurses (10.2%). Slightly greater than half of the queries (51.9%) were focused on therapeutic clinical information. 39.6% of drug related queries related to infectious disease case scenarios, followed by cardiovascular cases in 21.3% of queries. More than half of (53.9%) and nearly one in five (19.4%) of the queries took 5 to 30 minutes and 30 minutes to 1 hour of literature searching to answer, respectively. Pharmacists (with odds ratio of 2.474(95% CI 1.373, 4.458)) and patients (with odds ratio of 4.121(1.403–12.105)) ask patient-specific questions in their drug related queries higher than other group of health professionals.

Conclusions: In conclusion, pharmacists are the primary drug information users and frequent drug related information inquirers at the DIC. Most of the queries targeted therapeutic indications, adverse drug events, infectious or cardiovascular disease related requests. Drug information services can assist the growing pharmacist's role in patient care and addressing patient specific drug related needs.

738 | Validation of maternal self-reported pregnancy complications using web-based questionnaires in a prospective cohort study

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Background: Evidence for the validity of maternal self-reports of common pregnancy complications is conflicting and these reports have not been validated for web-based questionnaires yet.

Objectives: To validate data on gestational diabetes, gestational hypertension, and preeclampsia from web-based questionnaires administered during pregnancy and two months after delivery.

Methods: We included 1,809 women who participated in the PRegnancy and Infant DEvelopment (PRIDE) Study and gave birth in 2012–2017, for whom the relevant data were complete. Sensitivity,

specificity, and positive and negative predictive values of self-reported diagnoses of gestational diabetes, gestational hypertension, and preeclampsia were determined using obstetric records as reference standard. Furthermore, we determined whether maternal characteristics affected the disagreement between the questionnaires and obstetric record.

Results: For gestational diabetes and preeclampsia, we observed very few false positive and false negative reports, yielding sensitivities of 93% (95% confidence interval [CI] 86–100) and 88% (95% CI 79–98), respectively, and specificities of 100%. The positive predictive values (PPV) were 91% (95% CI 90–92) and 88% (95% CI 87–90). Depending on the definition of gestational hypertension, sensitivity ranged from 62% to 89% with PVVs of 64% and 88%. The odds of disagreement on gestational hypertension seemed to be lower for women 25–29 years of age (odds ratio [OR] 0.6, 95% CI 0.3–1.0), with low/intermediate education (OR 0.6, 95% CI 0.3–1.1), and/or having had one or more previous births (OR 0.5, 95% CI 0.3–0.9).

Conclusions: We showed that maternal self-reports of preeclampsia and gestational hypertension in web-based questionnaires are valid. Gestational hypertension seemed to be of somewhat lower validity due to relatively high numbers of false positive reports, but it is questionable whether an appropriate reference standard exists to validate this pregnancy complication.

739 | Validation of a comorbidity index for use in obstetric patients: A Nationwide cohort study

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Background: A previously developed Obstetric Comorbidity Index has been validated in highly selected cohorts. Validation of the index in an unselected population as well as in other health care settings is, however, of high importance to determine external validity.

Objectives: To validate the Obstetric Comorbidity Index by examining the tool's ability to predict the incidence of maternal morbidity (end-organ injury) or death.

Methods: Using the Danish National Birth Register, we formed a nationwide cohort including completed pregnancies (both live and stillborn) in Denmark (2000–2014) linked to the National Patient Register. Maternal age and 20 comorbid conditions were assessed and weighted. Outcomes were maternal end-organ injury or death within 30 days postpartum. The predictive and discriminative ability of the index was estimated by Brier score and the area under the receiver operating characteristic curve, respectively. Logistic regression analysis was used to estimate odds ratios (OR) with 95% confidence interval (CI).

Results: In 876,496 completed pregnancies by 527,079 women, 1.40% (*n* = 12,314) experienced an outcome. The majority of women (64.1%) did not have any record of a condition included in the Obstetric Comorbidity Index, 35.6% scored 1–6, and only 0.3% (*n* = 3,044) had a score > 6. The incidence of an outcome increased with increasing comorbidity score from 0.9% (95% CI 0.8–0.9) in women with a score of 0 to 10.4% (95% CI 7.6–13.9) in women with a score 9–10. The odds of the outcome increased by 41% (OR 1.41, 95% CI 1.39–1.42) with each one-point increase in the Obstetric Comorbidity Index. Compared to women scoring 0, the OR for experiencing the outcome increased with each increase in index category: Scoring 1–2 yielded an OR of 2.34 (95% CI 2.25–2.44), 3–4 an OR of 5.16 (95% CI 4.81–5.54), 5–6 an OR of 4.84 (95% CI 4.31–5.44), and 8–9 an OR of 7.97 (95% CI 6.54–9.72). The index had a Brier score of 0.01 and an area under the receiver operating characteristic curve of 0.64.

Conclusions: The Obstetric Comorbidity Index showed a moderate ability to discriminate and predict end-organ injury and death in a nationwide unselected cohort and performed in accordance with previous findings in other settings. These results suggest that the index may be a useful tool to control for confounding in health research and to identify women at high risk for adverse maternal outcomes.

740 | Social media monitoring on the safety of medication use during pregnancy: A case study from the Netherlands

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Background: An increasing number of women rely on the Internet for information about medication safety during pregnancy. Online pregnancy-related information is available through many sources, each with different levels of credibility. However, a complete overview of the quality and quantity of social media information available to pregnant women is lacking.

Objectives: To evaluate the availability and accuracy of social media content on the safety of medication use in pregnancy.

Methods: We performed a systematic search of posts related to medication safety during pregnancy in the Dutch language published on social media, blogs, and forums between May 2012 and April 2016 using Coosto, a tool for social media monitoring. The perceived safety in the posts was compared with the Dutch Teratology Information Service (TIS) safety classifications using descriptive statistics and logistic regression analysis.

Results: We included 1,224 online posts, which described 1,441 scenarios about medication safety in pregnancy. A total of 820 (57%) scenarios described were in line with the TIS classification. Incorrect perception was higher for prescription medication compared to medication available over-the-counter (odds ratio [OR] 4.6; 95% confidence interval [CI] 3.7–5.8). Furthermore, the safety classification of

medications with a TIS classification on strict indication or second line drugs (OR 46.1, 95% CI 28.1–75.4) and medications with insufficient knowledge on their safety during pregnancy (OR 10.1, 95% CI 6.8–15.0) was more likely to be incorrectly perceived by the public compared to medications considered safe during pregnancy according to the TIS.

Conclusions: Social media monitoring may be useful for surveillance of potentially unsafe use of medications in pregnancy. There is an abundance of social media posts related to the safety of medication use during pregnancy, but a large proportion of these posts provides inaccurate information. As this information may influence women's perceptions and decisions, accurate communication between healthcare providers and pregnant women regarding the benefits and risks of medications is vital.

741 | Implementation of ICD-10-CM Z3A% codes in real-world evidence studies of pregnancy outcomes

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Background: Healthcare claims databases are a source for real-world evidence and drug safety evaluation, but ICD-9 codes often cannot capture gestational age with sufficient accuracy. This limitation could impact the validity of database studies of pregnancy outcomes. The Z3A% code category is part of the ICD-10-CM codes that accurately describes gestational age and is required reporting for service reimbursement. We used administrative claims data to assess how often Z3A% codes are being used since the introduction of ICD-10-CM codes in October 2015.

Objectives: To assess potential implementation of new ICD-10-CM Z3A% code category as it pertains to better pregnancy clinical practices, by evaluating the occurrence of these codes in a large administrative claims database.

Methods: This study was conducted in the HealthCore Integrated Research DatabaseSM (HIRD), which contains claims data from across the US. The time period used in this study is between January 1, 2015, and October 31, 2018.

Results: An algorithm for defining pregnancy episodes based on pregnancy outcomes identified 408,236 female members between the ages of 15–49 years with at least one pregnancy outcome. Pregnancy outcomes were defined as codes in medical claims indicating specific pregnancy outcomes, i.e., live-birth, and still-birth; abortion which includes, elective abortion, spontaneous abortion, and miscarriage; and ectopic pregnancy. Among the identified live-birth, and still-birth cases, at least five unique Z3A% codes were reported for 95.57%, while for the identified abortion and ectopic, the percentage of reporting was 85.63% and 80.86%, respectively.

Conclusions: The proper designation of the gestational age of any pregnancy is integral to improving mother and child maternal health outcomes. It is imperative for maternal research to accurately determine the start of any pregnancy for situations like assessing drug exposure, as incorrect assessment may lead to inaccurate drug safety profiles for use during pregnancy. Our results show the extensive use of Z3A% codes even at the beginning of any pregnancy. These findings prove to be fruitful for future maternal research, specifically for drug safety surveillance during the time of pregnancy.

742 | Use of adverse events spontaneous reporting for drug safety surveillance in pregnancy

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Background: The U.S. FDA Adverse Events Reporting System (FAERS) database is used postmarketing spontaneous reporting surveillance of drug safety. However, the use of spontaneous reports for drug safety in pregnancy has serious limitations and remains unclear.

Objectives: To detect drugs associated with specific adverse pregnancy outcomes as signals among reproductive-age women who reported pregnancy outcomes with or without anticonvulsants.

Methods: We conducted data mining in U.S. FAERS database from 2008 to 2017. To minimize heterogeneities and potential confounding bias, the population was restricted to pregnant women aged 12 to 55 years old. Valproate was used as the exposure since it was one of the most common anticonvulsants with a known risk of malformations. To identify the reference groups, we first defined the use of non-valproate drugs in the entire pregnancy population as the reference group, and then restricted only the use of non-valproate anticonvulsants. We included only reports for the pregnancy outcomes to increase the comparability of the population in exposed and reference groups. The data mining algorithms including proportional reporting ratios (PRR) and reporting odds ratios (ROR) were estimated.

Results: A total of 75817 pregnancy outcomes were identified. Among them, spontaneous abortion was the most frequent outcome (11.66%), followed by ectopic pregnancy (3.20%), stillbirth (1.95%), and malformations (1.59%). Compared to non-valproate use, valproate use was associated with a malformation signal (PRR: 2.49; ROR: 2.56; the number of co-occurrences: 3.62). The association between valproate use and malformation remained significant after restricting the comparison to non-valproate anticonvulsants (PRR: 3.06; ROR: 3.14; the number of co-occurrences: 3.47). We did not find any signals of spontaneous abortion and stillbirth among valproate users as compared with non-valproate users and non-valproate anticonvulsant users separately.

Conclusions: We confirmed utility of US FAERS to detect valproate associated with malformations restricted the population to pregnant women of reproductive age. FAERS database may be a robust resource for surveillance of drug safety in pregnancy.

743 | Every mother counts: Target sample size estimates for pregnancy exposure registries

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Background: Pregnancy exposure registries (PERs) are often required as post-marketing commitments to prospectively collect safety information among women and their infants who may be exposed to medicines during pregnancy. Meaningful analysis is often limited by insufficient sample size. Enrollment challenges include lack of registry awareness, few patient-level benefits, limited medication use during pregnancy, and the ability to capture women early in pregnancy.

Objectives: With these known enrollment challenges, we demonstrate how varying the parameters for powered sample size calculations reach target enrollments beyond what is feasible for many of the exposures under study in PERs.

Methods: For an internal comparator, sample size was calculated in PASS v13.2 using Fisher's Exact test of two independent proportions. Assumptions of a minimum detectable risk ratio (RR) for major congenital malformations (CMs) ranging from 2.0–3.0 and a 1:1 ratio of exposed to unexposed patients were used with 80% power and alpha = 0.05. An additional calculation for a single proportion compared with the general population was performed using the same software and parameters, with the baseline prevalence of major CMs among live births in the general population set to 3%. A range of projected live birth rates (LBRs), in addition to accounting for loss-to-follow-up (15%), were applied to increase enrollment targets to achieve the number pregnancy outcomes needed.

Results: By varying the minimum detectable RR (2.0–3.0) and LBR assumptions (62% - 100%), PER enrollment targets ranged from n = 148 to n = 676 for comparison of risk of major CMs relative to the general population. PER enrollment targets to compare with an internal comparator cohort ranged from n = 328 up to n = 1545 per arm.

Conclusions: This exercise demonstrates that small variations in the assumed parameters for sample size calculations can greatly impact PER planning and commitments to regulatory agencies. PERs can be used as supportive evidence, considered with the broader safety and efficacy context reported across the clinical development portfolio. However, high enrollment targets impact study cost, timelines, analysis and interpretation of results, and come with ethical considerations. PERs are long-term obligations and in many PERs, sample sizes will not be reached despite best efforts. Without sufficient numbers of patients, the opportunity for adjusted analyses are limited. Sample size calculations, although useful, should be adapted to the nature of the underlying disease and anticipated exposure prevalence during pregnancy.

744 | Calculating prevalence of spontaneous abortion in pregnancy registries: Slippery slope

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Background: When studying drug safety in pregnancy, it is important to examine multiple outcomes, such as congenital anomalies, prematurity, small for gestational age, and spontaneous abortion (SAB). Calculating the prevalence of SAB (defined as spontaneous fetal loss before 20 weeks' gestation) is complicated due to varying times during gestation at which women enroll in registries and the natural variation of SAB by gestational age: SAB occurs at a higher prevalence prior to gestational week 12 and a lower prevalence after gestational week 14. To obtain an accurate estimate of SAB, it is critical to examine SAB as a function of gestational age at enrollment. If SAB is an outcome of interest, the prevalence should be calculated among women enrolled prior to 20 weeks' gestation, and, if feasible, using survival analysis to account for varying gestational age at enrollment and censoring at 20 weeks' gestation.

Objectives: To examine the robustness of pregnancy registry methods for the calculation of SAB prevalence.

Methods: Registries were identified from multiple sources: FDA website, clinicaltrials.gov, and PubMed. Data were gathered on primary and secondary outcomes of interest and methods for calculating SAB prevalence. Data were analyzed descriptively.

Results: The search identified 21 pregnancy registries with published results. For those with multiple publications, the most recent was included. Eight of 21 focused exclusively on congenital anomalies and did not report SAB except 4 which descriptively reported SAB in a frequency distribution of pregnancy outcomes. For 13 of the 21, SAB was listed as a primary or secondary outcome. These registries calculated SAB prevalence using a variety of methods. Nine of the 13 calculated SAB prevalence as the number of SABs over the total number of pregnancy outcomes; prevalence ranged from 2.2% to 11.8%. Three registries calculated the SAB prevalence as the number of SABs over the subset of pregnancies enrolled prior to 20 weeks' gestation; the prevalence was 3.4%, 8.6%, and 9.4%. Only 1 registry used a survival function accounting for gestational age at enrollment and censoring at 20 weeks' gestation; the prevalence was 3.9%.

Conclusions: This study found wide variability in reported SAB prevalence and the methods used for calculation. Most registries calculated SAB prevalence based on all women regardless of gestational age at enrollment which leads to spurious SAB prevalence. Three registries appropriately limited the calculation to pregnancies enrolled prior to 20 weeks' gestation, and only 1 used survival analysis to account for varying gestational age at enrollment and censoring.

745 | Development of pregnancy identification and trimester algorithm in US claims data

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Background: Using administrative claims databases to examine medication use during pregnancy is challenging due to limited information available to estimate the timing of exposure. The pregnancy start date is not routinely recorded in claims and gestational age is not always available. Claims data algorithms are needed to accurately identify women exposed to medications during pregnancy and time periods of exposure.

Objectives: To create a standard method of identification of pregnancies in US Marketscan using ICD-9, ICD-10 and procedure codes.

Methods: Women 10 to 64 years of age from 2014 and 2016 were identified in Marketscan Commercial and Medicaid. Algorithms were developed; medical codes, including ICD-9, ICD-10 and CPT codes, were identified and assigned (1) an estimated trimester (2) pregnancy outcome (3) and pregnancy start and end date.

Results: Three challenges arose in development of the algorithm. Conflicting trimester codes, conflicting outcome codes and/or conflicting gestational age occurred on the same day or within 30 days of each other. Hierarchy algorithms were created to reassign these codes. Estimated trimester codes were classified into four tiers ranging from most to least specific trimester time period and assigned to the code in the lowest tier. Second, if a record had a gestation weeks code, the weeks were used to calculate the correct trimester for those with conflicting codes either before and/or after. Then, the frequency of trimester codes was assessed and those with the most instances was used. To assign pregnancy outcomes, a set of rules was created to address conflicting outcomes occurring within 30 days of each other. For example, a record could not have an ectopic pregnancy and a delivery on the same day. In this instance ectopic pregnancy was assigned a priority in the hierarchy and thus classified as an ectopic pregnancy. A hierarchy was created for all types of pregnancy losses and deliveries. Finally, to identify start and end dates of the pregnancy, ICD-10 and ICD-9 codes that identified gestation weeks were used, if multiple codes occurred, the latest claim date was used as the maximum number of gestation weeks. Outcome and trimester specific codes were then used to calculate start and end dates. This algorithm identified 97.42% of pregnancy claims with a start and end date.

Conclusions: Medical coding inconsistencies need to be addressed to ensure an algorithm is valid. Using hierarchy algorithm to systematically resolve conflicting codes allowed for trimester, birth outcome and start and end dates to be assigned. Study funded by GSK 208777.

746 | Timing of routine prenatal screening tests relative to the last menstrual period estimated from an ICD-10 based algorithm

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Background: Accurate estimation of the last menstrual period (LMP) is essential in pregnancy studies. Several chart validated ICD-9 based algorithms of varying complexity and accuracy are available to estimate the LMP in administrative claims data. These methods anchor estimates of LMP on the presence of pregnancy outcomes, which may result in a potentially biased pool of pregnancies used for a study. A new code category in ICD-10 (Z3A) specifically ties medical encounters to the pregnancy weeks of gestation. The validity of these codes in estimating the LMP is not yet fully described.

Objectives: To characterize the timing of routine prenatal screening tests relative to the estimated LMP derived from an ICD-10 based algorithm.

Methods: Using the Optum Dynamic Assessment of Pregnancies and Infants (DAPI) database, pregnancies of women who were enrolled in their health plan from at least 6 months prior to the beginning of pregnancy through the end of their pregnancy were identified from January 2016 through December 2017. For each pregnancy, LMP was estimated by subtracting the number of specific weeks from the first observed Z3A code. Gestational weeks of pregnancy were calculated relative to the estimated LMP, and the proportion of pregnancies with at least one claim for each of the prenatal screening tests was estimated, per gestational week. Results were compared with clinical guidelines for routine prenatal care of low-risk pregnancies to assess concordance. Non-specific Z3A codes (Z3A.00, weeks of gestation of pregnancy not specified and Z3A.01, less than 8 weeks gestation of pregnancy) were not utilized.

Results: A total of 139,993 pregnancies were observed in the 2-year study period. From 22,724 pregnancies with at least 1 claim for pregnancy-associated plasma protein A (PAPP-A), 77% occurred between 11–14 weeks gestation. 49,564 pregnancies had a claim for Alpha-fetoprotein (AFP) test, 70% of which occurred between 15–20 weeks gestation. The glucose screening test was observed in 104,195 pregnancies, 60% occurring between 24–28 weeks gestation, and the Streptococcus B screening test was observed in 32,351 pregnancies, of which 75% occurred between 35–37 weeks gestation.

Conclusions: A high proportion of pregnancies with at least 1 claim for each of the prenatal screening tests had testing performed within the recommended weeks of gestation based on clinical guidelines, showing that utilization of the first observed Z3A code may allow for accurate estimation of the LMP in administrative claims data.

747 | Evaluation of a pregnancy and trimester algorithm in US claims data

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Background: Creation of algorithms to identify pregnancies and trimesters in automated health care claims databases is important to study medication use and pregnancy outcomes. Comparing new algorithms to existing ones and external benchmarks assesses how the algorithm performs.

Objectives: To compare percentages of select medications in pregnancy, overall and by trimester, and selected pregnancy outcomes obtained from a newly created algorithm to external data and published literature.

Methods: A pregnancy and trimester algorithm, which utilized gestational code and pregnancy outcome hierarchies, was used to identify the number of pregnancies among women aged 10–64, 2014–2016 in Marketscan Commercial and Medicaid respectively. Influenza, TDAP vaccine and anti-epileptic use in pregnancy and by trimester were calculated and compared to published literature. The prevalence of selected pregnancy outcomes, live births, C-sections, preterm, twin and multiple births were compared to US national rates and published literature.

Results: The percent of women with a code for TDAP vaccine during pregnancy was lower in Medicaid than in the Commercial population and differed by year. The distribution by trimester was similar across years. The overall estimates in pregnancy were in line with those from Sentinel Distributed network publication, though there wer differences in the 2nd and 3rd trimester distributions. The percent of pregnant women with a code for influenza vaccine differed in Medicaid and Commercial populations. The distribution of use was approximately equivalent across trimesters for both databases and consistent with published literature. The percentage of anti-epileptic medications was similar in Commercial and Medicaid as well as a Sentinel analysis, however distributions varied slightly by trimesters. The rates of live births from the Commercial population followed similar age trends to other privately insured population published rates. Medicaid had a larger proportion of live births in the younger age groups as would be expected given the population. In both Commercial and Medicaid, the rates of C-section, preterm, twin and multiple births were similar to 2016 CDC rates with the exception of a slightly lower preterm birth rate in claims data.

Conclusions: The information obtained from the newly created pregnancy algorithm was comparable to published estimates when used on a Commercial database. The rates of vaccine use in the Medicaid population and the population distribution make it difficult to use this data source as a basis of comparison to national data sources. Study funded by GSK 208777.

748 | Study of the Association of Uterine Perforation and IUD expulsion with breastfeeding and postpartum timing at IUD insertion (APEX IUD)—Study size estimation to actuality

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Background: The FDA required a study to determine the extent to which breastfeeding and timing of postpartum intrauterine device (IUD) insertion practices in the United States (US) are associated with risk of uterine perforation and IUD expulsion. Uterine perforation is an uncommon event: 1.3 cases per 1,000 IUD insertions, based on a prospective European cohort of 61,448 women. Therefore, adequate sample size to assess this outcome was critical for study feasibility. A validation study was conducted to ensure adequate sample size, availability of breastfeeding data, and validation of outcome variables in four US health care systems (3 Kaiser Permanente sites—Northern California, Southern California, and Washington state—and Regenstrief Institute in Indiana) The validation study data accrual ended September 30, 2015.

Objectives: We present the approach to projecting sample size and the estimated and actual sample sizes in APEX IUD.

Methods: The APEX IUD start of patient inclusion varies by site between January 1, 2001 and January 1, 2009; the end of patient accrual for all sites is April 30, 2018. The cohort and postpartum estimates for APEX IUD were based on the validation study's findings of the total number of women aged ≤50 with IUD inserted after a minimum 12-month look-back, the number of women with IUD inserted within 52 weeks postpartum, and the percentage of those who had a postpartum insertion with breastfeeding status available. Projections to estimate APEX IUD sample size involved including 31 additional months of patient accrual beyond the validation study timeframe; and, based on the validation study's results, estimating that 30% would have an IUD inserted within 52 weeks postpartum, and that 90% of those with an IUD insertion within 52 weeks postpartum would have breastfeeding data (exact percentages from validation study projected by site). The estimated and actual numbers of women in these categories are presented.

Results: Based on results from the validation study, the estimated number of women in APEX IUD with an IUD insertion was 264,706, those with insertion within 52 weeks postpartum was 79,412 and

with breastfeeding status available was 71,471. The actual numbers were 329,689, 98,576, and 95,529 respectively, about 25% higher than estimated.

Conclusions: The numbers in the validation study used to estimate sample sizes for the full-scale study provided a basis for study feasibility, but accounting for a higher trajectory of IUD use over time could have improved the projections.

749 | Prevalence of CYP2C19 genetic polymorphisms in 26 population affecting safety or efficacy of medications

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Background: Individual genetic make up may regulate drug responses. Genetic polymorphisms of *CYP2C19* may affect safety or efficacy of many clinically important medications.

Objectives: This study was aimed to determine the predictive phenotypes based on genetic polymorphisms of *CYP2C19*2,*3 and *17* variants collectively in 26 population participated in 1000 Genomes project. Subsequently, it was aimed to linking predicted phenotypes with the safety or efficacy of clinically important medications.

Methods: The genotype data were obtained from 1000 Genomes project Phase III in line with Fort Lauderdale principles. Based on the carrier of characteristics alleles, predictive phenotypes were assigned using international standardized consensus terms. International pharmacogenomics working groups such as clinical pharmacogenetics implementation consortium (CPIC) etc. guidelines were used to determine the association of predicted phenotypes with the safety or efficacy of clinically important medications.

Results: Out of the 2504 world population (26 population) participated in the 1000 Genomes projects (Phase III), 23.4% (95% CI 22%–25%) were predicted to be CYP2C19 Ultrarapid metabolizers (*CYP2C19*1/*17,*17/*17*), 47.6% (95% CI 46%–50%) of extensive metabolizers (*CYP2C19*1/*1*), 25.4% (95% CI 24%–27%) of intermediate metabolizers (*CYP2C19*1/*2,*1/*3,*2/*17,*3/*17*) and 3.6% (95% CI 3%–4%) of poor metabolizers (*CYP2C19*2/*2,*2/*3,*3/*3*). The predicted phenotypes may affect safety or efficacy of 39 clinically important drugs as outlined by different international pharmacogenomics working group. Of these, at least eleven drugs have dosing guidelines having strong evidence level based on the genetic variability of *CYP2C19*2, *3, or *17* that may need either alternative therapy or dose adjustments. Overall, ~52% of world population had predicted risk phenotypes in which at least 29% had high risk phenotypes potentially leading to either therapeutic failure or increased toxicities of standard therapy.

Conclusions: Genetic epidemiology of *CYP2C19* variants may potentially involved in drug safety or effectiveness. Translation of pharmacogenomics in the form of precision medicine into routine clinical practice is not too far away.

750 | Medication related problems among post-renal transplant patients at the renal unit of a referral Hospital in Kenya: A cross sectional study

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Background: Medication related problems are unwanted events or outcomes that may arise as a consequence of or lack of drug therapy. Post-renal transplant patients are at risk of medication related problems due to complex multiple medications they receive during therapy.

Objectives: To determine the prevalence, types and risk factors for medication related problems in adult post -renal transplant patients in a tertiary referral hospital in Kenya.

Methods: We conducted a cross sectional study of adult patients 18 years and older who underwent renal transplant and were on treatment and follow up at Kenyatta National Hospital, between July and September 2018. We excluded patients who were undergoing haemodialysis before and after renal transplant and pregnant women. Data were collected using a pretested questionnaire. Descriptive and bi-variable analysis was done. The Hepler and Strand Classification was used to identify and classify medication related problems.

Results: Fifty post renal transplant patients were recruited into the study. The prevalence of medication related problems was 100%. The most common types of medication related problems were adverse drug reactions (40%), failure to receive drugs (23%), and drug interactions (16%). Risk factors for development of medication related problems were pill burden (41%), non-adherence (25%), adverse reactions (17%), inability to afford medication (14%), and medicine stock-outs (3%).

Conclusions: All the patients in the study had one or more medication related problems. Comprehensive pharmaceutical care is required to reduce this prevalence.

751 | 20 years of major and minor malformations in Danish health registries: A descriptive study

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Background: The prevalence of congenital malformation over time may be an indicator for changes in environmental or lifestyle conditions that effect health. The characteristics of malformations and trends over time have not been systematically studied. Different overall prevalence rates of major malformations have been reported,

indicating differences in the quality of the underlying data, the definitions of malformations or different study periods.

Objectives: To describe the prevalence and changes in registration of malformations among liveborn singletons in Denmark from 1997 to 2016.

Methods: Using nationwide Danish registries, we identified all deliveries of liveborn singletons from January 1st, 1997 to May 31st, 2016 and followed these for 1 year. Within this population, we identified the 10 most commonly registered major and minor malformations, as well as the overall rate of malformations over time.

Results: We identified 1,179,956 liveborn singletons by 683,551 women during the study period. Of these, 59,466 newborns had a record of any malformation within the first year of life when using the Danish Medical Birth Registry alone (5.0%). Using EUROCATs definition of malformations, 35,942 (3% of liveborn singletons) had major malformations, and 29,877 (2.5%) minor malformations. Adding data from the Danish National Patient Registry (DNPR) these numbers increased to 39,322 (3.3%) and 31,895 (2.7%) respectively. The registration of major malformations ranged from 2.9% in 1998 to 4.1% in 2014, while minor malformations ranged from 1.6% in 1997 to 4.3% in 2014. During the 1-year follow-up in the DNPR, only 0.9% of children had a recording of a major malformation within 24 hours of delivery. By utilizing 1, 3, 6, and 12 months of follow-up data, this number increased to 1.5, 2.1, 2.4, and 2.8% respectively.

Conclusions: Within this nationwide cohort, 5.0% had a recorded diagnosis of a malformation. The prevalence of major and particularly minor malformations increased from 1998 through 2014. Completeness of malformation diagnoses increased when including data from both the Medical Birth Register and the DNPR. These trends in prevalence must be interpreted cautiously as they could reflect changes in reporting practices, improvements in quality of diagnostic tools, as well as represent true changes in the prevalence of malformations.

752 | In utero exposure to antibiotics and risk of congenital malformations: A population-based study

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Background: Antibiotics are commonly prescribed during pregnancy. While the safety of many penicillins are well established, the pregnancy safety evaluation of other common antibiotics suffers from inconsistent and inadequate data. Consequently, clinical decision support is largely insufficient and does not provide prescribing physicians information based on a reassuring level of evidence.

Objectives: To determine the risk of overall-, major-, and cardiac congenital malformations following first trimester in utero exposure to the 10 most commonly prescribed antibiotics in Denmark.

Methods: This was a cohort study comprising all singleton liveborn children in Denmark between 2000 and 2015. Merging validated and comprehensive population-wide Danish health-care and civic registries, we merged data on pregnancy, prescription drugs purchases during first trimester and congenital malformations. The exposed cohorts were compared to a cohort exposed to either of four penicillins (ampicillin, pivampicillin, benzylpenicillin, and phenoxymethylpenicillin) considered safe during pregnancy (primary analysis) and an unexposed cohort (sensitivity analysis). Using logistic regression, we calculated odds ratios (OR) for congenital malformations (any), major congenital malformations and cardiac congenital malformations for the 10 most commonly prescribed antibiotics (excluding the four penicillins that served as control). Covariate adjustments were made for maternal age at conception, year of delivery, pre-pregnancy BMI, parity, smoking, educational status, employment status and household income.

Results: We found no increased risk of congenital malformations related to first trimester in utero exposure to the 10 most commonly prescribed antibiotics in Denmark compared to a cohort of pregnant women exposed to penicillins that are considered safe during pregnancy. Compared to unexposed pregnancies, small increased risks for major malformations and cardiac malformations were apparent for pivmecillinam (aOR 1.13; CI 1.06–1.19 and 1.19; CI 1.08–1.31, respectively), sulfamethizol (aOR 1.15; CI 1.07–1.24 and 1.25; CI 1.10–1.41, respectively) and azithromycin (aOR 1.19; CI 1.02–1.38 and 1.29; CI 1.01–1.66, respectively).

Conclusions: In this large population-wide cohort study, we found no increased risk of congenital malformations following first trimester exposure to 10 commonly prescribed antibiotics: doxycyclin, amoxicillin, pivmecillinam, dicloxacillin, sulfamethizol, erythromycin, roxithromycin, azithromycin, ciprofloxacin and nitrofurantoin.

753 | Asthma medication use and risk of birth defects: National Birth Defects Prevention Study 1997–2011

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Background: Asthma affects 4–8% of pregnant women. Evidence regarding associations between asthma medication use during pregnancy and the risk of birth defects is mixed. Previous publications from the National Birth Defects Prevention Study (NBDPS) found associations between asthma medications and certain birth defects, including gastroschisis (based on 1997–2002 births) and oral clefts (based on 1997–2005 births).

Objectives: We estimated associations between early pregnancy asthma medication use (one month before through the third month

of pregnancy) and 52 specific birth defects using NBDPS data from 1997–2011.

Methods: The NBDPS was a population-based, multicenter, case–control study in 10 US states. Cases were identified via birth defects surveillance systems and controls were randomly sampled non-malformed, live-born infants from the same areas. Exposure information was collected from women via telephone interview. We analyzed early pregnancy asthma medication use and further grouped by most common types: bronchodilator use only, anti-inflammatory use only, or both. The reference group was women without asthma or asthma medication use during pregnancy. We used logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI), adjusting for maternal age, race/ethnicity, body mass index, smoking, folic acid-containing supplement use, and parity.

Results: In our analysis of 27,270 birth defect cases and 10,894 controls, 5% (n = 1,308) of case and 4% (n = 449) of control women reported early pregnancy asthma medication use. Of the exposed, 57% (n = 742) of case and 57% (n = 255) of control women reported using only a bronchodilator, 13% (n = 168) of case and 15% (n = 66) of control women reported using only an anti-inflammatory, and 24% (n = 317) of case and 24% (n = 109) of control women reported both. Early pregnancy bronchodilator use was significantly associated with choanal atresia (OR 2.19; CI 1.01–4.75), cleft palate (OR 1.52; CI 1.13–2.05), cleft lip (OR 1.63; CI 1.15–2.30), longitudinal limb deficiency (OR 2.28; CI 1.51–3.44), and truncus arteriosus (OR 2.43; CI 1.11–5.30). Early pregnancy anti-inflammatory use was not associated with any birth defect examined. Early pregnancy use of both types of asthma medications was associated with biliary atresia (OR 3.54; CI 1.53–8.19) and pulmonary atresia (OR 2.42; CI 1.05–5.57).

Conclusions: Early pregnancy asthma medication use was not associated with most of the 52 birth defects examined. We observed modestly elevated ORs for the association between bronchodilators and several birth defects, but did not confirm all previous findings.

754 | Phthalate exposure from drugs during pregnancy and risk of preterm birth and small for gestational age

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Background: Phthalates are thought to be endocrine disruptors and previous studies suggest that environmental phthalate exposure may increase the risk of preterm birth, whereas studies of phthalate exposure and birth weight have been contradictory and inconclusive. Phthalates are used as plastic softeners in consumer products such as cosmetics, food containers, toys, medication, and other soft plastics. Users of medicinal drugs have been shown to have up to 50-fold higher urine phthalate metabolite concentrations than the general population.

Objectives: To assess the effect of phthalate exposure from pharmaceutical drugs on preterm birth (PTB) and small for gestational age (SGA).

Methods: Using Danish nationwide health registries, we performed a case–control study nested within a cohort of 30,837 singleton deliveries from 2004 to 2015 who were exposed to ≥1 of 23 selected drug groups available in both phthalate-containing and phthalate free formulations. Using conditional logistic regression, we estimated associations between phthalate exposure and the risk of PTB and SGA. SGA was defined by INTERGROWTH-21st grow charts (SGA-I) and by Marsal's equation for expected birthweight (SGA-M).

Results: We included 1,965 PTBs, 1,315 SGA-Is, and 891 SGA-M cases, matched to 19,537, 12,008, and 7,573 controls, respectively. Ortho-phthalate exposure during the third trimester was positively associated with PTB with a crude OR of 1.36 (95% CI: 1.06–1.76). The association was mainly due to diethyl phthalate. No associations were found between ortho-phthalate exposure and SGA. Exposure to polyvinyl acetate phthalate and hypromellose phthalate in late pregnancy were associated with a risk of PTB with crude ORs of 5.13 (95% CI: 1.51–17.44) and 3.02 (95% CI: 1.21–7.50), respectively. However, the number of exposed individuals was low. No strong associations were found between cellulose acetate phthalate exposure and either PTB or SGA.

Conclusions: We found an increased risk of PTB with exposure to DEP and phthalate polymers used as drug excipients. As the use of phthalates as drug excipients is easily avoided (all drugs are already marketed in phthalate free versions), regulatory agencies should reconsider the use of phthalates in pharmaceuticals until their safety has been clarified.

755 | Estimating the causal effect of prenatal Lead on Prepulse inhibition: A prospective study in children and adolescents

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Background: During pregnancy, maternal lead from earlier exposures mobilizes and crosses placental barriers, placing the developing fetus at risk for lead exposure and neurodevelopmental deficits. Some neuronal circuits known to be affected in neurodevelopment disorders can be probed with simple physiological behavioral paradigms. One such neural biomarker is Pre-Pulse Inhibition (PPI), an indicator of adequate sensorimotor gating processing. In clinical studies, impairments in PPI have been associated with neurodevelopmental deficits in human subjects. To our knowledge, no studies have examined the

use of PPI as a biomarker of toxicant effects on the brain in epidemiological studies.

Objectives: We aimed to estimate the causal effect of prenatal lead exposure, as assessed by maternal cortical bone lead concentrations, on PPI in 279 children from Mexico City.

Methods: *In vivo* maternal cortical bone lead measurements were taken at four weeks postpartum at the mid-tibia shaft using a K-Shell X-ray fluorescence instrument. PPI recording occurred in an isolated clinical setting and eye blink responses were measured using electromyography. We assessed if the conditions for causal inference held in our study population and used the results of our assessment to estimate the effect of prenatal lead exposure on PPI using an ordinary least squares regression model, a marginal structural model, and the parametric g-formula.

Results: Results were consistent across the three modeling approaches. For the parametric g-formula, a one standard deviation (10.00 μg/g) increase in prenatal lead significantly reduced PPI by approximately 13.32% (95% CI: 2.12%, 25.48%).

Conclusions: In a population of children from Mexico City, we estimated the causal effect of prenatal lead exposure on PPI deficits. Our results are consistent with findings from other studies establishing an association between lead exposure and neurodevelopmental disorders in children and suggest that PPI may be useful as an objective biomarker of toxicant effects on the brain.

756 | Oral corticosteroids during pregnancy and offspring risk of congenital heart defects - a Nationwide cohort study

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Background: Pre-pregnancy diabetes is a strong risk factor for congenital heart defects (CHDs), suggesting a role for glucose in the causal pathway. Oral corticosteroids may cause hyperglycemia, and maternal use could affect embryonic heart development.

Objectives: The objective was to determine the association between maternal intake of oral corticosteroids 0–8 weeks after conception and CHDs in offspring.

Methods: A register-based nationwide prevalence study including all live singleton births, Denmark, 1996–2016 was conducted. In total 1,194,687 individuals and their mothers were identified and linked with information on CHDs and their mothers' use of oral corticosteroids in early pregnancy. Corticosteroid use was defined as a filled prescription for maternal use of oral corticosteroid 0–8 weeks after conception. CHDs were identified through International Classification of Diseases codes. The association was estimated by prevalence (odds) ratios using logistic regression and propensity score-matched analyses.

Results: Among 1,194,687 live births, 2,032 had a mother who had used oral corticosteroids 0–8 weeks from conception. Of these, 32 had a heart defect. Among offspring of never-users of oral corticosteroids, 10,534 had a heart defect. Adjusted prevalence ratio (PR) was 1.29, 95% confidence interval (CI) 0.90–1.84 comparing offspring prevalence of heart defects in oral corticosteroid users with that in oral corticosteroid never-users. Propensity score-matched analysis yielded similar results, PR 1.38, 95% CI 0.95–2.02.

Conclusions: This study does not support an association between maternal use of oral corticosteroids in the first 8 weeks after conception and CHDs.

757 | The safety of amoxicillin and Clavuladoodles#123nic acid use during the first trimester of pregnancy

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Background: Penicillins are widely used during pregnancy for various infectious indications, but the safety of use during pregnancy was not fully assessed.

Objectives: The goal of the current study was to assess the risk for major congenital malformations following first-trimester exposure to and amoxicillin and clavulanic acid (ACA).

Methods: A population-based retrospective cohort study was conducted, by linking four computerized databases: maternal and infant hospitalization records, drug dispensing database of Clalit Health Services in Israel and data concerning pregnancy terminations. Multivariate negative-binomial regressions were used to assess the risk for major malformations following first-trimester exposure, adjusted for mother's age, ethnicity (Bedouin vs. Jewish), parity, diabetes mellitus, lack of perinatal care (LOPC) and the year of birth.

Results: The study included101,615 pregnancies, of which 6,919 (6.8%) were exposed to amoxicillin: 1,045 (1.0%) to amoxicillin only, and 6,041 (5.9%) - to ACA. No significant association was found, in both univariate and multivariate analysis, between first-trimester exposure to amoxicillin or ACA and major malformation in general (Crude OR = 1.05 95%CI 0.95 to 1.16, Adjusted OR = 1.09 95%CI [0.98 to 1.20) or for major malformations according to organ systems. No dose–response was found between exposure in terms of the defined daily dose (DDD) and major malformations.

Conclusions: Exposure to amoxicillin and ACA during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations.

758 | Maternal early pregnancy use of specific antidepressant medications and risk for birth defects

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Background: Antidepressants are commonly used to treat depression and anxiety. Data on individual antidepressant medication safety during pregnancy are relatively limited.
Objectives: To examine associations between maternal use of commonly prescribed antidepressant medications during early pregnancy (1 month before through the third month) and specific birth defects.
Methods: We used data from the NBDPS, a U.S. multicenter, population-based case–control study (1997–2011). Cases were from active birth defects surveillance systems; controls included liveborn infants without major defects. Medications were examined if used by >0.2% of control mothers in early pregnancy, and included sertraline (1.1%), fluoxetine (0.7%), paroxetine (0.4%), bupropion (0.4%), citalopram (0.3%), escitalopram (0.3%), and venlafaxine (0.2%). We used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between each medication and birth defects with ≥4 exposed cases, controlling for maternal education, race, smoking, and pre-pregnancy body mass index. We compared early pregnancy-exposed women to those who were unexposed to an antidepressant in the three months before or during pregnancy, and to account for treated indication, women who reported antidepressant use only outside of the early pregnancy period.
Results: Sertraline was associated with 6/38 defects (highest aOR: some types of double-outlet right ventricle (aOR: 3.3, 95% CI: 1.2–9.3)). Fluoxetine was associated with 11/33 defects (highest aOR: Dandy Walker malformation (aOR: 4.0, 95% CI: 1.4–11.2)). Paroxetine was associated with 7/27 defects (highest aORs: total anomalous pulmonary venous return (aOR: 4.0, 95% CI: 1.4–11.3); anencephaly (aOR: 3.0, 95% CI: 1.3–7.1)). Of 25 defects examined, bupropion was associated with spina bifida and diaphragmatic hernia. Of 24 defects examined, citalopram was associated with one defect. Escitalopram had no increased risk for the 21 defects examined. Venlafaxine was associated with an increased risk for 16/20 defects, with aORs for seven defects >3.0. Controlling for treated indication attenuated associations for many defects, although new associations were seen for some medication and defect combinations, and most associations between venlafaxine and individual defects remained.
Conclusions: Except for escitalopram, each of the antidepressant medications was associated with some birth defect risk. These results may assist healthcare providers in counseling women about the safest antidepressant treatment options during pregnancy.

759 | Effect of N-acetylcysteine supplementation on women undergoing assisted reproductive techniques: A systematic review and meta-analysis

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Background: N-acetylcysteine (NAC) possesses antioxidant, mucolytic and insulin-sensitizing properties, and has been proven to be a reasonably good candidate as a supporting therapy in women undergoing assisted reproductive techniques (ART).
Objectives: To determine the effect of NAC supplementation on women undergoing ART.
Methods: A systematic review and meta-analysis study was conducted on randomized controlled trials (RCTs) which compared the effect of NAC supplementation with placebo or no treatment on women undergoing ART. An electronic search was done on PubMed, EMBASE, Cochrane and Ovid databases which included data till December 2018. This search was limited to articles conducted on humans and published in English. The estimation of ovulation rate and pregnancy rate were the primary outcomes of this study. However, the miscarriage rate and multiple pregnancies were the secondary outcomes. The results were presented in an odd ratio (OR) with heterogeneity and confidence intervals (95% CI).
Results: Nine RCTs, in accordance with the inclusion criteria, were considered, which involved 1617 women for meta-analysis. It was observed that NAC supplementation was associated with an increased ovulation rate (I^2 = 60%; 3.62; 95% CI, 1.80 to 7.27) and pregnancy rate (I^2 = 69%; 1.94; 95% CI, 1.04 to 3.64) when compared to placebo or no treatment. Although there was no significant association with miscarriage (I^2=0%; 0.94; 95% CI, 0.56–1.55) and multiple pregnancy (I^2 = 29%; 1.13; 95% CI, 0.33–3.81).
Conclusions: Evidence has suggested that NAC supplementation may be beneficial to increase the ovulation rate and pregnancy rate in women undergoing ART. However, high quality of evidence is required to confirm these results.

760 | In utero opioid exposure and risk of ADHD in childhood: A Scandinavian registry study

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Background: Prescriptions for opioid analgesics increased sharply over the past two decades. Knowledge about long-term consequences of *in utero* exposure to opioids is scarce.
Objectives: The aim of this study was to examine the association between prenatal exposure to opioids and risk of ADHD in childhood

a) in population of women with a history of chronic opioid prior to pregnancy and b) among short- and long- term opioid users.

Methods: We used data from nationwide health registers in Norway and Sweden, and linked data using personal identification numbers. We identified exposure to opioids (ATC code N02A) from the Prescription Databases. ADHD was identified as an ADHD diagnosis (ICD-10 F90) in specialist health care system or at least one ADHD drug dispensed. a) Among women with chronic opioid analgesic exposure one year prior to pregnancy start (n = 6 202), we compared those who continued to use opioids during pregnancy (filled 30 Defined Daily Doses (DDD) or more during pregnancy) (n = 3178) with discontinuers (no opioid prescriptions during pregnancy) (n = 3024). b) We studied dose–response by comparing long-term (30 DDD or more) (n = 8224) with short-term (less than 30 DDD) (n = 38 578) analgesic opioids in-utero exposure. We followed the cohorts of live born infants up the age of ten years. The association between exposure and the cumulative risk of ADHD was analyzed using Cox proportional hazard regression, with attained age as the time scale. Inverse probability of treatment weights based on the propensity scores was applied to adjust for measured confounders.

Results: a) The mean follow-up time after age of three was 3.3 years in the exposed group and 3.4 years in the discontinuers. There were 110 ADHD cases (3.5%) in the opioid exposed group and 61 (2.0%) in the discontinuer group. The unadjusted HRs for the risk of ADHD was 1.77 (95% Confidence Interval 1.29 to 2.41). After adjustment the HR decreased to 1.16 (0.72 to1.85). b) In the comparison between short and long term use of opioids during pregnancy the unadjusted HRs for the risk of ADHD was 1.77 (1.51 to 2.08). After adjustment the HR decreased to 1.43 (1.18 to1.72).

Conclusions: We did not observe increased risk of ADHD among children of women who used opioids long-time during pregnancy when compared with children of opioid discontinuers. Analysis of dose–response indicated increased risk among long-term exposed when compared to short-term exposed. Short-time users may use small amounts of opioids and be quite similar to the general pregnant population. Increased risk of ADHD in long term compared to short term exposed children might thus be a result of residual confounding.

761 | Outcome measurement in pregnancy exposure registries: A preliminary review of publicly available resources

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Background: Pregnancy exposure registries (PERs) can improve medication safety information for mothers and their infant(s) and can be used to update drug labeling. Accurate outcome measurement is critical. Currently there are no standardized recommendations to measure pregnancy and infant outcomes, leading to possible variation across PERs.

Objectives: To review and describe outcome measurement elements for PERs conducted in North America and Europe.

Methods: We reviewed publicly available information from the U.S. Food and Drug Administration List of Pregnancy Exposure Registries, ClinicalTrials.gov, and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance E-Register of Studies. Protocols or other posted materials were reviewed from ongoing, completed or terminated registries through Jan. 2019; planned studies were excluded. We extracted primary/secondary outcomes, infant follow-up time, and reporting sources (e.g. patients, healthcare providers [HCPs]) as well as exposure details that influence outcome measurement (e.g. medication class, lactation-based exposure). Descriptive statistics were calculated using SAS 9.4.

Results: Our initial search yielded 357 entries. We then restricted to prospective registries and after excluding planned registries, we examined 78 PERs in North America (n = 53), Europe (n = 7), or both regions (n = 14) (missing n = 4). Among 69 PERs with available primary objectives, 76.8% included congenital malformations (major and/or minor) as the primary outcome; 29.0% included spontaneous abortion, and 23.2% included stillbirth. Few PERs (5.8%) included outcomes of lactation-based exposure in the objectives. Median follow-up time for infant across registries was 1 year (range: 0–18 years). Over half (56.4%) followed infants for ≥1 year after delivery. The most common exposure medication class was monoclonal antibody (25%). Planned sample size for ongoing registries (N = 56) varied from 1 to 10,200 patients (median 363). Among 44 PERs with posted information, 24 (54.5%) included HCPs as reporters for infant outcomes.

Conclusions: We observed variability in outcome ascertainment across publicly available resources. A large proportion of PERs included congenital malformations as a primary outcome; however, just over half followed infants for ≥1 year after delivery. Sample size and follow-up length varied substantially. HCPs were not universally included as reporters. As registering PERs is voluntary, our results may not be generalizable to PERs that are not currently publicly listed.

762 | Risk of early neurodevelopmental outcomes associated with prenatal exposure to antiepileptic drugs: A Nationwide cohort study based on the French National Healthcare Databases

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Background: Valproate is known to be a cognitive and behavioral teratogen. However, evidence for most of the 'newer' antiepileptic drugs (AEDs) is still limited.

Objectives: To assess the association between prenatal exposure to monotherapy with the most commonly used AEDs other than valproate during pregnancy and the risk of various neurodevelopmental outcomes.

Methods: This cohort study was based on the French national healthcare databases, which cover 99% of the 67 million inhabitants in France. The cohort included children born alive between 2011 and 2014 and prenatally exposed to an AED in monotherapy. Women were considered to be exposed to an AED during the 30 days following each dispensing. Children prenatally exposed to lamotrigine were used as the reference group. Outcomes included neurodevelopmental disorders (NDDs), defined using long term diseases and hospital discharge diagnoses with ICD-10 codes F70 to F98 - pervasive developmental disorders (F84) and mental retardation (F70-F79) were studied separately - and visits to a speech therapist. Children were followed up until outcome, loss to follow-up, death or 31 December 2016. We performed inverse probability of treatment weighting analyses using the propensity score, which included maternal (age, socioeconomic status, psychiatric history, comedications...) and infant (gender, gestational age and birth weight) characteristics. Hazard ratios (HRs) were then calculated using Cox models.

Results: The cohort included 9,034 exposed children, with a median follow-up of 3.7 years. Of these, 2,916 were exposed to lamotrigine, 1,627 to pregabalin, 1,246 to clonazepam, 621 to levetiracetam, 502 to carbamazepine, 477 to topiramate, 378 to gabapentin and 143 to oxcarbazepine. None of the studied AEDs were associated with increased risks of neurodevelopmental outcomes compared with lamotrigine (e.g. levetiracetam and NDDs: 8 cases, HR = 0.7 [0.3–1.5]; pregabalin and NDDs: 28 cases, HR = 0.6 [0.4–1.0]). Similar results were observed among children of women considered treated for epilepsy. Furthermore, the expected positive association between valproate and NDDs or visits to a speech therapist was confirmed in this cohort.

Conclusions: This nationwide cohort study based on claims data provides reassuring results for all AEDs except valproate. Because of the small numbers of cases, these results should be interpreted with caution. In addition, due to the nature of the neurodevelopmental outcomes investigated, a longer follow-up is necessary to confirm the findings.

763 | Fetal outcomes associated with maternal asthma: Evidence from a large healthcare database in the United States

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Background: Asthma complicates between 3% and 10% of pregnancies. Consequently, drugs used to treat asthma have become among the most commonly prescribed medications in pregnancy. Poor maternal asthma control has been associated with worse pregnancy outcomes. However, results have been inconsistent and often from small and selected samples.

Objectives: To quantify the risk of fetal and neonatal adverse events associated with asthma during pregnancy in a large population, with a focus on asthma severity and control.

Methods: This study was conducted within the Truven MarketScan Commercial Claims and Encounters Database for 2011–2015. Asthma was identified by diagnoses and treatments, severity was based on medications dispensed, and control was based on hospitalizations, emergency room admissions, and rescue oral corticosteroid dispensations. We estimated the relative risks (RRs) of stillbirth, spontaneous abortion, preterm birth (PTB), small for gestational age (SGA), neonatal intensive care unit admission (NICUA), and congenital malformations, comparing pregnancies with differing asthma status, severity, and control. Log-binomial generalized linear models were used to adjust for socio-demographics, lifestyle factors, and comorbidities.

Results: Among 1,026,743 eligible pregnancies, we identified 29,882 pregnancies (2.9%) with asthma. Among these, 17% had severe asthma and 24% had poorly-controlled asthma. Neither asthma (vs. no-asthma) nor severity was associated with any of the outcomes considered; and we observed no meaningful associations between asthma control and pregnancy losses, SGA, or major congenital malformations. However, compared to women with controlled asthma, pregnancies with poorly-controlled asthma were more likely to result in PTB (RR = 1.30; 95% confidence interval 1.08–1.56) or NICUA (RR = 1.24; 1.02–1.51). When we stratified by asthma severity, the RRs associated with poor control were greatest among women not taking asthma control medications.

Conclusions: Maternal asthma during pregnancy was associated with an elevated risk of PTB and NICUA only when it was poorly controlled. We did not observe associations between asthma severity, based on medications received, and adverse fetal outcomes. Funding: GSK (206948).

764 | Risk of attention deficit hyperactivity disorder in childhood after exposure to serotonergic antidepressants in pregnancy

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Background: The time-dependent effect of prenatal exposure to serotonergic antidepressants on attention deficit hyperactivity disorder (ADHD) risk remains unresolved.

Objectives: To quantify the effect of time-varying prenatal exposure to serotonergic antidepressants on ADHD risk in childhood, as clinical diagnosis and parent-reported symptoms.

Methods: We used data from the Norwegian Mother and Child Cohort Study, the Medical Birth Registry, the Prescription Database, and the Patient Registry of Norway, limited to women with depressive/anxiety disorders in pregnancy. The windows of self-reported antidepressant exposure were mid (week 16–28) and late pregnancy (> week 28). Symptoms of ADHD at 5 years were parent-reported via the Conners' Parent Rating Scale-Revised; ADHD diagnoses were retrieved from the specialist health care system, the Patient Registry (ICD-10 F90). We fit general linear and Cox marginal structural models (MSM) to account for time-varying exposure and confounders (depressive/anxiety symptoms as measured by SCL, co-medication with other psychotropics and analgesics), and time-fixed maternal and paternal factors.

Results: We included 3232 pregnancy-child dyads within women with self-reported depressive/anxiety disorders in pregnancy. Overall, 481 (14.9%) children had been prenatally exposed to serotonergic antidepressants and 90 children (2.8%) had a clinical diagnosis for ADHD. Relative to children born to women with non-medicated depression/anxiety (n = 2751), those exposed to serotonergic antidepressants in mid (weighted HR: 1.74, 95% CI: 0.41–7.15) or late pregnancy (weighted HR: 1.66, (0.41–6.82)) did not have an increased risk for an ADHD diagnosis. Likewise, there were no differences on symptoms of ADHD according to timing of exposure (midpregnancy: weighted β: -0.02, 95% CI: −0.30, 0.34; late pregnancy:weighted β: −0.04, (−0.32, 0.25)).

Conclusions: In a population of children born to women with depressive/anxiety disorders in pregnancy, there was no evidence for a substantial association between prenatal exposure to serotonergic antidepressants at different timings in pregnancy, and risk for ADHD symptoms and diagnosis. However, we were unable to confirm or refute whether a smaller increased risk exists.

765 | Prenatal antibiotics use and the risk of attention deficit hyperactivity disorder

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Background: Prenatal antibiotic exposure induces changes in infants' gut microbiota composition and is a possible contributor in the development of Attention-Deficit/Hyperactivity Disorder (ADHD).

Objectives: In this study, we examined the association between prenatal antibiotic exposure and the risk of ADHD.

Methods: This was a population-based cohort study that included 187,605 children born in Manitoba, Canada between April 1, 1998 and March 31, 2017. Exposure was defined as having filled one or more antibiotic prescription during pregnancy. The outcome was ADHD diagnosis identified in hospital abstracts, physician visits or drug dispensations. Risk of developing ADHD was estimated using Cox proportional hazards regression models in a high dimensional propensity scores-matched cohort and an exposure-discordant sibling cohort. Several sensitivity analyses were planned to test the robustness of the risk estimates.

Results: A total of 102,974 children were included in the matched-cohort. During a follow-up of 1,098,717 person-years, 9717 (9.4%) children received an ADHD diagnosis. Prenatal antibiotic exposure was associated with increased ADHD risk (HR 1.14, 95% CI 1.09–1.19). The highest risk was observed in those receiving 3 or more antibiotic courses or for a duration longer than 2 weeks (HR 1.37, 95% CI 1.19–1.58 and HR 1.28, 95% CI 1.16–1.42, respectively). In the sibling cohort of 64,019 children, prenatal antibiotic exposure was associated with a small increase in the risk of ADHD, though it was not statistically significant (HR 1.06, 95% CI 0.98–1.14).

Conclusions: Prenatal antibiotic use appears to increase the risk of developing ADHD. However, much of this risk may have been overestimated as a result of unmeasured confounding by genetic and shared familial factors. Cautious interpretation of study finding is warranted.

766 | The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis

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Background: Past studies assessing whether exposure to interferon-beta during pregnancy can adversely affect foetal development have been inconclusive, although evidence leans toward no association. Adverse pregnancy outcomes such as spontaneous abortion have been the focus of many studies, however foetal development can also be assessed through birth measurements accounting for gestational age, which will be used as outcomes in this study.

Objectives: To assess whether infants of women with multiple sclerosis (MS) exposed to interferon- beta show evidence of smaller size at birth relative to infants of women with MS which were not exposed to any MS disease modifying drugs (DMDs).

Methods: All pregnancies to women with MS between 2005 and 2014 in Sweden and Finland were identified using register data. For this study, only births with a record of birth weight, height, and head

circumference were included. Exposure was defined as having occurred if an ATC code indicating a dispensation of interferon-beta was recorded in the 6 months prior to last menstrual period up until the end of pregnancy. Generalized estimating equations, which used mothers' ID number as a cluster, were used with continuous measures of birth weight, height, and head circumference included as the outcomes in separate models.

Results: Of pregnancies to women with MS in Sweden, 427 pregnancies were exposed to interferon-beta, and 974 unexposed to any MS DMDs. The corresponding numbers for Finland were 233 and 331 respectively. Infants prenatally exposed to interferon-beta were on average 36 grams heavier (p = 0.16) in Sweden, and 50 grams lighter (p = 0.26) in Finland than those unexposed. For birth height, those exposed to interferon-beta were 0.03 cm longer (p = 0.81) in Sweden, and 0.03 cm shorter (p = 0.87) in Finland compared to those unexposed. For head circumference, those in Sweden had measurements 0.16 cm larger (p = 0.05) and in Finland 0.21 cm smaller (p = 0.17) relative to those unexposed.

Conclusions: This study provides evidence that exposure to interferon-beta during pregnancy does not adversely affect foetal growth in infants of mothers with MS exposed to IFN beta.

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767 | Determinants of missing or delayed prenatal screening in Florida, New Jersey, and Texas Medicaid populations 1999 to 2010

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Background: Prenatal screening can detect and attenuate pregnancy complications, but limited evidence exists regarding determinants of missing or delayed prenatal screening in the Medicaid population.

Objectives: To examine prevalence and determinants of missing or delayed prenatal screening in Florida, Texas, and New Jersey Medicaid populations during 1999–2010.

Methods: We conducted a retrospective cohort study using the 3-state Medicaid Analytic eXtract data linked to birth certificates. Mothers had to be enrolled from ≥1 year before last menstrual period (LMP) to delivery date. Evaluated outcomes were missing aneuploidy screening (AS, defined as missing all of these tests: nuchal translucency measurement, pregnancy associated plasma protein A, human chorionic gonadotropin, alpha-fetoprotein, estriol, and inhibin-A tests), missing or delayed (>20 gestational weeks) first anatomical ultrasound (AU), missing group B streptococcus test among term and post-term deliveries (GBS), and missing or delayed (>28 weeks) first gestational diabetes screen (GDS). To evaluate GDS, we excluded mothers with diabetes diagnosed before LMP. Candidate determinants were maternal sociodemographic and clinical conditions based on the Centers for Medicare and Medicaid Services' hierarchical condition categories and assessed during one year prior to LMP. Stepwise selection and generalized estimating equation models were used to identify determinants for each outcome.

Results: A total of 65,477 deliveries were included (64,186 deliveries without diabetes diagnosis before LMP). We observed a high proportion of missing AS (29%) and GBS (30%), and a high proportion of missing or delayed AU (44%) and GDS (49%). Non-Hispanic Black, maternal age < 18 years (except for GBS), receiving cash subsidy, having previous pregnancy with no or minor complication, newborn, or having serious perinatal complications, and having drug or alcohol disorder within one year before LMP were associated with a larger proportion of missing or delayed screening for IPS, AU, GBS, and GDS. Mothers enrolled in Medicaid due to disability or poverty, with previous ectopic, molar, miscarriage, or terminated pregnancy, and a variety of chronic and acute disease conditions were significantly likely to have less missing or delayed screening.

Conclusions: Important determinants of having missing or delayed IPS, AU, GBS, and GDS were identified and highlight significant disparities in screening involving socio-economic and clinical factors.

768 | Prevalence of ectopic pregnancy among an under-represented population in electronic health records: Results of the 2011–2015 National Survey of family growth

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Background: Ectopic pregnancy (EP) is a rare yet significant contributor to maternal morbidity and mortality in the United States (US). Due to changes in management and a shift from inpatient to outpatient care, traditional surveillance data cannot be used to validly quantify EP rates. Electronic health record (EHR) data do not produce representative estimates of the disease rate at national levels as it does not identify or capture all women at risk of EP including non-users of any contraceptive methods and uninsured women.

Objectives: To assess the prevalence of EP among subpopulations of women at risk of pregnancy not represented in EHR systems including women who are non-users of any contraceptive methods and uninsured women between 2011 and 2015 in the US.

Methods: We utilized data from the 2011–2013 and 2013–2015 National Survey of Family Growth, conducted by the Centers for

Disease Control, which captures a nationally representative sample of women aged 15 to 44 years in the US. The study population included women who were at risk of pregnancy. Information regarding pregnancy outcomes, method of contraceptive use, reproductive history, and surrogates of socioeconomic status were used. Crude and age-standardized EP prevalence and corresponding 95% confidence intervals (CIs) were estimated.

Results: A total of 6,029 women were enrolled to the study. 562 women were non-users of any contraception. Sixteen percent (1,115/6,029) of the study population did not have health insurance. EP was reported in 29 women, six of which were among non-users of contraceptives. Age standardized EP prevalence was 0.5% (0.3%, 0.9%) for all and 0.5% (0.2%, 1.5%) for non-contraceptive users. EP prevalence among uninsured and insured women (private and Medicaid/government) was 0.7% (0.4%, 1.5%) and 0.5% (0.2%, 1.0%), respectively.

Conclusions: Results of this study shows comparable EP risk among populations under-represented in EHR. The complexity of capturing accurate information on disease and sexual habits further adds to the need for innovative approaches that can accurately capture such information and estimate disease burden at the national level.

769 | Preconception use of asthma medication and Fecundability: A prospective study

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Background: Asthma is a chronic inflammatory disease of the lungs. It has been associated with irregular menses and infertility in some studies, but there are limited data on the relation between asthma medication use and fecundability.

Objectives: We used data from Pregnancy Study Online (PRESTO), a North American preconception cohort study, to examine the association between asthma diagnosis and medication use with fecundability.

Methods: During 2013–2018, we enrolled 6,868 female pregnancy planners who had been trying to conceive for ≤6 cycles at entry. Participants completed a baseline questionnaire and bimonthly follow-up questionnaires for up to 12 months or until pregnant. At baseline, participants reported if they had ever been diagnosed with asthma and their asthma medication use in the past four weeks.

Results: We used proportional probabilities models adjusted for factors such as socio-demographics and comorbidities to estimate fecundability ratios (FR) and 95% CIs. The referent for all comparisons was women without an asthma diagnosis. Overall, 1,149 women (17%) reported an asthma diagnosis, of whom 395 (34%) reported use of asthma medication in the past four weeks. Of those who used asthma medication, 60% reported use when having symptoms, 22% reported daily use, and 18% reported daily use plus more when having symptoms. Overall, an asthma diagnosis had little association with fecundability (FR = 0.98, 95% CI: 0.90–1.06). For women with asthma who reported medication use only when having symptoms, daily asthma medication use, daily asthma medication use with additional dosing for symptoms, or no medication use, FRs were 1.08 (95% CI: 0.91–1.28), 0.98 (95% CI 0.78–1.29), 0.79 (95% CI: 0.59–1.07), and 0.97 (95% CI 0.89–1.07), respectively.

Conclusions: Despite the near-null findings overall, we found slightly reduced fecundability for the heaviest users of asthma medication, which might be a chance departure, confounding by asthma severity, or an effect of greater asthma medication use.

770 | Prenatal and infant exposure to paracetamol and ibuprofen and the risk of asthma in children at 24 months of age: Findings from a cohort study

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Background: Some studies have suggested that prenatal paracetamol exposure might associate with the risk of child asthma. However, some systematic reviews, indicate that despite knowing pathophysiological mechanisms that could explain this association, the evidence regarding the use of paracetamol and the development of asthma is still inconclusive.

Objectives: the aim of this study was to analyze the prenatal and infant exposure to paracetamol and ibuprofen and the risk of asthma in children at 24 months of age.

Methods: this is a cohort study conducted in Pelotas, Brazil, in 2015. This cohort recruited pregnant women during the prenatal period n = 4,275, in order to collect variables related to pregnancy. The outcome of the study was asthma in children at 24 months. The exposure was the use of paracetamol, ibuprofen and both drugs during gestation and in childhood, 3 months, 12 months and 24 months. The independent variables were: maternal age, maternal schooling, maternal asthma, infection during pregnancy, child birth weight and breastfeeding status. The analyzes were performed using poisson regression.

Results: the cohort comprised 4,014 children at the 24 months follow-up. 71.9% of mothers reported white skin color, 47.1% were between 20 and 29 years old, 34.1% had 9 to 11 years of study. Tobacco use was observed in 16.5% of the women. The prevalence of exposure to paracetamol during gestation was 64.2%, ibuprofen was 2.5% and of both drugs was 3.2%. Exposure to paracetamol and ibuprofen in children up to 24 months was, respectively, 17.2% and 13.6%. The relative risk of having asthma among those exposed to paracetamol

during pregnancy was 1.05 IC95% 0.96–1.15 in the crude analysis and 1.03 CI95% 0.93–1.16 in the adjusted analysis. The relative risk of taking ibuprofen was 1.17 CI95% 0.91–1.51 in the crude analysis and 1.16 IC95% 0.91–1.48 in the adjusted analysis. No association was found when analyzing the simultaneous use of paracetamol and ibuprofen during the pregnancy. When analyzing the children's exposures to the medicines at 12 and 24 months, we observed a significant association with the use of paracetamol and ibuprofen: relative risk of 1.11 CI95% 1.01–1.23 and 1.16 CI95% 1.04–1.30 in the adjusted analysis, respectively.

Conclusions: the findings suggest that there is no association between prenatal exposure to paracetamol and ibuprofen and increased risk of developing asthma at 24 months. However, the use of paracetamol and ibuprofen from birth to 24 months of age increased the risk of asthma in the children.

771 | Use of iron salts, hemoglobin levels in gestation and the development of diabetes mellitus Gestacional in the 2015 Pelotas birth cohort, Brazil

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Background: Prophylactic iron supplementation in pregnant women is a universal practice of antenatal care. However, there is evidence that high iron intake increase the risk of gestational diabetes mellitus (GDM) for women with hemoglobin levels >11 g/dL in early pregnancy.

Objectives: To evaluate the association between the use of iron salts in pregnant, hemoglobin levels, and development of GDM.

Methods: Longitudinal study with women who participated in the perinatal study (n = 4270) in 2015 Pelotas Birth Cohort, Brazil. Participants were interviewed at the maternity about the antenatal period. The analyzes were performed with all non-anemic women before the 24th week of gestation (n = 2463). The GDM outcome was based on maternal self report. All women with a previous history of diabetes were excluded. The exposure "use of prophylactic iron in the first or second trimester of gestation", was defined as iron use in non-anemic pregnant women. In order to characterize this exposure, was used the variable of use of vitamins and salts of iron in the gestation. It was considered "yes" for the use of iron all the compounds with ferrous sulfate and all the vitamins with iron. Descriptive analyses were performed between exposed and unexposed and factors associated with the development of GDM were evaluated using Poisson regression with robust variance. Variables with $p < 0.2$ were included in adjusted analysis. The regression followed a hierarchical backward selection model. The distal level included socio-demographic variables and family history of diabetes; the second level includes pre-gestational body mass index (BMI), parity and smoking; and proximal level included the use of iron salts. The significance level was set at 0.05.

Results: Younger non-anemic women (19 years or younger) used more iron salts (79.4%) than older women (71.0%, p = 0.02). Sociodemographic characteristics, pre-gestational BMI, parity, smoking and family history of diabetes did not show statistically significant differences. The adjusted analysis did not find association between the use of iron salts and the risk of GDM (Risk relative = 1.0, 95%CI 0.7–1.4).

Conclusions: Prophylactic supplementation of iron salts in non-anemic pregnant women is not a risk factor for GDM. To confirm our results, future studies should include baseline hemoglobin levels and additional markers of iron status.

772 | Safety outcomes among infants exposed to Omalizumab via breastfeeding: Results from the Xolair pregnancy registry (EXPECT)

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Background: EXPECT is an observational study with the primary objective of evaluating pregnancy outcomes in women exposed to Xolair.

Objectives: Explore the potential risk to newborn infants exposed to Xolair via breast milk within the EXPECT pregnancy registry.

Methods: This analysis report on safety outcomes for 230 infants born to these women and for whom data were available on breastfeeding status and long-term outcomes. Data on infant outcomes were collected from the mother and relevant healthcare providers at 6 and 12 months after delivery (follow-up was extended to 18 months after delivery if the mother continued Xolair treatment while breastfeeding). Outcomes of interest were serious and non-serious adverse events, infections (used as a potential proxy for immune system development) and thrombocytopenia. Analyses were descriptive and results summarized as percentages.

Results: Among the 230 infants included in the analysis, 44 were not breastfed, 154 were exposed to Xolair through breastfeeding, and 32 were breastfed without being exposed to Xolair. The overall frequency of Serious Adverse Events (SAEs) reported was similar across the 3 groups: 54.5%, 48.1% and 46.9% respectively. The most frequently reported SAEs not related to infections were conditions identified in the immediate perinatal period (most common: prematurity, jaundice, and fetal distress syndrome) and minor congenital anomalies (most common: ankyloglossia, dacryostenosis, and hydrocele). The frequency of reported SAEs categorized as "infections and infestations" was 11.4%, 10.4% and 12.5% respectively. There was only one infant diagnosed with thrombocytopenia, identified on her day of birth.

Conclusions: The results of this analysis are not suggestive of a relationship between Xolair exposure via breastfeeding and an increased risk of overall adverse events or deficiencies in immune system function in infants. Limitations of the data include the observational nature of the registry, and the potential for under-reporting of infections, particularly those that were clinically mild.

773 | Prenatal drug exposure in children using psychiatric care: A study conducted in the POMME cohort

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Background: More and more studies suggest a potential impact of prenatal drug exposure, in particular to psychotropic medicines, on the occurrence of neuropsychiatric disorders in the offspring.

Objectives: This study aimed to describe prenatal drug exposure in children receiving psychiatric care.

Methods: The study was conducted using the POMME cohort (PrescriptiOn Médicaments Mères Enfants), which holds anonymous medical information as well as drug and healthcare reimbursements to more than 8,000 children, from the day of their conception. The children recorded in POMME were born between July 2010 and June 2011, thus they have reached 7 years of age. Data included i) drugs and medical care reimbursements to children and their mothers during pregnancy and ii) health certificates at birth, 9 and 24 months. Children were included if they i) consulted at least once a psychiatrist, neurologist or psychiatrist, ii) presented at least two signs of psychomotor development disorders mentioned in their health certificates and/or iii) were prescribed at least one psychotropic medicine (ATC classes N05 and/or N06).

Results: A total of 1,785 children were included (21.3% of the POMME cohort). Among them, 442 (24.8%) consulted a neuropsychiatrist, neurologist or psychiatrist, 856 (48.0%) presented at least two signs of psychomotor development disorders and 670 (37.5%) were prescribed psychotropic medicines. Children were prescribed 10.4 ± 6.2 medicines during intrauterine life (versus 9.8 ± 6.1 in the entire POMME cohort) and they were mostly exposed to medicines for the digestive system during their intra-uterine life. 68.6% were prenatally exposed to nervous system drugs (67.1% in the POMME cohort), the majority of whom was exposed to analgesic. Prenatal exposure to psycholeptics and psychoanaleptics concerned 6.3% and 2.4% of the children respectively (4.8% and 1.9% in the POMME cohort) and exposure was higher during the first trimester of pregnancy.

Conclusions: More than two thirds of the children using psychiatric care were prenatally exposed to nervous system drugs. A case–control study nested in the POMME cohort will assess the association between neuropsychiatric disorders in the offspring and prenatal exposure to psychotropic drugs.

774 | Antibiotic use during pregnancy and infancy and the possible impact on overweight in early childhood. Analysis from 2015 Pelotas birth cohort, Brazil

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Background: Antibiotics alter the composition of intestinal microbiota, even after discontinuation of use, influencing metabolic programming. There are indications that intestinal microbiota may play a role in the development of obesity. Some studies suggest that antibiotic use may influence negatively weight gain in childhood. However, few studies have examined this association during gestation and the first years of life. Thus, the best knowledge can contribute to clarify this possible association.

Objectives: To evaluate the association between antibiotic exposure in pregnancy and infancy and overweight in the first childhood through body mass index (BMI).

Methods: Longitudinal cohort study of children born in 2015 in Pelotas (Brazil), whose mothers lived in the urban area of the city. Data of this study are from the hospitalization to the delivery (perinatal study), and from the follow-ups of three, 12 and 24 months of the children. The use of antibiotics (ATC/DDD level 1 group J) was self-reported during pregnancy, at three, 12 and 24 months of the children. Variables of cumulative exposure to antibiotics was constructed for each outcome period. The outcomes (at three, 12 and 24 months) were operationalized by the BMI in z-score according to WHO parameters (≤ −2dp to >2dp: low weight/eutrophic; ≥ 2dp: overweight). The weight and height of the children were measured in all follow-ups by standard interviewers.

Results: Our cohort comprised 4,014 children at the 24 months follow-up. 71.9% of mothers with skin color white, 47.1% with age between 20 and 29 years old, 34.1% with 9 to 11 years of study, about 20.0% with low income, and 44.5% were primiparous. Tobacco use was observed in 16.5%. The prevalence of use of antibiotics by mothers during pregnancy was 43.4%. The prevalence of use of antibiotics in children was 3.1%, 10.0%, 8.9% at 3 months, 12 months and 24 months, respectively. The prevalence ratio of cumulative exposures to antibiotics at the 3 months was PR = 1.24 (95%CI 0.87; 1.77), at 12 months it was PR = 1.14 (95%CI 0.96; 1.34) and at 24 months PR = 1.04 (95%CI 0.83; 1.30). The use of antibiotics at 3 months,12 months and 24 months, as well as during pregnancy, were not statistically associated with an increase in BMI.

Conclusions: Our findings suggest that the use of the antibiotics increase the probability of higher BMI in the infancy, but these associations were not statistically significant.

775 | Trends in use of antiepileptic drugs during pregnancy

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Background: Exposure to antiepileptic drugs (AED) such as valproate, topiramate and carbamazepine has been associated with increased risk of fetal malformations and is therefore contraindicated during pregnancy. There is a current need for population-based data on trends in AED treatment during pregnancy in order to facilitate contextualisation and decision making in this field.

Objectives: The objective of this study was to describe trends in the use of AED during pregnancy in the Netherlands.

Methods: A cross-sectional analysis was conducted using linked pharmacy dispensing and pregnancy records from the Dutch Birth Cohort (DUBC). Pharmacy dispensing records were obtained from the PHARMO Database Network (PHARMO) - a population-based network of electronic healthcare databases combining data from different healthcare settings in the Netherlands. Pregnancy records were obtained from the Perinatal Registry of the Netherlands (Perined) - a nationwide registry containing maternal and neonatal characteristics and data on perinatal care. Pregnancies between 1999 and 2015 of women registered in Perined as well as PHARMO were included in the study. Types of AED were assessed per year among pregnant women dispensed at least one AED (ATC N03A).

Results: The DUBC included 486,025 pregnancies of 355,448 women (mean ± SD age at delivery 31.0 ± 4.8 years) during which 2,038 women (mean ± SD age at delivery 31.6 ± 5.0 years) used AED. In 1999, carbamezapine was the most commonly used AED (42%), followed by valproate (27%) and in 2015 this was lamotrigine (24%), followed by levetiracetam (19%). From 1999 to 2015, decreasing trends in prevalence of exposure were observed for carbamazepine (−28%) and valproate (−23%). Increasing trends were observed for levetiracetam (+19%), lamotrigine (+17%), pregabalin (+11%) and topiramate (+9%).

Conclusions: Although prevalence of exposure decreased over time for most of the teratogenic AED, increasing trends were observed for topiramate, as well as for new AED with ill-defined risks such as pregabalin. This highlights the need for an expansion of medication-risk knowledge and communication in the Netherlands in terms of teratogenic effects of AED used during pregnancy.

776 | Inflammatory bowel disease treatment in pregnancy in the US and Sweden

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Background: Many women with inflammatory bowel disease (IBD) may require treatment with immunomodulatory agents during pregnancy to avoid disease activity, which in turn is associated with adverse pregnancy outcomes. Population level data describing medication use in pregnant women with IBD are scarce.

Objectives: To study treatment patterns of systemic corticosteroids, sulfasalazine/5-ASA, thiopurines and anti-TNF for IBD in pregnancy in the US Medicaid program and in Sweden over time.

Methods: We identified a cohort of pregnant women who gave birth in 2000–2013 who were enrolled in the US Medicaid and pregnant women who gave birth in 2006–2015 in the national health registers in Sweden with a diagnosis of either Crohn's disease or ulcerative colitis, assessed in the 90-day baseline period before pregnancy. The proportion of women who filled prescriptions for drug classes indicated for IBD during is presented by drug class and by calendar year. We further assessed continuation patterns for each drug class and presented the proportion of those on treatment at pre-pregnancy baseline who were still on treatment in the third trimester.

Results: We identified 3,219 pregnant women with IBD from the Medicaid cohort and 1,713 from the Swedish cohort. The proportion with any treatment during pregnancy was 47.5% for Crohn's disease and 49.3% for ulcerative colitis in Medicaid, and 60.9% for Crohn's disease and 64.7% for ulcerative colitis in Sweden; proportions which remained stable over time in both countries. In Medicaid, 26.7% were treated with systemic corticosteroids and 28.8% with sulfasalazine/5-ASA and the corresponding numbers were 20.0% and 42.3% in Sweden. Thiopurines were more frequently used in Sweden (22.6%), than in the Medicaid cohort (6.6%). Anti-TNF treatment increased over time from 3.6% in 2006 to 9.5% in 2013 in Medicaid and from 2.7% to 9.8% in the same time period in Sweden. Continuing anti-TNF treatment throughout pregnancy was more common in the Medicaid (43.0%) than in Sweden (22.6%).

Conclusions: In this large population-based study from two countries, a higher proportion of women with IBD received treatment during pregnancy in Sweden than in Medicaid, however, the pattern of used drug classes differed. We further documented an increasing trend in use of anti-TNF in pregnant women with IBD over study years in both countries, emphasizing the need for research on the safety of these medications in pregnancy.

777 | Switching patterns of antidiabetic medications during pregnancy in women with pre-gestational diabetes in publicly or privately insured US populations

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Background: Pre-gestational diabetes (pre-GDM) affects around 1% of pregnancies in the US, with pre-existing type II diabetes being the most common. The American Diabetes Association and American College of Obstetrics and Gynecology have recommended insulin as the preferred agent for management of diabetes in pregnancy due to a lack of evidence on oral agents. However, it is unclear to which extent treatment of pre-GDM during pregnancy follows these guidelines.

Objectives: To characterize prescription patterns in women with pre-GDM treated with non-insulin antidiabetic medications before the start of pregnancy.

Methods: The source cohorts consisted of women aged 12 to 55 years with pregnancies resulting in a delivery, and continuous eligibility in their health insurance plan from 3 months prior to the date of their last menstrual period (LMP) to 3 months after the date of delivery (DoD) using nationwide Medicaid Analytical eXtract (MAX) data from 2001 to 2014, and OptumClinformatics data from 2004 to 2015. Pre-GDM was identified by 2 or more diabetes diagnostic codes (250.xx, 648.0x) in out- or inpatient claims, and 1 or more prescriptions for a non-insulin antidiabetic medication during the 3 months before LMP. Based on the prescription dispensing date, we describe use of antidiabetic agents in 5 time windows (3 months before pregnancy, first, second, third trimester, and 3 months after DoD), and medication switching patterns.

Results: The study cohorts consisted of 6933 pregnancies in MAX and 942 in Optum treated with a non-insulin antidiabetic medication before pregnancy. The most common treatments before pregnancy were metformin alone (53% in Optum; 35% in MAX), and metformin in combination with other antidiabetics (35% in Optum; 47% in MAX). The proportion of women that switched to insulin alone during pregnancy was 42% in MAX and 27% in Optum by the second trimester, and 47% and 35% respectively by the third trimester. Switching to insulin has decreased in both cohorts over the study period. During the first 3 months after delivery, the proportion on insulin alone decreased to 15% in MAX and 10% in Optum, while the proportion on metformin increased to 20% and 24%, respectively.

Conclusions: Less than half of women using non-insulin antidiabetic medications before pregnancy had switched to insulin by the second trimester. Switching to insulin was more common among publicly compared to privately insured women but has decreased in both groups over time. These findings highlight the need for additional information on safety of oral medications during pregnancy.

778 | Use of sildenafil and other PDE-5 inhibitors among pregnant women in Scandinavia

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Background: Phosphodiesterase 5 inhibitors (PDE-5-I) may improve the uteroplacental circulation and in 2014 a multinational randomized clinical trial was initiated to assess the effect of the PDE-5-I, sildenafil in growth restricted fetuses. The trial was halted prematurely due to excess risk of neonatal lung problems and mortality.

Objectives: To describe women who filled prescriptions with PDE-5-I before and during pregnancy and their singleton infants born in Denmark, Norway or Sweden 1995–2015.

Methods: From the Scandinavian national birth and drug registers, we obtained information on maternal and infant characteristics among women who had filled a prescription with any marketed PDE-5-I product from 90 days before the last menstruation period (LMP) until delivery. Small-for-Gestational-Age (SGA) was defined as a birthweight below two standard deviations from the mean by gestational age and sex. Numbers and proportions are presented. Due to restrictions for reporting small numbers from the Danish national registers, numbers less than three are reported as such.

Results: At least one prescription of a PDE-5-I drug was filled by 68 women and 52 had filled a prescription with sildenafil. Of the 68 women, 35 (51%) filled a prescription before LMP and 31 (46%) in the first trimester. Twelve women (18%) filled a prescription only in the second or third trimester. The women were generally of higher age and 31 (46%) were 35 years of age or older. There were nine (13%) who reported smoking in early pregnancy and four (6%) had a cardiovascular diagnosis. Twenty-one (31%) delivered by cesarean section and 48 (71%) had filled a prescription with another drug during the exposure period of interest. Most infants (52, 76%) were born 2006–2015, and 58 (85%) were born at term. Five infants (7%) had an APGAR score below 8 and five were born SGA. A total of 18 (26%) had been admitted to a neonatal intensive care unit (NICU) and seven (10%) had a respiratory or a cardiovascular disease. There were less than three stillbirths, no neonatal deaths and less than three postneonatal deaths.

Conclusions: Prescriptions with PDE-5-I have been filled by Scandinavian women when pregnant. The prescribing indication is not known and though only a handful had a cardiovascular diagnosis, the generally high age and the high rate of cesarean section and co-medication indicate a less healthy population. Some of the women may have filled their prescriptions due to suspected intrauterine growth restriction as the filling was only in the second or third trimester and the rate of SGA was higher than expected.

779 | Hypertensive disorders of pregnancy and utilization of antihypertensive therapies

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Background: Hypertensive disorders of pregnancy (HDP) affect 5–10% of pregnancies and are associated with mortality and morbidity in offspring and in mothers. Use of antihypertensive therapies, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) is contraindicated in pregnancy, and is therefore rare and not well characterized.

Objectives: To describe utilization of antihypertensive therapies in HDP, focusing on ACEi and ARBs overall and by pregnancy trimester.

Methods: We conducted a nationwide cross-sectional study using routinely and prospectively collected data from the Danish Medical Birth Registry, the Danish National Patient Registry, the Danish National Prescription Registry, and the Danish Civil Registration System. The study population consisted of all pregnancies ending at ≥22 gestational weeks as a live or still birth in 1997–2016. We reported prevalence of ACEi, ARBs and other HDP therapies utilization as measured by dispensings during pregnancy. Whenever necessary, reported frequencies were rounded ('clouding') to comply with data protection regulations. Prevalences are reported based on unrounded frequencies.

Results: Among the 1,218,633 included pregnancies, 73,960 (6.1%) were complicated by a HDP. Of those, 19.3% (14,249/73,960) had at least one dispensing of any antihypertensive therapy. Of women with pregnancies complicated by a HDP, 1.0% had at least one dispensing of ACEi or ARBs (735/73,960). The number of pregnancies with dispensings of ACEi or ARBs was small and decreased with trimester (*N* = 695 in first trimester vs. *N* = 50 in second trimester vs. *N* = 25 in third trimester). The most frequently dispensed ACEi and ARB were enalapril (255/73,960, 0.3%) and losartan (145/73,960, 0.2%), respectively. Of pregnancies with a dispensing of any antihypertensive therapy, the most prevalent condition was chronic hypertension (7,745/14,250, 54.3%), followed by gestational hypertension (2,890/14,250, 20.3%), preeclampsia-eclampsia (1,890/14,250, 13.3%), and by preeclampsia superimposed on chronic hypertension (1,720/14,250, 12.1%). ACEi or ARBs were dispensed in pregnancies with chronic hypertension (720/735, 98.0%), of whom (130/720, 17.7%) developed preeclampsia superimposed on chronic hypertension, and in pregnancy with gestational hypertension (15/735, 2.0%).

Conclusions: As expected, the utilization of ACEi or ARBs for therapy of HDP was low, but not absent.

780 | Use of anti-migraine medications among commercially insured pregnant women in the United States

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Background: Migraine headache is a debilitating pain condition affecting 30% of reproductive-age women, considered by the World Health Organization to be one of the 20 most disabling conditions. Management of migraine includes medications to prevent attacks (beta blockers, tricyclic antidepressants (TCA), and anti-seizure drugs) and medications to treat symptoms (triptans, opioid and non-opioid analgesics). These medications have varying pregnancy safety profiles.

Objectives: To study treatment patterns of medications used by pregnant women with migraine in a cohort of commercially-insured US women.

Methods: We used data from commercial insurers in the United States gathered between 2011 and 2015. We identified pregnancies resulting in a live or stillbirth, in which the insured women also had klcomplete prescription drug coverage, and where there was at least one diagnosis of migraine in the 90 days before last menstrual period (LMP). We calculated proportions of women with at least one prescription fill for medications of interest, for the 90 days prior to LMP and each pregnancy trimester.

Results: We included 30,793 women with a diagnosis of migraine in the 90-day baseline period. Opioids were the most widely used medications in women with migraine, with 20% filling at least one prescription before pregnancy, and slight reductions during pregnancy (17, 16, and 15% in 1st, 2nd, and 3rd trimesters). 16% of the sample used triptans prior to pregnancy, 8% in the 1st trimester and 3% and 2% in the 2nd and 3rd trimesters, respectively. Non-steroidal anti-inflammatory drugs were used by 11% before LMP, 4% in 1st trimester, 1% in 2nd trimester, and 2% in 3rd trimester. 20% of the sample filled prescriptions for one class of preventive therapy, 6% filled for 2 classes, and < 1% filled for 3 classes. Antidepressants were the most commonly-used preventive medication, with 17% filling a prescription before pregnancy (10% SSRI and 4% TCA), 12% in the 1st trimester (8% SSRI and 2% TCA), 7% in the 2nd (5% SSRI and 1% TCA), and 7% in the 3rd (6% SSRI and 1% TCA). Antiepileptic drugs were used by 9% pre-pregnancy, 5% in the 1st trimester, 2% in the 2nd, and 2% in the 3rd; topiramate was most common, with 6% using before pregnancy, 3% in the 1st trimester, and < 1% in later trimesters. Antihypertensives were used by 7% of the sample before pregnancy, 6% in the 1st trimester, 6% in the 2nd and 9% in the 3rd; beta blockers were the most common with 5% filling a prescription in each period.

Conclusions: In this population-based study of pregnant women with migraine, we noted highly prevalent use of multiple medications, some of which had uncertain pregnancy safety profiles.

781 | The association between annual hospital delivery volume and discharge opioid prescriptions after vaginal deliveries

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Background: Opioid use after vaginal delivery is highly variable, although reasons for this variability are not well understood. Delivery hospital characteristics, especially delivery volume, may be associated with differences in discharge opioid prescribing.

Objectives: To examine whether annual hospital delivery volume is associated with filling a discharge opioid prescription after vaginal delivery.

Methods: We conducted a cross-sectional study of women aged 15–44 years enrolled in Tennessee Medicaid (TennCare) with a vaginal delivery at a Tennessee hospital with ≥50 annual births (62 hospitals) from 2007–2015. Patients were continuously enrolled in TennCare and had no evidence of opioid use disorder in the 180-day period prior to delivery. Hospital data were obtained from the American Hospital Association Annual Survey and Tennessee Hospital Joint Annual Reports. Delivery volume was defined as the total number of births reported by the hospital in the year of delivery and was categorized into quartile groups (1–4): <400, 400–799, 800–1599, ≥1600. Deliveries and opioid prescriptions were identified using TennCare claims data supplemented with State hospital discharge and birth certificate information. We used multilevel multivariable logistic regression to assess whether delivery volume was associated with filling an opioid prescription within 5 days of hospital discharge, controlling for relevant risk factors and delivery year, and random effect of hospital.

Results: Of 145,094 women with vaginal deliveries who met study inclusion criteria, 49% filled an opioid prescription within 5 days of hospital discharge. The median (interquartile range) annual proportion (%) of women who filled an opioid was 58 (32–72), 59 (24–78), 65 (47–75), 62 (35–72) for hospitals in quartiles 1–4, respectively. Compared to patients who delivered at a hospital with a delivery volume < 400, those who delivered at a hospital with a delivery volume of 400–799 had lower odds of filling a discharge opioid prescription (adjusted odds ratio [OR] 0.76, 95% confidence interval 0.67–0.86). The odds of filling a discharge opioid prescription was similar in hospitals with higher delivery volumes (800–1599 and > =1600) compared to <400 (adjusted OR 1.12 [0.98–1.27] and 0.92 [0.80–1.07], respectively).

Conclusions: Preliminary findings show that delivery at hospitals with low-intermediate delivery volume (2nd quartile) was associated with the lowest odds of filling an opioid prescription after vaginal delivery. We found no evidence that high delivery volumes were associated with lower opioid use.

782 | Phosphodiesterase-5 (PDE5) inhibitor use among pregnant women and women of child-bearing age in the sentinel distributed data network

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Background: In July 2018, a Dutch clinical trial was terminated prematurely because of an unexpectedly high neonatal death rate associated with use of sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, in pregnancies complicated with early severe fetal growth restriction (FGR). The prevalence of PDE5 inhibitor use in pregnant and reproductive-aged women in the US is unknown.

Objectives: To assess the prevalence and potential indications of PDE5 inhibitor use among pregnant and reproductive-aged women in the US.

Methods: We examined PDE5 inhibitor use during pregnancy in the Sentinel Distributed Database (SDD), a distributed administrative claims database of mostly commercially-insured patients. We identified women aged 15–50 years with a live-birth between January 2001 and March 2018. We examined PDE5 inhibitor outpatient dispensing data recorded within 90 days preconception through the end of pregnancy, and identified potential indications, labeled and off-label, using pre-defined ICD-9/10 diagnosis codes. Separately, we used IQVIA's Total Patient Tracker™ (TPT, a nationally-estimated dataset derived from retail pharmacy dispensed prescriptions) data to estimate the number of female patients aged 15–50 with a dispensed prescription for PDE5 inhibitors from outpatient retail pharmacies during 2013–2017.

Results: In SDD we identified over 3.3 million pregnancies during 2001–2018, 96 of which had PDE5 inhibitor use any time during pregnancy, yielding an overall prevalence of 2.85 per 100,000 live-born pregnancies (95% CI: 2.31–3.48). Sildenafil was the most commonly-used PDE5 inhibitor in pregnancy (89%). The prevalence of any PDE5 inhibitor use was 2.61, 0.62, and 0.62 per 100,000 live-born pregnancies during the 1st, 2nd, and 3rd trimesters, respectively. Among women exposed to a PDE5 inhibitor from 90 days preconception to the end of the pregnancy, 25.0%, 31.1%, and 15.5% had a diagnosis code for FGR, preeclampsia, and pulmonary arterial hypertension, respectively. The TPT analysis revealed that an estimated 3.7 million US patients received prescriptions for PDE5 inhibitors in 2017, of whom approximately 15,000 (0.4%) were female patients aged 15–50 years.

Conclusions: Despite the limitations of data source (e.g., cannot assess PDE5 inhibitor use in non-live birth pregnancies in SDD; pregnancy status and indication for use unavailable in TPT), we found a low

prevalence of PDE5 inhibitor use in pregnant and reproductive-aged women. These drug utilization data help to inform the public health impact of PDE5 inhibitor exposure in pregnancy in the U.S.

783 | Exposure to Fosfomycin trometamol during pregnancy: A descriptive study using the EFEMERIS database

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Background: Fosfomycin trometamol has been recommended as first-line bactericidal antibiotic for urinary tract infections in pregnant women since 2015 in France. However, too few studies have assessed the risk of fosfomycin on pregnancy outcomes.

Objectives: The aim of this study was to compare pregnancy outcomes between women exposed to fosfomycin during pregnancy and the general population.

Methods: We performed a comparative study in EFEMERIS, the French database including expecting mothers declaring their pregnancy to the French Health Insurance System of Haute-Garonne from July 1st, 2004 to December 31th, 2017. EFEMERIS contains prescribed and dispensed reimbursed drugs during pregnancy and pregnancy outcomes. Women receiving at least one prescription and dispensation of fosfomycin during pregnancy were selected.

Results: A total of 5,887 women (4.3%) were included. Among them, 44.3% received at least one prescription of fosfomycin during the first trimester, 38.9% during the second and 25.8% during the third trimester. The mean maternal age was 30.6 ± 5.2 years (EFEMERIS: 30.6 ± 5.1 years; p = 0.99). A significantly higher percentage of women suffering from a declared long-term adverse health condition (3.2% *versus* 2.6%; p = 0.003), number of ultrasound scans during pregnancy (4.0 ± 1.8 *versus* 3.8 ± 1.8; p < 0.0001), number of maternal pathologies during pregnancy (9.6% *versus* 8.6%; p = 0.01) and number of drugs prescribed during pregnancy (excluding fosfomycin) (11.7 ± 7.4 *versus* 9.1 ± 6.6; p = 0.0001) were observed in the fosfomycin group compared to general population. The average duration of pregnancy (36.2 ± 5.6 *versus* 36.4 ± 5.2; p = 0.004) and the parity (1.7 ± 1.0 *versus* 1.7 ± 0.9; p = 0.004) were slightly lower than in the general population. Pregnancy loss concerned 6.5% of the outcomes (n = 387) (EFEMERIS: 5.8%; p < 0.0001). Among live births (n = 5,579 (93.5%)), preterm birth, newborn weight, size, head circumference, neonatal pathology and psychomotor development were similar between the two groups. The rate of congenital anomalies (according to EUROCAT classification) was comparable between pregnancies exposed to fosfomycin and the EFEMERIS population (2.2% *versus* 2.4%; p = 0.39).

Conclusions: This study showed reassuring results about pregnancy outcomes after prenatal exposure to fosfomycin. In order to minimize confounding by unmeasured family-level risk factors, further analysis using a sibling approach will be carried out.

784 | Prescription patterns before, during and after pregnancy among Dutch women: A drug utilization study

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Background: As knowledge about safety of drug use during pregnancy is still limited, monitoring of prescription patterns is important.
Objectives: Analyze prescribing patterns in Dutch women from 2 years before until 3 months after pregnancy between 2004 and 2014.
Methods: A descriptive drug utilization study was performed by using a large mother-infant subset extracted from the IADB.nl database. All mothers who were present in the database from 2 years before the theoretical conception date (= 273 days before birth date child) till 3 months after giving birth were selected. Only first known pregnancies and singleton pregnancies were included in the analysis. Drugs were classified into three categories: (1) drugs for chronic conditions, (2) drugs for occasional and short-time use, (3) drugs for pregnancy-related symptoms. The prescription rate was calculated as the number of women per 100 women who received one or more prescriptions for a given drug within a specified time period.
Results: About 64,4% of the women received at least one prescription (excluding contraceptives) during pregnancy. Although the prescription rate for most drugs for chronic diseases decreased during pregnancy, a sharp increase is noticed in the use of antihypertensives (1,5%) and glucose lowering medication (1,33%) in the third trimester. Antibacterials, especially penicillins, are the most prescribed drugs for occasional and short term use (first trimester: 7,0%, third trimester: 9,1%). Most prescribed drugs for pregnancy related symptoms were antiemetics (8,6%) during the first trimester and iron preparations (10,1%) during the third trimester.
Conclusions: Although the use of drugs during pregnancy seems to decrease compared to data describing drug utilization between 1994–2003, still almost two-third of all pregnant women use one or more drugs. Close monitoring of the safety for both the mother and unborn child is still warranted.

785 | Spontaneous reporting systems as proxy for drug utilization in pregnancy: The example of insulin maternal exposure

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Background: There are challenges in characterizing insulin treatment during pregnancy, and using adverse event reporting systems as a proxy to characterize maternal exposure has not been employed before.

Objectives: To describe the distribution of pregnancy exposure reports submitted for insulin therapies in the US.

Methods: The FDA Adverse Event Reporting System (FAERS) was used to identify maternal exposure reports spontaneously submitted between Q2/2000 and Q2/2017 for insulin products that have pregnancy exposure events. Insulin products identified by generic names, and MedDRA preferred terms (PT) corresponding to fetal and maternal exposures were used to create a maternal exposure (ME) custom term. Reporting Rates (EBGM) and 95%CI were used to assess insulin-related ME during pregnancy, and compared to those in other anti-diabetes medications (ADM). Rates with 95%CI lower limit ≥2.0 are considered significant insulin-ME associations.

Results: During the analysis period, a total of 3,912 and 1,253 ME reports were submitted for all insulins and other ADM, respectively. Compared to other ADM, insulins showed significant reporting rates of ME (EBGM = 0.38; 95%CI = 0.37–0.40 and EBGM = 2.23; 95%CI = 2.14–2.32, respectively). Number of ME reports and reporting rates for individual insulin products were: aspart (*n* = 522; EBGM = 5.06; 95%CI = 4.72–5.42), NPH (*n* = 29; EBGM = 4.55; 95%CI = 3.32–6.11), detemir (*n* = 360; EBGM = 4.54; 95%CI = 4.16–4.95), human (*n* = 128; EBGM = 3.57; 95%CI = 3.08–4.12), glulisine (*n* = 80; EBGM = 2.38; 95%CI = 1.97–2.84), degludec (*n* = 37; 2.25; 95%CI = 1.71–2.93), lispro (*n* = 1153; EBGM = 2.05; 95%CI = 1.95–2.15), and glargine (*n* = 562; EBGM = 1.40; 95%CI = 1.30–1.50). Numbers and reporting rates of specific PT for insulins were: ME timing unspecified (*n* = 21; EBGM = 1.91), ME during pregnancy (*n* = 1769; EBGM = 2.60), ME before pregnancy (*n* = 30; EBGM = 1.23), maternal drugs affecting fetus (*n* = 371; EBGM = 1.30), fetal exposure during pregnancy (*n* = 835; EBGM = 2.07), and fetal exposure during breast feeding (*n* = 217; EBGM = 2.72). Corresponding PT-specific EBGM for other ADM were: 0.23; 0.46; 0.17; 0.45; 0.30; and 0.14.

Conclusions: Reporting of ME for insulin therapy appears to reflect the guidelines of diabetes management during pregnancy. These events do not reflect safety outcomes, rather a proxy for insulin treatment during pregnancy. Signal detection of congenital anomalies or fetal exposures in diabetes therapies using FAERS should be interpreted with caution due to confounding by indication.

786 | The French pregnancy cohort: Prevalence and trend of medication use during pregnancy in the French population

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Background: The French Pregnancy Cohort (FPC) is a representative cohort of pregnant women.

Objectives: We evaluated the potential usefulness and the validity of FPC as a research tool in perinatal pharmacoepidemiology.

Methods: The FPC was built with the sampling of all pregnant women included in the French Echantillon généraliste des bénéficiaires (EGB), which is a 1/97th representative sample of the population covered by the French health insurance. The EGB includes anonymous information on the socio-demographic and medical characteristics of beneficiaries, and the health care services they have received such as diagnoses and procedure codes, as well as data on reimbursed filled medication; EGB also includes data on hospital stays in all public and private French health facilities. Each prescription record contains information on drug brand and generic names, date of prescription and date of dispensing, quantity dispensed, mode of administration, duration of prescription, dosage, and prescribing physician specialty. The FPC includes data on all pregnancies of women sampled in the EGB between 2010 and 2013 with long-term follow-up. Date of entry in FPC is the first day of pregnancy regardless of pregnancy outcome (spontaneous and planned abortion, livebirth, and stillbirth), and data on women are collected retrospectively one year before pregnancy, and prospectively during pregnancy, and after delivery. Prevalences of prescribed medications before, during and after pregnancy were compared; comparison was also done between trimesters.

Results: The FPC includes data on 36,065 pregnancies. Among them, 27,253 (75.6%) resulted in a delivery including 201 stillbirths (0.7%). The total number of spontaneous abortions was 6,718 (18.6%), and planned abortions was 2,094 (5.8%). The prevalence of prescribed medication use was 91.1%, 89.9%, and 95.6% before, during and after pregnancy, respectively. Although there was a statistically significant decrease in the proportion of use once the pregnancy was diagnosed (first trimester exposure, 76.4% vs. exposure in the year prior to pregnancy 87.2% ($p < .01$)), post-pregnancy medication use was above the pre-pregnancy level (95.6%). Maternal depression was the most prevalent comorbidity during pregnancy (20%), and post-partum depression was higher in those who delivered a stillborn infant (38.8%) as well as in those with a spontaneous (19.5%) or planned abortion (22.4%) compared to those with a liveborn (12.0%).

Conclusions: The FPC has the advantage of including a representative sample of French pregnant women, and study medications only available in France.

787 | A systematic review on prescribing patterns of Antidepresssants before, during, and after pregnancy

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Background: Although depression is common in pregnancy, many women discontinue antidepressant (AD) treatment before or during pregnancy due to a possible increased risk of adverse neonatal outcomes. Limited information is available on how many of these women restart AD therapy after pregnancy.

Objectives: To assess: (1) the prevalence of AD use in women before, during, and after pregnancy, (2) associations between AD use in women before, during, and after pregnancy, (3) the choice of AD prescribed during pregnancy, and (4) time trends in gestational AD use.

Methods: We conducted a systematic review and narrative synthesis. PubMed/Ovid MEDLINE and EMBASE databases were searched from conception to September 2018 by using multiple keywords relating to pregnancy and antidepressant drugs. Observational studies on AD drug use in pregnant women were included in the review. A modified version of a Joanna Briggs Institute critical appraisal tool was used to assess study quality.

Results: A total of 21 cohort studies from Europe, the US, and Canada were included in the review: three studies examined only selective serotonin reuptake inhibitors (SSRIs), the rest considered various types of ADs. Prevalence of AD use decreased in the months before and during pregnancy and rose after delivery, and most women who were using ADs before conception stopped using before or during their first trimester. SSRIs were the most common class of ADs prescribed during pregnancy. In the Netherlands, Canada, Italy, and France, paroxetine was one of the most popular SSRIs for gestational use, while it declined in popularity during the early 2000s in the US, the UK, and Nordic countries. From the mid-1990s to the mid-2000s, the use of ADs during pregnancy increased. It has remained relatively stable since then.

Conclusions: While many women stop the use of ADs when they get pregnant, the prevalence of AD use during pregnancy has increased since the 1990s to the mid-2000s. Numerous studies report on the prevalence of AD use before, during, and after pregnancy, but further research is needed to explore the associations between AD treatment before conception and after delivery.

788 | Maternal early pregnancy antidepressant use by medication class and birth defect risk

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Background: Depression and anxiety, common conditions for women during pregnancy, are often treated with antidepressants. Safety data during pregnancy for each antidepressant class have yielded mixed results.

Objectives: To examine associations between any maternal early pregnancy (1 month before through the third pregnancy month) antidepressant use by medication class and specific birth defects.

Methods: We analyzed data from the NBDPS (1997–2011), a U.S. population-based multicenter case–control study; cases were identified from surveillance systems and controls were liveborn infants without major defects. We used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for associations between maternal early pregnancy use of each antidepressant class (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic (TCAs), other antidepressants, multiple classes) and birth defects with ≥4 exposed cases, controlling for maternal education, race, smoking, and pre-pregnancy body mass index. Comparisons were made to women who were unexposed to any antidepressant three months before or during pregnancy, and, to control for treated indication, women who were only exposed to an antidepressant outside of early pregnancy.

Results: SSRIs were associated with an increased risk for 12/58 defects (highest aORs: partial anomalous pulmonary venous return (aOR: 6.1, 95% CI: 3.2–11.7), cerebellar hypoplasia (aOR: 2.9, 95% CI: 1.1–7.4)). SNRI use was associated with an increased risk for 15/22 defects (highest aORs: anencephaly (aOR: 4.4, 95% CI: 1.7–11.6), gastroschisis (aOR: 4.5, 95% CI: 1.9–10.5)). TCA use was not significantly associated with an increased risk for the six defects examined; other antidepressant medication use had an increased risk for 4/27 defects (highest aOR: glaucoma/anterior chamber defects (aOR: 5.7, 95% CI: 2.0–16.2)). Multiple class use in early pregnancy was associated with 8/23 defects, with the highest aOR for omphalocele (aOR: 4.7, 95% CI: 1.8–12.1). Controlling for treated indication resulted in attenuated associations for most classes, with the exception of SNRI use, which retained a significant association with more than half of the examined defects.

Conclusions: Each antidepressant class was associated with some birth defect risk, which was attenuated when accounting for treated indication, except for SNRIs. Results support the need for evidence-based guidance for healthcare providers to select the safest options to treat mental health conditions before and during pregnancy.

789 | Prevalence and trends in depression and anxiety, antidepressant use and key maternal conditions during pregnancy, 1998–2015

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Background: Depression, anxiety and use of antidepressants are known to be common among women of reproductive age. However, the prevalence of both during pregnancy and their potential association with maternal obesity, and pregnancy related conditions (induced hypertension and gestational diabetes) are unknown. Since these adverse pregnancy outcomes could lead to substantial maternal and child morbidity, an updated prevalence of these concomitant conditions are needed.

Objectives: To estimate the prevalence and time trends of 1) maternal depression and anxiety, 2) antidepressant use (overall and class-specific), and 3) key maternal comorbidities including obesity, pregnancy-induced hypertension, and gestational diabetes.

Methods: Using data from the Quebec Pregnancy Cohort, we defined a cohort of pregnant women who delivered between 1998–2015. Annual prevalence of antidepressant use identified in pharmacy records, and annual prevalence of maternal comorbidities identified using ICD-9 and ICD-10 codes were calculated. Time trend analyses of prevalences, over the 17-year span, were performed using Cochran-Armitage test.

Results: We included 249,234 deliveries with a mean gestational age of 38.7 weeks (standard-deviation (SD) 2.0). The prevalence of depression and anxiety during pregnancy slightly increased from 5.2% in 1998 to 6.9% in 2015, corresponding to a 1.3-fold increase (Cochran-Armitage Trend test: $p < 0.01$). From 1998 to 2015, antidepressant use in pregnant women with deliveries increased 3-fold from 2.2% to 6.2% (Cochran-Armitage Trend test: $p < 0.01$), driven by an increase in selective serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) use. Between 1998–2015, we observed a 6.5- fold increase in maternal obesity; 2-fold increase in gestational diabetes; and 1.3-fold increase in pregnancy-induced hypertension (Cochran-Armitage Trend test: $p < 0.01$).

Conclusions: Our study found an overall and large increasing trend in gestational antidepressant use, mainly due to the increase of SSRI and SNRI use, despite a small increase in maternal depression and anxiety prevalence. Concomitantly, increases have been observed for maternal obesity, gestational diabetes, and pregnancy induced hypertension, which could be partly related to antidepressant use or maternal depression and anxiety. These results suggest that antidepressants are used beyond known indications during pregnancy.

790 | Asthma medication use during pregnancy: Does timing of asthma diagnosis matter?

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Background: Use of asthma medications during pregnancy is recommended by international guidelines to achieve disease control. Newly diagnosed asthma during pregnancy may put the fetus at a higher risk of perinatal outcomes due to more severe asthma caused by hormonal fluctuations or delay in the initiation of controller therapy during pregnancy.

Objectives: To explore whether asthma medication use during pregnancy differs in women newly diagnosed with asthma during the first 19 weeks of pregnancy compared to those newly diagnosed with asthma in the 2 years prior to pregnancy.

Methods: We conducted a retrospective cohort study using the Quebec asthma and pregnancy database, formed by the linkage of Quebec healthcare administrative databases between January 1, 1998 and March 31, 2010. Pregnant women were included if they were aged 15–45 years with new-onset asthma at any point in time 2 years prior to pregnancy or in the first 19 weeks of pregnancy. We compared the proportions of asthma medications use during pregnancy between women newly diagnosed with asthma prior to pregnancy and those diagnosed during the first 19 weeks of pregnancy. Use of asthma medications during pregnancy was defined as filling at least 1 prescription from 20 weeks post-pregnancy until delivery or filling a prescription with a duration that covers week 20.

Results: The final cohort included 2007 pregnancies with 1749 women newly diagnosed with asthma 2 years prior to pregnancy and 258 women newly diagnosed with asthma during the first 19 weeks of pregnancy. Mean age of enrolled women was 25 years. Inhaled corticosteroids (ICS) use during pregnancy was slightly higher among women with pregnancy-onset asthma (10.9%; 95% CI: 7.1–14.8) compared to those with new-onset asthma prior to pregnancy (9.1%; 95% CI: 7.8–10.5), but this difference was not statistically significant. Proportions of use of short-acting ß2-agonists (15.0%; 95% CI: 13.3–16.7 vs 13.3%; 95% CI: 9.1–17.4), ICS and long-acting ß2-agonists fixed combination (0.9%; 95% CI: 0.4–1.3 vs 0.8%; 95% CI: 0.0–1.8), nasal corticosteroids (4.2%; 95% CI: 3.2–5.1 vs 2.7%; 95% CI: 0.7–4.7) and oral corticosteroids (1.2%; 95% CI: 0.7–1.7 vs 0.8%; 95% CI: 0.0–1.9) during pregnancy did not significantly differ between women newly diagnosed with asthma prior to pregnancy and those diagnosed during the first 19 weeks of pregnancy.

Conclusions: Regression analyses will be done to adjust for potential confounding variables and confirm or infirm the absence of significant differences in the use of asthma medications during pregnancy between women diagnosed with asthma prior to pregnancy and those diagnosed during pregnancy.

791 | Antihypertensive drug use among pregnancies in South Korea, 2003–2013

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Background: Hypertensive disease is among the most common medical conditions of pregnancies, occurring in approximately 12–22%; however, there is limited safety data to inform use of antihypertensive drugs (AD) in pregnancies.

Objectives: To describe patterns of AD use before and during pregnancy and assess the AD use by maternal characteristics.

Methods: We used the Korean national claims database to identify pregnancies with live births aged 15–44 years between 2003 and 2013. Pregnancy onset was estimated by subtracting 39 weeks from the delivery date and all forms of AD examined by pregnancy stage (pre-conception [PC: 90 days before pregnancy onset], first trimester [1 T], second trimester [2 T] and third trimester [3 T]), where the time-period of seven days before delivery was excluded. Labetalol, hydralazine and nifedipine were considered as 'recommended drugs' and angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) as 'contraindicated drugs'; all other AD except thiazide diuretics were considered as 'non-recommended drugs.' The prevalence of AD use was calculated as the proportion of pregnancies to women who received at least one AD. We also conducted multivariable logistic regression to evaluate predictors of the AD use, such as maternal age, urbanity, income, medical aid, history of obesity and diabetes, nulliparity and multiple gestation. Statistical significance was determined by 95% confidence interval of adjusted odds ratio.

Results: Among total 88,248 pregnancies, 788 (0.89%) had exposure to any AD during pregnancy. The AD use declined from 0.61% in PC to 0.36% in 1 T and 0.25% in 2 T, but it was most common in 3 T (0.64%). Nifedipine (0.27%), hydralazine (0.18%) and amlodipine (0.16%) were most commonly used during pregnancy, while that of in PC was propranolol (0.19%), hydrochlorothiazide (0.17%) and amlodipine (0.07%). The use of recommended drugs increased with trimesters (0.09%, 0.16% and 0.46% in 1 T, 2 T and 3 T, respectively) compared with non-recommended drugs (0.29%, 0.12% and 0.32%). Despite the large decrease in the use of contraindicated drugs from 0.10% in PC to 0.01% in 3 T, 49 (0.06%) and 13 (0.01%) pregnancies received ACEI and ARB, respectively, during pregnancy. The AD use during pregnancy was significantly more prevalent in women 35–44 years of age, those living in rural areas, with lower income, medical aid, multiple gestation and history of obesity and diabetes.

Conclusions: The prevalence of AD use in Korea (0.89%) was lower than that in the US (3.1%) and Italy (1.2%). AD use was dominated by recommended drugs in 2 T and 3 T, although non-recommended drugs were more prevalent in PC and 1 T.

792 | Knowledge of the new Food and Drug Administration pregnancy and lactation labeling rule (PLLR) among physicians and pharmacists

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Background: In December 2014, the U.S. Food and Drug Administration (FDA) issued a final Pregnancy and Lactation and Labeling Rule. This new system eliminated the letter system (A, B, C, D and X) designations, and introduced several new sections to provide more comprehensive information on medication safety in pregnancy and lactation. Assessment of the knowledge and level of awareness of the new Food and Drug Administration (FDA) Pregnancy and Lactation Labeling Rule (PLLR) among providers is important.

Objectives: To assess knowledge of the FDA PLLR among pharmacists and physicians.

Methods: A cross-sectional study was conducted among pharmacists and physicians who were affiliated directly or engaged externally as clinical preceptors, alumni or program participants with the Howard University Health Sciences Enterprise and Howard University Hospital. The main outcome for this study was knowledge of the FDA PLLR. Descriptive statistics of all study variables were estimated. Linear regression analyses were conducted to assess predictive factors of knowledge of the FDA PLLR. SPSS version 25 was utilized, and all analyses were conducted at an alpha value of 0.05.

Results: A total of 167 participants were recruited in the study in 2018. Majority of them were pharmacists (78.4%) and provided direct patient care to women who are pregnant or of reproductive age. The mean age of the participants was 38.6 years and the mean number of years in practice was 9.0 years. Findings on knowledge of the PLLR showed that 40% of respondents were unsure about the new "Females and Males of Reproductive Potential" and "Pregnancy" subsections within the PLLR. Additionally, almost half were unsure about the PLLR's effect on over-the-counter medications (47.3%). Findings from multivariable linear regression analysis showed that gender ($P < 0.01$) and knowledge score of the older pregnancy letter category system ($P < 0.05$) were significant predictors of PLLR knowledge, adjusting for the other factors. Type of provider was only a significant predictor in the unadjusted analysis. Nearly all of the participants (94.2%) acknowledged their need to learn more about the new PLLR.

Conclusions: Efforts are needed to increase pharmacists' and physicians' knowledge of the new PLLR.

793 | Direct-acting Oral anticoagulants (DOACs) in pregnancy: New insight from VigiBase®

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Background: To date, the largest case series that investigated pregnancy outcome data with Direct-Acting Oral Anticoagulants (DOACs) suggests that "there is no indication that DOACs exposure in pregnancy carries a high risk of embryopathy". However, the study lacked of a disproportionality analysis and a case-by-case assessment to investigate the role of comorbidities, concurrent teratogenic drugs (whenever

reported), temporal and biological plausibility of drug-event couples, i.e. the presence of confounders that could potentially explain the outcome and/or reduce the strength of the individual causality between the drug and the adverse event.

Objectives: We aimed to perform an analysis of individual case safety reports retrieved after the Standardized MedDRA Query "Pregnancy and neonatal topics" for which DOACs were claimed as suspected/interacting drugs. Additionally, to investigate if exists a disproportion of cases reporting "Pregnancy and neonatal topics" adverse events rather than other adverse events for DOACs in comparison with all other drugs registered in VigiBase or warfarin.

Methods: VigiBase, the World Health Organization (WHO)'s global database of individual case safety reports was used as data source.

Results: Forty-two cases of abortion were detected of which 18 (42.8%) had alternative causes for its occurrence. Fourteen cases reported congenital anomaly (8 cases) or low birth weight baby/fetal growth restriction (6 cases) of which 62.5% and 33.3% had at least one confounder, respectively. In the disproportionality analyses, a potential safety signal for spontaneous abortion emerged for rivaroxaban (Reporting Odds Ratio, ROR 2.70; 95%CI 1.79–4.07) and apixaban (ROR 6.76; 95%CI 2.99–15.25). However, when the same analyses were performed using only cases without alternative causes, no statistically significant associations for rivaroxaban when compared to all other drugs (ROR 1.05; 95%CI 0.54–2.02) or warfarin (ROR 0.79; 95%CI 0.47–1.32) were found. For apixaban, we found a statistically significant ROR for induced abortion when compared to all other drugs or warfarin.

Conclusions: For the majority of cases claiming DOACs-induced teratogenic effects, spontaneous or induced abortion there was at least one alternative cause explaining the occurrence of the adverse events. For rivaroxaban, when cases without confounders were considered, no safety signals emerged. However, for apixaban, we found a potential safety signal suggesting an increased probability of reporting spontaneous/induced abortion rather than other events when compared to all other drugs or warfarin.

794 | Complications and medication patterns in preeclampsia patients: A retrospective analysis of a large United States electronic health record database

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Background: Preeclampsia is a pregnancy-related complication characterized by the onset of high blood pressure occurring after 20 weeks of gestation and up to six weeks postpartum. Risk factors include age, race, and certain preexisting medical conditions. Medication prescribing is generally dependent on preeclampsia severity.

Objectives: The main objective of the present study was to examine risk factors, complications, and medication prescribing in preeclampsia patients.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All outpatients (≥ 12 years) between 2012 and 2016, with an ICD9/10 diagnosis of preeclampsia, were included in the analysis. Complications and comorbid conditions were characterized by corresponding ICD9/10 diagnosis codes. Medications were grouped into three major classes (antihypertensives, corticosteroids, and anticonvulsants) for evaluation.

Results: The study included 864,450 pregnant patients, with 18% of patients having severe preeclampsia. Preeclampsia occurred in the third trimester in majority of patients (81.1%) and was more prevalent in the age group of '35+ years' (1.4%) as compared to other age groups. In addition, African-American women had the highest preeclampsia rates (1.0%) as compared to Asian/Pacific Islander (0.9%), Caucasian (0.9%), and Hispanic (0.4%). Three percent of preeclampsia patients had preexisting hypertension. Rates of eclampsia and HELLP syndrome were 1.6% and 1.1%, respectively, in preeclampsia patients. Corticosteroids and anticonvulsants were highly prescribed across both preeclampsia severity types (73.1% and 80.7% of severe cases vs. 53.7% and 48.6% of non-severe cases). Among severe preeclampsia patients, the most commonly prescribed anticonvulsant medication was magnesium sulfate (80.7%).

Conclusions: This large database analysis examined risk factors of preeclampsia and provides detailed description of several clinical characteristics of preeclampsia patients including relevant complications and medication usage.

795 | Use of medicines by mothers and duration of breastfeeding in 2015 Pelotas (Brazil) birth cohort study

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Background: Use of medicines by mothers may influence the success of breastfeeding. These women may discontinue breastfeeding or not consume medicines for fear of exposing the baby to drugs through breast milk. In addition, many women are mistakenly advised to stop breastfeeding or avoid treatment by health care providers.

Objectives: To evaluate the impact of the use of medicines on breastfeeding duration.

Methods: Cohort, composed by all women who gave birth in Pelotas, Southern Brazil, in the year of 2015. Data were collected at birth, at three months and at 12 months of life of the children. Children of HIV-positive women were excluded, as well as the children who were not breastfed for other reasons. Socioeconomic and demographic data, information about use of medicines by mothers up to 3 months

postpartum and information on breastfeeding were collected through questionnaires. Medicines were classified according criteria of Brazilian Ministry of Health. Duration of breastfeeding was analyzed according to the exposure variables using Cox regression models and Kaplan–Meier curves.

Results: Our final cohort comprised 4192 children. 71% of the mothers were white, 47.4% with age between 20 and 29 years old, 34.3% with 9 to 11 years of schooling, 49.6% with middle income, and 49.9% were primiparous. The prevalence of use of medicines by mothers in the first three months postpartum was 89.4%, with a total of 9,874 medicines used (195 distinct medication types). About 39.1% (*N* = 3848) of the medicines were used up to 7 days and 18.4% (*N* = 1810) were considered as chronic use (60 days or more). About 89.2% (*N* = 6872) of the medicines were considered compatible with breastfeeding, 6.3% (*N* = 488) were considered of judicious use and 4.4% (*N* = 341) as contraindicated in breastfeeding. At 12 months of life of the children, 1689 mothers (42.4%) still were breastfeeding. 45.3% of the mothers breastfed their children at least for 6 months. For the survival analysis, we only considered children who were still breastfeeding at 3 months (*N* = 2940). Women who used at least one contraindicated drug had a 16% higher hazard ratio of not breastfeeding at 12 months, compared to women who only used breastfeeding-compatible medications and adjusted for schooling, gestational age, and maternal labor at 3 months. However, this association was not statistically significant.

Conclusions: In the adjusted analysis, there was no difference in the duration of breastfeeding regarding the use of medicines by the mothers, according to the Brazilian Ministry of Health's classification of adequacy for breastfeeding.

796 | Antimalarial prescription pattern among pregnant women attending antenatal Clinic in a Nigerian Tertiary Hospital

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Background: Malaria in pregnancy is a serious public health problem. World health organization recommend interventions including malaria treatment with antimalarials.

Objectives: To assess the antimalarial prescription pattern among pregnant women in Jos university teaching hospital.

Methods: This descriptive retrospective study was carried out at the Antenatal Clinic of Jos University Teaching Hospital from March 2018 to July 2018, we assessed type of antimalarial prescribed/trimester of use.

Results: A total of 41(25%) were prescribed sulfadoxine/pyrimithamine of which 7 was in first trimester. Most women (92) used the antimalarials in second trimester. Arthemether-Lumefantrine was the most frequently prescribed antimalarial (59%), with quinine the least(2%) and was only in the first trimester.

Conclusions: Arthemeter-lumefantrine (AL) was the most prescribed antimalarial, prescription pattern was in line with WHO guidelines for pregnancy except few uses of AL and SP in the first trimester.

797 | Monitoring of adverse events following zoster vaccine (Shingrix) in Department of Veterans Affairs

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Background: In October 2017, a new zoster vaccine (Shingrix) was approved for the prevention of shingles in adults aged ≥50 years by the US Food and Drug Administration (FDA). Shingrix is a non-live vaccine to be administered intramuscularly in two doses separated by 2 to 6 months. Shingrix like other vaccines has the potential to cause adverse events (AE). The Department of Veterans Affairs implemented a pilot project to track the utilization of Shingrix and potential AEs in Veteran patients.

Objectives: The objective of this rapid cycle analysis of Shingrix is to track utilization of both doses and monitor pre-specified adverse events (AEs) following Shingrix in a near-real time setting.

Methods: Patients who received Shingrix were identified in Corporate Data Warehouse (CDW) based on the name of vaccine and by procedure codes (90750) from January 2018 to December 2018. Both ICD-9 and ICD-10 codes only were used to identify AEs following the initiation of Shingrix and the calculation of historical rates based on patients who received Zostavax from 2006 to September 31, 2017. Pre-specified AEs include anaphylaxis, polymyalgia rheumatica, rheumatoid arthritis, psoriasis, autoimmune thyroiditis, multiple sclerosis, Guillain Barre Syndrome, idiopathic thrombocytopenia, optic neuritis, inflammatory bowel diseases, Still's disease adult onset, leukocytoclastic vasculitis, gout, temporal arteritis, and optic ischemic neuropathy. The Poisson-based maximized sequential probability ratio test (MaxSPRT) was applied.

Results: Approximately, 293 K patients received one dose of Shingrix in 2018. Of these, 133 K (45%) received a second dose, and 55 K (19%) did not receive a second dose within 7 months. Approximately 70% were aged between 60 and 79 years old and 94% were male. By December 31, 2018, the most commonly observed AE was gout (270) followed by psoriasis (88). For each AE, the observed number of AEs was compared with the expected number of AEs based on the historical background rate. There were 10 observed cases of leukocytoclastic vasculitis compared to 5.0 expected but test statistics did not exceed a threshold. The observed rate of rheumatoid arthritis in patients who did not receive a second dose was higher than those who received second dose (4.8 vs 1.8 per 10000 patients, $p < = 0.001$).

Conclusions: VA used weekly data to rapidly detect pre-specified AEs following administration of Shingrix. No signal was generated for any of the pre-specified AEs as of Dec. 2018. To date rheumatoid arthritis appeared to occur more often in patients who did not receive a second dose but further investigation and chart validation is needed.

798 | Tetanus, Diptheria, acellular pertussis (Tdap) vaccination during pregnancy and risk of pertussis in the newborn in publicly and privately insured mother-infant pairs in the United States

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Background: Triggered by an increase in pertussis cases, the Advisory Committee on Immunization Practices modified the guideline for Tdap vaccination to provide more protection to vulnerable infants and, since 2011, recommends Tdap vaccination to women during pregnancy.
Objectives: The objective of this study is to describe the patterns of prenatal Tdap in both publicly and privately insured women and to determine the effectiveness of this maternal Tdap vaccination for the prevention of pertussis in infants.
Methods: This study analyzed the insurance claims from 1,830,578 livebirth deliveries between 2000–2013 in women enrolled in Medicaid, and 457,980 livebirth deliveries between 2011–2015 in privately insured women from the Truven Marketscan database. Women were required to be enrolled from 90 days prior to pregnancy through 30 days postpartum, and infants were required to be enrolled at least 60 days after birth. Prenatal exposure was defined as any CPT or NDC code for Tdap vaccination between the last menstrual period to 1 day before delivery. Pertussis outcomes were defined using inpatient and outpatient diagnosis codes, laboratory tests, and antibiotic treatments.
Results: In the Medicaid cohort, the proportion of women receiving prenatal Tdap rose from 0% in 2000, to 1.33% in 2011 (when Tdap was recommended), to 7.24% in 2013. Of 11,102 prenatally exposed pregnancies, 12 (0.11%) infants developed pertussis by age 6 months. In the 1,801,499 pregnancies without Tdap exposure, 2,875 (0.15%) infants developed pertussis. In the Truven Marketscan cohort, the proportion receiving Tdap during pregnancy rose from 5.93% in 2011 to 49.35% in 2015. Of 114,616 prenatally exposed pregnancies, 52 (0.045%) infants had pertussis. In the 326,189 pregnancies without a Tdap exposure, 220 (0.06%) infants developed pertussis. In both cohorts, the distribution of factors potentially associated with neonatal infections (e.g., maternal age, baseline comorbidities) were similar for exposed and unexposed.
Conclusions: Adherence to the 2011 Tdap vaccination guidelines for pregnancy remained low by 2013–2015. Preliminary findings suggest a lower risk of pertussis following prenatal vaccination. Continued surveillance of vaccination rates and pertussis cases can inform the need for public health and clinician education programs.

799 | Influence of comorbidity status on seasonal influenza vaccine effectiveness in Canada: A systematic review and meta-analysis of test-negative design studies

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Background: Comorbidity status influences seasonal influenza vaccine effectiveness (VE) but not much is known on how the influence differs across influenza types and subtypes.
Objectives: To summarize and compare seasonal influenza VE from test-negative design studies in Canada by comorbidity status.
Methods: We systematically searched appropriate bibliographic databases and relevant websites from January 2011 to July 2018 for full-text articles from test-negative design studies of seasonal influenza VE against laboratory-confirmed (PCR or culture) influenza conducted in outpatient primary care settings during the 2010/11 to 2017/18 influenza seasons in Canada. Two reviewers independently screened retrieved citations against the eligibility criteria using a two-stage sifting approach (screening of titles/abstracts and full-text articles) and extracted data from all included studies. Disagreements were resolved by consensus or by involving a third reviewer. We included only final seasonal influenza VE estimates. Pooled VE was calculated using inverse variance, random-effects model for all influenza, H1N1, H3N2, influenza A, and influenza B.
Results: Five full-text articles met our eligibility criteria and were included in the meta-analysis. Pooled VE against all influenza was 50% (CI: 23–68%; I^2 = 89.3%; n = 5) for studies involving individuals without comorbidity compared with 44% (CI: -26-75%; I^2 = 84.2%; n = 2) for studies involving individuals with comorbidity. Pooled VE for studies involving individuals without comorbidity was 75% (CI: 64–82%; I^2 = 0%; n = 4) against H1N1, 36% (CI: -14-64%; I^2 = 86.6%; n = 4) against H3N2, 44% (CI: -6-71%; I^2 = 90.6%; n = 4) against influenza A, and 53% (CI: 26–61%; I^2 = 36.4%; n = 4) against influenza B. The observed high heterogeneity in some pooled VE estimates was due to one study (2014/15 influenza season) during which the available vaccine performed very poorly. There was only one study each involving individuals with comorbidity and VE was 58% (CI: 24–77%) for H1N1, 11% (CI: −42-44%) for H3N2, 14% (CI: −36-46%) for influenza A, and 37% (CI: −37-71%) for influenza B.
Conclusions: The available but limited evidence suggests that comorbidity status influences seasonal influenza vaccine effectiveness against all influenza in Canada. More test-negative design study

comparisons of seasonal influenza VE by comorbidity status are needed for influenza types and subtypes.

800 | Coverage rates, completeness, and timeliness of recommended basic immunizations in Swiss preschool children: A descriptive analysis using claims data

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Background: Low vaccination coverage rates and incomplete vaccinations are a risk for the individual and population protection from vaccine-preventable diseases.

Objectives: To describe vaccination patterns for nationally recommended basic vaccinations in a cohort of Swiss children aged up to 37 months.

Methods: We conducted a descriptive study based on administrative claims data in cohorts of Swiss non-preterm children born between January 2010 and December 2016 insured with a single health insurer (Helsana). We assessed coverage rates and completeness for the nationally recommended basic vaccinations (i.e., diphtheria, tetanus, acellular pertussis [DTaP], *Haemophilus influenzae* type b [Hib], poliomyelitis [IPV], measles, mumps, and rubella [MMR]) for each birth cohort at the age of 13, 25, and 37 months. Additionally, we analyzed timeliness of the vaccinations using inverse Kaplan–Meier curves and standardized the results to the Swiss population.

Results: The study population comprised 563,216 children. At 13 months of age, overall coverage rates for the first dose of DTaP, Hib, IPV, and MMR amounted to 93.8%, 93.2%, 93.7%, and 67.2%, respectively. At 25 months of age, we found a complete vaccination status for DTaP, Hib, IPV (4 doses each), and MMR (2 doses) in 68.0%, 65.9%, 67.1%, and 62.9% of the children, respectively, with slightly increased rates at 37 months of age. In contrast, 4.1% of all analyzed children received none of the recommended basic vaccinations at 25 months of age. Overall, we observed continuously increasing coverage rates across birth cohorts for all vaccinations, leveling off after a peak in the 2015 birth cohort. Children were mainly vaccinated within the recommended time window for each vaccination.

Conclusions: National and international goals for vaccination coverage were not reached in Swiss preschool children. However, vaccination coverage rates increased over time, and the majority of vaccinated children received the vaccines under study within the recommended time windows.

801 | Signal detection of human papillomavirus vaccines using the Korea adverse events reporting system database, 2005–2016

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Background: Human papillomavirus (HPV) vaccine is known to prevent about 70% of cervical cancer, and its safety and risk-benefits ratio confirmed by many HPV vaccine safety studies. However, new adverse events (AEs) have recently been reported in young girls following immunization.

Objectives: To compare AEs of HPV vaccines with all other vaccines using the Korea Adverse Event Reporting System (KAERS) database, and to identify new AE-signals not listed in the HPV vaccine labels of South Korea and the United States.

Methods: We detected AE-signals of HPV vaccines using information on the spontaneously reported AEs from the Korea Institute of Drug Safety and Risk Management KAERS Database (KIDS-KD). We extracted and compared all vaccine-related AE pairs with AEs pairs related to the following HPV vaccines between 1 January 2005 and 31 December 2016: 9-valent human papillomavirus vaccine, 4-valent human papillomavirus vaccine, and 2-valent human papillomavirus vaccine. AE-signals were determined by meeting all three data mining criteria: proportional reporting ratio ($\geq$2, no of case$\geq$3), reporting odds ratio ($\geq$2, no of case$\geq$3), and information component (lower limit of 95% confidence interval $\geq$ 0). We then compared identified AE-signals with the HPV vaccine labeling information in Korea and the United States.

Results: A total of 24,105 AE reports for all vaccines and 125,437 AE-pairs were selected from the KAERS database. Of those, the number of HPV vaccine-related AE reports and AE-pairs were 2,566 (10.65%) and 4,748 (3.79%), respectively. Among the 97 detected signals, 13 AE-signals were not listed on the HPV vaccine labels of Korea and the United States; the most frequent AEs were tremor (49), back pain (15), hypotension (12), neuritis (12), anxiety (11), and circulatory failure (11).

Conclusions: We have identified new AE-signals that were not listed in the HPV vaccine labels. However, further studies are needed to investigate the causal relationship between the AE-signals identified from the study and the HPV vaccines to update the safety information of HPV vaccines in Korea.

802 | Monitoring the safety of high-dose, trivalent influenza vaccine in the vaccine adverse event reporting system (VAERS), 2010–2018

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Background: In December 2009, a high-dose, trivalent inactivated influenza vaccine (IIV3-HD, Fluzone High-Dose®) was licensed for adults aged ≥65 years. Injection site (8.9%–35.6%) and systemic reactions (16.8%–21.4%) were the most commonly observed adverse events in pre-licensure studies.

Objectives: To characterize reports to the Vaccine Adverse Event Reporting System (VAERS), a US spontaneous reporting system among older adults who received IIV3-HD.

Methods: We searched VAERS for reports of persons aged ≥65 years who received IIV3-HD from July 1, 2010 through December 31, 2018. We conducted an automated analysis of the characteristics of these reports and the following pre-specified conditions: Guillain-Barré syndrome (GBS), and anaphylaxis. We compared the proportion of serious events, pre-specified conditions, and adverse events (AEs) with those of Fluzone trivalent and Fluzone quadrivalent (IIV-SD) vaccines.

Results: VAERS received 12,755 reports after IIV3-HD; 754 (5.9%) were serious which included 52 deaths. Females comprised 9,209 (72.2%) reports. Median age was 71 years (range 65–102 years). The most common reported AEs were injection site erythema (15.9%), fever (15.4%), pain in extremity. (15.3%), injection site pain (13.8%), pain (13.8%) and chills (13.3%). There were 97 (0.8%) reports of GBS and 43 (0.3%) of anaphylaxis after IIV3-HD. Reports of serious events, GBS, and anaphylaxis for IIV-SD vaccines in adults ≥65 years (n = 2,590) were 9.7%, 2.9%, and 0.3%, respectively. The most common AEs for IIV-SD vaccines were injection site erythema (17.2%), injection site pain (15.3%), pain in extremity (14.9%), fever (13.4%), and pain (13.3%). Serious and GBS reports were reported less frequently after IIV3-HD when compared with IIV-SD vaccines and the proportion of the most common AEs were similar for both IIV3-HD and IIV-SD.

Conclusions: AEs after IIV3-HD were similar to those observed during pre-licensure studies and those reported after IIV-SD in VAERS. No new or unexpected safety concerns were identified for IIV3-HD reported to VAERS during 2010–2018. CDC will continue to monitor the safety of IIV3-HD and other influenza vaccines.

803 | Variation in vaccination for respiratory infections and associated outcomes across long-term care facilities

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Background: Pneumonia and influenza (P&I) cause substantial harm to frail older adults, especially those residing in long-term care facilities (LTCFs). Vaccination has proven to be an effective means of preventing P&I, however little is known about LTCF-level pneumococcal and influenza vaccination rates and their association with resident outcomes.

Objectives: To examine the association between LTCF vaccination rates and P&I hospitalizations while accounting for differences in resident characteristics. We hypothesized that LTCFs with higher pneumococcal and influenza vaccination rates would have fewer P&I hospitalizations for both short-stay and long-stay residents.

Methods: We conducted a retrospective cohort study using 2013–2015 Medicare claims linked to Minimum Data Set (MDS) assessments and LTCF data. Short-stay (<100 days) and long-stay (100+ days) LTCF residents were followed from admission (short-stay) or day 100 (long-stay) to hospitalization, discharge, Medicare disenrollment, or death. Exposure was LTCF-level pneumococcal and influenza vaccination rates, calculated using MDS data through a previously defined algorithm. The outcome was risk-standardized incidence rates (RSIRs) for P&I hospitalization per 1,000 person-years, calculated by adjusting for over 30 LTCF resident covariates using hierarchical logistic regression. LTCFs with vaccination rates above the median were compared to those below.

Results: We included 1,767,241 short-stay (13,683 LTCFs) and 922,863 long-stay residents (14,495 LTCFs). The overall LTCF-level pneumococcal and influenza vaccination rates were a median of 66.67% (IQR: 47.84%–79.48%) and 53.85% (40.54%–66.46%) among short-stay residents, and 73.33% (59.41%–83.63%) and 66.67% (55.74%–75.44%) among long-stay residents, respectively. LTCFs with higher pneumococcal vaccination rates had lower RSIRs (per 1,000 person-years) for short-stay residents [Mean (SD); Difference (95% CI): 106.73 (24.40) vs. 108.58 (24.35); −1.85 (−2.66, −1.03)] and no difference for long-stay residents [94.60 (39.64) vs. 93.52 (35.96); 1.08 (−0.15, 2.31)]. LTCFs with higher influenza vaccination rates had lower RSIRs for short-stay residents [106.82 (24.67) vs. 108.49 (24.09); −1.67 (−2.48, −0.85)] and higher RSIRs for long-stay residents [95.43 (40.32) vs. 92.69 (35.14); 2.74 (1.50, 3.96)].

Conclusions: Higher LTCF-level vaccination rates likely reduce P&I hospitalizations among short-stay residents. The absence of an association between LTCF-level vaccination rates and reduced P&I events for long-stay residents requires further study.

804 | Causality assessment of fatal outcomes following vaccination errors reported in EudraVigilance

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Background: Death following vaccination has occasionally been described in the context of appropriate use, but also in the context of

immunization errors. There is no thorough evaluation of spontaneously reported fatal vaccination errors available in the literature.

Objectives: The aim of this study is to systematically review reported Individual Case Safety Reports with a fatal outcome describing immunization errors as captured by EudraVigilance.

Methods: A case-series analysis of Individual Case Reports on cases reporting vaccination errors and a fatal outcome. Causality was assessed by two independent reviewers using the WHO tool for "Causality assessment of an Adverse Event Following Immunization". Causality was classified as consistent, indeterminate, inconsistent/coincidental, or unclassifiable. In addition, the impact of reported errors on the fatal outcomes was estimated. Error impact was classified as large, moderate, small, none, or unclassifiable.

Results: Preliminary data (based on one reviewer) show that there were 151 evaluable cases. Vaccines reported most frequently were pneumococcal (34), rabies (26) and influenza vaccines (24). Most frequently reported errors were incorrect schedule of vaccination (62), vaccination errors (23) and inappropriate age at vaccination (18). The most frequently reported vaccine-error combinations were rabies vaccines with incorrect schedule of vaccination (22), pneumococcal vaccines with incorrect schedule of vaccination (13), and influenza vaccines with inappropriate age at vaccination (12). Ten cases were classified as consistent with large error impact. These cases concerned use of poor-quality measles vaccines (6), administration of live varicella or rotavirus vaccines to immunocompromised patients (4). All but one of these cases was described in the literature. A third of the cases (35%) was also described in the literature, local newspapers or by regulatory authorities.

Conclusions: It is reassuring that very few cases were classified as consistent with large error impact. Continued publication of vaccination errors in the medical literature aids in transparency and detection of errors that need to be minimized. Delayed start of vaccination remains an issue in rabies post-exposure prophylaxis. More education and availability of rabies vaccines is necessary to limit incorrect schedule of vaccination and unnecessary deaths.

805 | Adverse events following adenovirus type 4 and type 7 live Oral vaccine in the vaccine adverse event reporting system (VAERS), United States, October 2011–July 2018

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Background: In March 2011, the U.S. Food and Drug Administration licensed adenovirus type 4 and type 7 live, oral vaccine (Teva Pharmaceuticals) (adenovirus vaccine) for use in military personnel 17 to 50 years of age. The vaccine was first universally administered to U.S. military recruits in October 2011.

Objectives: We investigated adverse event (AE) reports following the adenovirus vaccine submitted to the Vaccine Adverse Event Reporting System (VAERS).

Methods: We searched the VAERS database for U.S. reports among persons who received adenovirus vaccine during October 2011 through July 2018 including participants in a military observational study. We reviewed all serious reports and accompanying medical records. Since the VAERS form does not specifically identify recruits, we compared the proportion of serious reports in a proxy recruit population i.e., reports to VAERS with a date of vaccination from July 1, 1999 through October 31, 2011 (when adenovirus vaccine was unavailable) in service personnel aged 17–24 years old and from the eight states having DoD initial entry recruit sites and 1 US Coast Guard site. We also reviewed all reports of suspected allergic reactions following adenovirus vaccination.

Results: During the analytic period, VAERS received 100 reports following adenovirus vaccination; 39 (39%) were classified as serious and of these 17 (44%) were from the observational study. One death was reported. Males accounted for 72% reports. Median age of patients was 19 years (range 17–32 years). The most frequently reported serious AEs were Guillain Barré syndrome (GBS) (n = 12) and anaphylaxis (n = 8); of these two GBS and all the anaphylaxis reports were reported from the observational study. 95% of reports documented concurrent receipt of multiple other vaccines and intramuscular injection of penicillin G.

Conclusions: The percentage of serious AE reports in VAERS following adenovirus vaccine was higher than with other vaccines administered in the recruit military population (39% vs 18%); however, 17 (44%) serious adenovirus vaccine (including eight anaphylaxis) reports were in the observational study. No serious anaphylaxis reports were identified among persons who were not included in the military observational study suggesting the observational study stimulated serious reports of anaphylaxis. Also, 95% of all reports documented co-administration of other vaccines and intramuscular penicillin G in this military population. These other exposures may have contributed to the GBS and anaphylaxis outcomes observed with the vaccine.

806 | 3 years of post-licensure safety data on a live attenuated tetravalent dengue vaccine (CYD-TDV)

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Background: The live attenuated tetravalent dengue vaccine (CYD-TDV) was first licensed in Dec 2015. Vaccine exposure through public campaigns started in The Philippines and Brazil. Of the 2.9 million doses distributed worldwide, ~2.3 million have been used in these campaigns as of Dec 2018.

Objectives: To provide an update of the initial post-licensure safety data of CYD-TDV over a 3-year period.

Methods: We have summarized the post-marketing safety reports for CYD-TDV from worldwide sources at the marketing authorization holder (MAH) pharmacovigilance department from 8 Dec 2015 through to 7 Dec 2018.

Results: As of 7 Dec 2018, 2,992 adverse event cases have been reported, including 553 serious cases. The most frequently reported adverse events (pyrexia, headache, dizziness, myalgia, and vomiting) are consistent with those observed in the clinical development program and in the product label. Treatment-emergent allergic and anaphylactic reactions were reported at an estimated frequency of <0.01%. There were 3 cases of anaphylactic reactions meeting the Brighton Collaboration case definition, and 134 allergic reactions within the first 7 days post vaccination, 69 of which occurred within the first 24 hours. A total of 151 dengue cases, of which 101 hospitalized, were reported post vaccination either spontaneously from market research studies, or from the Post-authorization Safety study (PASS) conducted by Sanofi Pasteur (DNG15; NCT02948933). Among them, 51 cases were virologically-confirmed dengue and 10 suspected cases with a negative dengue NS1 antigen rapid diagnostic test. No cases of yellow fever vaccine-associated viscerotropic (YEL-AVD) or neurotropic (YEL-AND) disease were reported. Of the 58 cases with a fatal outcome, 16 had a dengue diagnosis, 5/16 were virologically confirmed, and 15/16 occurred in the Philippines. In a report from July 2018, the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that, as it was not possible to differentiate cases linked to vaccine failure from cases caused by vaccine-related immune enhancement in The Philippines, individual cases should not be attributed to one or the other but classified as indeterminate.

Conclusions: Safety surveillance in the initial post-marketing stage has been key to better assess the safety profile of CYD-TDV vaccine. The WHO GACVS considered indeterminate cause in fatal dengue cases. Overall, the MAH considers that the safety profile of CYD-TDV in persons with previous dengue exposure is favorable.

807 | Vaccination and risk of atrial fibrillation in the active component United States military

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Background: Reports of atrial fibrillation following vaccination are uncommon. Atrial fibrillation was a priority topic in the collaborative Vaccine Analytic Unit's research agenda to investigate rare or longer term adverse events potentially associated with anthrax vaccine (AVA). Atrial fibrillation is the most common sustained cardiac arrhythmia, with a lifetime risk of approximately one in four for men and women aged 40 years and older. Substantial morbidity and mortality is associated with atrial fibrillation primarily as result of ischemic stroke, thromboembolism, heart failure, dementia and impaired quality of life. Older age and several medical conditions predispose to atrial fibrillation but this outcome may also occur in the absence of identifiable underlying risk factors or comorbidities ("lone atrial fibrillation").

Objectives: To evaluate the hypothesis that receipt of anthrax vaccine adsorbed (AVA) increases the risk of atrial fibrillation in the absence of identifiable underlying risk factors or structural heart disease (lone atrial fibrillation).

Methods: We conducted a retrospective population-based cohort study among U.S. military personnel who were on active duty during the period from January 1, 1998 through December 31, 2006. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to identify individuals diagnosed with atrial fibrillation in the Defense Medical Surveillance System, and electronic records were screened to include only individuals without evidence of predisposing medical conditions. We used multivariable Poisson regression to estimate the risk of lone atrial fibrillation after exposure to AVA. We also evaluated possible associations with influenza and smallpox vaccines.

Results: Our study population consisted of 2,957,091individuals followed for 11,329,746 person-years of service. Of these, 2,435 met our case definition for lone atrial fibrillation, contributing approximately 8,383 person-years of service. 1,062,176 (36%) individuals received at least one dose of AVA; the median person time observed post-exposure was 3.6 years. We found no elevated risk of diagnosed lone atrial fibrillation associated with AVA (adjusted risk ratio = 0.99; 95% confidence interval = 0.90, 1.09; p = 0.84). No elevated risk was observed for lone atrial fibrillation associated with influenza or smallpox vaccines given during military service.

Conclusions: We did not find an increased risk of lone atrial fibrillation after AVA, influenza or smallpox vaccine. These findings may be helpful in planning future vaccine safety research.

808 | Pandemrix exposure and the risk of narcolepsy in children and adults: Validation study comparing results from patient-file-verified and register-based data in Finland

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Background: Register-based health studies have been commonly critized for poorly specific outcome definitions due to misclassification bias resulting in biased false negative findings.

Objectives: To evaluate the validity of register-based research with previous research based on validated data from patient files on association between Pandemrix vaccination and narcolepsy risk.

Methods: Methods: The child cohort included all children born during the years 1991–2005 and living in Finland at any time during the years 2009–10. The adult cohort included persons born during 1945–1990. Cases of narcolepsy (ICD-10 G47.4) diagnosed in all Finnish hospitals during 2009–10 were identified from the national hospital discharge register including all ambulatory hospital visits and in-patient

hospitalizations. In the original study, all the relevant records of the narcolepsy patients belonging to the cohort and diagnosed during the follow-up time were validated by reviewing the patient records. Information on the vaccination was obtained from the National Vaccination Register. The association of the Pandemrix exposure on the risk of narcolepsy was analyzed using Poisson regression method. The vaccination exposure was used as a time-dependent covariate in the analyses. The results were expressed as incidence rate ratios (IRR) with 95% confidence intervals (CI).

Results: The number of narcolepsy cases and the follow-up time, as well as the IRR for narcolepsy was similar between the original study (IRR 14.5, 95% CI 6.8–37.7) and the register study (IRR 13.1, 95% CI 6.4–31.3) in children. In adults, the number of narcolepsy cases was higher and the follow-up time was longer in the register study than in the original study. For the adults, IRR for narcolepsy was lower in the register study (IRR 1.7, 95% CI 1.2–2.3) than in the original study (IRR 3.1, 95% CI 1.8–5.5).

Conclusions: Our study showed that the previously observed associations between Pandemrix and narcolepsy in the original study could be identified also using the register data only. Further validation studies on other vaccination exposures and outcomes are needed.

809 | Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2018–19

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Background: It has been speculated that the low influenza vaccine effectiveness (VE) observed during the 2017–18 season may have been due to vaccine virus adaptation to growth in eggs. During this influenza A(H3N2)-predominant season, for the first time, we evaluated the relative VE (RVE) between cell-cultured and egg-based vaccines among 13 million Medicare beneficiaries and found that cell-cultured vaccines had a modestly higher VE than the comparable quadrivalent egg-based vaccines in preventing influenza hospital encounters (RVE 10.0%, 95% CI: 7.0% to 13.0%). In an interim analysis during weeks with a clearer A(H3N2) dominance, we found a slightly larger RVE (RVE 16.5%, 95% CI: 10.3% to 22.2%). The High-dose (HD) vaccine was also more effective than the Standard-dose egg-based vaccines.

Objectives: To analyze the RVE between the cell-cultured and egg-based influenza vaccines during the 2018–19 influenza season among Medicare beneficiaries ages ≥65 years.

Methods: Retrospective cohort study on beneficiaries ages ≥65 years who receive an influenza vaccine (cell-cultured, recombinant, egg-based quadrivalent; egg-based HD, adjuvanted, or standard-dose trivalent) during the 2018–19 season. We will use inverse probability of treatment weighting to adjust for potential confounders and Poisson regression to evaluate RVE in preventing influenza hospital encounters (inpatient hospitalizations and emergency room visits).

Results: Preliminary data as of January 31, 2019 indicate that, so far, influenza A(H1N1) has predominated. Among 13,596,330 vaccinated Medicare Fee-for-Service beneficiaries ages ≥65 years, 817,680 (6%), 270,992 (2%), 8,414,613(62%), 2,206,196 (16%), 1,551,096 (11%), and 335,753(3%) beneficiaries had received the quadrivalent cel-cultured, quadrivalent recombinant, egg-based high dose, adjuvanted, quadrivalent and trivalent standard-dose influenza vaccines, respectively. The preliminary demographic breakdown of vaccinees showed that their median age was 74 years, 5,712,809 (42%) were male, and 1,126,012 (8%) had low income (dual eligible) status.

Conclusions: Once the (ongoing) 2018–19 season study is completed, the findings will provide new evidence for evaluating whether the cell-cultured vaccine is more effective than the comparable egg-based vaccines during influenza A(H3N2) and A(H1N1)-dominated seasons.

810 | Safety of trivalent Adjuvanted influenza vaccine (aIIV3; Fluad), vaccine adverse event reporting system (VAERS), United States, July 2016–June 2018

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Background: Trivalent adjuvanted influenza vaccine (aIIV3; Fluad®) was approved in the United States (U.S.) in 2015 for adults aged ≥65 years and has been in use since the 2016–17 influenza season.

Objectives: To assess the safety profile of Fluad vaccine.

Methods: We analyzed U.S. reports for aIIV3 submitted from July 1, 2016 through June 30, 2018 to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system. Medical records were reviewed for serious reports. Among individuals ≥65 years of age, the relative frequency of the most commonly reported adverse events (AEs) after aIIV3 were compared with non-adjuvanted inactivated influenza vaccines given to adults aged ≥65 years, high-dose trivalent influenza vaccine (IIV3-HD) and trivalent or quadrivalent vaccines (IIV3/IIV4). Data mining analyses were undertaken to identify whether AEs for aIIV3 occurred disproportionately more than expected compared to all influenza vaccines.

Results: VAERS received 630 reports after aIIV3, of which 521 (83%) were in adults aged ≥65 years; 79 (13%) in persons <65 years and in 30 (5%) reports age was missing; 19 (3%) reports were serious, including two deaths (0.4%) related to cardiac condition and Sjogren's syndrome. The most common AEs reported in adults aged ≥65 years were injection site pain (21%) and erythema (18%), with similar proportions reported for IIV3-HD (17% and 19%, respectively) and for IIV3/IIV4 (15%, each). Except for reports related to vaccination of

inappropriate age (n = 79) and syringe malfunction (n = 6), data mining did not identify other disproportionately reported AEs.

Conclusions: Although our review of aIIV3 in VAERS did not identify any unexpected health conditions of concern, we observed more than twice the expected number of reports with administration of the vaccine to persons outside of the age range for which the vaccine is approved in the U.S. Health care providers should be educated on the age groups for whom aIIV3 is recommended.

811 | Opportunities and challenges for near real time monitoring (NRTM) of vaccine exposures and outcomes in the participating databases of the ADVANCE consortium

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Background: The Accelerated Development of VAccine beNefit–risk Collaboration in Europe (ADVANCE) is a public-private collaboration aiming to develop and test a system for rapid Benefit–Risk (B/R) monitoring of vaccines using electronic health record databases in Europe. Rapid B/R monitoring or Near Real Time Monitoring (NRTM) is a periodic collection and analysis of several key variables (e.g. coverage, adverse events, and vaccine preventable diseases) where an alert is triggered when these data suggest variations in the expected B/R profile in the population. NRTM can serve as an important tool for various stakeholders such as public health institutes, vaccine manufacturers and regulatory authorities.

Objectives: To understand opportunities and challenges of conducting NRTM (defined as a weekly refresh of data for analyses and visualization) using databases of the ADVANCE consortium.

Methods: A survey was developed and administered to all databases (DB) of ADVANCE Consortium (N = 10) that participated in the prior DB characterization activities. Responses were further discussed during an in-person meeting. The survey assessed delays and barriers to NRTM including **data entry delay**: an interval between the health encounter and system dates (the date on which the record is actually entered in the system that feeds the DB) and **data release delay**: an interval between the system or last collection date (the date on which data are last entered into a DB) and internal release date (the date on which the data are ready for querying internally).

Results: Information was received from 9 out of 10 DBs. These included 3 DBs from Italy: Val Padana, Tuscany, PEDIANET; 2 from the UK: the Health Improvement Network, Royal College of General Practitioners Research and Surveillance Centre (RCGP-RSC); 2 from Denmark: Statens Serum Institut (SSI), Aarhus Universitets Hospital; and 2 from Spain:the Primary Care Research Informatics Network (SIDIAP), Base de datos para la investigación Farmacoepidemiológica en Atención Primaria (BIFAP). Five DBs (Val Padana, Tuscany, SIDIAP, RCGP-RSC and SSI) concluded that they would in principle be able to implement NRTM of various types of outcomes during the ADVANCE project. Estimated data entry delay varied from <24 hours to several months depending on the DB and outcome of interest and data release delays varied from being instantaneous to up to 12 months.

Conclusions: NRTM is deemed feasible in some databases within ADVANCE, based on the qualitative assessment. Specific challenges will become clear upon the implementation of the NRTM.

812 | Uptake of Papanicolaou testing by HPV vaccination status

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Background: Although the annual incidence of cervical cancer in Israel is relatively low (5.4 per 100,000), the Ministry of Health recommends HPV vaccination among females and males at 8th grade as part of the national childhood immunization program. It is unclear whether young Israeli women who initiated HPV vaccination are more likely than unvaccinated women to report having a Papanicolaou (Pap) test later in life.

Objectives: To evaluate the impact of the HPV vaccine on cervical cancer screening program and to examine if uptake of Pap testing differed across subgroups of age and income by vaccination status.

Methods: Design and settings: This retrospective cohort analysis was carried out at Maccabi Healthcare Services (MHS), a 2.3-million-enrollee integrated care provider in Israel. From all women immunized with at least one dose of HPV vaccine from its introduction in Israel in June 2007 to Dec. 2018, we excluded those who had a Pap test prior vaccination as well as women who were no longer members of MHS on Dec. 2018. Over 20 thousand eligible vaccinated women were individually matched with non-vaccinated MHS members on one to one basis by exact birth year, socioeconomic level, and district of residence. Exposure: HPV immunization was collected from the women's electronic medical records (EMR) as well as information on demographic factors (date of birth, district of residence, enumeration area), body mass index, and ever smoked cigarettes. Socioeconomic status

was categorized according to the poverty index of the member's enumeration area. Main outcome: Data on the uptake of Pap smears were extracted from MHS central laboratory, and the number of Pap smears for each woman during the study period was counted. Statistical analysis: We started follow-up at the date of purchase of first vaccination dose and then followed them forward until Pap test or Dec 2018, whichever occurred first. We used Cox proportional hazards regression, with days of follow-up as the time scale.

Results: Proportion of women having Pap was significantly higher among HPV vaccinated women (27%) compared to 22% in non-vaccinated (aHR = 1.34; 95%CI: 1.29–1.41). Higher adherence with Pap smear tests among women vaccinated women was significantly higher compared to non-vaccinated across all relevant age groups.

Conclusions: We found no indication for lower adherence with Pap tests among women who were immunized with HPV vaccine in the past.

813 | BCG vaccination against *Mycobacterium tuberculosis* infection in pediatrics: A systematic literature review and meta-analysis

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Background: Tuberculosis (TB) is contributing a major cause of morbidity and mortality in pediatrics worldwide, and *Mycobacterium tuberculosis* infection are at increased risk of developing active TB.

Objectives: The objective of this study to determine the effect BCG vaccination against *Mycobacterium tuberculosis* infection as assessed by interferon γ release assays (IGRA) in pediatrics.

Methods: A systematic search on MEDLINE and Cochrane Central Register of Controlled Trials, was performed with pairing relevant keywords to identify English language articles published between January 2008 to December 2018. The eligible studies reporting vaccinated and unvaccinated aged under 18 years old with known recent exposure with pulmonary TB. A meta-analysis was conducted to calculate the risk ratio and 95% confidence intervals (CI) using random effect model. Statistical analysis was performed using RevMan 5.3 software. Publication bias was assessed by using Begg funnel plots.

Results: A total 13 relevant studies met the inclusion criteria, ranging in age from 1 month to 18 years. Included studies comprised of total 2230 patients in the vaccinated group and 840 patients in the unvaccinated group. The patients were screened for infection with *Mycobacterium tuberculosis* with the two types of interferon γ release assays (ELISpot or QuantiFERON) across the studies. The estimated overall risk ratio was 0.67 (95% CI 0.62, 0.73), indicating a significantly protective efficacy of 33% against infection among vaccinated after exposure compared with unvaccinated pediatric population. Sub group analysis showed protection against infection was 37% (risk ratio 0.63, 0.57 to 0.69) compared with 25% (0.75, 0.64 to 0.87) against active TB. No significant asymmetry was observed, suggested no evidence of publication bias.

Conclusions: The current meta-analysis found that, the BCG vaccination showed protective effect against *Mycobacterium tuberculosis* infection. However, further RCTs and real world studies with long term follow-up warranted to make this finding more robust.

814 | Effect of expanding Pharmacist's prescriptive authority on influenza and pneumococcal vaccination rates in the United States

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Background: Vaccines are essential tools in prevention of infectious diseases including influenza and pneumococcal disease. However, Vaccination rates remains below goals set by the United States government. Pharmacists can play a role in improving vaccination rates by expanding their prescriptive authorities.

Objectives: The aim of this study is to evaluate the effect of recent changes in vaccination laws on influenza and pneumococcal vaccination rates.

Methods: Data from the Behavioral Risk Factor Surveillance System (BRFSS) were used to calculate weighted proportions for influenza and pneumococcal vaccination rates from 2012 to 2016 along with the 95% confidence interval for the states of Arizona, California, Idaho, Louisiana, Maine, Montana, New Hampshire, West Virginia and Wyoming. Chi-square test was used to compare count data for the year before and the year in which law changes took effect. Further subgroup analysis was done on high risk groups including adults of age 65 or older, those who did not graduate high school and those with no personal doctor.

Results: A statistically significant ($P < 0.001$) increase in influenza vaccination rates in the states of Arizona, Maine, Wyoming (Absolute difference (AD): 1%), Montana and New Hampshire (AD: 3%) was observed. Meanwhile, there was no difference in vaccination rates in the states of Idaho and West Virginia. Contrarily, there was a significant decrease in vaccination rates in the states of California (AD: 3%) and Louisiana (AD: 2%). Furthermore, there was a significant increase in Pneumococcal vaccination rates in Arizona, New Hampshire and Wyoming (AD: 1%), Maine, Montana and West Virginia (AD: 3%), Idaho (AD: 4%), Louisiana (AD: 5%). Dissimilarly, in the state of California a statistically significant decrease was found (AD: 2%).

Conclusions: Changes in pharmacist's vaccine prescriptive authority were associated with an increase in influenza and pneumococcal vaccination rates in most of the states understudy and a decrease in two states. A number of demographic, socioeconomic and logistical factors

could have contributed to the inconsistent effects found, which emphasize the importance of post-regulatory steps in adopting pharmacist's role in vaccination.

815 | Trends in overall vaccine-related adverse event reports and vaccination during pregnancy, 2000–2016

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Background: Vaccine safety surveillance is critical to maintain confidence in national immunization. Although the trends of overall adverse events (AEs) following immunization are being established, information on the vaccine utilization and safety during pregnancy are still in need.
Objectives: To present the overall trend of reported AEs following immunization and describe the number and type of AEs reported from immunization during pregnancy over the 17-year period.
Methods: We described the trend of AEs following immunization and detected signals using the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System database (KIDS-KD), between January 2000 and December 2016. A total of 17 vaccines were included. The number of reported AEs were calculated by year, and AE reports were classified by vaccine and types of AEs. To identify vaccine-related AEs in pregnant women, WHO-ART Code 2221, "Exposure during pregnancy", was used to define pregnant women who were vaccinated and experienced the AEs. The vaccine-AE pairs were detected as signals by meeting all three indices: proportional reporting ratio (≥2, no of case≥3), reporting odds ratio (≥2, no of case≥3), and information component (lower limit of 95% confidence interval ≥ 0).
Results: Vaccine-related AE reports remained relatively consistent up until 2011 and increased remarkably in 2013 (*n* = 2406), three-fold higher compared with 2011 (*n* = 774). Of total 11,042 reported AEs for all vaccines, influenza vaccine accounted for more than half (56.7%), followed by pneumococcal (11.6%), Bacillus Calmette-Guérin (BCG) (5.0%), *Haemophilus influenzae* type b (4.5%), human papilloma virus (4.5%). The majority of reported AE pairs were non-serious events: injection site pain (23.6%), muscle pain (9.1%), fever (7.0%). In pregnant women, human papilloma virus vaccine (*n* = 27), smallpox (*n* = 9) and measles-mumps-rubella (n = 2) were the most reported vaccines. Abortion (*n* = 5), fetal death (*n* = 1), and small for gestational age (n = 1) were rarely reported during pregnancy. The most predominant signals detected in influenza vaccines, pneumococcal and BCG were injection site pain, cellulitis, and lymphadenopathy, respectively.
Conclusions: The findings on the overall trend of reported AEs following immunization was mostly consistent with the previous reports from the United States and Australia, except for BCG vaccine since routine vaccination is not recommended in those countries. Lastly, HPV vaccine safety during pregnancy needs to be investigated promptly as suggested by our preliminary findings on the vaccine exposure during pregnancy.

816 | Detection of adverse events after pneumococcal vaccines immunization from Korea adverse events reporting system database, 2005–2016

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Background: As part of Korea's National Immunization Program, Pneumococcal polysaccharide vaccines and Pneumococcal conjugate vaccines are being used. However, safety concerns regarding these vaccines persists as undetected adverse events (AEs) may exist.
Objectives: We aimed to compare adverse events of Pneumococcal vaccines with all other vaccines using Korea Adverse Events Reporting System (KAERS) database and to determine the signal of Pneumococcal vaccines by comparing the information with the drug labels of Korea.
Methods: We analyzed the cases of adverse events for Pneumococcal vaccines and all other vaccines reported through KAERS Database from 2005 to 2016. In this study, adverse events which were detected by all three indices of data-mining, PRR (Proportional Reporting Ratio), ROR (Proportional Odds Ratio) and IC (Information Component) were defined as a signal. After then, we determined the signals by comparing the information on the drug labels of Korea.
Results: Of total 24,105 reports corresponding to 125,437 vaccines-AE pairs, 4,748 (26.4%) AE-pairs were Pneumococcal Vaccines related. The detected signals for Pneumococcal vaccines by met the criteria of three data mining indices were 97 AEs. Among them, the total number of 13 AEs were not listed on the drug label of Korea: the most frequent AEs were tremor (49), back pain (15), hypotension (12), neuritis (12), anxiety (11), and circulatory failure (11); all AEs were reported in more than 10 cases.
Conclusions: Our signal detection found 13 new AEs associated with Pneumococcal vaccines which may be causal, with respect to other vaccines. Further research is needed to confirm causality associated with Pneumococcal vaccines.

817 | Treatment patterns of checkpoint inhibitors in metastatic melanoma

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Background: Melanoma incidence is rising and the 5-year survival for melanoma with distant metastasis is 23%. Checkpoint inhibitors are

indicated as first-line therapy for metastatic melanoma, and discontinuation may be required due to disease progression or immune-related adverse events.

Objectives: To describe recent treatment patterns of ipilimumab (IPI), pembrolizumab (PEM), and nivolumab (NIVO) for metastatic melanoma in the US.

Methods: We assembled a retrospective cohort study of adults with metastatic melanoma using MarketScan® Databases. All patients were assigned a time-zero as the date of first exposure to IPI, PEM, NIVO, or combination IPI/NIVO over Jan 2012-Dec 2016. We required patients to have health/drug plan coverage for 12 months before and 12 months after time-zero. We described baseline (year prior to time-zero) characteristics and treatment patterns during the first year of follow-up.

Results: We studied 710 patients initiating IPI (*n* = 442), PEM (*n* = 121), NIVO (*n* = 68), and IP/NIVO (*n* = 79). Median age was 59 (interquartile range 52–65) years and 61% were male. IPI was the only drug available from 2012–2014; use of other agents increased over time with PEM being most common (39%) as of 2016. Overall, at baseline, 11% had prior BRAF inhibitor use (vemurafenib, dabrafenib, and trametinib), 22% prior radiotherapy, 27% prior melanoma-related surgery, and 34% prior conventional chemotherapy (mostly cisplatin, dacarbazine, vinblastine) (non-mutually exclusive proportions). Use of conventional chemotherapy prior to checkpoint inhibitors declined from 50% in 2012 to 32% in 2016 (95% confidence interval, CI, for difference in proportions 6–28%). Use of conventional chemotherapy during the first year of follow-up also declined (26% in 2012/2013 vs 14% in 2016/2017, 95%CI for difference 3–21%) as did melanoma-related surgery (18% in 2012/2013 vs 9% in 2016/2017, 95%CI for difference 1–17%). During the first year of follow-up, additions of BRAF inhibitors ranged from 8% in PEM to 19% in IPI/NIVO. Switching to another checkpoint inhibitor ranged from 17% in IPI/NIVO to 34% in IPI. Among patients using IPI (alone or with NIVO), 64% completed the recommended course (4 doses within 16 weeks from initial dose). At one year, 62% of NIVO users and 55% of PEM users remained on therapy (without a gap of more than 6 weeks between doses).

Conclusions: The melanoma therapeutic landscape has changed considerably throughout 2012–2017, with increasing checkpoint therapy use. Over one-third of IPI users did not complete 4 doses and a large proportion discontinued NIVO and PEM at one year. Further analyses will investigate reasons for discontinuation.

818 | Measuring treatment intensification in patients with type 2 Diabete: An electronic health records based study

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Background: Delayed treatment intensification of glucose-lowering therapy (GLT) is a major contributor to suboptimal glycemic control in patients with type 2 diabetes (T2D). Measuring treatment intensification, however, is fraught with conceptual and methodological issues when using secondary databases.

Objectives: We sought to quantify treatment intensification using an existing electronic health records (EHR)-based cohort and to identify issues around operationalizing this clinical phenomenon.

Methods: This was a retrospective, observational study of adults, ≥21 years of age, with T2D and incident users of an oral GLT from a community-based healthcare delivery system in northern California (2003–2017). We quantified the proportion of patients with treatment intensification, defined as a daily-dose increase of first-line GLT or a prescription for second-line GLT (of a different class) in the 3 to 12 months following treatment initiation. We further classified delayed treatment intensification as lack of intensification ≤6 months of uncontrolled hyperglycemia (HbA1c >7% for ages 21–75 of HbA1c >8% for ages >75). Lastly, we highlighted potential issues in operationalizing treatment intensification, and its timeliness, given the nature of retrospective databases.

Results: Among 58,586 patients with first-line GLT, 77% initiated treatment with metformin, 16% with a sulfonylurea, and 7% with a different oral GLT. During follow-up, 21% had treatment intensified between 3 and 12 months after treatment initiation: 9.5% with a daily-dose increase and 11% with a second-line GLT. Most common second-line GLTs were sulfonylureas (30%) or metformin (28%) among patients who did not initiate treatment on these agents, followed by insulin (14.3%) and insulin sensitizing agents (14.1%). Mean time to intensification was 184.9 days (median = 168 days). Only 8% of patients had treatment intensified within 6 months of first evidence of uncontrolled hyperglycemia. Follow-up HbA1c was missing among 23% of patients.

Conclusions: In a cohort of patients with T2D from a community-based healthcare system, approximately one-fifth of patients initiating GLT had treatment intensified within a year. Among patients with evidence of uncontrolled hyperglycemia at follow-up, the vast majority had delayed or no treatment intensification. Determining when intensification should occur is complicated by missing lab values, individualized glycemic targets, and patient/physician preferences. Multiple sensitivity analyses should be employed.

819 | Trends in blood pressure thresholds for initiation of antihypertensive treatment in patients with type 2 diabetes

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Background: There have been changes in the recommended systolic blood pressure (SBP) threshold for initiating antihypertensive treatment in patients with type 2 diabetes (T2D). Particularly, attention for a more patient-centered approach has increased over time, including higher thresholds for the elderly population.

Objectives: To assess trends in SBP thresholds at antihypertensive treatment initiation in T2D patients, and the influence of patients' age on these SBP thresholds.

Methods: We used the Groningen Initiative to Analyze Type-2 diabetes Treatment (GIANTT) database, which includes data about patients with T2D treated in primary care in the north of the Netherlands. For each calendar year between 2007 and 2013, patients were included if they had initiated antihypertensive treatment, and had an SBP measurement within 365 days before treatment initiation. The influence of the year on SBP level at initiation was assessed using a linear regression analysis. ANOVA was conducted per year to assess the influence of age groups (<60 years; 60–69 years; 70–79 years; ≥80 years) on the SBP level at initiation.

Results: A total of 3,397 patients initiating treatment (296 in the year 2007; 366 in 2008; 486 in 2009; 490 in 2010; 623 in 2011; 587 in 2012 and 549 in 2013) were included (48% female, average age 65 years). The average SBP levels at treatment initiation significantly decreased over time (β = −0.604, P = 0.002), from 157 mmHg to 154 mmHg. For patients aged <60 years a decrease from 155 mmHg in 2007 to 152 mmHg in 2013 was seen, whereas in older patients the thresholds seemed to peak in 2010 (around 160 mmHg) and decreased to 156, 156, and 154 mmHg for the three higher age groups in 2013, respectively. Statistically significant differences between the age groups were observed in the years 2008, 2010, 2011 and 2012.

Conclusions: Over time, antihypertensive treatment was initiated at lower SBP levels among patients with T2D treated in primary care. In general, elderly patients initiated antihypertensive treatment at higher SBP levels than younger patients, but the thresholds for the older age groups also decreased in more recent years. This does not appear in line with changes in treatment guidelines.

820 | Incidence of direct Oral anticoagulation use for non Valvular atrial fibrillation and characteristics of users in six European countries (2008–2015): A cross-National Drug Utilization Study

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Background: The newer direct oral anticoagulants (DOACs) have been approved by the European Union since 2008. Utilization of DOACs for stroke prevention in non-valvular atrial fibrillation (NVAF) and their effectiveness and safety in clinical practice have been assessed in several European countries. However, little is still known about their use beyond the clinical trial conditions, especially in patients with hepatic or renal impairment.

Objectives: To estimate the incidence of Direct Oral Anticoagulant Drugs use in non-valvular atrial fibrillation (NVAF) and to describe user and treatment characteristics in 8 European health databases (Mondriaan, Bavarian CD, AOK Nordwest, BIFAP, SIDIAP, CPRD, EGB and DNR) representing 6 European countries (The Netherlands, Germany, Spain, United Kingdom, France and Denmark).

Methods: Descriptive cohort study from January 2008 to December 2015. A common protocol approach was applied. Annual period incidences and direct standardization by age and sex were performed. An incidence percentage change in DOAC use, dose adjustment related to change in age and by renal function as well as concomitant use of potential interacting drugs during first DOAC episode were assessed.

Results: A total of 186,405 new DOAC users (≥18 years) were identified. The standardized incidence increased for all DOACs over the study period, with the highest increase for apixaban (554.5%) followed by rivaroxaban (80.7%). The highest incidence for all DOACs was found in Denmark and Germany, with lower values and slight differences among the remaining databases. The incidence of DOAC use increased for both genders in most databases and especially in those older than 75. Concomitant use of contraindicated drugs varied between 16.4% (SIDIAP), and 70.5% (EGB) and dose adjustment ranged from 4.6% in the Spanish (BIFAP) to 15.6% in the French (EGB) population.

Conclusions: The overall incidence of new DOAC users increased, with the highest increase for apixaban. Cross national drug utilization studies with a standard protocol may help to compare drug use and enable health care decisions. This study was funded by the European Medicines Agency (EMA/2015/27/PH; EU PAS Register No: 16014).

821 | Assessment of the Calcium Channel blocker, lower extremity edema, loop diuretic prescribing Cascade: A prescription sequence symmetry analysis

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Background: Dihydropyridine calcium channel blockers (DH-CCB) are commonly used first-line medications used to treat hypertension; however, they are associated with lower extremity edema (LEE). A previous case report and cross-sectional study identified the potential for a prescribing cascade (PC), in which DH-CCB associated LEE was treated with a loop diuretic instead of discontinuing the DH-CCB.

Objectives: To assess temporality of the DH-CCB associated LEE, Loop PC and the estimated percentage of patients impacted by this PC.

Methods: A prescription sequence symmetry analysis (PSSA) was used to assess the initial prescribing of a loop diuretic relative to the initial prescribing of a DH-CCB among patients in outpatient clinics of a university health system. Patients who initiated on a DH-CCB and loop diuretic on the same day were excluded. Patients with congestive heart failure (CHF) were excluded, since the use of a loop diuretic in this population was likely due to volume overload. Crude (cSRs) and adjusted sequence ratios (aSRs) with 95% confidence intervals (CI) were calculated within a 360-day window of the DH-CCB initiation. Stratified analyses were performed on the basis of age (<65 and ≥ 65), sex, initial DH-CCB dose (low/standard dose and high dose, and number of other antihypertensive classes (0–1, 2–3, 4 or more) at the time of the DH-CCB initiation. The estimated percentage of patients impacted by the DH-CCB, LEE, Loop PC was calculated by the difference in the number of initial loop diuretics after and before DH-CCB initiation divided by the number of DH-CCB initiators.

Results: We identified 5,153 DH-CCB initiators without a diagnosis of CHF. A total of 106 patients were initiated on both a DH-CCB and a loop diuretic within the 360-day window. Among DH-CCB initiators without CHF, the cSR was 2.21 and aSR was 2.10 (95% CI 1.39–3.17). There appeared to be no differences in the aSR between age, sex, and initial DH-CCB dose. When stratified by number of other antihypertensive classes, there were differences in aSR of 0–1 (2.35, 95% CI 1.29–4.26), 2–3 (1.96, 95% CI 1.12–3.45), and 4 or more (0.80, 95% CI 0.34–1.90) classes. We estimated that 1% of DH-CCB initiators without CHF experienced the DH-CCB, LEE, Loop PC.

Conclusions: Patients with CHF were two times more likely to be prescribed a loop diuretic after a DH-CCB relative to before, confirming the temporality of the PC. Although a small percentage of DH-CCB initiators experienced a potential PC, the overall number of patients impacted by this PC is likely substantial since DH-CCB are commonly used to treat hypertension.

822 | Appropriate prescribing in nursing homes demonstration project: A pragmatic, cluster-randomized trial

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Background: Inappropriate medication use in the nursing home setting is associated with preventable harms. Antipsychotics are a major culprit of inappropriate medication use. Inappropriate antipsychotic use has been the focus of significant clinical, research, and policy attention. The province of Ontario launched standard feedback tools to nursing homes in the province which helped reduce antipsychotic use. Additional proposed strategies to reduce inappropriate use of antipsychotics centre on educational and interdisciplinary interventions, such as academic detailing (AD). AD has been shown to have considerable variation in effectiveness and unknown long-term sustainability.

Objectives: To assess the real-world effectiveness of AD into nursing homes targeting appropriate prescribing of antipsychotics.

Methods: We conducted a pragmatic, cluster-randomized trial comparing AD (intervention) to audit and feedback (comparator) on prescribing of antipsychotic medications in nursing homes in Ontario, Canada. We used patient-level administrative claims data to assess changes in antipsychotic use. The primary outcome was the proportion of antipsychotics dispensed to residents in the past 7 days. Secondary outcomes included prescribing of other psychotropic medications and clinical outcomes such as falls and hospitalizations. Descriptive statistics were reported for all home and patient characteristics of interest at baseline. Outcomes were assessed at baseline and 3,6, and 12 months after randomization. Data were analyzed using home-level repeated measures analysis with generalized linear mixed effects regressions.

Results: A total of 40 nursing homes with 5,363 residents were randomized (18 intervention homes and 22 control homes). At 12 months, the proportion of residents with daily antipsychotic use in the past 7 days was similar between arms with 25.2% in the intervention group and 25.6% in the control group (p = 0.49). Among a subgroup of homes with higher baseline antipsychotic prescribing rates, there was a higher rate of reduction in antipsychotic use. There was no statistically significant difference between arms in clinical outcomes (e.g. falls) but the intervention group did experience a greater reduction in pain (P < 0.001) and depression scores (P < 0.001).

Conclusions: AD may not reduce antipsychotic use in an environment where standard quality improvement interventions are already achieving needed changes in prescribing. There may be a potential benefit of a data-driven approach to target homes with higher rates of antipsychotic use.

823 | Identifying signals of warfarin drug–drug interactions: A translational biomedical informatics approach using real world clinical evidence

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Background: Drug–drug interactions (DDIs) with warfarin are associated with increased risk of serious bleeding. Warfarin is susceptible to numerous DDIs via various mechanisms.

Objectives: To systematically evaluate all potential interacting drugs used concomitantly with warfarin (i.e. the object drug) in clinical practice to affect international normalized ratio (INR, a quantitative biomarker of warfarin-induced anticoagulation) and to cause serious bleeding.

Methods: We identified all oral medications frequently co-prescribed with warfarin in OptumInsight Clinformatics Data Mart (Optum), 2000–2016 as potential interacting precipitants. We conducted three independent studies in parallel. First, we predicted potential DDIs to affect the rate of serious bleeding using physiologically based pharmacokinetic (PBPK) modeling for each warfarin-precipitant drug pair (R- and S-warfarin examined separately). Second, we conducted a series of cohort studies in Optum to identify which precipitants were associated with an increased or decreased INR in warfarin users. Change in INR after vs. before precipitant initiation was estimated using conditional mixed effect model adjusted for warfarin dose change. Third, we conducted a series of self-controlled case series studies using Optum to identify which precipitants were associated with increased rate of serious bleeding. Conditional Poisson regression was used to estimate rate ratios (RR) comparing precipitant exposed vs. unexposed time for each warfarin-precipitant drug pair. Pravastatin was examined as a quantitative negative control object drug. In the latter two studies, multiple estimation was adjusted via Semi-Bayes shrinkage.

Results: We predicted 5 weak DDIs, 3 with S-warfarin and 2 with R-warfarin based on PBPK modeling. We identified 63 precipitants associated with statistically significantly elevated INR and 51 precipitants associated with statistically significantly reduced INR following precipitant initiation. There were 128 precipitants associated with increased rate of serious bleeding. After adjusting for pravastatin, 20 (16%) precipitants were associated with increased rates of serious bleeding. There was a positive association between pharmacokinetic prediction for S-warfarin and RR for serious bleeding (coefficient = 0.086, $p = 0.006$).

Conclusions: The translational approach of combining pharmacokinetic prediction and pharmacoepidemiologic screening of biomarker and clinical endpoint could be useful for systematic identification of DDIs.

824 | Drug safety signal detection in a Chinese regional healthcare database using the tree-based scan statistic and comparison to 3 other statistical methods

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Background: The tree-based scan statistic (TreeScan) is a statistical data mining tool that has been used for drug safety signal detection. Little is known, however, about its performance when compared to other signal detection methods.

Objectives: To evaluate the relative performance of Tree-based Scan Statistic (TreeScan), crude cohort study, Bayesian confidence propagation neural network (BCPNN) and Gamma Poisson Shrinker (GPS) methods for detecting statins-related Adverse Events (AEs) in electronic healthcare database.

Methods: Patients older than 18 years with a diagnosis of hypertension in Yinzhou healthcare database from 2010 to 2016 were included in our study. We identified statin users according to the prescription information of out/in-patients. The AEs were defined by using the ICD-10 codes of out/in-patient diagnosis. We established a set of reference signals to better evaluate the performance of each method. Then the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, youden index and area under the curve (AUC) of methods were calculated for evaluation. Moreover, our study compared the evaluation indicators of 4 signal detection methods. For AUC, we tested the statistical significance of the difference between the areas under two curves with the method of DeLong. In sensitivity studies, we compared these 4 methods in 2 different situations, including new-user cohorts and propensity score matched (PSM) cohorts.

Results: The sensitivities of TreeScan, BCPNN and GPS were the same (69%) and larger than the crude cohort (46%). The specificity, PPV, NPV, accuracy, youden index of TreeScan were the largest in 4 methods, 82%, 31%, 96%, 81%, 52%, respectively. And AUC of TreeScan (0.75, 95%CI: 0.62–0.89) was significantly larger than other 3 methods. In new-user cohort and PSM cohort, the results remained consistent in original cohort design. The AUC of TreeScan were 0.79 (95%CI: 0.65–0.93) and 0.77(95%CI: 0.64–0.92), which was significantly larger than the other 3 methods, respectively.

Conclusions: In this example, TreeScan performs better than crude cohort, BCPNN, and GPS. It is proposed as a complement for other signal detection methods in drug safety active surveillance.

825 | Contribution of natural language processing in predicting risk of pleural and pericardial effusions in small cell lung cancer by line of therapy

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Background: The use of electronic health records (EHR) with natural language processing (NLP) has been rising in pharmacoepidemiology and pharmacovigilance.

Objectives: To evaluate the contribution of NLP use when combined with diagnosis and procedure codes in predicting risk of pleural (Pl) and pericardial (Pc) effusions in small cell lung cancer (SCLC), by line of therapy (LOT), in Optum EHR.

Methods: Optum's EHR database consists of de-identified EHR data from a network of healthcare provider organizations in the US. In addition to structured data tables, Optum Analytics utilizes NLP computing technology to extract critical facts from physician notes into usable datasets. Of 8,291 patients with newly diagnosed SCLC between 01/01/2008 and 09/30/2016, 3,633, 1,211 and 428 patients received 1st, 2nd and 3rd LOT, respectively. Pl and Pc effusions were each identified according to 3 criteria: criterion 1 (ICD-9/ICD-10 codes), criterion 2 (ICD-9/ICD-10 or procedures), and criterion 3 (ICD-9/ICD-10, procédures, or NLP SDS term and sentiment). Incidence of Pl and Pc effusions in each LOT was calculated by dividing number of patients with at least one new occurrence from start of LOT to the earlier of (30 days after end of current LOT or start of next LOT) by number of patients at risk at start of LOT.

Results: At diagnosis, median age was 69, 46% were male, 84% had extensive disease. The incidence of Pl and Pc effusions in SCLC were similar according to criterion 1 and criterion 2; adding procedures to criterion 1 did not generate additional Pl or Pc cases. By further adding NLP SDS term and sentiment to criterion 2, the incidence of Pl effusion increased from 8.4% (95% CI, 7.5–9.5%) to 19.0% (95% CI, 17.5–20.7%) in 1st LOT, 7.0% (95% CI, 5.5–8.8%) to 11.8% (95% CI, 9.6–14.4%) in 2nd LOT, and 7.4% (4.9–10.7%) to 15.0% (95% CI, 11.0–19.7%) in 3rd LOT. The incidence of Pc effusion increased from 0.7% (95% CI, 0.4–1.0%) to 4.8% (95% CI, 4.1–5.6%) in 1st LOT, 0.4% (0.1–1.0%) to 4.5% (95% CI, 3.3–5.9%) in 2nd LOT, and 1.4% (95% CI, 0.5–3.1%) to 7.4% (95% CI, 4.9–10.6%) in 3rd LOT.

Conclusions: NLP use improves pleural and pericardial effusion case identification in small cell lung cancer when combined with diagnosis and procedure codes in Optum EHR. Future studies on the validity of NLP-based algorithm in adverse event detection are warranted (such as positive predictive value).

826 | Text mining to identify drug–drug interactions (DDIs) in elderly patients admitted to emergency department

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Background: Clinically Significant drug–drug interactions (CS-DDIs) can have serious consequences, and lead to emergency department (ED) visit, in particular in elderly. The Bordeaux ED has set up, for patients over 75 years, a questionnaire to evaluate the usual treatments at the entry of ED.

Objectives: To evaluate the performances of a text-mining based-tool for the detection of CS-DDIs in elderly admitted to ED, and to estimate the prevalence of CS-DDIs in this population.

Methods: Design: A retrospective study based on medical records of ED of Bordeaux was performed. Patients ≥75 years old, admitted between September, 2016 and August, 2017, with at least one declared drug were included. Setting: Geriatricians interviewed patients or caregivers through a standardized questionnaire, filled-in directly in the hospital information system in free text. An automated program identified and coded drugs via Natural Language Processing techniques. Then, the text-mining and knowledge-based algorithm developed within the Synapse tool was used to identify automatically CS-DDIs using the French Drug Agency interaction thesaurus. Data analysis: A subset of randomly selected 400 drug-pairs was used to evaluate the specificity of the tool in identifying CS-DDIs compared to a Gold Standard (GS) in which CS-DDIs were selected by a pharmacologist and an ED physician. A second analysis was performed using all CS-DDIs found by the tool among the completed questionnaires in order to determine the positive predictive value (PPV) of the tool. The prevalence of DDIs was calculated as the rate of CS-DDIs on the total number of questionnaires.

Results: Overall, 5860 questionnaires were completed (median of 5 treatments per questionnaire). Among these questionnaires, the tool found 375 CS-DDIs, for a prevalence of 6.4% (95% CI, 5.8%–7.0%). The specificity of the tool was of 100%. Among the 400 analyzed drug-pairs, GS and tool found 398 non CS-DDIs and two same CS-DDIs. The PPV was of 99.7 (95% CI, 99.2%–100%), as 374 of the 375 CS-DDIs found by the tool were confirmed by the GS.

Conclusions: The automated identification of clinically significant DDIs appeared reliable but needs to be confirmed on a larger data set. The prevalence of CS-DDIs found in the elderly admitted to ED was higher than expected.

827 | Nationwide adverse drug reaction screening using high process computing

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Background: Detecting adverse drug reactions has a very important role in minimizing drug-related harms, particularly in older adults. Previous studies have mainly focussed on ascertaining known adverse drug reactions (ADRs). We present here a sequence-symmetry based approach aided by high process computing (HPC), to systematically detect all putative signals of abrupt ADRs and improve efficiency of screening of administrative health databases.

Objectives: The aim of this study is to identify all signals of significant drug-event associations that can be abrupt ADRs, in the New Zealand (NZ) 65 yr + population by parallelizing sequence-symmetry calculations.

Methods: We sourced hospital events and prescription data (2005–2016) from the NZ Ministry of Health. We processed the data using the HPC facility at Bath University and created a self-matched cohort. The day an individual started a drug of interest is the index-date, and this ascertains non-exposure before the index-date. We defined a pre-initiation window and a post-initiation window before and after the initiation respectively. We identified a first-time diagnosis of interest in both windows. Window lengths of 7, 15 and 30 days were considered. Short window lengths ascertain current or recent first-time exposures at occurrences of new events, and that the new events can be abrupt ADRs. We calculated adjusted sequence ratios (ASR) to measure the increased odds of first-time event post-initiation relative to the background using the Hallas' method, with modifications that the calculations are within the pre-post window-pairs. We stratified the cohort by drug and diagnosis and used HPC to calculate all ASRs in parallel. Starting with 7-day windows, we detected signals with 100% odd increases (log (ASR) > 0.69), and then detected more signals with longer windows.

Results: Our dataset has 2,170,393 new events, covering 9009 ICD-10-AM codes; and 37,359,480 drug initiations, covering 914 drugs. We found a total of 183 strong drug-event associations including well-known ADRs, for example ibuprofen and GI-bleeding (K92.2, log (ASR) = 0.79 [0.41–1.16]), as well as warfarin and subdural hemorrhage (I62.0, log (ASR) = 1.94 [0.52–3.36]). A number of less well-known associations that can be ADRs were also detected, for example bendrofluazide and hyponatremia (E87.1, log (ASR) = 1.89 [1.22–2.56]), codeine and enterocolitis (A04.7, log (ASR) = 0.76 [0.34–1.17]).

Conclusions: With the aid of HPC, the symmetry-based algorithm has the potential for the development of an efficient, big-data ADR-signal detection software to improve medication safety and advance post-marketing surveillance.

828 | Detecting rare diseases: A case study using machine learning semi-supervised networks to identify under-diagnosed patients

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Background: Patients affected by rare diseases may present with a combination of symptoms that mimic more common conditions, making it challenging for physicians without specific therapeutic area experience to diagnose. These patients often spend years with a misdiagnosis, or no diagnosis at all. With careful guidance, machine learning within insurance claims can help identify likely rare disease cases in as-yet undiagnosed populations and provide key insights for diagnoses and treatment. Precise predictive modeling is challenged, however, by the high dimensionality of medical features for rare disease patients coupled with the small number of confirmed diagnoses. Together, these issues limit the ability to "train" the machine to detect undiagnosed patients.

Objectives: Develop and implement a novel machine learning method to boost the ability to accurately predict undiagnosed rare disease patients.

Methods: Deep learning models have achieved significant results in recent years, but they require a large amount of "labeled data"- in this case, diagnosed patients- to train. We created a Semi-supervised Generative Adversarial Network (SGAN) to support rare disease detection. Model training techniques such as feature mapping and pull away terms were applied to improve prediction accuracy. Synthetic patients were then generated within the claims to boost weak signals and inform machine algorithms. Due to the imbalanced nature of rare disease data, Precision-Recall and Area Under the Curve (PR-AUC) was used to measure model performance.

Results: These techniques were able to boost weak signals within small samples to train a better predictor relative to the more comment Logistic Regression and Random Forest techniques. The SGAN had 0.34 PR-AUC, meaning that it can identify 34 out of 100 undiagnosed rare disease patients. This is a 3-fold improvement relative to Random Forest techniques and 29% over standard Deep Neural Networks.

Conclusions: Predicting symptomatic but undiagnosed rare disease patients out of millions is a challenge to understanding these diseases and providing the right treatment. Machine learning techniques are needed to combat this issue, but they must work within a complicated medical population and small available samples with which to train the machine. The innovative network architecture of the SGAN model provided the ability to leverage unlabeled patient samples within claims data to improve precision and performance of predictive models. This technique can be applied in similar "big data" settings with only small populations of firmly diagnosed patients.

829 | Evaluation of bias in case-crossover analyses of persistent drug exposures

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Background: Previous empirical investigations suggest that a case-crossover analysis may be biased when the population includes a mix of transient and persistent medication users; however, these results may have conflated other sources of bias.

Objectives: To evaluate the performance of the case-crossover design in the context of chronic therapy using simulated data.

Methods: We simulated cohorts, where either all patients were exposed to (1) 180-day therapy; (2) 30-day therapy; or (3) some patients were exposed for 30 days while the remaining portion did not stop therapy following initiation (i.e., stayed on therapy until the end of the study period). For scenario (3), we varied the percentage of patients with persistent exposure (10%, 30%, 50%, and 70%). We evaluated all scenarios under the null (true odds ratio [OR] of 1.0), and scenario (3) with varying non-null true ORs (0.5, 0.8, 1.25 and 2.0). Cases were analyzed using conditional logistic regression that compared odds of exposure on the outcome date to the odds of exposure on a day 30 days prior to the outcome. We generated 1,000 cohorts for each scenario and compared mean estimates for the effect of exposure on the outcome and mean bias.

Results: Case-crossover estimates were unbiased in scenarios where all patients were exposed for either 30 days or 180 days. In scenarios where some patients had persistent exposure, the estimates showed upward bias, which increased from 0.11 on the log scale (OR, 1.12) when 10% of patients stayed on therapy to 1.21 (OR, 3.36) when 70% stayed on therapy. We did not observe substantial changes in magnitude of bias when the true OR was varied.

Conclusions: The case-crossover design can provide unbiased estimates when evaluating prolonged, but finite, exposures; however, in situations where patients stay on therapy indefinitely, case-crossover analyses will incur upward bias.

830 | Empirical assessment of case-based methods for the identification of drug-related health outcome of interest in the French Nationwide Healthcare Database (SNDS)

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Background: With long-term data for over 66.6 million patients, the French Nationwide Healthcare Database (*Système National des Données de Santé* - SNDS) offers great potential for drug-related risk identification. However, it is not known how different study designs compare for large-scale screening in the database.

Objectives: To evaluate and compare the performance of 3 case-based methods - self-controlled case series (SCCS), case control (CC), and case-population (CP) - as tools for risk identification in the SNDS.

Methods: All hospitalized cases of acute liver injury (ALI), acute kidney injury (AKI), myocardial infarction (MI), and upper gastrointestinal bleeding (UGIB) in 2009–2014 were extracted from SNDS. The AKI, UGIB and MI cases were sampled randomly at fractions of 1/3, 1/10 and 1/20, respectively, to reduce execution time. 139 positive and negative drug controls corresponding to 273 drug-outcome pairs were screened; those with a minimum detectable relative risk (MDRR) <1.30 were analyzed. The pairs were used to compare 196 SCCS, CC, and CP design variants (e.g., varying regarding risk windows, different adjustment approaches). We evaluated each method based on its discriminative ability using area under the receiver operating curve (AUC). Mean square error (MSE) was calculated for negative controls, assuming that the true relative risk was 1.

Results: Over 6 years, there were before sampling, 5 152 cases of ALI, 12 317 KI, 304 369 MI and 139 172 UGIB. The number of drug-outcome pairs with a MDRR<1.30 ranged from 61 for MI to 25 for ALI. SCCS variants achieved the best performance across all outcome definitions with AUC $\geq$0.9 for ALI, $\geq$0.8 for KI and UGIB and $\geq$ 0.7 for MI. MSE associated with the SCCS variants with highest AUCs ranged from 0.07 to 0.47. The best predictive accuracy was observed for UGIB ($0.07 \leq MSE \leq 0.10$) and MI ($0.19 \leq MSE \leq 0.22$). CC achieved higher AUC than CP for ALI ($\geq$0.89 *vs.* $\geq$0.85), KI ($\geq$0.62 *vs.* $\geq$0.58) and MI ($\geq$0.62 *vs.* $\geq$0.57). CP performed better for UGIB ($\geq$0.67 *vs.* $\geq$0.60). MSE was lower for the most discriminating CC variants ($0.23 \leq MSE \leq 1.34$) as compared to the most discriminating CP variants ($1.07 \leq MSE \leq 3$).

Conclusions: This empirical assessment showed that SCCS designs variants tended to achieve results with a higher discriminative ability and predictive accuracy than CC and CP for screening of drug-related ALI, AKI, MI and UGIB. For each outcome of interest, a

specific SCCS variant should be considered for drug-related event detection in the SNDS.

831 | Using active comparators in self-controlled studies

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Background: When self-controlled designs are used to study the triggering of medication-related adverse effects, time-varying confounding by indication can occur if the indication or its severity varies over time.

Objectives: We aimed to describe how self-controlled designs might mitigate or eliminate such confounding by indication by incorporating active comparators with similar indications, illustrated by an empirical example.

Methods: Practical approaches to incorporating active comparators will be described for case-crossover, case-time-control, self-controlled case-series and symmetry analyses.In the empirical example, we used nation-wide data from Denmark to study the association between narrow-spectrum penicillin and venous thromboembolism (VTE), using a case-crossover design. Macrolide antibiotics were selected as active comparator. This example was chosen because upper respiratory infection - the main indication for narrow-spectrum penicillin and macrolides - is a transient risk factor for venous thromboembolism, i.e., representing time-dependent confounding by indication.We identified Danish VTE patients, born 1950 or earlier, during the period 1995–2012. If patients had more than one VTE, we included only the first. The focal window was the 14-d period before VTE diagnosis. We compared the odds of exposure in that window with one reference window 29–42 days before the VTE. We counted a window as exposed if one of the two antibiotics (penicillin or macrolide) was dispensed within it. We used a Wald-based method and an interaction term in a conditional logistic regression model to estimate the exposure odds ratio (OR) with 95% confidence limits (CI) for the narrow-spectrum penicillin users, having the macrolide users as active comparators, i.e. adjusted for transient confounding by indication.

Results: We identified 57486 patients, of whom 4898 (8.5%) were dispensed penicillin during the focal window, and 2226 (3.9%) during the reference window. Corresponding figures were 1192 (2.1% and 572 (1.0%) for macrolide antibiotics. The case-crossover estimate for penicillin was 2.45 (CI: 2.32–2.59) and 2.22 (CI: 2.00–2.47) for macrolide antibiotics. The Wald-based estimate for penicillin with macrolide antibiotics as active comparator was 1.10 (CI: 0.98–1.24), and the interaction-term based estimate was 1.22 (CI: 1.07–1.39).

Conclusions: The strong association of penicillin and macrolides with VTE suggests both are due mostly to time-varying confounding by indication. Such confounding can be mitigated by applying an active comparator drug that has an similar indication.

832 | Development and application of a hybrid matching algorithm to refine the prevalent new-user cohort Design for Comparative Drug Effect Studies

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Background: The prevalent new-user (PNU) cohort design was recently introduced to accommodate the circumstance where incident new users of a target drug are very scarce; most study drug users have used the comparator old drug previously. The PNU cohort design used either time- or prescription-based exposure sets to compute time-conditional propensity scores (PS) of initiating the study drug and to identify matched individuals receiving the comparator drug to achieve the comparability between two study groups.

Objectives: We adapted the PNU cohort design to propose a refined matching algorithm which accounted for medication history before the initiation of the study drug, and we illustrated this approach with a comparative safety study of glucagon-like peptide-1 receptor agonist (GLP-1ra) vs. sulfonylurea (SU) on the risk of cardiovascular diseases (CVDs) in patients with type 2 diabetes (T2DM).

Methods: To achieve the baseline comparability between the study and comparator drug users, we defined stable users and developed an enhanced hybrid algorithm with three-step matching for (1) index date at which the study drug was initiated (inspired by time-based exposure set), (2) medication possession ratios (MPRs) which quantified past exposures [e.g., exposure to all glucose-lowering drugs before the GLP-1ra initiation in T2DM] (modified by prescription-based exposure set), and (3) PS estimated based on confounder patient characteristics. We illustrated this refined approach with data from Taiwan National Health Insurance Research Database 2009–2015. Cox models were applied to compare the hazard of the composite CVD and 3-point major adverse cardiovascular event (MACE) between the matched GLP-1ra and SU groups.

Results: During 2011–2014, there were 3,195 and 773,026 stable users of GLP-1ra and SU, respectively. Most of 3,195 GLP-1ra users have been exposed to SU previously. After applying for our matching algorithm, 1,573 stable users of GLP-1ra were 1:1 matched to 1,573 stable sets of SU. With a mean follow-up of 2,520 and 2,591 person-years, the use of GLP-1ra compared to SU was associated with a significantly reduced risk of the composite CVD [hazard

ratio (HR): 0.71, 95% CI: 0.54–0.95] but not MACE [HR: 0.71, 95% CI: 0.44–1.15].

Conclusions: The refined PNU cohort design not only allows the use of most subjects with prior medications but applies the enhanced three-step matching algorithm to comprehensively consider the past exposure to all potential comparator drugs before initiating the study drug, thus enhancing the study validity.

833 | Classes and prevalence of prevalent new users: An example in Medicare

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Background: The prevalent new user (PNU) design has been proposed to increase sample size and include a clinically relevant patient subset in research. Few applied examples exist in large longitudinal claims databases and whether all PNUs should be treated as one group has yet to be examined.

Objectives: Determine sizes of potential classifications of PNUs and sample size increase from implementing a PNU design in a comparative effectiveness study of dabigatran versus warfarin among a sample of Medicare beneficiaries.

Methods: We identified new users of dabigatran and warfarin in a 20% Medicare random nationwide sample from January 2010 to October 2015 using 60-day washout and 30- and 45-day grace periods, respectively. Next we found dabigatran initiators who did not meet the washout criterion and divided them into three mutually exclusive groups: true PNUs (TPNUs) whose initiation was directly preceded by an eligible period of new use of warfarin in the study period with no intervening gap; gap PNUs (GPNUs) whose initiation was preceded by an eligible period of new use of warfarin in the study period with a gap between 0 and 60 days; and other PNUs (OPNUs) whose initiation was preceded by a period of warfarin use in the study period that did not qualify as new use, regardless of gap. We included each individual once, taking first chronological new use then first PNU period. We compared covariates and hazard ratios (HR) for as-treated all-cause mortality across these categories.

Results: We identified 11,240 dabigatran new users, 1,683 TPNUs, 263 GPNUs, and 1,332 OPNUs. The populations differed in many covariates including cardioversion in the past year (9.3% in new users, 16.9% in TPNUs, 19.8% in GPNUs, and 6.3% in OPNUs), major bleeding event in the past year (8.5% vs 12.2% vs 17.5% vs 14.3%), and deep vein thrombosis in the past year (3.4% vs 6.6% vs. 10.3% vs. 9.0%). Mortality comparisons showed similarity between new users and TPNUs (new user vs TPNU HR: 0.93, 95% CI 0.79–1.09) but improved survival for new users vs GPNUs and OPNUs (new user vs GPNU HR: 0.72, 95% CI 0.51–1.01; new user vs OPNU HR: 0.63, 95% CI 0.54, 0.73).

Conclusions: Adding all PNUs to the study would increase sample size by 29%. However, these PNUs had different distributions of potential confounders and GPNUs and OPNUs had poorer survival. TPNUs had similar mortality to new users despite the presence of more comorbid conditions. Matching the type of PNU to the appropriate type of warfarin user will be key for accurate estimates. Investigators conducting PNU analyses should articulate differences between the PNU and new user populations as well as how they change the causal questions being examined.

834 | Comparative performance of trend-in-trend design and instrumental variable methods in an active comparator new user setting

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Background: Trend-in-trend (TT) design has been proposed as an extension of instrumental variable (IV) methods to compare prevalent vs. never users. Time varying confounding and time varying hazards could however violate TT assumptions and bias estimates. Relative performance of TT design and IV methods in the active comparator, new user (ACNU) setting, where drug initiation patterns change over time, has not been evaluated.

Objectives: To evaluate the TT design in ACNU setting, as compared with calendar time IV methods and traditional new user cohort design, using thiazolidinediones (TZDs) versus dipeptidyl peptidase-4 inhibitors (DPP4i) and TZDs known effect on congestive heart failure (CHF) hospitalizations as a positive control example.

Methods: Using Medicare fee-for-service claims data 2007–14, we identified new users of TZD and DPP-4i, aged over 65 years, after a 6-month drug-free period, during which there was no TZD or DPP-4i prescription. We compared short-term (3-year) risks of inpatient CHF with diagnosis in 1st or 2nd positions among TZD vs. DPP-4i initiators, starting from 2nd prescription dates until death or administrative censoring. We estimated this intent-to-treat (ITT) treatment effects 3 ways: (i) TT odds ratio (OR), and 95% confidence intervals (CI) evaluating the trend in TZD vs. DPP4i initiation in 6-monthly calendar time intervals (crossover around 2011) (ii) binary calendar time IV estimator (before and after 2011) using 2-stage generalized method of moments and (iii) cohort ORs based on inverse probability of treatment weighting to control for measured confounding.

Results: TZD (n = 45,218) and DPP-4i initiators (n = 87,338) had similar baseline characteristics. With the overall inpatient CHF risk of 5.3%, we identified 2,323 events among TZD and 4,786 among DPP-4i initiators. TZD has a higher risk of CHF than DPP-4i with TT OR (95% CI) of 1.16 (1.02, 1.33) and the weighted OR (95% CI) of 1.31 (1.24, 1.37). IV estimate (risk difference) from 2-stage least square estimator is 0.08 (95% CI: 0.07, 0.09), while pseudo-OR calculated from the risk difference (and unscaled by treatment compliance) is 1.62, revealing consistent direction of estimates.

Conclusions: We were able to extend the TT design to ACNU which allows us to implement TT in settings with time varying confounding or time varying hazards. In our positive control ACNU example, TT results were consistent with other methods, likely due to limited unmeasured confounding. We will further vary ITT risk periods and implement IV estimator with 2-stage probit regression to get comparable OR estimates.

835 | Concomitant use of quinolones and stimulants and the risk of cardiovascular adverse events: A comparative safety study

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Background: Stimulants can increase blood pressure and heart rate. Cases of cardiac arrest and torsades de pointes have occurred with the concomitant use of quinolones and other pro-arrhythmic drugs. Despite the plethora of evidence suggesting cardiac toxicities with quinolones or stimulants, to date, no study has evaluated cardiac outcomes related to their pro-arrhythmic properties when used concomitantly.

Objectives: To examine whether concomitant use of quinolones and stimulants is associated with an increased risk of cardiac events in adults.

Methods: Methods: A retrospective cohort study using IBM MarketScan® commercial claims data from 2008 to 2015. Setting: Adults between 18 and 64 years old with prescription fills of stimulants (methylphenidate or mixed amphetamine salts) and continuous enrollment in MarketScan® for the 6 months (baseline) prior to the date of first dispensation (index date) of oral quinolones or comparators. Exposure: Initiation of quinolones versus amoxicillin (amoxicillin/clavulanate) during stimulant use. Main outcomes measures: Emergency room visits or hospital admission related to palpitations or tachycardia. Analysis: We adjusted for baseline covariates through inverse probability treatment weighting. Adults were followed for up to 10 days after the index date. The hazard of cardiac symptoms in stimulant/quinolones-exposed adults was compared to those who had stimulants/amoxicillin using a weighted Cox proportional hazard model. We performed sensitivity analyses to challenge the results' robustness.

Results: The study cohorts comprised 390,490 stimulants users who initiated either quinolones or amoxicillin. The unadjusted incidence rate for cardiac symptoms was 471 cases per 10,000 patient-years in stimulant/quinolones users and 244 cases per 10,000 patient-years in stimulant/amoxicillin users. The adjusted hazard ratio for cardiac symptoms was 1.61 (95%CI, 1.30–1.98) with stimulant/quinolones use. The sensitivity analyses findings including restriction to patients without respiratory infections, censoring at stimulant discontinuation during the 10-day follow-up, no censoring when antibiotics were switched, and exclusion of patients who initiated stimulants within 30 days of index date were consistent with the primary analysis.

Conclusions: Concomitant use of stimulant and quinolones was associated with an increased hazard of cardiac symptoms in comparison to stimulant and amoxicillin concomitant use. Sample size constraints limited our ability to examine severe arrhythmias.

836 | An unnecessary risk: Lack of benefit of fluoroquinolone antibiotics in uncomplicated exacerbations of chronic obstructive pulmonary disease

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Background: Fluoroquinolone antibiotics are associated with rare, but severe adverse events. Their effectiveness in treating severe exacerbations of COPD (AECOPD) requiring hospitalization has been well documented. However, they are frequently also used for the treatment of mild and moderate acute exacerbations. The potential benefit of fluoroquinolone antibiotics in the ambulatory setting is less clear, especially in uncomplicated patients with AECOPD.

Objectives: To compare health outcomes in patients treated with fluoroquinolones compared to other antibiotics in uncomplicated patients with AECOPD.

Methods: We carried out a retrospective cohort study in multiple health care databases from six Canadian provinces comparing 30-day outcomes in subjects with uncomplicated COPD visiting their physician for an AECOPD and dispensed either a quinolone or other antibiotics. Differences between the treatment groups were adjusted for using high dimensional propensity scores. Aggregate data from each province was combined by random effects meta-analysis.

Results: We identified 286,866 AECOPD events among 203,642 unique individuals. The level of fluoroquinolones use, mostly levofloxacin and moxifloxacin, varied by province and ranged from 8% to 32% of AECOPD antibiotic prescriptions. The risk of a repeat ambulatory care visit was increased among patients dispensed a fluoroquinolone, OR 1.32, 95% CI 1.27–1.36. The risk of a hospitalization for AECOPD for subjects dispensed a fluoroquinolone was higher than for subjects prescribed other antibiotics; OR 1.52, 95% CI 1.33–1.74. There was no difference in subsequent antibiotic prescriptions; OR 1.00, 95% CI 0.94–1.07.

Conclusions: There was no apparent benefit in short term outcomes with fluroquinolones as compared to other antibiotics for the ambulatory treatment of AECOPD in uncomplicated patients. These findings support curent recommendations that fluoroquinolones be reserved for AECOPD in patients with recurrent exacerbations, significant co-morbidity or requiring hospitalization.

837 | Excess risk of tendon rupture due to fluoroquinolones with and without concomitant corticosteroid use

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Background: Fluoroquinolone antibiotics have been associated with an increased risk of Achilles tendon rupture. However, the rate of Achilles and other tendon rupture attributable to fluoroquinolones, with and without concomitant corticosteroid use, has not been well described.

Objectives: To estimate the relative, absolute, and attributable risk of non-traumatic tendon rupture, at various sites, associated with use of fluoroquinolones, with and without concomitant corticosteroids.

Methods: We conducted cohort and nested case–control studies among fluoroquinolone users in the United Kingdom Clinical Practice Research Datalink GOLD. From the population of fluoroquinolone users (ages 10–80), cases of tendon rupture were identified using Read codes and matched 4:1 with controls on age, sex, calendar time and general practice. Cases of traumatic tendon rupture, including cases within 90 days of a major trauma, were excluded, as were cases and controls with a history of tendon rupture or strong risk factors for rupture (e.g. organ transplant). We estimated the excess risk (incidence rate differences) using Byar's method (cohort analysis) and odds ratios (ORs) using conditional logistic regression (case control) of tendon rupture by use of fluoroquinolones (current, recent and past use verses unexposed) and corticosteroids (current versus unexposed). Effect modification was assessed for age, sex and corticosteroids.

Results: We identified 3957 cases of tendon rupture among 740,926 patients with a fluoroquinolone prescription. In the case–control analysis, ORs with 95% confidence intervals (CI) among current fluoroquinolone users versus unexposed patients were elevated: any tendon rupture 1.60 (1.22–2.09), Achilles tendon 2.71 (1.76–4.17) and bicep tendon 1.53 (0.85–2.73). The risk of any tendon rupture was higher among women (OR 2.27 (1.54–3.34)), patients aged 60+ (OR 2.42 (1.74–3.37)), and concomitant corticosteroid users (OR 6.64 (3.99–11.1)). The excess risk due to current fluoroquinolone use was low: any tendon rupture 3.73 cases (95% CI, 2.08–5.39) per 10,000 PY, Achilles tendon rupture 2.91 (1.71–4.11) per 10,000 PY and bicep tendon rupture 0.59 (−0.14–1.32) per 10,000 PY. The excess risk of any tendon rupture was much higher for current concomitant fluoroquinolone and corticosteroid use versus corticosteroids alone: 21.2 cases (11.3–31.2) per 10,000 PY.

Conclusions: Fluoroquinolones increase the risk of Achilles tendon rupture and, to a lesser extent, bicep tendon rupture, but the attributable risk is low. The risk is materially increased with concomitant use of corticosteroids.

838 | Early childhood antibiotics use and the risk of attention-deficit/hyperactivity disorder: A population-based cohort study

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Background: Early childhood antibiotic exposure induces changes in infants' gut microbiota composition reportedly associated with the development of Attention-Deficit/Hyperactivity Disorder (ADHD).

Objectives: In this study, we examined the association between antibiotic use in the first year of life and the risk of ADHD.

Methods: This was a population-based cohort study utilizing the Manitoba Population Research Data Repository. The cohort included 187,605 children born in Manitoba, Canada between April 1, 1998 and March 31, 2017. Exposure was defined as having filled one or more antibiotic prescriptions during the first year of life. The outcome was ADHD diagnosis identified in hospital abstracts, physician visits or drug dispensations. Risk of developing ADHD was estimated using Cox proportional hazards regression models in a high dimensional propensity scores-matched cohort and a sibling cohort.

Results: A total of 69,738 children were included in the matched-cohort. During follow-up, 6087 (8.7%) children received an ADHD diagnosis. ADHD risk was not found to be associated with antibiotic exposure in early life (HR 1.02, 95% CI 0.97–1.08). In secondary analyses, an association was observed in those receiving three or more antibiotic courses or for a duration longer than three weeks (HR 1.57, 95% CI 1.23–2.00 and HR 1.38, 95% CI 1.17–1.64, respectively). In the sibling cohort of 67,671 children, antibiotic exposure was not associated with the risk of ADHD (HR 0.96, 95% CI 0.89–1.03). No association was observed in any of the secondary analyses.

Conclusions: Antibiotic use in the first year of life does not appear to pose an ADHD risk on a population level.

839 | Comparative safety and cost assessment of prescribing systemic steroids for acute respiratory tract infections

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Background: Evidence and guidelines do not support use of systemic steroids for acute respiratory tract infections (ARTIs), but about one-in-ten patients in the US receive this treatment.

Objectives: To assess how treating ARTI with systemic steroids impacts clinical outcomes and health care costs.

Methods: We used a large US national commercial claims database, the IBM MarketScan, to identify patients aged 18–65 from 2007–2016, who entered the study cohort after an ambulatory visit with an ARTI diagnosis (acute bronchitis, sinusitis, pharyngitis, otitis media, allergic rhinitis, influenza, pneumonia, and unspecified upper respiratory infections; ARTI diagnosis date was the cohort entry date [CED]). Steroid user group consists of those receiving systemic steroids within 7 days of the ARTI diagnosis and non-user group was selected by risk-set sampling among the non-use person-time within 7 days after CED. Those with systemic steroid use and an extensive list of steroid-indicated conditions in the prior year before CED were excluded. We used Cox Regression to calculate the hazard ratios (HR) of sepsis, gastrointestinal bleeding (GIB), and fracture in 30, 31–90, 91–180 days after the index date (steroid dispensing date for users and selection date for non-users). We also examined association with some negative control outcomes, including pancreatitis, seizure, and acute kidney injury. We used generalized linear models to calculate difference in mean health care costs. Propensity-score (PS) matching was used to adjust for 55 selected confounders.

Results: Our study cohort included 1,291,810 steroid users and 1,291,810 non-users (855,535 of each group matched based on PS). Most (84%) of the users were prescribed steroid for ≤7 days. Comparing steroid users vs. non-users, adjusted HR (aHR) was 1.26 (95% confidence interval [CI] 1.07–1.48) for sepsis, 1.58 (1.01–2.48) for GIB, and 1.04 (0.98, 1.11) for fracture for the first 30 days. The corresponding risks of sepsis and GIB attenuated to null before 90 days but the increased risk of fracture from steroid use persisted in 90–180 days (1.14 [95% CI, 1.09–1.19]). The adjusted mean total health care costs were $346.34 (95% CI $324.08–368.60) more in steroid users than in non-users after the ARTI diagnosis, largely driven by outpatient costs ($260.33 [95% CI $247.45–273.21]). All the HRs for the negative control outcomes were null.

Conclusions: Prescribing systemic steroids for ARTI was associated with elevated risks of GI bleeding and sepsis and increased health care costs as early as the first 30 days after ARTI diagnosis.

840 | Antibiotic use and colorectal cancer recurrence and mortality: A Danish Nationwide prospective cohort

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Background: Despite advances in screening and treatment, colorectal cancer (CRC) remains the 4th most common cause of cancer related deaths globally. Nearly 3.5 million CRC survivors worldwide are at risk of adverse CRC outcomes, including death from CRC, which is preceded by a recurrence. The human gut microbiome plays a vital role in the host's gut physiology and potentially contributes to CRC progression and response to treatment. Antibiotic (ABX) use has been associated with reduced diversity and altered composition of the gut microbiota in humans. Given the frequency of antibiotic use in the adult population and their effects on the gut microbiome, the potential influence of antibiotics on the clinical course of CRC is of great public health interest.

Objectives: To assess the association of pre-diagnostic and post-diagnostic ABX use with the risk of CRC recurrence and mortality.

Methods: Using data from Danish registries, we followed 21,152 patients (5,036 recurrences, 7,084 deaths) diagnosed with stage I-III CRC during 2001–2011 and registered in the Danish Colorectal Cancer Database. We ascertained information on potential confounders from Danish population-based and medical registries. We examined the association between pre-diagnostic and post-diagnostic antibiotic use and CRC recurrence and mortality, controlling for age, sex, year of diagnosis, tumor stage, tumor location, treatment, comorbidities, history of inflammatory bowel disease, and the use of NSAIDs, aspirin, and statins.

Results: After adjustment for potential confounders, any ABX prescription 90 days prior to CRC diagnosis was not associated with recurrence [adjusted hazard ratio (aHR) = 1.06, 95% confidence interval (CI): 0.98, 1.14]. ABX use after CRC diagnosis was also not associated with recurrence (aHR = 1.03, 95% CI: 0.97, 1.09). However, both pre-diagnostic and post-diagnostic use of ABX was associated with overall and CRC-specific mortality (90 days prior to diagnosis: overall mortality aHR = 1.13, 95% CI: 1.06, 1.20, CRC mortality aHR = 1.09, 95% CI: 1.01, 1.19; after diagnosis: overall mortality aHR = 1.38, 95% CI: 1.32, 1.45, CRC mortality aHR = 1.29, 95% CI: 1.21, 1.38). The association of pre-diagnostic ABX use and overall mortality was stronger for more than one prescription of ABX compared to none (aHR = 1.16, 95% CI: 1.05, 1.27), and for broad spectrum ABX (aHR = 1.47, 95% CI: 1.39, 1.55).

Conclusions: Our results suggest ABX use not to be associated with cancer recurrence in this group of CRC patients. A higher risk observed for overall and CRC-specific mortality is possibly due to confounding by indication.

841 | Staying on treatment matters: estimating effects of dabigatran vs warfarin in Medicare

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Background: There are many studies of the relative efficacy and safety of dabigatran and warfarin in patients with atrial fibrillation (AF), but little evidence exists on the risk differences (RD) necessary for benefit-harm assessment. In addition, few studies contrast as-treated (AT) and initial treatment (IT) designs or estimate treatment effects in all new users.

Objectives: Estimate 2-year RDs in ischemic stroke (IS), death, and gastrointestinal bleeding (GIB) comparing new use of dabigatran versus new use of warfarin using AT and IT designs in dabigatran new users or new users of either drug.

Methods: We identified new users (60-day washout period) of warfarin and 150 mg of dabigatran with AF in a Medicare 20% nationwide random sample from January 2010 through October 2015, including first period of new use eligible for the RE-LY trial. In the AT design, we censored users after switching oral anticoagulants or 45- and 30-day gaps in drug supply for warfarin and dabigatran users respectively, with anticoagulation management procedure codes refreshing warfarin supply. In the IT design, we followed users until death or October 2015. We estimated 2-year outcome risks with a weighted Aalen-Johansen estimator to allow for the competing risk of death and obtained RD variances via nonparametric bootstrap. We used both inverse probability of treatment weights (IPTW) and standardized morbidity ratio (SMR) weights targeting dabigatran users, incorporating censoring weights in the AT.

Results: We identified 10,623 dabigatran users and 74,194 warfarin users. Dabigatran users were younger (median age 75 vs 78 years) with lower predicted probability of frailty (median 5.0% vs 7.3%) and fewer comorbid conditions. IPTW 2-year AT RDs showed decreased IS risk with dabigatran versus warfarin (−0.7%, 95% CI -1.4%, −0.1%) while IT RDs showed increased risk (RD 0.6%, 95% CI -0.1%, 1.4%). AT RDs for death were more favorable than IT RDs, though both were protective (AT RD: −3.2%, 95% CI: −5.3%, −1.2%; IT RD: −1.0%, 95% CI -2.6%, 0.6%). GIB RDs increased in the AT design (AT RD: 1.8%, 95% CI -0.2%, 3.9%; IT RD: 1.1% 95% CI 0.1%, 2.1%). SMR showed more benefit and less harm than IPTW, particularly for GIB (AT RD: 0.6%, 95% CI -0.3%, 1.4% IT RD: 0.4%, 95% C.I. -0.1%, 0.8%).

Conclusions: Our AT estimates suggest dabigatran is protective for mortality and IS if patients stay on treatment; these effects diminish or reverse in IT analyses. Dabigatran new users appear to be at lower risk of experiencing harms than all new users. Future research on possible mortality benefits of oral anticoagulants in older adults and ways to keep patients on anticoagulants are vital for AF patients.

842 | Comparative effectiveness and safety of concomitant use of antiplatelets and anticoagulants in acute coronary syndrome patients with atrial fibrillation

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Background: Current treatment guidelines for patients with acute coronary syndrome (ACS) and arterial fibrillation (AF) recommend antiplatelets and anticoagulants. However, the optimal strategy to balance the prevention of cardiovascular disease (CVD) and bleeding risk remains unclear. There is limited evidence on the comparative effectiveness and safety of concomitant antiplatelet-anticoagulant use in the era of direct-acting anticoagulants (DOACs).

Objectives: We aimed to assess the comparative effectiveness and safety of antiplatelet-DOACs compared to antiplatelet-warfarin in patients with ACS and AF.

Methods: A retrospective cohort analysis of Truven Commercial and Medicare supplemental database (2010–2016) was conducted for treatment-naive ACS patients with AF. Patients who were (1) $\geq$ 18 years (2) had a diagnosis of ACS (ICD-9, 410.xx; 411.xx; ICD-10: I21, I22) (3) a diagnosis of AF (ICD-9, 427.31; ICD-10, I48) within the one year preceding the first ACS diagnosis and (4) used concomitant antiplatelet-anticoagulant within 30 days of their first admission of ACS were included. The study outcomes including CVD and major bleeding events were compared between users of antiplatelet-DOACs and antiplatelet-warfarin. Cox-proportional hazard models after propensity score matching (PSM; 1:3) were used to obtain the hazard ratio (HR) and 95% confidence interval (CI).

Results: It is worth noting that even prior to PSM, most baseline characteristics were comparable between the two groups including age (69 yrs vs. 69 yrs), presence of comorbidities including liver disease (0.6% vs. o.6%), cancer (7.0% vs. 8.0%) and use of medications such as thiazide diuretics (2.0% vs. 2.0%). After PSM, a total of 1,783 were included (n = 506 patients for antiplatelet-DOACs and n = 1,277 for the antiplatelet-warfarin). The incidence rate of CVD was 10 and 23 per 100 person-years in the antiplatelet-DOACs and antiplatelet-warfarin groups, respectively. The incidence of major bleeding was 4 and 11 per 100 person-years in the antiplatelet-DOACs and antiplatelet-warfarin groups, respectively. In the Cox model, compared to antiplatelet-warfarin the use of antiplatelet-DOACs was associated with a lower risk of CVD (HR, 0.47; 95% CI, 0.30, 0.73) and major bleeding (HR, 0.40; 95% CI, 0.20, 0.78).

Conclusions: Our findings suggest that when the combination therapy is considered, DOACs with antiplatelets appears to be superior to warfarin -antiplatelets in preventing the development of CVD and bleeding events in treatment naïve ACS patients with AF.

843 | Safety and effectiveness of direct oral anticoagulants versus vitamin K antagonists, results from three Italian regions

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Background: In Italy, direct oral anti-coagulant drugs (DOACs) were authorized for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) in 2013. There is conflicting evidence on their benefit–risk profile under real world conditions.

Objectives: A population based study was funded by the Italian Medicines Agency with the aim to investigate effectiveness and safety of DOACs compared to standard therapy with vitamin K antagonists (VKAs) in three Italian regions (Lazio, Lombardy, Tuscany) accounting for almost 20 million residents.

Methods: An observational study was conducted with a sequential propensity-score (PS)-matched new user parallel-cohort design in the period July 2013–December 2015 using administrative health data. DOAC (dabigatran, rivaroxaban, apixaban) users with NVAF diagnosis were 1:1 matched to VKA (warfarin, acenocoumarol) users based on a PS which accounted for over 90 potential confounders (socio-demographic, comorbidity, drug consumption, CHA_2DS_2-VASc and HAS-BLED scores) at baseline. Applying an as-treated approach with a 90-day renewal grace time, patients were followed from the day after the first prescription of the study drug until occurrence of the outcome, death, discontinuation, switch, end of health plan enrolment, or study end. Outcomes were total mortality, cardiovascular mortality, acute myocardial infarction, ischemic and haemorrhagic stroke, and gastrointestinal bleeding. The 30 months were broken down into 9 time windows, and at the end of each interval, analyses were performed, using Cox proportional hazard models. The results of the regional analyses were combined through a random-effects meta-analysis.

Results: During the first 30 months of authorisation for NVAF, DOACs were increasingly prescribed and at the end outweighed VKAs. Overall, 72,429 new anticoagulant users were enrolled, 34% of whom received a DOAC. After PS matching, 37,266 patients contributed to the analysis. No differences between the two study groups were found for total and cardiovascular mortality, myocardial infarction and ischemic stroke. DOAC users were at higher risk of gastrointestinal bleeding (HR:1.41, 95%CI:1.07–1.86), and at lower risk of haemorrhagic stroke, which did not reach statistical significance due to small numbers (HR:0.36, 95%CI:0.10–1.33).

Conclusions: The present study confirms findings from previous research. Future investigations on head-to-head comparison between single DOAC active agents and on population subgroups who may particularly benefit from the new treatment options are warranted.

844 | Comparative effectiveness and safety of direct oral anticoagulants in non-valvular atrial fibrillation: a multi-center observational cohort study

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Background: Atrial fibrillation is the most common cardiac arrhythmia, with lifelong anticoagulation generally recommended to prevent cardio-embolic stroke. Direct oral anticoagulants (DOACs) are widely replacing vitamin K antagonists for anticoagulation in non valvular atrial fibrillation (NVAF). No randomized trials have compared DOACs head to head, and large observational studies are needed, especially to compare the newer apixaban to the other two available DOACs.

Objectives: To compare safety and effectiveness among DOACs in NVAF.

Methods: We conducted multi-center observational cohort studies with meta-analyses using data from seven Canadian healthcare databases, US MarketScan®, and the UK's Clinical Practice Research Datalink. All adults with NVAF initiating anticoagulation therapy with dabigatran, rivaroxaban, or apixaban between January 1st, 2009 and March 31st, 2017 were included. Patients were matched on a propensity score including sex, age, date of cohort entry, and clinically-defined potential confounders. The outcomes included ischemic stroke, major bleeding and a composite of stroke, major bleeding, or all-cause mortality. For each of the matched cohorts and for each outcome, we fit a Cox marginal structural proportional hazards model to estimate the marginal hazards ratios contrasting the different types of DOACs. Meta-analysis techniques with random effects were used to estimate pooled hazard ratios (pHR) across the databases.

Results: The cohorts included 73,414 new users of dabigatran, 92,881 of rivaroxaban, and 61,284 of apixaban. After matching, the pHRs (and 95% confidence intervals) comparing rivaroxaban initiation to dabigatran were: 1.11 (0.93 to 1.32) for ischemic stroke, 1.26 (1.09

to 1.46) for major bleeding, and 1.17 (1.05 to 1.30) for the composite outcome. For apixaban vs dabigatran, they were: 0.91 (0.74 to 1.12) for ischemic stroke, 0.89 (0.75 to 1.05) for major bleeding, and 0.94 (0.78 to 1.14) for the composite outcome. For apixaban vs rivaroxaban, they were: 0.85 (0.74 to 0.99) for ischemic stroke, 0.61 (0.53 to 0.70) for major bleeding, and 0.82 (0.76 to 0.88) for the composite outcome.

Conclusions: This large multi-center observational study suggests that apixaban is more effective at preventing stroke and safer with respect to bleeding risks compared with rivaroxaban. Apixaban appears to have similar effectiveness and safety compared with dabigatran. In the absence of head-to-head trials, this large, multi-database observational study adds important evidence to guide clinical use of DOACs.

845 | Comparative effectiveness and safety of direct acting oral anticoagulants and warfarin in cancer patients with venous thromboembolism

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Background: There is limited evidence to support the use of direct-acting oral anticoagulants (DOACs) in cancer patients with venous thromboembolism (VTE).

Objectives: The study aimed to assess the comparative effectiveness and safety of DOACs compared to warfarin in patients with VTE and active cancer.

Methods: A retrospective cohort analysis using the Truven Commercial and Medicare supplemental database (2013–2016) was conducted. Patients who (1) were ≥ 18 years (2) had a diagnosis of VTE (ICD-9: 415.1, 451.1, 453.2, 453.4, 453.5, 453.8, or 453.9 and ICD-10: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1, I26.9, I26.0) (3) had a diagnosis of an active cancer within the 6 months period preceding their initial VTE and in treatment with radiotherapy or chemotherapy and (4) initiated DOACs (apixaban, rivaroxaban, dabigatran, edoxaban) or warfarin within 30 days of their first VTE diagnosis were included. The risk of recurrent VTE and major bleeding was compared between DOACs and warfarin using Cox-proportional hazard models after propensity score matching (PSM) (1:1). In the subgroup analysis, we stratified the study outcomes into pulmonary embolism vs. deep vein thrombosis (for the recurrent VTE outcome), and gastrointestinal bleeding [GI] vs. intracranial bleeding (for the major bleeding outcome).

Results: After PSM, a total of 10,006 patients were included in the cohort (*n* = 5,003 DOACs users and n = 5,003 warfarin users). The incidence of recurrent VTE was 5 and 9 per 100 person-years in the DOACs and warfarin groups, respectively. The incidence of major bleeding was 3 and 6 per 100 person-years in the DOACs and warfarin groups, respectively. In Cox regression models, the use of DOACs compared to warfarin was associated with a lower risk of recurrent VTE (HR, 0.61; 95% CI, 0.48, 0.77) and major bleeding events (HR, 0.60; 95% CI, 0.45, 0.81). Study results remained consistent when stratifying the study outcome into PE (HR, 0.65; 95% CI, 0.47, 0.90) and DVT (HR, 0.51; 95% CI, 0.35, 0.73) (P interaction = 0.13), and GI bleeding (HR, 0.63; 95% CI, 0.46. 0.87) and intracranial bleeding (HR, 0.45; 95% CI, 0.19, 1.03) (P interaction = 0.98).

Conclusions: Our findings suggest that among cancer patients with VTE, DOACs offer superior effectiveness for the secondary prevention of VTE as well as a lower risk of bleeding when compared to warfarin.

846 | Risk of major bleeding associated with the use of individual direct oral anticoagulants compared to vitamin K antagonists in patients with non-valvular atrial fibrillation: a meta-analysis of results from multiple population-based cohort studies using a common protocol in Europe and Canada

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Background: Several observational studies have been carried out before to investigate the real world benefit–risk balance of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs) in patients with non-valvular atrial fibrillation (NVAF). However, information on the differences in performance within the class of DOACs and for different subgroups of patients is still inconclusive due to the lack of statistical power.

Objectives: The aim of this study was to establish the risk of major bleeding in DOAC users (overall and by class) versus VKA users using healthcare databases from four European countries and six provinces in Canada.

Methods: All research groups used the same protocol to perform a retrospective cohort study. First-users of VKAs or DOACs with a diagnosis of NVAF were included. The main outcome of interest was major bleeding and secondary outcomes included gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH). Incidence rates of events per 1,000 person years were calculated. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were estimated using a Cox proportional hazard regression model. VKA or DOAC exposure and confounders were measured and analyzed in a time dependent way. Risk estimates were pooled using meta-analysis techniques with a random effect model.

Results: In total, 421,523 patients were included in the period of 2008–2015 of which 37.2% used a DOAC and 62.8% used a VKA. The risk of major bleeding for the group of DOACs compared to VKAs showed a pooled HR of 0.94 (95% CI: 0.87–1.02). Risk differed by age group; for those ≥75 years old, HR was 1.01, 95% CI 0.94–1.09, while for those <75 HR was 0.83, 95% CI 0.73–0.95. Rivaroxaban showed a modestly increased risk (HR 1.11, 95% CI 1.06–1.16). Apixaban and dabigatran showed a decreased risk of respectively HR 0.76 (95% CI 0.69–0.84) and HR 0.85 (95% CI 0.75–0.96) compared to VKAs. The observed risk on GI bleeding was elevated around 20% for dabigatran and rivaroxaban and lowered with around 30% for apixaban. The observed risk on ICH was for all DOACs lower than for VKAs.

Conclusions: This study confirms that the risk of major bleeding of DOACs compared to VKAs is not increased when combining all DOACs. However, we observed a modest higher risk of major bleeding for rivaroxaban, whereas for apixaban and dabigatran lower risks of major bleeding were observed compared to VKAs.

847 | Impact of the publicly funded herpes zoster immunization program on burden of disease in Ontario, Canada

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Background: Herpes zoster (shingles) infections are associated with considerable morbidity and healthcare costs. In September 2009, a live, attenuated herpes zoster (HZ) vaccine (Zostravax) became available in Canada. This was subsequently provided free of charge to all Ontario residents aged 65 to 70 through a publicly-funded immunization program commencing in September 2016.

Objectives: To examine the impact of the HZ vaccine availability and Ontario's immunization program on HZ incidence and associated health service use in Ontario.

Methods: We conducted a population-based time-series analysis among Ontarians aged 65 to 70, between January 2005 and June 2018. We report monthly rates of herpes zoster incidence, defined as 1) physician visit for HZ with a HZ antiviral prescription dispensed within +/− 5 days, or 2) emergency department (ED) visit or hospitalization for HZ. Secondary outcomes included monthly rates of HZ related ED visits and hospitalizations. We stratified outcomes by sex, income quintile and rural/urban residence. We used interventional autoregressive integrated moving average (ARIMA) models to examine the impact of the HZ vaccine availability and Ontario's immunization program on our outcomes.

Results: The availability of a herpes zoster vaccine did not significantly impact trends of incidence or related hospitalizations among Ontarians aged 65 to 70 (p = 0.43 and p = 0.97, respectively). In contrast, the subsequent implementation of Ontario's immunization program significantly reduced the rate of incidence among our population by 25.3% between August 2016 and June 2018 (p < 0.01; from 4.8 to 3.6 individuals per 10,000 population). The rate of ED visits and hospitalizations for herpes zoster were relatively stable between January 2005 and August 2016, but significantly decreased following Ontario's immunization program by 36.2% (p < 0.02; from 1.7 to 1.1 hospitalizations per 10,000 population between August 2016 and June 2018). Findings were consistent when stratified by sex, income quintile and rural/urban residence.

Conclusions: Ontario's publicly-funded immunization program for herpes zoster led to significant reductions in the incidence of disease and related hospitalizations among individuals aged 65 to 70 in the province. Our future work will evaluate the cost savings associated with the reduction in herpes zoster-related health service use.

848 | Trends in human papillomavirus vaccination uptake in girls and boys in the United States: real-world evidence from 2003 to 2016

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Background: Human papillomavirus (HPV) vaccination is recommended at age 11 and 12 to prevent HPV infection and subsequent occurrence of HPV-related cancers. The Healthy People 2020 goal for HPV vaccination coverage is 80% by 15 years of age. In the U.S. there is a lack of nationwide population-based data on HPV vaccination.

Objectives: To describe the trends in HPV vaccination in children in the U.S.

Methods: We identified a pediatric cohort within the Truven MarketScan healthcare database between January 2003 and December 2016. Children were followed from the year they turned 9 until the first dose of HPV vaccination, end of insurance coverage, the end of the year when they turned 17, or death, whichever came first.

HPV vaccination was defined using current procedure terminology (CPT) codes. The monthly vaccination rate was calculated as the number of children that received the HPV vaccination in that month divided by the sum of person-months contributed by the eligible children that month. The cumulative incidence of HPV vaccination was estimated by using survival analyses to account for censoring. The study population was stratified by birth year and gender. The cumulative incidence of HPV vaccination at age 15 was mapped across 50 States. To test the robustness of our methods, we examined the use of two vaccines: pneumococcal conjugate vaccine (PCV) and measles vaccine, with an expected coverage over 88% in infants.

Results: The study included 7,500,397 children (49% females) and 18.8 million person-years. The proportions of 15 years old girls and boys who had received HPV vaccination increased from 38% and 5% (1996-birth cohort) in 2011 to 54% and 45% (2001-birth cohort) in 2016. HPV vaccination tended to be higher in the Northeast than in Southern states but varied substantially across states, from a 78% coverage in girls in Rhode Island to 20% coverage for boys in Mississippi. Restriction to children with continuous enrollment from ages 9 to 17 yielded almost identical estimates. For our positive controls, by 2016 the proportion of 3-year-old infants with at least one dose of PCV and measles vaccination was 98% and 88%, respectively.

Conclusions: Despite the increasing trends in uptake, HPV vaccine coverage in the U.S. remains behind target rates, with significant regional disparities. Although HPV vaccination increased faster in boys, since boys' recommendation lagged 5 years behind girls, it was still lower in boys than in girls by 2016.

849 | Vaccination before first symptom of central demyelination

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Background: Few studies have documented the role of vaccination before first signs of central demyelination. HBV and HPV vaccines have been the subject of distrust in some countries.

Objectives: To study the association between vaccines exposure and central demyelination (CD), before CD's first symptom.

Methods: From a systematic national registry assembled in neurology, patients with a first lifetime symptom of demyelination affecting the brain, spinal cord or optic nerve were identified and documented for their exposure to vaccines up to 24 months before the first symptom. This exposure was compared to that of a representative sample of general practice patients without a history of demyelination, randomly selected in a national database (referents). Referents were matched to CD cases on age, gender, index date (first symptom in cases) and region of residence (northern or southern France). Vaccines against influenza, hepatitis B (HBV), human papilloma virus (HPV), diphtheria-tetanus-pertussis-poliomyelitis haemophilus (DTPPHae) and others were studied. The associations between vaccination and the occurrence of CD were assessed using multivariable conditional logistic models, controlled for potential confounding factors including family history of autoimmune diseases, geographic origin and co-vaccinations.

Results: 564 cases of CD were matched to 1128 randomly selected referents identified within the registries, with an age range of 2 yo to 79 yo. 123 (22%) cases and 320 (28%) referents had received at least one vaccine within the 24 months before the index date: adjusted odds ratios (OR) were 0.69; 95%CI[0.54–0.88] for any CD first sign (0.68 [0.51–0.90] for myelitis, 0.70 [0.42–1.17] for optic neuritis). Similar results were observed for the 6-month and 2-month time windows. Adjusted OR for any CD were 1.02 [0.71–1.47] for flu vaccines and 0.72 [0.53–0.99] for DTPPHae vaccines; vaccines against HBV and HPV were used respectively by 1.1% and 1.3% of cases and 2.9% and 3.2% of referents which statistically explained the odds ratios below 1 observed for vaccination as a whole.

Conclusions: No increased association between vaccination and CD was observed. Lower rates for vaccination against HBV and HPV in patients with CD, may be due to an early withdrawal from exposure in patients at risk of demyelination.

850 | Incidence of outcomes relevant to vaccine safety monitoring in Europe using two distinct data sources: National Healthcare Registries (Sweden) and electronic medical records (UK)

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Background: Readily available access to population-based background incidence rates (IRs) is critical for monitoring real world safety profiles of vaccines in order to assess whether observed event rates exceed expected rates that may be temporally but not causally associated with vaccination. However, IRs may differ between regions due to differences in population, outcome definition, disease reporting/recording biases, and health care delivery system.

Objectives: To systematically estimate background IRs of 46 pre-specified outcomes including autoimmune, allergic, and neurologic conditions in Sweden (SE) and United Kingdom (UK) and evaluate the extent to which these IRs differ given the potential underlying variability.

Methods: The source populations were derived from national registers in SE with hospital/speciality care and the Health Improvement

Network (THIN) database, a UK primary-care database. All patients aged 0 to 100 years (yrs) from January 1, 2010 to December 31, 2016 were included. IRs were calculated as the number of events divided by the total person-time at risk (per 100,000 Person Years) assuming a Poisson distribution with a 95% Confidence Interval (CI).

Results: 10,203,759 (SE) and 5,239,238 (UK) persons were included with approximately 50% female in each cohort and mean age of 37.9 yrs (standard deviation (sd) = 25.1) in SE and 39.4 yrs (sd = 24.4) in UK. Differences were seen in IRs between SE and UK, e.g. allergic urticaria, SE: 40.3 (95% CI:39.8–40.7) vs. UK: 17.0 (95% CI:15.4–16.5); anaphylactic shock, SE: 19.4 (95% CI 19.1–19.8) vs. UK: 5.9 (95% CI:5.6–6.2); arthritis, SE: 431.3 (95%CI: 429.7–433.0) vs UK: 783.1 (95% CI:779.3–786.9). Further divergence was seen in age groups, e.g. in 0 to 5 yrs, IRs diverged for febrile seizures and myopathies but not for Guillain-Barre syndrome and angioedema; in 65+ yrs, IRs diverged for acute disseminated encephalomyelitis and Raynaud's disease but not for Idiopathic thrombocytopenic purpura and multiple sclerosis.

Conclusions: This study systematically estimated IRs for a wide range of pre-specified outcomes in two large population-based cohorts in Europe. The differences in the magnitude of IRs between the two were aligned with expectations of variability in population and health care delivery systems and emphasize the importance of considering these when conducting safety monitoring studies. This has the potential for significant impact in determining observed vs expected rates of events in establishing or refuting the existence of a true safety issue.

851 | ADVANCE: towards near-real time monitoring of vaccination coverage, benefits and risks using European electronic health record databases

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Background: The Accelerated Development of VAccine beNefit–risk Collaboration in Europe (ADVANCE) is a public-private collaboration aiming to develop and test a system for near real-time (NRT) benefit–risk (B/R) monitoring of vaccines using electronic health record (eHR) databases in Europe.

Objectives: To test the feasibility of NRT monitoring (NRTM) of vaccination coverage, benefits and risks based on multiple eHR databases in Europe (EU), using acellular pertussis vaccination in children (< 6 years) as test case.

Methods: Among participating databases in the ADVANCE consortium, which expressed interest in this NRTM study based on a preliminary qualitative feasibility assessment, a dynamic cohort study was conducted containing two distinct observation periods: a first period (Jan 2014 - Feb 2018) to establish a baseline and a second period (March 2018–May 2018) to test the actual feasibility of NRTM of vaccination coverage, benefits and risks. The events were dose-specific vaccinations (coverage), pertussis (benefit) and febrile convulsions, fever, hypotonic-hyporesponsive episodes, somnolence and persistent crying (risks). Data latencies, differences in time between the date of diagnosis and the data release date, were derived from consecutive data extracts and an interactive web-application was developed for visual monitoring. Five databases from 4 European countries (Denmark: SSI; Italy: ARS, ATSVP; Spain: SIDIAP and UK: RCGP RSCS) participated in this study.

Results: Five databases provided baseline data. Three databases (SSI, ATSVP and RCGP RSC) successfully provided weekly data extractions for a period of three months. The median data latency was 2 (SSI), 2 (ATSVP) and 1 week (RCGP RSC) for vaccinations and varied between 2 weeks and 3 month for the majority of benefit and risk events, depending on type of event and database. ARS and SIDIAP did not obtain approval in time to perform repeated data extractions.

Conclusions: This test case demonstrated that visual NRTM of vaccine benefits and risks is possible with multiple EU eHR databases. Getting the required approvals is a potential barrier.

852 | Variation in rotavirus vaccination coding in US state Medicaid data

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Background: US state Medicaid claims databases may be an attractive option for research into childhood vaccination use, safety, or effectiveness. Variation in US state Medicaid reimbursement policies and coding practices may present challenges for vaccination research that seeks to use state Medicaid data. Rotavirus vaccines are the only oral vaccine licensed for US infants, thus providing a useful test case for exploring differences in the use of vaccine-specific procedures codes versus oral administration codes.

Objectives: We quantify state-specific differences in procedure coding for rotavirus vaccination in Medicaid programs by identifying rotavirus vaccine-specific codes and oral vaccine administration codes.

Methods: We identified infants born between January 1 and June 30, 2010 in four US states' (California, Georgia, North Carolina, Texas)

Medicaid programs. We identified all rotavirus vaccine-related claims in the cohort during the first 6 months of life and categorized each claim as either vaccine-specific or vaccine administration. As one vaccination could result in multiple codes of different types, we defined unique vaccination events as discrete 7-day periods during which at least one rotavirus-related vaccine code was present; all codes occurring in the period were assumed to result from the same vaccination event. We calculated the state-specific proportions of eligible newborns with rotavirus vaccination claims and described the code types used in each state.

Results: 59.4% of 273,312 eligible children had ≥1 rotavirus vaccine-related code in the first 6 months of life. We identified 259,857 unique vaccination events (~1.6 events/vaccinated child). The proportion of vaccinated children with vaccine-specific and oral vaccine administration codes differed substantially across states: California and Georgia used vaccine-specific codes almost exclusively (96.7% and 99.1%,); North Carolina had only oral vaccine administration codes (>99.9%); Texas had a mixture (32.1% vaccine-specific codes alone, 40.0% oral vaccine administration codes alone, and 27.9% had both).

Conclusions: Rotavirus vaccination coding varied substantially across states. Vaccine-specific codes were not used in all states, and Medicaid data in states without (or with incomplete) vaccine-specific coding may make -research on specific vaccine types infeasible. Investigators should carefully evaluate state Medicaid policies and patterns of vaccination uptake, as vaccine reimbursement policies and availability of vaccine claims may vary.

853 | Analysis of data from distributed pharmacoepidemiologic networks

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Background: Distributed data networks allow us to address otherwise inaccessible questions, such as the effects of uncommon treatments, risks of rare adverse drug reactions and heterogeneity in the effects of medicines across populations. Challenges in multi-database studies include both practical barriers, such as restrictions on data access, and methodological issues, such as variation in the collection and coding of information across centers.

Objectives: This symposium will address the challenges of using distributed data for pharmacoepidemiologic analyses. Specialists will present current solutions, weigh the advantages and limitations and highlight areas for further research. The practical recommendations provided will benefit any researcher interested in conducting multicenter studies.

Description: The symposium will consist of a series of talks, summarized by a moderator-led discussion. 1. "Dealing with differences in healthcare systems in multi-database studies". Examples of the impact of differences, such as the capturing and registration of exposure and outcomes, across healthcare systems will be presented. Different approaches to deal with this, including common data models and standardized protocols, will be discussed *(20 min)*. 2. "Methods for meta-analytic pooling of results from distributed networks: random effects, fixed effects and Bayesian methods". Distributed networks usually work with site-specific analyses pooled via meta-analysis. The strengths, weaknesses, and assumptions underlying different methods as well as a proposal of best practices for the analysis of distributed networks will be presented *(20 min)*. 3. "Distributed analytic and data-sharing methods that enable robust statistical analysis without the need to share individual-level data". Methods that ensure consistent data processing and statistical analysis across data sources, and methods that allow database-specific analysis (e.g., covariate selection) will be presented. Different analytic options based on different types of outcomes and different adjustment methods will also be discussed *(20 min)*. 4. "Making the most of it: how to handle systematically missing information in multi-database studies". Several approaches exist to handle missing data across a distributed network. A hierarchy of approaches to leverage information across a network, along with a hierarchy of their requirements will be presented for discussion *(20 min)*. 5. Panel discussion *(10 min)*.

854 | Causal inference in pharmacoepidemiology

Laura Pazzagli[1]; Elizabeth A. Stuart[2]; Miguel Hernán[3]; Sebastian Schneeweiss[4,5]

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Background: When investigating associations between drugs and outcomes of interest, researchers are generally interested in establishing whether it is a causal link: whether the drug itself led to increased (or decreased) risk of the outcome. The fact that two or more events are associated does not imply a causal effect; confounding or other challenges can lead to misleading results. Trying to draw inferences regarding causal links between exposures (such as drugs) and outcomes is obviously an important research field, however there are multiple statistical difficulties.

Objectives: The aim of the symposium is to disseminate recent advances in methods for estimating causal effects among researchers within the pharmacoepidemiological community via the voices of speakers with acknowledged expertise in the field. The symposium is also devoted to opening a constructive dialog between speakers and audiences interested in providing possible solutions to the challenges.

Description: The invited speakers will introduce important concepts fundamental to the estimation of causal effects, as well as some methods for estimation of those effects in non-experimental studies or when dealing with complications in randomized experiments. The

symposium will end with a panel discussion with emphasis on speaker-audience interaction. The symposium will be moderated by Laura Pazzagli, PhD, postdoctoral researcher at the Centre for pharmacoepidemiology of Karolinska Instituted, and will include the following speakers: Elizabeth A. Stuart, Professor at Johns Hopkins Bloomberg School of Public Health, will discuss "*Complications in randomized trials: Dealing with non-compliance and non-representative samples*"; Miguel Hernán, Kolokotrones Professor at Harvard T.H. Chan School of Public Health, will discuss "*Causal Inference from observational data as the emulation of a (hypothetical) target trial*"; Sebastian Schneeweiss, Professor at Harvard Medical School and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital will talk about "*Causal inference principles augmented by machine learning: Can we automate confounding adjustment in database studies?*"

855 | Pharmacoepidemiology and rare cancer research

Wei Zhou[1]; Leigh Marcus[2]; Anton Pottegård[3]; Bruce Carleton[4]; Andrew Freedman[5]; Hans-Georg Eichler[6]

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Background: Rare cancers are a heterogenous group, and there is no internationally agreed definition of rare cancers. The estimated annual incidence rate of all rare cancers in Europe was about 541,000 new diagnoses. The overall public health burden of rare cancers has not been adequately estimated.

Rare cancers are often inadequately diagnosed and treated due to lack of knowledge and insufficient clinical expertise, including many pediatric cancers. Recently, particular genomic markers or biomarkers have been identified to subdivide common cancers into different subtypes qualifying as "rare cancers". The American Society of Clinical Oncology names "Progress in Treating Rare Cancers" as the Advance of the Year 2018.

Rare cancers may develop as a consequence of common chronic diseases and/or their therapies. More collaboration is needed across different regions and databases or registries, to understand the epidemiology, treatment, and outcomes of rare cancers.

Objectives: 1). To provide an overview on the significant disease burden and unmet medical need related to rare cancers in different regions of the world.

2). To discuss the progress and gaps of research on rare cancers, including regulator perspectives of rare cancer treatment and real-world data in supporting regulatory decisions, pediatric cancers, rare cancer subtypes defined by specific genomic markers or biomarkers, and drug-cancer associations.

3). To foster future collaborations between diverse stakeholders in different geographic regions on rare cancer research.

Description: The workshop will start with a short introduction of the panel members and topics, and continue with presentations from 3 speakers. The workshop will end with an 8 min summary and then panel discussions, including response to questions from audiences. The presentation topics of each panel member are as below:

a. Introduction and summary of the disease burden of rare cancers (5 min, Wei Zhou).

b. Overview of rare cancer treatment development: Regulatory approaches, methodological opportunities and challenges in the clinical development of drugs (e.g., umbrella and pragmatic trials) (Leigh Marcus, 20 min).

c. Rare cancers in pediatric population and in the precision medicine era (Bruce Carleton, 20 min).

d. Progresses and challenges of understanding risk of rare cancers as outcome of long-term medical exposures or chronic diseases (Anton Pottegård; 15 min).

e. Summary of the key messages and US NCI perspective (Andrew Freedman, 8 min).

f. Panel discussion: How pharmacoepidemiology expertise will help research and foster the collaboration between regulator, academic, and industry (20 min, all panel members, moderated by Wei Zhou).

856 | Emerging solutions to addressing challenges in measuring adherence to multiple medications

Julie Lauffenburger[1]; Caroline Walsh[2]; Sarah-Jo Sinnott[3]; Jessica Franklin[1]; Petra Denig[4]

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Background: The *Annals of Internal Medicine* recently published reporting guidelines for medication adherence research. While they clarify aspects of reporting research, they fall short of providing guidance on how to measure adherence in standardized ways, especially in the setting of multiple medication use.

Many patients require several medications to manage chronic conditions. Most efforts to measure adherence focus on single drug regimens, which are increasingly less clinically relevant. While prior research has improved methods for measuring adherence to one medication, directly applying them in multiple medications presents challenges. For example, one common measure categorizes patients as adherent based on being at least 80% adherent to at least one medication, but this and most other measures do not distinguish among adherence to different medications and also compress long-term behaviors into a single measure.

Even though calculating adherence to multiple agents is an area of increasing importance, consensus on optimal approaches has yet to be achieved. These different approaches impact estimates of the benefits or harms of interventions/policies on adherence or adherence on

outcomes. As a research community, we need to better standardize methods for measuring adherence to multiple medications.

Objectives: 1. To review the challenges of measuring adherence to multiple medications in pharmacoepidemiologic studies, particularly in claims databases, and potential health and economic implications of the variety of measures being used.

2. To provide a balanced review of emerging solutions to address deficits in adherence measurement standardization to multiple medications and their strengths/limitations.

Description:

The symposium is organized by topic and each identified speaker:

1. Introduction/Background
    1. Short overview of new EMERGE adherence guidelines
    2. Most common measurements in claims data and their strengths/limitations for multiple medications
2. Challenges of adherence measurement
    1. Specific research examples showing how measurements of adherence to multiple medications as both an outcome and exposure differ depending on researcher choices
3. Implications of measurements on outcomes
    1. Specific research examples about implications that different measurements have on their association with health outcomes, like utilization, mortality and quality of life
4. Emerging areas in measurement/possible solutions
    1. Application of group-based trajectory modeling to multiple medications
    2. New adherence software (AdhereR) for measurement in claims databases
5. Moderated panel/audience discussion

857 | Mixing it up: implementing qualitative & mixed methods in pharmacoepidemiology research

M. Elle Saine[1]; Julia E. Szymczak[1]; Irene Petersen[2]; Rachel E. Sobel[3]

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Background: Qualitative methodologies allow researchers to better understand the processes underlying health behaviors and outcomes. Despite the ability of mixed-methods research to minimize limitations associated with quantitative and qualitative approaches independently, these methods have largely been ignored in pharmacoepidemiology research.

Objectives: This symposium will highlight how qualitative methods can enrichen pharmacoepidemiologic research designs by adding interpretation and context to quantitative findings. Four panelists will discuss a range of study designs and populations, underscoring the diversity of questions that these methods may answer.

Description: Timeline (90 Min): Introduction (10 min); Presentations (15 min each); Discussion & Q&A (20 min).

Julia E. Szymczak *The Social Determinants of Antimicrobial Prescribing: Using Qualitative Methodology to Understand the Drivers of Antimicrobial Overuse* The objectives of this talk are to review the sociobehavioral factors that shape antimicrobial prescribing and evidence for interventions that leverage social science theory to improve prescribing. Best practices and practical approaches will be discussed. Specific methodologies, including ethnography and semi-structured interviews, and techniques to establish rigor will be reviewed.

Irene Petersen *Understanding the perspectives of women with severe mental illness concerning the use of psychotropic medicines while pregnant* The research presented in this study provides women's accounts of decisions concerning the use of psychotropic medicines while pregnant. Through interviews with women who had to take the decision on whether to stop or continue treatment in pregnancy we gain their perspectives.

Rachel E. Sobel *How Industry Can Use Mixed Methods to Assess the Effectiveness of Risk Minimization Activities* The objectives of this talk are to review the regulatory framework and to provide some examples of how mixed methods can support the pharmaceutical industry and others in performing effectiveness evaluations of risk minimization activities such as required FDA Risk Evaluation and Mitigation Strategies (REMS) and EU additional Risk Minimisation Measure (aRMM) evaluations.

M. Elle Saine *Using Mixed-Methods Research to Identify Barriers to Treatment of Hepatitis C Virus Infection in Philadelphia's Opioid Crisis* This talk explores how mixed-methods research allows deeper insight into social and patient-level barriers to antiretroviral treatment and adherence. The advantages and challenges of research among vulnerable and marginalized populations will be presented.

858 | Improved real-world outcomes for type 2 diabetes patients on basal-bolus insulin therapy switching to insulin glargine 300 U/ml vs. insulin glargine 100 U/ml and insulin Detemir

Jasmanda Wu[1]; Timothy S. Bailey[2]; Zsolt Bosnyak[3]; Jukka Westerbacka[3]; Rishab A. Gupta[4]; Arjun A. Menon[4]; Charlie Nicholls[5]; Lawrence Blonde[6]

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Background: Randomized controlled trials have indicated that insulin glargine 300 units/mL (Gla-300) is associated with less hypoglycemia than insulin glargine 100 U/mL and insulin detemir (1st generation basal insulins, 1G-BI) in adults with type 2 diabetes (T2D).

Objectives: To comparatively evaluate real-world clinical outcomes in T2D patients on basal-bolus insulin therapy (BBT) who switched their BI to either Gla-300 or 1G-BI.

Methods: This retrospective observational study used electronic medical records from the Predictive Health Intelligence Environment database (IBM Explorys). Adults (≥18 years) with T2D on BBT who switched their BI were studied. Patients in the Gla-300 and 1G-BI cohorts were propensity-score matched (1:1). Endpoints were: glycated hemoglobin (A1C) change from baseline and target attainment (<7.0% and < 8.0%) at 6 months; hypoglycemia (ICD-9/ICD-10 and/or plasma glucose ≤70 mg/dL, or inpatient/emergency department [ED]-associated), with 6 months or variable (until discontinuation or 6 months) follow-up.

Results: Baseline demographics and clinical characteristics were similar: Gla-300 (*N* = 1486) vs. 1G-BI (N = 1486; insulin glargine 100 U/mL, 29.4%; insulin detemir, 70.6%). Comparing matched groups at 6 months, mean A1C reduction was similar (0.52% vs. 0.45%; $p = 0.317$), as was attainment of A1C goals <7.0% (16.0% vs. 19.0%; $p = 0.054$) and < 8.0% (43.5% vs. 41.8%; $p = 0.483$). At 6 months (fixed duration), adjusting for baseline hypoglycemia, Gla-300 patients had significantly fewer all hypoglycemia events (0.76 vs. 0.95 events per patient per year [PPPY]; $p = 0.036$). With variable follow-up, Gla-300 patients had significantly fewer all hypoglycemia events (0.63 vs. 0.77 PPPY; $p < 0.001$) and inpatient/ED-related events (0.15 vs. 0.25 PPPY; $p < 0.001$).

Conclusions: In patients with T2D on BBT, switching to Gla-300 vs. 1G-BIs was associated with similarly improved glycemic control, but significantly lower risk of hypoglycemia and inpatient/ED-related hypoglycemia.

859 | Metformin use and risk of benign prostatic hyperplasia

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Background: Benign prostatic hyperplasia (BPH) is a common age-related condition. Metformin inhibits proliferation of prostate cells and use of metformin seems to reduce the risk of prostate cancer compared with use of other glucose lowering drugs (GLD). Yet, few studies have examined the association between use of metformin and risk of BPH.

Objectives: To compare the risk of BPH in men with type 2 diabetes who initiated either metformin or sulfonylurea between 2000 and 2006 in Northern Denmark. In this period, Danish guidelines recommended initiation of either a sulfonylurea or metformin as first line oral GLD treatment.

Methods: We conducted a population-based cohort study among men with type 2 diabetes in Northern Denmark using Danish medical databases. We identified 9,911 men who initiated treatment with either metformin or sulfonylurea and filled at least 2 prescriptions for the same GLD within 6 months (the index date). We used an intention to treat (ITT) approach and computed rates and hazard ratios of BPH (using Cox regression), comparing metformin users with sulfonylurea users overall and stratified by HbA1C-level achieved at the index date. We adjusted for age, comorbidity, presence of micro- or macro-vascular complications, obesity, marital status as a marker of social support, and calendar year. We also used an as-treated approach in which we censored patients 30 days after change of type of monotherapy regimen.

Results: In the ITT analysis, the overall rate of BPH (diagnosis or prescription) in 3953 metformin users (Median follow-up 10.1 years) was 33.4 (95% CI, 31.4–35.4) per 1000 person-years. Compared with 5958 sulfonylurea users (median follow-up 8.0 years), the crude hazard ratio (HR) for BPH was 0.83 (95% CI, 0.77–0.89) but after adjustment it was 0.97 (95% CI, 0.90–1.05). In the as treated analysis, BPH risk was lower in metformin compared with sulfonylurea users, adjusted HR = 0.91 (95% CI, 0.83–1.00). When stratified by baseline HbA1c level we observed a slightly lower risk of BPH in metformin compared with sulfonylurea use in those with HbA1c level below 7% (adjusted HR 0.91 (95% CI, 0.80–1.03) but not among those with HbA1c ≥ 7% in the ITT analysis. In the as-treated analysis, adjusted HRs associated with metformin were 0.88 (95% CI, 0.76–1.01) in those with HbA1c below 7%, 0.92 (0.73–1.15) if HbA1C was ≥7% and < 8%, and 1.10 (0.81–1.48) when HbA1c was ≥8%.

Conclusions: Compared with sulfonylurea, metformin did not seem to substantially reduce the risk of BPH in men with diabetes overall. However, in men achieving good glycemic control metformin treatment may have a small benefit in relation to BPH risk.

860 | Comparative cardiovascular and hypoglycemic safety of glimepiride in type 2 diabetes: a population-based cohort study

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Background: Ongoing cardiovascular outcome trials will report on the efficacy and safety of newer antidiabetic drugs, including dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, compared with the sulfonylurea glimepiride. However, the pharmacologic heterogeneity among sulfonylureas could limit the generalizability of these trials regarding non-glimepiride compounds.

Objectives: To assess the risk of cardiovascular and hypoglycemic adverse events associated with use of glimepiride compared with other second-generation sulfonylureas among patients with type 2 diabetes in a real-world clinical setting.

Methods: We used the United Kingdom Clinical Practice Research Datalink and linked it to the Hospital Episode Statistics and Office for National Statistics databases to identify all patients initiating a sulfonylurea between January 1998 and June 2017. Using a prevalent new-user cohort design, we matched 1:4 patients initiating glimepiride with those initiating other second-generation sulfonylureas on calendar time, prior use of sulfonylureas, and time-conditional high-dimensional propensity score. The two groups were compared using Cox proportional hazards models to estimate adjusted hazard ratios (HRs)

and 95% confidence intervals (CIs) of myocardial infarction, ischemic stroke, severe hypoglycemia, cardiovascular death, and all-cause mortality.

Results: Among 66,032 initiators of sulfonylureas, 6,438 were initiators of glimepiride matched to up to 20,582 initiators of other second-generation sulfonylureas. During a mean follow-up of 1.3 years, glimepiride was associated with a similar risk of myocardial infarction (8.3 vs 8.7 per 1000/year; HR, 0.99; 95% CI, 0.75 to 1.30), ischemic stroke (7.8 vs 8.1 per 1000/year; HR, 0.96; 95% CI, 0.72 to 1.27), or severe hypoglycemia (7.2 vs 5.9 per 1000/year; HR, 1.24; 95% CI, 0.92 to 1.68) compared with other second-generation sulfonylureas. However, glimepiride was associated with a decreased risk of all-cause mortality (27.8 vs 37.0 per 1000/year; HR, 0.77; 95% CI, 0.67 to 0.89), and a non-significant but similar trend for cardiovascular death (10.7 vs 12.9 per 1000/year; HR, 0.83; 95% CI, 0.65 to 1.05).

Conclusions: In this population-based study, glimepiride was associated with a decreased risk of all-cause mortality and possibly of cardiovascular death compared with other second-generation sulfonylureas. These findings will help in interpreting the upcoming results of trials using glimepiride as an active comparator in the context of other sulfonylureas.

861 | Major adverse cardiovascular events associated with sodium glucose co-transporters versus other antidiabetes drugs: population-based cohort study

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Background: Randomized clinical trial data suggest sodium-glucose co-transporter inhibitors (SGLT2i) reduce major adverse cardiovascular events (MACE), but their effectiveness in real-world practice is poorly understood.

Objectives: To study the association between SGLT2i and MACE compared to patients treated with dipeptidyl peptidase-4 inhibitors (DPP4i), or sulfonylureas (SU).

Methods: We undertook a cohort study of adult patients with diabetes in British Columbia, Canada. Patients were eligible for the study if they initiated second-line therapy with an SGLT2i, DPP4i or SU between June 2014 and December 2017, having previously received metformin as first-line treatment. The metformin criterion was used to reflect normal practice. Patients were ineligible if they were less than 18 years of age, or had a record of gestational diabetes, malignancy, renal disease, human immunodeficiency virus infection, or organ transplant within a year prior to cohort entry. Our primary outcome was risk of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke). A secondary outcome was emergency admission to hospital for any reason. SGLT2i patients were matched to DPP4i patients (cohort 1) and SU patients (cohort 2) on propensity score using nearest neighbor matching. We estimated hazard ratios (HR) using cox proportional hazards regression.

Results: There were 18,534 patients eligible for analysis after all inclusion and exclusion criteria were applied. These comprised 6,360 SGLT2i users, 3,921 DPP4i users, and 8,253 SU users. After matching into 3,172 SGLT2i-DPP4i pairs, and 5,391 SGLT2i-SU pairs, 0.3% of patients on each drug experienced the primary outcome. SGLT2i exposure was not significantly associated with risk of MACE compared to DPP4i exposure (HR 0.70, 95% confidence interval [CI] 0.38–1.29), or SU exposure (HR 0.74, 95% CI 0.47–1.18). However, a paucity of events prevented precise estimation of the primary outcome. For the secondary outcome, SGLT2i exposure was not associated with reduced emergency admission to hospital compared to DPP4i exposure (HR 1.03, 95% CI 0.78–1.36), but was associated with reduced emergency admission to hospital when compared to SU exposure (HR 0.71, 95% CI 0.57–0.87).

Conclusions: Although a paucity of events prevented precise estimation of the primary outcome in second-line treated patients in British Columbia, observed hazard ratios for SGLT2i and MACE were comparable to those reported in randomized trials. Larger studies are needed to explore this association in a real-world setting.

862 | Comparative risk evaluation for cardiovascular events associated with empagliflozin vs. dapagliflozin: a multi-institutional cohort study

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Background: Clinical trials have proved the cardiovascular benefits of sodium-glucose co-transporter 2 (SGLT2) inhibitors. However, the comparative cardiovascular effects in real-life patients with SGLT2 inhibitors (i.e., empagliflozin and dapagliflozin) remain unclear.

Objectives: To compare the risk of cardiovascular events in patients without atherosclerotic cardiovascular disease receiving empagliflozin versus dapagliflozin.

Methods: We analyzed a multi-institutional electronic medical records database (Chang Gung Research Database, CGRD) containing about 6% of the Taiwan population for this study. We used a retrospective cohort design and included adult patients with type 2 diabetes who were newly receiving SGLT2 inhibitors from 2016 to 2017. We excluded patients with a history of cardiovascular events (e.g., ischemic stroke, myocardial infarction and heart failure). The primary outcome was a composite of cardiovascular death, ischemic stroke, myocardial infarction and heart failure. We performed intention-to-treat analyses and followed up patients from initiation of SGLT2 inhibitors until the occurrence of cardiovascular events or the last clinical visit date recorded in CGRD before December 31, 2018. We

performed multi-variate Cox proportional hazard modeling, taking into consideration patients' age, sex, baseline blood glucose level indicators, renal functions, lipid profiles, comorbidities, and co-medications.
Results: We identified 12,868 new SGLT2 inhibitor users with a mean age of 58.9 years, of whom 43.8% were male. A total of 12,089 person-years of empagliflozin and 10,426 person-years of dapagliflozin were included. There were similar risks of primary composite outcome (adjusted HR: 0.94; 95% CI: 0.76–1.17), but higher risk of ischemic stroke (adjusted HR: 1.19; 95% CI: 0.83–1.64) and lower risk of heart failure (adjusted HR: 0.68; 95% CI: 0.48–0.96) were found for dapagliflozin than empagliflozin users. Different sensitivity analyses (e.g., propensity scores matching and per-protocol approach) showed trends consistent with the main analysis.
Conclusions: The findings indicated that dapagliflozin and empagliflozin pose different risk profiles for cardiovascular events. Clinicians should consider patients' baseline risk profiles for specific cardiovascular events when selecting SGLT2 inhibitors.

863 | Empagliflozin selected cardiovascular and safety outcomes in routine care: first results from theempagliflozin comparative effectiveness and safety (EMPRISE) study

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Background: The EMPA-REG OUTCOME trial showed that empagliflozin (EMPA), a SGLT2 inhibitor (SGLT2i), reduces the risk of cardiovascular (CV) death and hospitalization for heart failure (HHF) in patients with type 2 diabetes (T2D) and established CV disease. The implications of these findings, as well as the potential risks observed for other SGLT2i agents or for the SGLT2i class, are yet to be evaluated for EMPA in real-world practice. EMPRISE studies the comparative effectiveness, safety and healthcare utilization of EMPA in routine care, using data from Medicare and 2 U.S. commercial claims datasets from 08/2014 through 09/2019.
Objectives: To evaluate the risk of CV and safety outcomes associated with the initiation of EMPA vs. DPP4 inhibitors (DPP4is) in an interim analysis from EMPRISE based on data from 08/2014 through 09/2016.
Methods: Within the three datasets (Medicare fee-for-service, Optum, and MarketScan), we identified 17,551 pairs of 1:1 propensity score (PS)-matched patients ≥18 years with T2D initiating EMPA or a DPP4i. We assessed a composite CV outcome (comprised of myocardial infarction, stroke, or all-cause mortality), an extended CV outcome (plus HHF or coronary revascularization), and their individual components. Safety outcomes of interest were lower-limb amputations (LLA), bone fractures, diabetic ketoacidosis (DKA), and acute kidney injury (AKI). We estimated pooled hazard ratios (HR) and 95% confidence intervals (CI) adjusting for >140 baseline covariates, including several proxies of diabetes progression.
Results: After PS-matching, covariates were well balanced with standardized differences <0.1, including laboratory test results available in a subset of the cohort and thus not included in the PS model. Compared to DPP4i, EMPA was associated with a trend to lower risk of the CV outcome [HR (95% CI) = 0.82 (0.62–1.10)] and its individual components, and a lower risk of the extended CV outcome [0.73 (0.60–0.88)], and HHF [0.56 (0.43–0.73)]. Despite small numbers, no increased risk of LLA [1.20 (0.57–2.53)], fractures [0.81 (0.41–1.57)], or AKI [0.64 (0.43–0.95)] was observed among EMPA users, though a numerical increase in DKA risk [1.74 (0.84–3.58)] was noted.
Conclusions: Early findings from EMPRISE showed that compared with DPP4i, EMPA was associated with a lower risk of CV outcomes with varying levels of precision, and a safety profile consistent with currently documented information.

864 | Real-world data on the use of biologics in the treatment of colorectal cancer: comparison between three European databases

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Background: An increasing number of biologics have been approved for treating metastatic colorectal cancer (CRC), but only little is known regarding their use in the real-world setting.
Objectives: To explore the potential of databases from different European countries to provide real-world data on the use of biologics in the treatment of CRC patients.
Methods: Based on three different databases (PHARMO Database Network from the Netherlands (NL), Caserta LHU from Italy (IT), GePaRD from Germany (DE)) we identified - for each database - persons treated with a biologic approved for metastatic CRC (bevacizumab, cetuximab, panitumumab, or aflibercept) and a diagnosis of CRC in 2010 (cohort 2010) or 2014 (cohort 2014; IT: only cohort 2014). The first dispensation date of one of these drugs in the respective year was defined as cohort entry. The cohort was followed for 12 months or until death, whichever occurred first. We characterized the patients regarding age, sex, presence of metastases and overall health (using the chronic disease score, CDS) at cohort entry and survival patterns during follow-up. We further described the type and number of biologics used.
Results: Cohort 2010 included 112 patients from NL and 2,176 from DE; cohort 2014 included 73 patients from NL, 49 from IT and

2,454 from DE. The cohorts were comparable regarding age (mean: 65–67 years) and sex (>53% male). Mean CDS and proportion of patients with metastatic disease were higher in DE and IT (~90%), compared to NL (<75%). Most patients (78–82%) received only one biologic. The proportion of dispensations of bevacizumab decreased between 2010 and 2014 by ~10% (NL: 93% to 85%, DE: 72% to 61%) while it increased regarding panitumumab (NL: 16% to 29%, DE: 5% to 13%). The second most frequently dispensed biologic was panitumumab in NL and cetuximab in IT and DE. The trends between 2010 and 2014 regarding the proportion of patients receiving ≥2 different biologics differed between countries: increase from 11% to 18% in NL and from 20% to 22% in DE. In all cohorts, 33–38% of patients died within one year; of these, ~20% died within 6 months.

Conclusions: The relatively high mean age and low 12-month survival indicate a less selective use of biologics among CRC patients in the real-world setting compared to clinical trials, including a potential off-label use given that no metastases were coded in ≥10% of patients. Overall, the analyses showed plausible results that were largely consistent across databases, underlining the potential of these databases for real-world monitoring regarding the use of novel oncologic drugs.

865 | Drug survival of targeted therapies for plaque psoriasis: evidence from a large U.S. claims database

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Background: Targeted therapies for plaque psoriasis (PsO) are associated with costly initiation regimens and may reduce the effectiveness of subsequent targeted treatments. For these reasons, characterizing drug survival (time to drug discontinuation) is essential for producing valid cost-effectiveness estimates for these drugs.

Objectives: To estimate drug survival for seven PsO drugs: adalimumab, apremilast, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab.

Methods: Using the Truven Health MarketScan Commercial Database from 2007 to 2017, we selected patients with at least one PsO diagnosis from a dermatologist. Patients enrolled for 12 months prior to the first PsO diagnosis were considered biologic-naïve at their first targeted therapy. The first treatment sequences for patients not fitting this definition were discarded, as we could not ascertain whether the patient was biologic-naïve. Two claims for the same drug were considered to be part of a single treatment sequence if the service date for the second claim occurred within a time period equal to twice the indicated days of supply for the first claim. Using Kaplan–Meier curves and proportional hazards regressions adjusted for age at initiation, year of initiation, sex, and region, we calculated median survival and hazard ratio (HR).

Results: We identified 145,637 treatment sequences among 56,355 patients totaling 104,986 person-years on targeted therapy. Of these sequences, 18,576 (12.8%) were among biologic-naïve patients. In biologic-naïve patients, secukinumab had the longest median drug survival with 477 days (95% confidence interval: 315 to 702); ustekinumab had the shortest with 149 days (129 to 209). In biologic-experienced patients, ixekizumab and secukinumab had the highest median survival with approximately 225 days, while apremilast, etanercept and infliximab had the shortest with approximately 145 days. The proportional hazards regression corroborated these results. We also found that female sex was associated with a higher risk of discontinuation (HR: 1.09 [1.08 to 1.11]) and that discontinuation has become more likely in recent years (HR: 1.02 year over year [1.01 to 1.02]).

Conclusions: We found that the interleukin-17A inhibitors ixekizumab and secukinumab provide superior drug survival in both biologic-naïve and -experienced patients relative to other targeted therapies. We also found that discontinuation is more likely as more targeted therapies have been released. With several new drugs for PsO recently released or forthcoming, it will be important to frequently update changes to drug survival.

866 | Risk of serious infections among new users of Interleukin-17, Interleukin-12/23 inhibitors, compared to tumor necrosis factor (TNF)-alpha inhibitors, for the treatment of psoriasis and psoriatic arthritis

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Background: Recently, interleukin-17 (IL-17) and interleukin-12/23 (IL-12/23) inhibitors have been approved by the U.S. Food and Drug Administration for the treatment of psoriasis (PsO) and psoriatic arthritis (PsA), yet existing evidence is mixed on the risk of serious infections associated with these products.

Objectives: To determine whether initiation of IL-17 or IL-12/23 inhibitors, compared with tumor necrosis factor-alpha (TNF-α) inhibitors, are associated with an increased risk of serious infection among patients diagnosed with PsO or PsA.

Methods: A retrospective cohort study evaluated U.S. commercially insured adults with PsO or PsA who received a first prescription of an IL-17 (ixekizumab and secukinumab), IL-12/23 (ustekinumab), or TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) between January 2015 and May 2018. Serious infection was defined as the first infection requiring hospitalization after biologic initiation. Incidence rates were calculated by drug class. Weighted Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (95% CI) for the risk of a serious infection after biologic initiation. We used inverse probability of treatment weighting (IPTW) propensity scores to address the imbalance of baseline covariates.

Results: Based on preliminary analysis, a total of 12,201 treatment episodes in persons diagnosed with PsO or PsA who were previously biologic-naïve were included: 2,228 (18%) with IL-17, 2,937 (24%) IL-12/23, and 7,036 (58%) TNF-α inhibitors. Overall, 200 (1.64% of episodes serious infections were identified (incidence rate per 100 person-years: 2.09 (95% CI 1.46–2.89) for IL-17 inhibitors, 1.32 (95% CI 0.92–1.83) for IL-12/23 inhibitors, and 2.39 (95% CI 2.01–2.82) for TNF- α. As compared to patients initiating a TNF- α, those initiating with IL-12/23 (adjusted HR 0.64, 95% CI 0.43–0.97), but not those with IL-17 inhibitors (adjusted HR 0.92, 95% CI 0.58–1.44) were less likely to be hospitalized for serious infection. The risk of serious infection was not different between IL-17 and IL-12/23 inhibitors: HR 1.21 (95%CI 0.71–2.05).

Conclusions: In this cohort, IL-12/23 inhibitors were associated with a lower risk of serious infection than TNF- α inhibitors in adults with PsO or PsA. No increased risk was observed in IL-17 inhibitors compared with TNF- α inhibitors.

867 | Risk of heart failure following exposure to non-TNFi compared to TNFi biologics in US patients with rheumatoid arthritis

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Background: Biologic disease modifying drugs have become the cornerstone of rheumatoid arthritis (RA) management. Case reports on new-onset heart failure (HF) following TNFi initiation led to an FDA black box warning released in October 2001, but subsequent observational studies have shown no association. There is a lack of knowledge regarding the risk of HF following exposure to the newer non-TNFi biologics.

Objectives: We aimed to assess the risk of incident HF following exposure to non-TNFi compared to TNFi biologics.

Methods: Using US claims data from Truven MarketScan (2004–2016), we conducted a cohort study of RA patients who initiated a 'TNFi' (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), or 'non-TNFi' biologic or targeted synthetic DMARD (abatacept, anakinra, tocilizumab, tofacitinib). Patients were excluded if they were < 18 years old, had previous HF, an implantable cardiologic device, or a loop-diuretics prescription. Patients were followed from the day after treatment initiation until the earliest event of the following: death, insurance disenrollment, treatment switching or discontinuation. The primary outcome of incident HF was defined based on primary inpatient diagnosis. Cox proportional hazards regression compared risk of HF among new users of non-TNFi compared to TNFi. To control for confounding, we used multivariable adjustment as well as propensity score (PS) adjustment by decile with trimming. Covariates in adjusted and PS models included year of cohort entry, age, gender, region, comorbidities, prior drug-use, and health utilization.

Results: A total of 13,290 non-TNFi patients were included, primarily consisting of abatacept (65%). For the TNFi group, we identified 67,892 patients, primarily consisting of etanercept (42%) or adalimumab (37%). More patients treated with non-TNFi were female, older, had higher proportion of co-morbidities and number of rheumatologist visits; but lower proportion of NSAID/Coxib use. There were 16 events of HF in the non-TNFi exposed group (incidence rate [IR] 1.08 per 1,000 person-years [py]), and 89 events in the TNFi group (IR 0.87/1,000py). The crude hazard ratio (HR) of HF after initiating a non-TNFi was 1.28 (95%CI 0.75–2.18) versus TNFi. After confounding adjustment in a multivariable model, the HR was attenuated to 1.08 (95%CI 0.57–2.05). The PS adjusted analysis showed consistent results.

Conclusions: In this large US-based cohort of 81,182 RA patients, we found no difference in the risk of incident HF after initiation of non-TNFi biologic or targeted synthetic DMARD versus TNFi.

868 | Risk of diabetes treatment intensification associated with use of abatacept versus other biologic drugs in patients with rheumatoid arthritis and diabetes mellitus

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Background: Rheumatoid arthritis (RA) patients have a high prevalence of cardiovascular comorbidities including diabetes mellitus (DM). Past studies have suggested a potential beneficial effect of abatacept on insulin sensitivity, but the effect of biologic therapy on DM severity in patients with RA and DM is unknown.

Objectives: To compare the rates of DM treatment intensification among patients with RA and DM (type 1 or 2), newly initiating abatacept versus other biologic disease-modifying antirheumatic drugs (DMARD).

Methods: We identified RA patients aged ≥18 years with ≥2 RA diagnoses separated by 7–365 days using insurance claims data from Truven MarketScan database (2005–2016). We included new users of abatacept, tumor necrosis factor inhibitors (TNFi) (adalimumab, etanercept, certolizumab, golimumab, and infliximab), rituximab or tocilizumab. The date of drug dispensing was defined as the index date. We required ≥365 days of continuous enrollment prior to the index date, defined as the baseline period. We excluded patients with history of malignancy. Among these RA patients, we identified patients with DM by using ≥1 diagnosis for either type 1 or type 2 DM and ≥ 1 anti-diabetic drug prescription during baseline. The primary outcome was DM treatment intensification defined as adding or switching to a different oral antidiabetic medication or insulin. We calculated incidence rates (IR) and hazard ratio (HR) of DM treatment intensification in patients initiating abatacept versus other biologics.

Results: We included 9,385 patients with RA and DM initiating abatacept (mean age 58.5, female 78%), TNFi (56.7, 71%), rituximab (58.1, 76%), or tocilizumab (57.6, 79%). Hypertension was present in

up to 74% and hyperlipidemia was present in up to 67% of patients. Baseline insulin use was highest in the rituximab group (44%) and lowest in the TNFi group (36%). Over 7,012 person-years of follow up, 1,565 DM treatment intensification events occurred. The IR per 1,000 person-years ranged from IR 209.0 (tocilizumab) to 236.7 (abatacept). After adjustment, the risk of DM treatment intensification was similar between abatacept and TNFi (HR 0.93, 95% confidence interval [CI] 0.83–1.08), rituximab (HR 0.96, 95% CI 0.79–1.18), and tocilizumab (HR 0.86, 95% CI 0.68–1.08).

Conclusions: In patients with both RA and DM, we found no difference in the risk of DM treatment intensification between patients initiating abatacept versus TNFi, rituximab, and tocilizumab.

869 | Intravitreal anti-vascular endothelial growth factor drugs and risk of serious non-ocular hemorrhage

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Background: Intravitreal (IVT) anti-VEGF drugs aflibercept and ranibizumab are used to treat neovascular retinal diseases. A meta-analysis reported inconsistent risk of hemorrhage but suggested that this may differ among single IVT anti-VEGF drugs. IVT dexamethasone, also used for various retinal diseases, can cause bleeding as well.

Objectives: To compare the non-ocular hemorrhage risk of IVT aflibercept vs. ranibizumab (primary aim) and for single IVT anti-VEGFs vs. IVT dexamethasone (secondary aim).

Methods: A cohort study was conducted using 4 Italian regional claims databases, covering 18 million inhabitants in a period ranging from 2011 to 2016. Incident aflibercept users were propensity score (PS)-matched 1:4 to incident ranibizumab users. The outcome was first non-ocular hemorrhage requiring hospitalization. Incidence of events per 1,000 person-years (PYs) was estimated. An intention to treat approach based on a Poisson distribution was used, whereby aflibercept and ranibizumab users were followed for 180 or 365 days in separate analyses. An as-treated (AT) approach was also employed as sensitivity analyses, with censoring on date of switching to another drug or discontinuation. All analyses were repeated for aflibercept vs. dexamethasone and ranibizumab vs. dexamethasone. Risk was expressed in hazard ratios (HR) with 95% confidence intervals (CI) using a Cox proportional hazards model.

Results: Overall 21,766, 3,150 and 3,900 incident users of ranibizumab, aflibercept and dexamethasone were identified from 2009–2016 in 4 Italian regions. After matching, mean age was 76 ± 10 and female–male ratio was 1.4 for ranibizumab and aflibercept users; slightly lower mean age and equal sex distribution was seen when matching anti-VEGFs to dexamethasone users. The incidence of non-ocular hemorrhage with low, at 4 events per 1,000 PYs for each drug. Aflibercept was not associated with increased risk of hemorrhage vs. ranibizumab at 180 days (HR: 0.97 (95%CI: 0.37–2.56)), which was confirmed at 365 days (HR: 1.01 (95%CI: 0.51–1.99)). Results were consistent in the AT analysis: HR: 1.19 (95% CI: 0.52–2.75). No increased risk of hemorrhage was found for aflibercept and ranibizumab at 180 days compared to dexamethasone (HR: 0.70 (95% CI 0.30–2.60) and 0.67 (95% CI: 0.33–1.38), respectively).

Conclusions: No association was identified between aflibercept and non-ocular hemorrhage compared to ranibizumab. A comparable risk for these IVT anti-VEGFs and IVT dexamethasone was observed. Given the known benefits of IVT anti-VEGF in retinal diseases, hemorrhage does not appear to be a significant risk.

870 | Heatwaves and heat-sensitizing medications in vulnerable older adults

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Background: Heatwaves kill people and have become more common and severe in the past decades. Some medications may sensitize vulnerable older patients with chronic conditions to the effects of heatwaves.

Objectives: To determine whether heat-sensitizing medications, e.g., diuretics, antipsychotics, increase the risk of heat-related hospitalizations during the warm summer months among older adults with debilitating conditions.

Methods: Linking 20% US Medicare Part A, B, and D data with daily maximum surface air temperature (tasmax) using residence ZIP codes, we identified patients with chronic kidney disease (CKD), diabetes on chronic insulin use (DM), chronic obstructive pulmonary disease (COPD), dementia, heart failure (HF), myocardial infarction (MI), and stroke during June–August of years 2007–2012. We assessed exposure to angiotensin blockers (ACE/ARB), loop diuretics (LD), antipsychotics (AP), beta-blockers (BB), and anticholinergic agents (AC). We defined heatwaves as at least two consecutive days with tasmax >95th percentile. We assessed heat-related hospitalizations (heat exhaustion, heat fatigue, heatstroke, dehydration, hyperosmolality, or excessive exertion) during follow-up. We conducted self-controlled case series analysis for censored or curtailed data to estimate risk ratios (RR) and 95% confidence intervals (CI) for heatwave and medication effects. We evaluated each medication separately, both overall in the full cohort and in each disease-specific cohort.

Results: Among 377,100 patients (73% female; 80% white; mean age = 80, SD 8; 41% living in South region; 42% CKD, 29% dementia, 26% HF, 19% DM, 12% MI, 9% COPD, 7% stroke), 33% experienced a heatwave. A heat-related hospitalization occurred in 11,244 (3%). Heatwaves were associated with modest increases in heat-related hospitalizations (RR 1.1 [1.0–1.2]). Medication exposure varied widely ranging from 9% (AP) to 75% (AC). After accounting for heatwaves, several drug classes moderately increased the risk for heat-related hospitalizations except for AC and AP: BB, 1.3 (1.1–1.6); LD, 1.4 (1.2, 1.7) and ACE/ARB RR = 1.6 (1.3–1.9). The effects of ACE/ARB and LD were pronounced in subgroups with CKD, DM, and HF, with RR >5 and lower CI bound >2.

Conclusions: Many of the heat-sensitizing medications increased the risk of heat-related hospitalizations among older patients with chronic disease. ACE/ARB posed greater risks in subgroups with CKD, DM, and HF. Large high-resolution cohort studies are needed to understand the interactions between heatwaves and medications on heat-related hospitalizations and other health outcomes in vulnerable older adults.

871 | Opioid intensification versus adjuvant gabapentin initiation and risk of hospitalization for falls and fractures in United States nursing home residents

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Background: Opioids are commonly used in nursing homes and residents receiving opioids are at higher risk for falls and fractures. Adjuvants (e.g., gabapentin) may be used with the pain medication regimen when residents are intolerant for opioid side effects. Data on the comparative safety of different strategies for intensifying pharmacologic pain management on fall and fracture risk are scant.

Objectives: To investigate the risk of hospitalization for falls or fractures among residents for whom gabapentin was added to an opioid regimen relative to residents whose oral morphine equivalent (OME) was increased.

Methods: We conducted a retrospective cohort study among fee-for-service Medicare beneficiaries aged ≥65 years living in 1790 nursing homes from 2011 to 2016 linking Minimum Data Set 3.0, Medicare Parts A and D. Using principles of a new user design, we identified residents for whom gabapentin was added to an opioid drug regimen and 1:1 propensity matched them to residents with an increase in oral morphine equivalent (OME). Residents contributed treatment episodes, and were followed up from the index date (date of gabapentin initiation or OME increase) until fall/fracture hospitalizations, death, or 180 days. We estimated the intention-to-treat effect from competing risks models from which we derived sub-distribution hazard ratios (aHR_{SD}) and 95% confidence intervals (CI).

Results: Overall, 3,171 residents contributed 5,528 treatment episodes: 2,764 gabapentin initiators were 1:1 propensity matched to residents whose opioid regimen was intensified. The incidence rate of hospitalizations for falls and fractures per 100 person-years was 2.98 (95% CI: 2.16–4.11) in residents with intensified opioid regimens and 2.56 (95% CI: 1.79–3.66) in residents initiating gabapentin while holding opioid dose constant. Gabapentin initiators had similar rates of hospitalizations for falls and fractures rates as those with OME increases (aHR_{SD} = 0.85, 95% CI: 0.44–1.67).

Conclusions: Use of gabapentin as an adjuvant to opioids was uncommon in US nursing homes. Given that nursing home residents typically have limited mobility, the fracture rates were lower than observed in community-dwelling older adults. The risk of hospitalizations for falls and fractures were similar regardless of pharmacologic pain management approach. Whether gabapentin as an adjuvant to opioid therapy is as effective as increased OME should be evaluated in older adults living in nursing homes.

872 | Comparative safety and effectiveness of apixaban and rivaroxaban versus warfarin among US nursing home residents

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Background: Research comparing direct-acting oral anticoagulants (DOACs) to warfarin has excluded nursing home residents, a vulnerable population at high risk for vascular and bleeding events.

Objectives: To compare the safety and effectiveness of individual DOACS (rivaroxaban, apixaban) versus warfarin in a contemporary (2014–2016) cohort of nursing home residents.

Methods: Residents aged ≥65 years with non-valvular atrial fibrillation newly initiating oral anticoagulation and enrolled in fee-for-service Medicare for ≥6 months were studied. Nursing home residence was determined using Minimum Data Set 3.0 assessments. Effectiveness and safety outcomes were identified from Part A claims and included 1) ischemic stroke or transient ischemic attack (IS/TIA); and 2) bleeding (extracranial or intracranial); 3) a composite of the IS/TIA, bleeding, myocardial infarction, venous thromboembolism, systemic embolism, and death; and 4) death. Follow-up continued until an outcome or 14-day treatment gap (as-treated). DOAC initiators were 1:1 propensity matched to residents initiating warfarin in the same year. Cox proportional hazards models estimated cause-specific hazard ratios.

Results: Among 3,326 apixaban and 2,855 rivaroxaban initiators, 84% and 99% were matched to warfarin initiators. Median age (84 years; Q1 77, Q3 89), CHA_2DS_2-Vasc (5; Q1: 4, Q3: 6) and ATRIA risk scores (3; Q1: 3, Q3: 6) were similar across treatments and cohorts. Crude IS/TIA incidence rates in the apixaban cohort were 0.93 events/100

person-years (PYs) for warfarin and 1.73 events/100 PYs for apixaban; event rates in the rivaroxaban cohort were 1.29/100 PYs for warfarin and 1.90/100 PYs for rivaroxaban. Bleeding rates were in the range of 6.58–6.84 events/100 PYs, with the exception of apixaban (4.24 events/100 PYs). Compared with warfarin, the IS/TIA rates were higher among apixaban (HR: 1.93; 95% CI: 1.02–3.65) and rivaroxaban users (HR: 1.48; 95% CI: 0.87–2.51). Bleeding rates were lower among apixaban users (HR: 0.63; 0.47–0.85) and similar to warfarin for rivaroxaban users (HR: 0.96, 95% CI: 0.74–1.23). Crude mortality rates ranged from 29.34 to 36.96 deaths/100 PYs. Apixaban (HR: 0.79; 0.70–0.88) and rivaroxaban (HR: 0.80; 95% CI: 0.71–0.89) were associated with lower mortality. Composite event rates were also lower among apixaban (HR: 0.80; 95% CI: 0.72–0.89) and rivaroxaban users (HR: 0.87; 95% CI: 0.79–0.96).

Conclusions: Nursing home residents initiating apixaban and rivaroxaban had lower mortality compared with warfarin and higher rates of IS/TIA hospitalizations. Bleeding was less common with apixaban.

873 | Statin use in older Danes: an analysis of discontinuation patterns

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Background: There is limited evidence on benefits and harms of statins in the oldest old. Current guidance suggests individualized decisions and discontinuation of statins may be considered in some.

Objectives: To investigate factors associated with statin discontinuation in new statin users ≥70 years of age over the first four years of use.

Methods: This was a register-based descriptive drug utilization study. The population was all Danish persons ≥70 years of age, starting statins between 2008 and 2012. We evaluated statin discontinuation at one year (early), two years, and four years. We also examined the annual rate of early discontinuation from 2008 to 2015. As possible factors associated with discontinuation, we considered age group, sex, indication, co-morbidities, concomitant medications, education, marital status, and region of residence. Factors associated with discontinuing were analyzed using logistic regression.

Results: We included 84,696 statin initiators. At one year, 13% had discontinued their treatment. At two years, an additional 13% discontinued, and at four years, another 17% discontinued. Increasing age was associated with increased odds of discontinuation at all timepoints (OR 1.95 [95% CI 1.28 to 3.00] at 1 year; OR 2.10 [95% CI 1.29 to 3.41] at 2 years; OR 2.51 [95% CI 1.17 to 5.41] at 4 years, for 95+ age group versus 70 to 74). Beyond one year, increasing co-morbidity scores (OR 1.85, 95% CI 1.60 to 2.15 for high versus zero at 4 years) and increasing numbers of medications (OR 1.29, 95% CI 1.20 to 1.40 for 10+ medications versus 0 to 4 at 4 years) were associated with increased odds of discontinuation. A secondary prevention indication was associated with reduced odds of discontinuation at one (OR 0.73, 95% CI 0.65 to 0.82) and four years (OR 0.85, 95% CI 0.76 to 0.96), but not at two years (OR 0.94, 95% CI 0.83 to 1.05). Use of cardiovascular medications was associated with reduced odds of discontinuation. The annual proportion of early discontinuers ranged from 14 to 17% for primary prevention and 10 to 12% for secondary prevention between 2008 and 2015.

Conclusions: Statin discontinuation appeared to be influenced by age, burden of co-morbidities and medication use, indication, and concomitant cardiovascular therapies. Decisions surrounding statin may have been made based on these person-specific factors. Future research should clarify reasons and discussions around statin discontinuation the oldest old to provide additional insight on this topic.

874 | Does use of acetylcholinesterase inhibitors prevent or delay the prescribing of psychotropic medications in people with dementia? Analyses of the Swedish dementia registry (SveDem)

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Background: Behavioral and psychological symptoms of dementia (BPSD) are common. Psychotropics, such as antipsychotics, anxiolytics and antidepressants, are often used to manage BPSD; however, they are associated with significant adverse effects.

Objectives: To investigate whether prescribing of acetylcholinesterase inhibitors (AChEIs) prevents or delays the subsequent initiation of psychotropic medication in people with Alzheimer's disease (AD) and Lewy body dementia (LBD).

Methods: This was a data linkage study of 17763 people with AD and LBD, who did not use a psychotropic at the time of dementia diagnosis, registered in the Swedish Dementia Registry (SveDem) from 2007 to 2015. Data on AChEI use, psychotropic use and comorbidities were linked using nationwide registers. Propensity-score matched Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between time-dependent AChEI use and risk of psychotropic initiation.

Results: During a median follow-up period of 2.6 [quartiles 1.3–4.2] years, 9959 people initiated a psychotropic. In comparison with matched controls, AChEI use was associated with a lower risk of antipsychotic (HR 0.80, 95%CI 0.73–0.88) and anxiolytic (HR 0.88, 95%CI 0.82–0.94) initiation, but no association with hypnotic or antidepressant initiation. Low doses of AChEI (<0.67 defined daily dose) were associated with a higher risk of anxiolytic, hypnotic and antidepressant initiation compared with non-use. In contrast, high AChEI doses (≥1.33 defined daily dose) were associated with a lower risk of initiation across all psychotropic drug classes.

Conclusions: AChEI use may be associated with a lower risk of antipsychotic and anxiolytic initiation in people with AD and LBD, particularly at higher doses. Further investigation into the potential benefits of AChEIs in BPSD management are warranted.

875 | Association rule analysis to evaluate frequent drug combinations associated with acute kidney injury in older adults

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Background: Older adults are at an increased risk of AKI because of aging, multiple comorbidities, and polypharmacy.
Objectives: The aim of this case-crossover study was to apply association rule analysis to ascertain drug combinations contributing to the risk of acute kidney injury (AKI) in adults aged 65 years and older.
Methods: We sourced a nationwide representative sample of New Zealanders aged ≥65 years from the pharmaceutical collections and hospital discharge information. Prescription records (2005–2015) of drugs of interest were sourced from New Zealand pharmaceutical collections (Pharms). We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines, diuretics, opioids, non-steroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with AKI in older adults. The first-time coded diagnosis of AKI was extracted from the National Minimal Dataset (NMDS). A unique patient identifier linked the prescription dataset to the event dataset, to set up a case-crossover cohort, indexed at the first AKI event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period), and the association of AKI with each frequent drug combination was tested by computing a matched odds-ratio (MOR) and its 95% confidence interval (CI).
Results: We identified 55747 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. Association rules revealed that frequently used drug combinations associated with AKI are trimethoprim (MOR = 1.68; 95%CI = [1.54–1.80]), ondansetron (MOR = 1.43; 95%CI = [1.25–1.64]), codeine phosphate plus metoclopramide (MOR = 1.37; 95%CI = [1.11–1.63]), and norfloxacin (MOR = 1.24; 95%CI [1.05–1.42]).
Conclusions: We applied association rules, a novel methodology, to big data to ascertain drug combinations associated with adverse drug events. Association rules identified several drug classes including antimicrobials, nonsteroidal anti-inflammatory medications and opioids are associated with AKI. The finding that ondansetron and amoxicillin plus clavulanic acid increases the risk of AKI requires further investigation.

876 | Pharmacy-based predictors of non-adherence, non-persistence, and re-initiation of antihypertensive drugs among patients on oral diabetes drugs in the Netherlands

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Background: Adherence to antihypertensive drugs in patients with diabetes is important. To support adherence, attention should be paid to the dynamic process of initiation, implementation and persistence on these drugs.
Objectives: To describe non-adherence, non-persistence, and re-initiation patterns of antihypertensive drugs in patients with type 2 diabetes, and to identify pharmacy-based risk factors of these processes.
Methods: We conducted a retrospective cohort study in patients on oral diabetes drugs who initiated antihypertensive drugs registered in the University of Groningen pharmacy database IADB.nl. Non-adherence was calculated in persistent patients and defined as a medication possession ratio < 80% for any antihypertensive drug. Non-persistence was defined as a gap >180 days for all antihypertensive drugs. We defined re-initiation as the dispensing of an antihypertensive drug within one year following a discontinuation. Logistic regression and Cox regression analysis were applied to assess independent associations with available sociodemographic and drug-related factors.
Results: Among 6,669 diabetes patients initiating an antihypertensive drug, non-adherence rates in persistent patients decreased from 11.0% in the first to 8.5% and 7.7% in the second and third year, respectively. Non-persistence rates decreased from 18.0% in the first to 3.7% and 2.9% in the second and third year. Of the 1,201 patients who discontinued in the first year, 22.0% reinitiated treatment within one year after discontinuation. Predictors of non-adherence were secondary prevention (OR: 1.45; 95% CI: 1.10–1.93) and the use of diuretics as initial drug class (OR: 1.37; 95% CI: 1.08–1.74). Predictors of non-persistence were female gender (HR: 1.18; 95% CI: 1.05–1.32), older age (HR: 1.33; 95% CI: 1.08–1.63), and the use of diuretics, beta-blocking agents, or calcium channel blockers as initial drug class. Longer duration of persistence (> 90 days) was a predictor of re-initiation.
Conclusions: Filling prescriptions for antihypertensive drugs in patients with diabetes is a dynamic process. The first year after initiation is the most crucial with regard to non-adherence and non-persistence, and risk groups are different for both processes. Since only a fifth of all patients re-initiated treatment within one year after discontinuation, more attention should be paid to these patients during this period.

877 | The social determinants of non-adherence to antihypertensive medications

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Background: Non-adherence to medications is a complex and multi-dimensional health behavior rooted in the complex web of interactions between patients and the social, physical, healthcare and policy environments. However, the role of these factors - collectively known as the social determinants of health (SDH) - as determinants of medication non-adherence has not been well interrogated.

Objectives: Therefore, we examined the role of SDH constructs as potential predictors of county-level non-adherence to antihypertensive medications (AHM).

Methods: We linked the Centers of Disease Control and Prevention (CDC) Atlas of Heart Disease and Stroke (2014–2016 cycle) and the 2016 County Health Rankings (CHR) datasets for this analysis. Both datasets contain >100 individual county-level variables in the following SDH domains per CHR definition: health behaviors, clinical care, social and economic factors and physical environment. County-level non-adherence to AHM is captured in the CDC Atlas dataset as the proportion of days covered using Medicare Part D claims data. Hierarchical linear models (HLM), weighted by the percent of county populations aged ≥65 years old, were used to quantify the variation and identify predictors of county-level non-adherence to AHM. Two measures of county-level SDH were assessed: 1) predefined SDH in the CHR data; 2) constructs of SDH created with principal component analysis (PCA). SDH constructs were modeled as level 1 predictors with states as a level 2 random intercept variable.

Results: PCA-derived SDH models were a better fit compared to those with CHR-defined SDH domains. In multilevel models - adjusted for county-level measures of race, sex and rural/urban status - six out of the 14 PCA-derived SDH constructs that accounted for >80% of variability in the data correlated strongly with non-adherence. These significant constructs are descriptors of the neighborhood (stress, affluence, disadvantage), healthcare access and health seeking behavior. Collectively, these SDH constructs accounted for 43% of county-level variation in non-adherence to AHM after accounting for between state variability.

Conclusions: This data confirms SDH as significant determinants of non-adherence to AHM. Future research will interrogate how these contextual factors interact with patient-level factors to influence non-adherence.

878 | Increased out-of-pocket costs lead to decreased adherence and delayed treatment reinitiation of branded diabetes drugs in Medicare patients

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Background: Studies have shown that high out-of-pocket costs for medications may negatively affect patients' adherence to antidiabetic treatment and clinical outcomes. For US Medicare beneficiaries who reach the "coverage gap", sudden increases in out-of-pocket costs may disrupt treatment.

Objectives: To compare changes in adherence to dipeptidyl peptidase-4-inhibitors (DPP-4i), a branded expensive drug class, before and after entering the coverage gap in 2015 between patients with and without a low-income subsidy (LIS). Analyses were repeated using sulfonylureas (SU), a cheaper alternative, to isolate cost-related adherence changes. We also explored seasonality of reinitiation, as patients are more likely to reinitiate in January when out-of-pocket costs are reduced.

Methods: Initiators of DPP-4i or SU aged >65 years were identified from a 20% random sample of 2014–2015 Medicare claims data. Patients must have filled at least one antidiabetic prescription and entered the coverage gap in 2015. We used difference-in-differences (DiD) Poisson regression analyses to compare adherence (proportion days covered ≥0.8) before and after entering the coverage gap between patients with and without LIS. Among patients who discontinued treatment during follow-up, we used Cox proportional hazard models to obtain monthly hazard ratios (HRs) for reinitiation relative to January 2015.

Results: Among DPP-4i initiators, 9,357 received LIS and 9,692 did not. Among DPP-4i users without LIS, adherence decreased from 65.5% to 46.8% when beneficiaries entered the coverage gap, differences were minimal in patients with LIS (71.6 vs. 68.8%). After accounting for differences in patients with LIS, the effect of facing higher costs reduced adherence by 16 percentage points (adjusted DiD:-15.9%; 95%CI:-18.0%,-13.8%). No such difference was observed among our low-cost control treatment (adjusted DiD:-0.1%; 95%CI:-2.2%, 2.1%). HRs for reinitiation were lower in months prior to January (HR = 0.4–0.5), demonstrating a strong seasonal pattern for unsubsidized DPP-4i group but not for those with subsidies. For SU, HRs of reinitiation were similar across groups and time.

Conclusions: Our study showed that increased out-of-pocket costs associated with entering the Medicare Part D coverage gap in 2015 were associated with poor adherence and delayed reinitiation of

DDP-4is. Despite the coverage gap steadily closing through 2019, these findings remain relevant as enrollment in high-deductible commercial health plans requiring large out-of-pocket payments continues to increase in the US.

879 | Abstract Withdrawn

880 | Does nonadherence with antidepressants differ by treatment indication?

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Background: Nonadherence with antidepressants for depression is a known problem, but physicians commonly prescribe antidepressants for other indications, many of which are off-label. No studies have measured antidepressant nonadherence for indications besides depression.

Objectives: To determine if rates of antidepressant nonadherence for depression differ from other treatment indications.

Methods: Cohort study using data from a Canadian primary care electronic prescribing system where physician documentation of treatment indications was mandatory. We identified all antidepressant prescriptions from Jan 2003-Dec 2012 for patients 18+ years old with public drug insurance. Study variables were measured using data from the prescribing system or patients' linked drug claims and medical billing data. The outcome was antidepressant nonadherence, defined as not filling a prescription for new or ongoing therapy within 90 days. Covariates included the treatment indication for the prescription (depression, anxiety, insomnia, pain, or miscellaneous) and other adjusting factors (eg, patient demographics, copay, illness severity, past adherence patterns, and past experience with drugs). We used multivariable alternating logistic regression to estimate odds ratios (ORs) for the independent association between 90-day nonadherence and treatment indication, using depression as the reference and an interaction term to stratify the ORs by therapy status.

Results: Among 37,801 antidepressant prescriptions (9,049 patients/152 physicians), the 90-day nonadherence rate for new and ongoing antidepressant therapy was 34.4% and 4.1%, respectively. Compared to depression, nonadherence rates for other indications differed. For new therapy, patients were more likely to be nonadherent if antidepressants were prescribed for anxiety (OR 1.26, 95% CI 1.03–1.54) but were less likely to be nonadherent if prescribed for insomnia (OR 0.73, 95% CI 0.55–0.98). For ongoing therapy, patients were more likely to be nonadherent if antidepressants were prescribed for insomnia (OR 1.58, 95% CI 1.25–1.99) or miscellaneous indications (OR 1.59, 95% CI 1.25–2.04).

Conclusions: Antidepressant nonadherence differed by treatment indication, particularly for insomnia where nonadherence rates were lower than depression for new therapy but conversely higher than depression for ongoing therapy. Since insomnia is an off-label indication for most antidepressants, further investigation is needed to determine whether the differing nonadherence rates between new and ongoing antidepressant therapy for insomnia is due to treatment ineffectiveness.

881 | A group based trajectory modeling to study adherence patterns of atypical antipsychotics in pediatrics and adolescents: a retrospective cohort study using Texas children health plan

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Background: The annual economic burden of pediatric mental health disorders in US is $247 bn. Medication non-adherence contributes to high cost of care. Due to sparsity of available literature in pediatrics, it is necessary to explore patterns of adherence to atypical antipsychotics or second generation antipsychotics (SGAs) in this population.

Objectives: To describe the adherence trajectory pattern of atypical antipsychotics (SGAs) among children and adolescents enrolled in a large pediatric Medicaid managed care plan in Texas.

Methods: Individuals enrolled during 2015 to 2016 were identified if they were under the age of 21, had one inpatient or two outpatient encounters with the primary diagnosis of bipolar disorder, autism spectrum disorder schizophrenia, ADHD or disruptive behavioral, and continuously enrolled for a period of three months prior and six months post to a SGA initiation. The monthly SGA adherence was measured using the proportion of days covered (PDC), and the monthly PDC was further modeled using Group Based Trajectory Model. After identifying the final number of latent trajectories, individuals were classified into a trajectory model according to their highest probability of membership. Comparison of mean PDC between groups was performed using ANOVA with Tukey's post hoc test.

Results: 393 patients who met the inclusion criteria were identified. Over half of the patients (55.43%) were prescribed aripiprazole (n = 218), followed by risperidone (n = 101; 25.7%), quetiapine (n = 44; 11.2%), olanzapine (n = 13; 3.31%), ziprasidone (n = 8; 2.04%), paliperidone (n = 6; 1.53%), asenapine (n = 3; 0.76%). The mean PDC was 40.2 ± 28.3%. A 3-group trajectory model was selected on the basis of their Akaike Information Criteria (AIC) value and clinical relevance. The patterns of the trajectories were identified as 1) Fully adherent (6.9%, mean PDC = 99.6 ± 2.5%), 2) Gradual decline (31.4%, mean PDC = 64.8% ± 15.2%) and 3) Rapid decline (61.7%, mean PDC = 21.5 ± 9.2%). The monthly PDC for the fully adherent group was more than 90% throughout the

6 month follow up period. The gradual decline group had above 80% PDC for 2 months, gradually declining to 30% at the end of the follow up period. Finally, the PDC of the rapid decline group quickly dropped to 20% within 2 months since the SGA initiation.

Conclusions: This study demonstrated that patterns of SGA adherence among pediatric patients may be described by three differing clinical trajectories. The gradual and rapid decliners both represent targets for interventions aimed at sustaining use.

882 | Current practice in reporting exposure in pharmacoepidemiological studies

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Background: Exposure definitions vary across pharmacoepidemiological studies. As different definitions can lead to different results, transparent reporting of the exposure definition is of utmost importance.

Objectives: This study assessed the current status of reported exposure definitions in pharmacoepidemiological research as baseline measurement compared to the ISPE-ISPOR taskforce reporting guideline published in 2018.

Methods: We systematically reviewed all observational pharmacoepidemiological studies that used routinely collected health data. We included studies with > = 250 subjects published in 2017 in six leading (pharmaco-)epidemiological journals. Information was extracted about all items regarding reporting of exposure as presented in the ISPE-ISPOR guideline. Primary outcome was the percentage of studies reporting each ISPE-ISPOR guideline item.

Results: 91 studies were included. Almost all studies reported the type of exposure (e.g. current use, cumulative dose) (*n* = 89, 97.8%), the exposure risk window in general terms (*n* = 77, 84.6%) and the exposure assessment window (n = 89, 97.8%). The operationalisation of the exposure window was poorly described: only 14 (15.4%) studies explicitly reported the presence or absence of an induction period, 5 (5.5%) respectively 21 (23.1%) studies reported how they handled stockpiling and bridging of exposure episodes, and 28 (30.8%) studies mentioned how long the exposure was extended. How switching between drugs was dealt with and specific drug codes were reported in 52 (57.1%) and 24 (26.4%) publications.

Conclusions: Reporting of exposure definitions in current pharmacoepidemiologic studies is suboptimal when compared to the ISPOR-ISPE guideline. Publications of pharmacoepidemiological studies should include more details on exposure ascertainment to allow both replication and quality assessment.

883 | Cause-specific and all-cause mortality associated with proton pump inhibitors: a cohort study

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Background: Previous studies report associations between proton pump inhibitor (PPI) use and a range of adverse outcomes, including all-cause mortality. It is unclear what is driving the association with all-cause mortality, and whether the association is causal or due to residual confounding.

Objectives: To evaluate the association between PPI usage and both all-cause and cause-specific mortality.

Methods: We conducted a cohort study comparing new users of PPIs (defined by first receipt of PPI prescription) to new users of an alternative acid-suppression therapy, H2 receptor antagonists (H2RA), and in a secondary analysis to non-users of acid-suppression therapy matched on age, sex, calendar year and general practice. We identified eligible individuals registered with practices contributing to the UK Clinical Practice Research Datalink (January 1998 to December 2015). Outcomes were defined based on International Classification of Disease (ICD) codes recorded in linked death registry data; and included all-cause mortality, communicable and non-communicable disease mortality, and mortality due to outcomes previously associated with PPI use. We used Cox regression models, weighted using average effect of treatment in the treated (ATT) weights, to estimate the association with mortality.

Results: A total of 733,885 new users of PPIs and 124,410 new users of H2Ras were identified. In secondary analysis, 689,602 PPI new users were matched 1:2 to 1,361,245 non-users. PPI users had a higher prevalence of most comorbidities and concurrent medication use in comparison to H2RA users and, particularly, compared to non-users. Weighted hazard ratios for all-cause mortality for PPI usage were 1.26 (95% CI 1.20–1.32) relative to H2RA use, and 1.98 (1.95–2.00) compared to non-use. Mortality from specific causes was frequently higher shortly after initiation. For example, the hazard ratio for PPI use over the first year of follow-up was 1.50 (1.37–1.65) for neoplasms, 4.08 (1.60–14.34) for *C. difficile* enterocolitis, and 1.70 (0.70–4.11) for liver cirrhosis, compared to H2RA use; and 5.52 (5.25–5.80), 4.11 (2.45–6.89), and 6.01 (3.99–9.05) respectively, relative to non-use.

Conclusions: First prescription for a PPI was associated with increased all-cause mortality and mortality from several specific causes. However, consistently higher hazard ratios when comparing PPI users to non-users rather than H2RA users, and some unexpected short-term associations in the first year with cause-specific mortality, suggest that observed associations with mortality are, at least in part, due to residual unmeasured confounding.

884 | Survival after Stevens-Johnson syndrome: a UK-based cohort study

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Background: Short-term mortality after Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is estimated between 5–17% and 15–46%, but evidence on long-term mortality is scarce.

Objectives: We aimed to describe short- and long-term mortality after SJS/TEN and to evaluate risk factors for death.

Methods: We performed a retrospective cohort study using a validated cohort of SJS/TEN patients (PPV = 87%) extracted from the UK-based Clinical Practice Research Database (1995–2013). We matched SJS/TEN patients 1:4 on a propensity score (PS) to patients without SJS/TEN, and followed them until death (primary endpoint) or censoring (max. Follow-up = 5 years [y]). We performed Cox proportional hazard (Cox PH) analyses to estimate hazard ratios (HR, 95% CI) for death during early (1–89 days [d]), intermediate (90–364 d) and late (365 d - 5 y) follow-up overall, and within subgroups of age. Using age-adjusted Cox PH analyses, we compared short-term mortality (90 d) in patients with (a) a cancer diagnosis within 1 year before or (b) an antiepileptic drug (AED) within 64 d before the SJS/TEN diagnosis to SJS/TEN patients without (a) or (b). To evaluate differential outcome misclassification (DOM), we compared short-term mortality between GOLD-standard confirmed (N = 80) and non-confirmed (N = 397) SJS/TEN patients.

Results: We included 477 SJS/TEN patients and 1908 matched comparator patients (mean age 38 y). In total, 12.4% of SJS/TEN patients died (4.8% within 90 d, N = 23). In patients aged ≥65 years, 45.1% died (16.5% within 90 d, N = 15) and in patients aged <65 years, 4.7% died (2.1% within 90 d, N = 8). After PS-matching, we observed an overall HR of 4.19 (95% CI 2.33–7.51) for death during early follow-up, HR of 0.99 (95% CI 0.54–1.83) during intermediate, and HR of 0.76 (95% CI 0.48–1.21) during late follow-up. Compared to patients without SJS/TEN, SJS/TEN yielded a HR of 4.94 (95% CI 2.35–10.39) in patients aged ≥65 years, and a HR of 10.5 (95% CI 2.79–39.62) in patients aged <65 years during early follow-up (HR around 1 thereafter). A previously recorded a) cancer diagnosis (vs. no diagnosis) and b) AED prescription (vs. no prescription) yielded a HR for death of a) 1.90 (95% CI 0.56–6.44) and b) 1.76 (95% CI 0.52–5.97) among SJS/TEN patients during early follow-up. Comparing death during early follow-up between confirmed and non-confirmed SJS/TEN patients resulted in a HR of 1.10 (95% CI 0.52–2.34).

Conclusions: Our results suggest that long-term survival after SJS/TEN is comparable to non-SJS/TEN patients after the first 90 days after diagnosis, irrespective of age. Cancer and AEDs were risk factors for early death (limited power), which was not explained by DOM.

885 | Real world effects of medications for chronic obstructive pulmonary disease: a UK population-based non-interventional cohort study with validation against randomized trial results

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Background: Chronic obstructive pulmonary disease (COPD) is a progressive disease affecting 3 million people in the UK, in which patients exhibit irreversible airflow obstruction. Treatment is largely informed by randomized controlled trial (RCT) results, but it is unclear if these findings apply to patient populations not studied in trials. Non-interventional studies could be used to study patient groups excluded from trials, but the use of these studies to estimate treatment effectiveness is in its infancy.

Objectives: To use (1) individual trial data and (2) trial results to validate non-interventional methods for assessing COPD treatment effectiveness.

Methods: First we obtained individual patient data from the landmark COPD TORCH trial. We matched these trial participants on a range of characteristics to people with COPD in the UK Clinical Practice Research Datalink (CPRD) between 1st January 2000 and 1st January 2017. We then determined whether analysis of this trial-analogous non-interventional data generated comparable results to the TORCH trial analysis of exacerbation rate for the following comparisons: (1) Seretide vs no Seretide (analogous to placebo in the TORCH trial) and (2) Seretide vs salmeterol. Cohort methodology with propensity score techniques was used to adjust for potential confounding.

Results: There were 2773 people from CPRD in each exposure group for the Seretide vs no Seretide analysis and 939 people in each exposure group for the Seretide vs salmeterol analysis. The propensity score matched exacerbations rate ratio (Seretide vs no seretide) was 1.25 (95% CI 1.14–1.37), compared to 0.75 (0.69–0.81) for the TORCH Seretide vs placebo analysis. For the Seretide vs salmeterol analysis, the rate ratio was 0.84 (0.73–0.97), compared to 0.88 (0.81–0.95) in TORCH.

Conclusions: While we were unable to replicate COPD trial results for analyses comparing treatment to no treatment using this methodology, our results indicate that it is possible to obtain very similar results for active comparator analyses in non-interventional data compared to trial data. The methodology applied here will now be used for further (active comparator) studies of COPD treatment effects for groups that were underrepresented or excluded from trials, and to compare between a range of treatments.

886 | Safety of Colobreathe: findings from the UK cystic fibrosis registry

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Background: Colobreathe (colistimethate sodium) is indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* (PA) in patients with cystic fibrosis (CF). Due to potential safety concerns, a long-term observational comparative study was conducted as part of the risk management plan in Europe.

Objectives: The primary objective is to monitor the long-term safety of Colobreathe compared to other inhaled antibiotics. Secondary objectives were to examine PA exacerbations (PEx) and rates of discontinuation.

Methods: A matched cohort study using data from the UK CF Registry was designed to compare outcomes of patients on Colobreathe to those on other inhaled antibiotics (comparator group) during 2014–17. Primary outcomes are defined as adverse safety events (AEs) (e.g. cough fracture) and those considered new complications (e.g. CF-related diabetes). Incidence rates and incidence rate ratios (IRR) were calculated for the primary outcomes and PEx. Rates of discontinuations were compared between Colobreathe and Tobramycin dry powder patients.

Results: A total of 1347 and 3469 patients were included in the Colobreathe and comparator groups respectively. Mean age was 26 years (standard deviation [SD] = 10) and 23 (SD = 12), and the proportion of males was 54% and 53%, respectively. Of the total patients, 1033 (77%) and 2571(74%) had AEs in the Colobreathe and comparator groups, respectively, including: cough fracture 7 (0.5%) and 13 (0.4%); pulmonary abscess 2 (0.1%) and 9 (0.3%); septicaemia −12 (0.9%) and 55 (1.6%) and Haemoptysis - 67 (5.0%) and 160 (4.6%). Most common new complications included CF-related diabetes - 197 (14.6%) and 461(13.3%); gastro-oesophageal reflux disease −160 (11.9%) and 518 (14.9%); and osteopenia - 228 (16.9%) and 453 (13.1%). The adjusted IRR for all types of primary event was 1.25, (95% confidence interval [CI]: 1.19, 1.31). However,when new complications that are a part of natural CF disease progression, and are unlikely to be influenced by antibiotic therapy,were excluded, there was no difference between the groups (adjusted IRR 1.12 [95% CI 0.97–1.43]). PEx were common in both groups (73.4% vs 77.1%, respectively), with annualized rates of 1.94 vs 1.85 per patient-year and IRR of 1.08, 95%CI (1.06–1.12). Rate of discontinuations of Colobreathe was similar to that of Tobramycin dry powder: 32% and 33.0% respectively.

Conclusions: There was no evidence of a difference in the incidence of safety events between the study groups. The observed excess risk of any primary event, including those expected as part of natural CF disease progression, is not considered to be related to antibiotic use.

887 | Where should I submit my manuscript? Applying machine learning to enhance communication of medical research

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Background: Neural networks have grown dramatically in sophistication over the last decade, with particular improvements in ability to identify and utilize subtle predictive patterns in complex data. This has created opportunities for predictions based on text and other high-dimensional input.

Objectives: Using 19 years of abstracts from PubMed, apply machine learning (ML) to create a predictor of journals likeliest to have published a particular abstract.

Methods: From PubMed data, we extracted 494,429 abstracts published in 92 epidemiology and general medicine journals between 2000–2018, and created a multi-layer neural network to predict the journal in which the abstract was published. The first layer used word embeddings of the 10,000 most frequent words to reduce the dimensionality of the data and capture the contextual similarity of the words. The embeddings were then passed to a convolutional layer, which identified 128 filters that brought out distinguishing features to best classify abstracts among the 92 journals. We then employed two dense layers as the core of the predictive model, followed by a dropout layer to reduce overfitting. The model yielded predicted probabilities for each of the journals. We characterized model accuracy using metrics of the correct journal appearing as (a) the highest-probability prediction ("exact match"), and (b) one of the 3 top predictions ("top 3"). The model was trained on 67% of the available data, with the remainder reserved for testing.

Results: Within the test data, we were able to predict exact matches for 64% of abstracts and top 3 matches for 82%. Journals with the highest likelihood of correct prediction included PLoS One, Circulation and Stroke (each ≥70% exact match and ≥ 90% top 3); that pattern was observed for many of the topic-specific publications. Pharmacoepidemiology and Drug Safety (PDS) was below average and was identified in the top 3 46% of the time. NEJM was identified in the top 3 76% of the time. Due to the non-explanatory nature of neural networks, no specific decision-making criteria could be observed.

Conclusions: ML methods are quickly improving, particularly as applied to subtle predictive questions. In this study, those journals with the clearest profiles had among the best predictive accuracy; PDS was not strongly distinguished by the algorithm. To apply ML more broadly, rich and publicly-available training data sets are beneficial; training sets to support causal analytics in pharmacoepidemiology (eg, selection of covariates, screening for valid study design, identification of instrumental variables) would be of high value to the field.

888 | Propensity score stratification and inverse probability weighting compared to surgical randomized clinical trial results in device epidemiology

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Background: Propensity scores are popular in pharmacoepidemiology. However, there is little data on their performance in the study of devices, where confounding is related to more complex mechanisms including not only patient but also surgeon characteristics.

Objectives: To test the performance of propensity score stratification and inverse probability weighting (IPW) to emulate an ongoing surgical RCT comparing partial to total knee replacement, the Total Or Partial Knee Arthroplasty Trial (TOPKAT).

Methods: Patients who underwent either a partial or total knee replacement were identified in the UK National Joint Registry linked to hospital inpatients data (Hospital Episode Statistics England) and patient reported outcome measures (PROMs). TOPKAT eligibility criteria were applied. Logistic regression was used to calculate PS for partial knee replacement using 28 covariates including demographics, preoperative PROMs, comorbidity, and procedures within 3 years before surgery. We compared different methods to the trial results: 1) stratification based on the entire cohort's PS (PSS_{cohort}); 2) stratification based on the PS of patients with partial knee replacement ($PSS_{exposure}$), and 3) IPW. Linear regressions were used to derive average treatment effect (ATE) estimates of difference in postoperative OKS between treatment groups with adjustment for imbalanced covariates (absolute standardized mean differences (ASMD) >0.1). A chi2 test was applied to test for significance differences between TOPKAT findings and each of the proposed methods. Tau2 was used to quantify between study variances.

Results: In total, 355 and 33,982 partial and total knee replacement, respectively, were analyzed. $PSS_{exposure}$ resulted in excellent covariate balance (all ASMD<0.1), while many covariates remained imbalanced in IPW and PSS_{cohort}. Postoperative OKS average differences were 1.2 (95%CI: 0.2, 2.1), 1.2(0.1, 2.2) and 1.2 (0.1, 2.2) in favor of partial knee replacement in IPW, PSS_{cohort}, $PSS_{exposure,}$ respectively, compared to 1.8 (0.2, 3.4) in TOPKAT. All methods obtained Chi2 $P > 0.05$ and small tau2 (<0.0001), suggesting no significant difference in ATE estimates compared to the TOPKAT RCT findings.

Conclusions: $PSS_{exposure}$ obtained better covariate balance than IPW and PSS_{cohort}, though all methods resulted in similar treatment effect estimates, all of them comparable to the TOPKAT RCT treatment effect estimate.

889 | The performance of preference-based instrumental variables to emulate a randomized clinical trial of comparative medical device effectiveness

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Background: Instrumental variables (IV) are used to minimize confounding in pharmacoepidemiology. There is a scarcity of data on the performance of preference-based IVs in medical device epidemiology.

Objectives: We aimed to test the use of surgeon, centre and regional preferences for partial knee replacement (PKR) as IVs to replicate an ongoing RCT comparing PKR vs total knee replacement (TKR), the TOPKAT trial.

Methods: Participants undergoing PKR or TKR according to the UK National Joint Registry, and with linked post-operative patient reported oxford knee scores (OKS) data were included. TOPKAT exclusion criteria were applied to maximize comparability. We calculated preference as the % of PKR in the last 20, 30 and 50 knee replacement surgeries for lead and consultant surgeon, and the last 100, 300, 500, and 1000 for surgical unit and regional area. We estimated IV strength using F-statistic and odds ratio (OR) on a regression between IV and exposure (PKR). We evaluated balance per groups (IV > median vs IV $\leq$ median) with standardized mean differences (SMD) for known confounders. IVs with confounding (SMD > =0.1) and those considered weak (OR 95% confidence intervals including 1 or F-statistic<10) were not further evaluated. A 2-stage IV regression was fitted to calculate the effect of PKR on one-year OKS compared to TKR. We used $x2$ to test differences in treatment estimates between TOPKAT and IVs results; and $\tau 2$ to quantify between-studies variance.

Results: A total of 69,269 patients were included for preference calculations; 34,576 had OKS data and were included, with 358 undergoing PKR. Lead surgeon preference based on 30 and 50 surgeries did not balance for age; while consultant preference based on previous 50 surgeries, and all area (surgical unit and region-based) IVs resulted in imbalances in socio-economic status. The results from lead surgeon preference IV based on 20 previous surgeries were comparable to TOPKAT: 9.1 (CI95: 0.1 to 18.1) vs 1.9 (0.2 to 3.6) respectively;

p = 0.12; =15. Conversely, consultant preference IV based on 20 and 30 previous surgeries yielded significantly different results, with p = 0.01 and p < 0.01 respectively.

Conclusions: Surgeon preference is a potentially valid IV, but treatment estimates are sensitive to decisions made during the construction of IVs. More research is needed on best practices for the estimation and diagnostics of surgeon preference IVs. Finally, caution is advised in the interpretation of area-based IVs, which fail to balance regional confounders such as deprivation.

890 | Development and validation of patient-level prediction models for adverse outcomes following total knee arthroplasty in osteoarthritic patients

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Background: Elective total knee replacement (TKR) is safe and cost-effective in treating severe knee osteoarthritis (OA). Post-operative complications, although rare, have been reported.

Objectives: We aim to develop prediction tools and assess its performance for predicting adverse outcomes after TKR in OA patients.

Methods: Through the Observational Health Data Sciences and Informatics (OHDSI) network we conducted a multinational, multi-database cohort analysis using five US and UK healthcare databases mapped to the Observational Medical Outcomes Partnership (OMOP) common data model. Subjects undergoing a first TKR aged 40 years or older, registered in any of the contributing databases for at least 1 year prior to surgery were included. Lasso logistic regression models were fit to predict post-operative outcomes including 90-day mortality, venous thromboembolism (VTE), infection, readmission and long-term (5-year) revision surgery. Models were evaluated for performance (discrimination and calibration), and those considered of value were then externally validated in other available datasets.

Results: A total of 504,103 participants were included, with size per data source ranging from 15,292 to 158,549. We found 0.20%–0.23% of post-operative 90-day mortality, 1.69%–2.99% of infection, 7.07%–8.98% of readmission, and 2.20%–4.79% of VTE after TKR. The incidence of 5-year revision surgery ranged from 1.99% to 3.13% among five databases. None of the models for VTE, infection or 5-year revision had good performance. Conversely, models for 90-day mortality and readmission had acceptable discrimination (AUC 0.78 and 0.69) and calibration internally. External validation for 90-day mortality developed in OPTUM and THIN yielded an AUC ranging 0.69–0.86 and 0.68–0.84, respectively.

Conclusions: We have developed models for the identification of subjects at high risk of short-term mortality and post-operative complications. We observed high predictability of short-term mortality and the unpredictability of the other outcomes. This suggests decision-making should be stratified based on variated risk of short-term mortality, but may not for other complications.

891 | Medications, device use, and non-device associated urinary tract infections in hospitalized patients

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Background: Catheter-associated urinary tract infection (CAUTI) rates have declined over the past several years, but rates of non-device associated UTI (ND-UTI) have remained stable. Because there is no national surveillance of ND-UTIs, there is a paucity of research on risk factors for these infections.

Objectives: Assess the effect of inpatient medications (anticholinergics, systemic antibiotics, sedatives, opioids, and neuroleptics) and device use (urinary catheters, suprapubic catheters, and nephrostomy tubes) on the incidence of ND-UTIs.

Methods: All adults (≥18 years) admitted to UNC Hospitals for >2 days between 2015–2017 were included. Electronic medical records from these hospitalizations were linked to the UNC Hospital Epidemiology database, which includes device and non-device associated infections captured during comprehensive, hospital-wide active surveillance using CDC case definitions and methodology. Only the first ND-UTI within a hospitalization was included. Multivariable Cox regression was used to assess the association between inpatient medications and devices with ND-UTIs, after adjusting for patient demographics, comorbidities, illness severity, urologic surgery, and trauma admission. Medications, device use, and surgery were treated as a time-varying. Correlation between patients with multiple hospitalizations was accounted for using robust sandwich covariance matrix estimates and death was treated as a competing risk.

Results: 87,718 hospitalizations (57,598 unique patients) were included and there were 412 ND-UTIs. 63% of patients received opioids, 58% received anticholinergics, 42% received antibiotics, 39% received benzodiazepines, and 10% received neuroleptics during risk period. Nephrostomy tube and suprapubic catheters were used in 1% of hospitalizations, and 41% had a urinary catheter. After adjustment, patients receiving opioids (HR 1.71, 95% CI 1.14, 2.56) or who had suprapubic catheters (HR 2.30, 95% CI 1.58, 3.34) were more likely to develop an ND-UTI. Receiving antibiotics (HR 0.21, 95% CI 0.15, 0.28) and neuroleptics (HR 0.66, 95% CI 0.48, 0.92) reduced patient risk. Anticholinergics (p = 0.49), benzodiazepines (p = 0.36), nephrostomy tubes (p = 0.35), and prior urinary catheterization (p = 0.72) had no effect.

Conclusions: Opioids and suprapubic catheters increased the risk of ND-UTI. Opioids are known to cause drug-induced urinary retention,

which is a known risk factor for UTIs. Future research should explore targeting opioid prescribing and non-urinary catheter device use for potential prevention strategies.

892 | Cardinality matching versus propensity score matching for causal inference in medical device research: an applied analysis of minimally-invasive versus open elective thoracic segmentectomy

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Background: Propensity score matching (PSM) is a mainstay of causal inference in observational research. A recently developed method—cardinality matching (CM)—uses integer programming to find the largest matched sample for which pre-specified balance criteria (e.g., standardized differences [SDiff]) are met for matching variables. In medical device research, balance on clusters (e.g., hospitals) between groups can be critical to internal validity.

Objectives: We describe the performance of PSM vs. CM when requiring perfect balance on clusters between groups in a retrospective, observational study comparing economic and clinical outcomes of minimally-invasive surgery (MIS) vs. open surgery (OS) for thoracic segmentectomy.

Methods: We extracted hospital discharge records from the Premier Healthcare Database for patients undergoing elective thoracic segmentectomy between 1-1-2010—6-30-2017 (first = index admission). Patients were classified as undergoing OS or MIS (video-assisted, robotic-assisted, conversions). PSM was conducted through nearest-neighbor matching (1:1 w/caliper) and exact matching on hospital. CM was conducted through 1:1 matching and exact distributional balance for all matching variables, including hospital. Matching variables included patient, procedure/admission, and provider/hospital characteristics. We evaluated PSM and CM on: post-match sample-size N, post-match SDiff for matching covariates, and outcome comparison results (index admission's length of stay [LOS], hospital discharge costs, respiratory failure, and inpatient mortality) between MIS vs. OS.

Results: Total post-match sample N's were: PSM = 852; CM = 1,702. Across 37 matching variables, post-match SDiffs were: PSM mean = 0.03 (range = 0.0—0.16); CM mean = 0.0 (range = 0.0—0.0). Outcome comparisons were similar between PSM and CM (expressed as OS minus MIS): LOS—PSM = 1.3 days ($P < 0.01$), CM = 1.1 days ($P < 0.01$); costs—PSM = \$1,779 ($P = 0.08$), CM = \$1678 ($P = 0.09$); respiratory failure—PSM = 1% ($P = 0.01$), CM = 2% ($P = 0.02$); inpatient morality—PSM = 0% ($P = 0.451$), CM = 0% ($P = 0.81$).

Conclusions: CM resulted in greater post-matching sample N, perfect distributional balance on all matching variables, and outcome estimates with smaller standard errors as compared with PSM. CM is an important advance in matching techniques for causal inference in observational research; further applied evaluation of CM vs. PSM is warranted.

893 | Self controlled case series in surgical epidemiology: checking the underlying assumptions in an empirical example

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Background: The self controlled case series (SCCS) is a within person study design which controls for all time fixed confounding. It has previously been shown to be useful for vaccine and drug safety studies, however its use in surgical safety has not been investigated. One key question is whether the assumptions underlying SCCS are likely to hold in surgical epidemiology.

Objectives: Demonstrate the checking of assumptions of the SCCS in a surgical safety setting.

Methods: Patients undergoing bariatric surgery who experienced an osteoporotic fracture within 5 years prior or post-surgery were identified in the clinical practice research datalink (CPRD) linked to hospital episode statistics (HES). The outcome, osteoporotic fracture, included all locations except skull and digits. An SCCS model, using a Poisson model, compared the 5 year risk of fracture post surgery to the 5 year risk pre-surgery. Three assumptions of the SCCS were tested in separate models: (I) The independence of the outcome and probability of further exposure (surgery); (II) the independence of recurring events; and (III) the lack of association between outcome and early departure from study. These assumptions were tested by comparing the incidence rate ratio (IRR) produced in the initial model to (I) a model with an 8 week wash out period prior to surgery, and (II) a model of each patient's first fracture. Assumption (III) was checked with a likelihood ratio test comparing models with and without an interaction with early departure. A histogram of the time between fracture and surgery was also used to check assumption (I).

Results: Of 5,492 patients undergoing bariatric surgery, 252 patients had 272 osteoporotic fractures within 5 years either side of surgery. Risk of osteoporotic fracture was not increased after bariatric surgery (IRR (95% confidence interval, CI) 1.17 (0.86, 1.60)). The histogram was uniformly distributed, suggesting fractures did not affect the likelihood of surgery. 12 fractures occurred in the wash out period, and 20 were subsequent fractures within patient and 145 patients departed early. The two adjustments to the dataset gave IRRs (95% CIs) of 1.14 (0.78, 1.50), and 1.10 (0.76, 1.61) for assumptions (I) and (II) respectively. The result of the LRT (assumption III) was 0.46. These results suggest no assumption was invalid.

Conclusions: The SCCS appears to be suitable for use in surgical safety settings in this specific example. The same assumption checks used for vaccine/drug safety studies can be used for surgical safety

studies using the SCCS. Different settings/surgical procedures would require further testing.

894 | Use of ondansetron during pregnancy and risks of spontaneous abortion, stillbirth and major congenital malformation: an international, multi-Centre cohort study

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Background: Ondansetron is frequently used off-label for treatment of nausea and vomiting during pregnancy. While there have been few important safety signals to date, few studies have been of sufficient size to properly consider rarer outcomes such as stillbirth or major birth defects.

Objectives: To study the association between ondansetron exposure during pregnancy and the risks of spontaneous abortion, stillbirth, and major congenital malformation.

Methods: We undertook an international, multi-centre cohort study of women aged 12–55 y who had a pregnancy event (spontaneous abortion, induced abortion, stillbirth, or live birth) between April 2002 and March 2016 recorded in administrative data from 4 Canadian provinces (British Columbia, Alberta, Saskatchewan, and Manitoba), the US MarketScan database, and the UK Clinical Practice Research Datalink. Our primary outcome was fetal death defined as a composite of spontaneous abortion or stillbirth. Secondary outcomes were the components of the composite and major congenital malformation. To minimize confounding by indication, exposure to ondansetron was compared with exposure to other antiemetics. We estimated hazard ratios (HR) and odds ratios (OR) using high dimensional propensity score-adjusted proportional hazards regression and logistic regression, as appropriate, with time-dependent drug exposures. Sensitivity analyses excluded pregnancy losses during the first 6 w, 20 w gestation; considered second-line exposures and those during 4–10 w gestation; and studied the first pregnancy per woman. Site-level results were pooled using random-effects models.

Results: Among the 163,952 pregnancies exposed to ondansetron, 7.9% resulted in fetal death vs 5.6% of 309,565 exposed to other antiemetics. After adjustment, ondansetron exposure during pregnancy was not associated with increased risks of fetal death (HR 0.92, 95% confidence interval [CI] 0.67–1.26), spontaneous abortion (HR 0.81, 0.65–1.02), stillbirth (HR 0.97, 0.79–1.20), or major congenital malformation (OR 1.07, 0.91–1.26). Results of sensitivity analyses were generally consistent with those of the primary analyses, although risks of stillbirth were increased in some settings.

Conclusions: In this large, multi-centre cohort study, there was no association between exposure to ondansetron during pregnancy and increased risks of fetal death, spontaneous abortion, stillbirth or major birth defects relative to exposure to other antiemetics. Larger studies are needed to evaluate risks for specific malformations.

895 | Medically assisted reproduction and the risk of being born small for gestational age

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Background: Medically assisted reproduction (MAR) includes assisted reproductive technology (ART) and ovarian stimulations (OS). These methods are known to increase obstetrical complications and adverse perinatal outcomes, including prematurity.

Objectives: We aimed to quantify the risk of being born small for gestational age (SGA) associated with MAR use overall and by method among those exposed.

Methods: *Design:* We conducted a cohort study in the Quebec Pregnancy Cohort (QPC), an ongoing population-based cohort, which includes all pregnancies of mothers covered by Quebec' prescription drug insurance and their children from 01/1998 and 12/2015. We included singleton liveborns between 05/08/2010 and 15/11/2015, whose mothers were covered by the RAMQ drug plan for at least 3 months prior to and during pregnancy. This time-period was used given that the MAR universal reimbursement program was active at that time in Quebec. *Exposure:* We considered MAR use dichotomously, using spontaneous conception as the reference. We then categorized MAR into 3 exposure subgroups: ART (reference), OS, and OS/ART combined. *Outcome*: We defined SGA as the lowest 10th percentile of gestational-age specific birth weight according to sex-specific population-based references in Canada. *Analyses*: Crude and adjusted odds ratios (aOR) and 95% confidence intervals (CI) were obtained using generalized estimation equation models. Covariates included maternal sociodemographics, history of pregnancy complications, comorbidities, and concomitant medication use, measured in the year before the 1st day of gestation. Subgroup analyses were performed within the MAR-exposed group.

Results: A total of 57,624 pregnancies met inclusion criteria and were considered for analyses. During the study period, 2,055 women were exposed to MARs, of which 419 (20.4%) to OS, 150 to ART (7.3%), and 1486 (72.3%) to a combination of both. We found no association between MAR use and being born SGA. Specifically, adjusting for potential confounders, no association was found between overall use of MAR and the risk of SGA (aOR, 1.08, 95%CI: 0.93–1.25, 202

exposed cases). In our sub-cohort of MAR users, we found no association between OS alone when compared to ART and the risk of SGA (OS: aOR, 1.20; 95%CI: 0.78–1.84, 46 exposed cases; and OS/ART combined: aOR, 0.98 95%CI: 0.69–1.38, 102 exposed cases).

Conclusions: We found no association between MARs and the risk of SGA, which is reassuring.

896 | Ondansetron use in early pregnancy and late pregnancy outcomes

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Background: The effect of ondansetron use during pregnancy on common adverse pregnancy outcomes and complications other than birth defects is understudied.

Objectives: Evaluate the risk of preterm birth and hypertensive disorders among women with orders for ondansetron during early pregnancy compared to alternatives antiemetics while accounting for competing risks.

Methods: A cohort of pregnancies was created using electronic health record (EHR) data from the UNC Health Care system. Pregnancies were identified at the date of first record of the pregnancy in the EHR and followed until the outcome of interest, a competing event, or loss to follow-up (last record with evidence of pregnant status). Pregnancies no longer at risk for the outcome of interest were classified as having competing events, e.g. miscarriage, or live birth without hypertension diagnosis. Pregnancies were included if an order for ondansetron or comparator antiemetics (metoclopramide or promethazine) was made during the first 140 days of gestation. Preterm birth was defined as live birth at <37 weeks and very preterm birth was defined at <32 weeks. Gestational hypertension was defined using diagnosis codes among pregnancies without existing hypertension. Preeclampsia was defined by evidence of 2 inpatient encounters with diagnosis codes. Cumulative incidence of all outcomes was estimated on the gestational age timescale. We report adjusted risk differences (RD) and 95% confidence intervals (CI). Confounding by antiemetic indication, maternal age, race, ethnicity, smoking status, comorbidities, and medication use was controlled using stabilized inverse probability of treatment weights.

Results: We identified 2730 eligible pregnancies with antiemetic orders; 66% had first ondansetron order and 34% had first comparator antiemetic order. Crude risk of preterm birth was slightly lower in the ondansetron group than the comparator group (11.7% and 13.8%, respectively); adjusted results suggested a small decrease in risk (RD -1.8%; 95% CI -5.0, 1.4). No difference was observed for very preterm birth (crude risk 2.4% in ondansetron group and 2.6% in comparator group; adjusted RD -0.2%; 95% CI -1.9, 1.5). Ondansetron exposed pregnancies were also observed to have lower risk of gestational hypertension (crude risk 5.4% and 7.0%, respectively; adjusted RD -1.5%; 95% CI -4.0, 0.4), and slightly lower risk of preeclampsia (crude risk 4.5% and 6.0%, respectively; adjusted RD -1.2%; 95% CI -3.3, 1.2).

Conclusions: We found no evidence of increased risk with ondansetron exposure compared to alternative antiemetics for any of these common adverse pregnancy outcomes.

897 | Misoprostol as an adjunct to oxytocin can reduce postpartum hemorrhage among pregnant women delivering in Bamenda Cameroon, 2015–2016: a propensity score-matched retrospective chart review

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Background: There is some evidence to suggest that misoprostol may supplement the action of oxytocin in preventing post-partum hemorrhage (PPH).

Objectives: Primary: To determine the effects of the administration of 600 μg misoprostol in addition to oxytocin versus oxytocin alone, on the risk of PPH among pregnant women after delivery. Secondary: To determine the effects of the above combination on maternal death and blood transfusion among pregnant women after delivery. To determine the prevalence of PPH, its case fatality, and the maternal mortality ratio in our hospital.

Methods: *Design and setting*: Retrospective chart review of 1736 women delivering at the Regional Hospital Bamenda Cameroon, between 2015–2016. This was a pre versus post study following a policy change in the prevention of PPH. *Exposure groups*: One group received oxytocin-misoprostol (January–April 2016: period after policy change), and the second group received oxytocin-only (January–April 2015: period before policy change) after delivery. *Outcomes*: The primary outcome was PPH, and the secondary outcomes were maternal death and blood transfusion. *Statistical analysis*: A 1:1 matching was done with the propensity score (PS). Covariates matched for included age, gravidity, parity, mode of delivery, birth weight etc. We used standardized mean differences to assert the quality of the matching. The groups were compared using propensity score matching with conditional logistic regression on the matched pairs as the main analysis. A sensitivity analysis was done using other propensity score adjustment methods and multiple regression.

Results: Of the 1736 patients included in this study, 1338 were matched and compared. Women who received oxytocin-misoprostol were less likely to have PPH as compared to those receiving oxytocin-only (odds ratio [OR] 0.22, 95% confidence interval [CI] 0.08, 0.59, $p = 0.003$). This reduced odds of PPH was upheld in the different sensitivity analyses. There were no significant differences in the odds of maternal death and the use of blood transfusions between the two groups: OR 0.26, 95% CI [0.03, 2.29], $p = 0.22$, and OR 0.89, 95% CI

[0.14–5.63], $p = 0.91$, respectively. Sensitivity analyses showed similar results. The prevalence of PPH was 2.9%, the case fatality rate was 1.96%, and the maternal mortality ratio was 293 maternal deaths/100000 life births.

Conclusions: We found that using 600 μg misoprostol as an add-on to oxytocin in preventing PPH significantly reduces the odds of PPH without affecting other maternal outcomes.

898 | Maternal opioid use and infant birth defects in RI Medicaid enrolled population

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Background: The rapid increase of opioid-related overdoses and deaths has become a public health threat in the United States. The utilization of prescription opioids in pregnant women has increased while the results from teratogenic studies remain controversial.

Objectives: To evaluate the association between maternal opioid use during pregnancy and the incidence of congenital malformations in infants.

Methods: This retrospective cohort study evaluated Rhode Island Birth Certificate data of live births from 2006 to 2016 for mothers who were enrolled in the Rhode Island Medicaid program. The study cohort included women who gave a live birth and had no opioid dispensing or opioid use disorders during the study period. Mothers' prescription opioid exposure was obtained through pharmacy claims and defined as filled at least one prescription opioid for non-cancer pain during pregnancy. Study outcomes were assessed using ICD-9 diagnosis codes and ascertained by medical records review. Conditional logistic regression models with propensity score (PS) fine stratification and weighting with 100 strata were applied to derive the effect estimates of maternal opioid exposure on infant birth defects after adjusting for other potential confounders.

Results: Of 25,205 pregnancies included in this study, 1,898 (7.5%) mothers filled prescription opioids and 1,024 (4%) infants were diagnosed with birth defects, either major congenital malformations (MCM) or minor anomalies (MA). Comparing opioid exposed vs unexposed, total birth defects were 9.5% vs 3.6% ($P < 0.0001$), MCMs were 7.0% vs 2.7% ($P < 0.0001$), and MAs were 3.1% vs 1.2% ($P < 0.0001$). Mother exposed to an opioid during pregnancy were older (27.35 ± 5.36), more likely to have smoked (52.6%), and had a higher number of prenatal care visits (13.04 ± 5.58). Infants with prenatal opioid exposure were more likely to be born preterm (gestational age, mean ± SD: 38.3 ± 2.3 vs 38.6 ± 2.1, $P = 0.07$; preterm born, N(%): 194 (11%) vs 2108 (9%), $P = 0.01$). The conditional logistic regression analysis with PS fine stratification and weighting with 100 strata also showed significant increases of MCM and MA in infants with maternal opioid exposure compared to those who were not exposed.

Conclusions: Our results suggest a significant association between opioid use during pregnancy and an increased incidence of birth defects. Further investigation is needed to examine the effects of maternal opioid exposure on infants' long-term health outcomes.

899 | Crowdsourcing as a novel method to assess the impact of drug exposure on Belimumab pregnancy registry enrollment

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Background: The belimumab (BEL) Pregnancy Registry (BPR; GSK Study 114256), a prospective, voluntary study of BEL during pregnancy in women with systemic lupus erythematosus (SLE), has demonstrated low enrollment ($N = 60$) despite awareness activities. Crowdsourcing platforms collect feedback from online general population or physician communities.

Objectives: Understand BEL use in pregnancy, ascertain BPR awareness, and identify study enrollment barriers via two crowdsourcing platforms.

Methods: Patients (women with SLE; pregnant [P]/recently pregnant [RP]/planning a pregnancy [PP]) completed an online Amazon Mechanical Turk (mTurk) questionnaire about their SLE medication use and BPR awareness. Rheumatologists (in 8 countries with active BPR) with a history of prescribing BEL in pregnancy were surveyed via SERMO on prescribing patterns and factors relating to BPR awareness/enrollment. Surveys were active for 3 months.

Results: Overall, 151 patients (across 3 months) and 169 rheumatologists (within 48 hours) responded, primarily from the US. Most patients were 26–35 years (58%), reported mild (42) or moderate (56%) SLE, and were P/RP (51%); 49% were PP. Exposure to BEL was reported by 42% of patients (of these: P, 29%; RP, 33%; PP, 38%), of whom 54% were exposed for ≤1 year (of these: P, 16%; RP, 14%; PP, 24%). Of patients with prior exposure to BEL, 51% were BPR-aware, versus 6% of those without exposure. Overall, 60% of patients stopped BEL due to pregnancy (of these: P, 32%; RP, 37%; PP, 32%); BPR awareness did not impact discontinuation. Among rheumatologists, 46% were BPR-aware, 92% of whom were willing to refer patients to the BPR. Rheumatologists reported 23% of their patients had no concerns on BEL use during pregnancy (multiple choices allowed); concerns included the unknown BEL safety profile (75%) and wanting to reduce medication in pregnancy (28%). Overall, 86% of physicians gave reasons for not prescribing BEL during pregnancy (multiple answers allowed) including unknown pregnancy safety profile (78%), preference for other treatments (41%), and mild disease or tolerable symptoms (33%). Rheumatologists (82%) reported treating ≤5 (52%), 5–10 (26%), or > 10 (23%) patients who were P/RP/PP with BEL.

Conclusions: Crowdsourcing platforms enable rapid, targeted, high-coverage, physician and patient feedback. Findings suggest women are BEL-exposed during pregnancy, but few take part in the BPR. Barriers to BPR enrollment include moderate BPR awareness, BEL discontinuation, and low knowledge of the BEL benefit/risk profile during pregnancy. Study funded by GSK.

900 | Discontinuation of anti psoriasis drug treatments during pregnancy. The PSO MOTHER cohort study

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Background: Psoriasis is a chronic condition with worldwide prevalence of about 2–3%. Fifty percent of patients are women, mostly diagnosed during childbearing age. Studies evaluating the effectiveness of anti-psoriasis treatments on mother during pregnancy are limited with no data regarding the impact of the pregnancy status on the compliance to different available drug therapies, both topical and systemic. The majority of the available treatments have important warnings on potential embryo-fetotoxicity, which might play a role on the decision to continue treatment or not.

Objectives: Our aim is to investigate quality of care for women with psoriasis in terms of use and discontinuation of different treatments before and during pregnancy.

Methods: This is the first analytical report from a large cohort study supported by the Italian Ministry of Health: Psoriasis in the Mother with Treatments and Health Endpoints Risk (PSO-MOTHER). All children born between 2009 and 2016 in a central Italian region (Lazio) by mothers with diagnosis of Psoriasis and with drug prescription before the conception date (six months) were identified. Anti-psoriasis drug patterns (biological, systemic or topical prescriptions) before and during pregnancy were analyzed according to women's socio-demographic and clinical characteristics at delivery. Furthermore, use of drugs specifically contraindicated in pregnancy (i.e methotrexate, acitretinoin) was analyzed.

Results: Among 1,876 deliveries by women affected by Psoriasis 525 (28%) had at least one prescription of anti-psoriasis drug treatments in the six months before the conception date. Median age at delivery was 33 years. For each class of drugs considered there was a general decrease in their use during pregnancy. In particular, considering the variations between the three months preceding the conception and the third trimester of pregnancy, the following prescriptive percentages were observed: from 8.4% to 0% for the biologicals, from 5.9% to 2.5% for the conventional systemic drugs and from 52.0% to 9.4% for the topical treatments. Eight women had methotrexate prescriptions in the three months before conception, only one had also a prescription during pregnancy (third trimester). No prescriptions of acitretinoin both before and during pregnancy were found.

Conclusions: Pregnancy appears to have a significant influence on the prescriptive patterns of different pharmacological treatments for psoriasis. In the context of the PSO-MOTHER project, we will aim to understand the impact of this phenomenon on the health outcomes of the mother with psoriasis and of their children.

901 | Long-term neurodevelopmental outcomes in children with prenatal opioid exposure

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Background: Several studies suggested that maternal use of opioids is associated with multiple maternal, fetal, and neonatal complications. However, the research gap remains in long-term effects of maternal opioid exposure on children.

Objectives: To determine the risk of long-term neurodevelopmental outcomes in children with prenatal opioid exposure.

Methods: This study included pregnant women aged 12 to 55 years and their liveborn infants enrolled in the Optum Clinformatics™ data from January 1, 2010 to July 1, 2012. Mothers were required to have continuous eligibility 3 months prior to the estimated last menstrual period (LMP) and throughout pregnancy. LMP was determined by counting back 2 weeks plus 35 weeks or 40 weeks for preterm and term births. Women with cancer, opioid-use disorder, opioid dispensing during baseline, or exposure to teratogenic drugs during pregnancy were excluded. Infants with diagnosis of chromosomal anomalies were excluded. Infants were considered exposed if mother received at least 1 prescription opioid during pregnancy. The children outcomes included the diagnosis of all mental disorders or specific development delays. Conditional logistic regression with propensity score greedy matching (PSGM) with 0.1 caliper width or propensity score fine stratification and weighting (PSFSW) with 100 strata were used to obtain adjusted risk ratios (RR). Maternal comorbidities and mental health diagnoses, measures of illness burden, and concomitant drugs were adjusted.

Results: Of the 83,332 mother-infant pairs, 8,874 (11%) mothers used opioids in pregnancies, 6,986 (0.8%) infants developed any types of mental disorders and 4,994 (0.6%) were diagnosed with specific development delays during the follow up period (median: 760 days). Unadjusted comparisons showed a statistically significant differences between exposed and unexposed in mental disorders (RR: 1.17, 95%CI: 1.10–1.26) and specific developmental delays (RR: 1.18, 95%CI: 1.09–1.29). After adjusting for confounding factors, the differences became insignificant for overall mental disorders (aRR from PSGM: 1.04, 95%CI: 0.95–1.15; aRR from PSFSW: 1.04, 95%CI: 0.96–1.10), and specific developmental delays (aRR from PSGM: 1.05, 95%CI: 0.93–1.18; aRR from PSFSW: 1.04, 95%CI: 0.96–1.13).

Conclusions: In this study, the association between maternal opioid exposure and risk for long-term mental disorders in children was not statistically significant. While future studies with larger cohort and longer follow up are needed to confirm the findings, a careful evaluation of the risk and benefits of opioids during pregnancy should be encouraged.

902 | Projected impact of pharmacogenetics on veteran pain management

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Background: Veterans have a high burden of chronic pain. Safely improving pain management is a priority for the Department of Veterans Affairs (VA). Pharmacogenetic (PGx) tests detect individual genetic variations associated with altered drug metabolism.

Objectives: To estimate the potential impact of PGx testing on pain management for Veterans, focusing on *CYP2D6* and opioid metabolism, *CYP2C19* and response to adjunct medications (antidepressants), and *CYP2C9* and celecoxib.

Methods: National retrospective study using data from VA Corporate Data Warehouse, VA Pharmacy and VA GDx database for molecular tests. We identified Veterans with ≥1 prescription for codeine, oxycodone, tramadol, or hydrocodone in 2012–2017. We built indicators for chronic opioid use defined as lasting 90+ days with 10+ prescriptions or 120+ day-supply, and for coprescriptions of pain medications. We summarized patient characteristics, healthcare utilization and PGx testing. We projected the prevalence of actionable phenotypes for *CYP2D6*, *CYP2C9 and CYP2C19* using published frequencies and race/ethnicity of the cohort.

Results: Among 2,687,831 patients with ≥1 opioid prescription in 2012–2017 (66% non-Hispanic white, 20% Black, 7% Hispanic), 36% experienced chronic use. Compared with non-chronic opioid users, chronic users were older (mean age 58 vs 55), more often white (70% vs 64%), and had higher healthcare utilization during the year of opioid prescription. The drugs most often coprescribed with opioids were antidepressants (27% of cohort), and 15% (*n* = 407,602) received a drug inhibiting *CYP2D6* that may decrease opioid response. We estimated that 3% of the cohort was at increased risk for codeine toxicity (*n* = 91,600 *CYP2D6* ultrarapid metabolizers) and 5% were at higher risk for undertreatment and drug interaction (*n* = 142,400 *CYP2D6* poor metabolizers). 33% of patients (*n* = 888,700) would have a *CYP2C19* phenotype relevant to antidepressant response, and 33% (*n* = 881,700). a *CYP2C9* phenotype influencing celecoxib treatment. Overall, 70% of the patients were estimated to have a clinically actionable phenotype. 2,768 patients (0.1%) had undergone PGx testing; 80% of the tests were *CYP2C9* ordered to guide anticoagulant therapy; 315 patients had been tested for *CYP2D6* and 411 for *CYP2C19*.

Conclusions: Coprescriptions of opioids and interacting drugs is frequent among Veterans. Although 70% of the patients would have an actionable phenotype relevant to pain therapy, PGx testing is infrequently used in this population. Our findings can help VA leadership develop a framework for comprehensive clinical implementation of PGx testing to inform pharmacotherapy decisions.

903 | Mountin' an expedition to find the truth: Alps Bayesian pathway modeling of tamoxifen pharmacogenetics

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Background: Tamoxifen and its metabolites compete with estrogens for binding of the estrogen receptor (ER). Adjuvant tamoxifen therapy is administered for 5—10 years at a dose considered to overwhelm the ER, thereby reducing the hazard of recurrence by half. Previous studies have examined some functional polymorphisms in genes that may alter tamoxifen effectiveness, but no study has evaluated the importance of the complete metabolic path in optimal tamoxifen response. No earlier study of genotype-guided tamoxifen therapy has included a large stratum of premenopausal women, for whom tamoxifen is guideline endocrine therapy.

Objectives: We evaluated the pharmacogenetics of tamoxifen metabolism and its impact on the hazard of breast cancer recurrence in a cohort of premenopausal women.

Methods: We identified a cohort of 6000 Danish non-metastatic premenopausal breast cancer patients, of whom 4600 with ER+ tumors received tamoxifen, and 1359 with ER− tumors did not receive tamoxifen. We also conducted a case–control study of 1082 predominately postmenopausal women in Denmark. In both study populations, women were followed for recurrence for up to ten years after initial diagnosis. We identified and collected formalin-fixed, paraffin-embedded primary tumor blocks from patients for whom samples were available (3959 ER+ and 1139 ER−). We genotyped 32 variants in 15 genes involved in tamoxifen metabolism or transport. We used the Algorithm for Learning Pathway Structure (ALPS), which incorporates well-established prior information about the tamoxifen metabolic pathway, to evaluate the importance of the total metabolic capacity and to identify interactions between variants in the pathway.

Results: No individual variant was notably associated with the hazard of breast cancer recurrence in either study population. For both the premenopausal and post-menopausal study populations, there was weak evidence for the importance of phase 1 metabolism to the clinical efficacy of adjuvant tamoxifen therapy [Bayes factor (BF) = 2.12 and 2.26, respectively].

Conclusions: Phase 1 metabolism is known to generate active tamoxifen metabolites, and consistent with this knowledge, our results support the importance of phase 1 metabolic capacity in optimal tamoxifen response. Nonetheless, no individual variant substantially

explained the overall phase 1 effect on metabolic capacity, and the level of evidence for the overall effect was weak. These results are consistent with existing guidelines recommending against genotype-guided tamoxifen prescribing, and provide the first large study in support in premenopausal women.

904 | Insurance coverage of pharmacogenomic testing

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Background: Pharmacogenomics (PGx), a component of personalized and precision medicine, focuses on how genetic variation contributes to inter-individual variability in drug disposition, response, and adverse effects. Many potentially actionable PGx drug-gene pairs exist, but few are routinely implemented in clinical practice. While clinical use of PGx testing is growing, little is known about how many patients receive PGx testing through their insurance.

Objectives: To identify patients who received PGx testing through their insurance; identify trends in PGx testing over time; and describe characteristics of patients who received PGx testing.

Methods: We leveraged a random sample of 10 million patients from an existing insurance claims dataset populated with medical and pharmacy claims for 89 million patients from 75 commercial health plans in the US. We identified a retrospective cohort of patients of all ages who had at least one claim with a procedure code indicating receipt of one of the following PGx tests: CYP2C19; CYP2D6; CYP2C9; VKORC1; and HLA Class 1 typing. Patients who paid for 100% of the costs of these PGx tests out-of-pocket are not represented in this data source. We calculated counts and frequencies for categorical characteristics, and means and medians for continuous characteristics.

Results: 5,695 patients received at least one of the PGx tests named above from January 2012–September 2017. The median number of tests received per patient was 3 (mean = 2.7, range 1–12; note patients may have received certain tests more than once). Just over half of the patients (55%) were female, and the average age was 43 years. For just over half (54%), the PGx test claim was processed through government insurance (i.e., Medicaid or Medicare); for 43%, the claim was processed through commercial insurance. Only a handful of patients (n = 12) received a PGx test in 2012. However, this number increased to 1,948 in 2013, then 4,126 in 2015 and 3,889 in 2016. The most common PGx test was CYP2C19 (n = 4,581), followed by CYP2D6 (n = 3,678) and CYP2C9 (n = 3,189). The most commonly documented diagnosis for CYP2C19, CYP2D6, CYP2C9, and VKORC1 was "long-term (current) use of other medications." The most common diagnosis for HLA Class 1 typing was HIV.

Conclusions: The number of patients receiving PGx testing through their insurance was low (less than 6,000 over nearly six years), but nearly doubled from 2013 to 2016. While PGx test results were not available from this data source, the most common diagnosis documented on the PGx test claims was related to medication use. This study emphasizes the need to better understand utilization patterns and insurance coverage for common PGx tests.

905 | β_2-adrenergic receptor haplotypes and risk of exacerbations in asthmatic children and young adults treated with long-acting β_2-agonists: a meta-analysis in the PiCA consortium

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Background: It is still unclear whether the haplotype combinations of polymorphisms at positions 16 and 27 of the β_2-adrenergic receptor (ADRB2) gene is associated with an increased risk of asthma exacerbations in patients treated with long-acting β_2-agonists (LABA).

Objectives: We investigated the association between haplotype combinations of polymorphisms at positions 16 and 27 of the *ADRB2* gene and asthma exacerbations in asthmatic patients using LABA and inhaled corticosteroids (ICS) from the multi-ethnic Pharmacogenomics in Childhood Asthma (PiCA) consortium.

Methods: We conducted a meta-analysis of 880 children and young adults aged (4–21) with asthma that were treated with LABA and ICS. Polymorphisms at positions 16 (rs1042713;16Arg > Gly) and 27 (rs1042714; 27Gln > Glu) of the *ADRB2* gene were extracted and their haplotypes were determined. Asthma exacerbations were defined as prescribed courses of oral corticosteroids and/or asthma-related hospitalizations/emergency room visits in the past 6 or 12 months prior to the study visit. The association between haplotypes and exacerbations was analyzed by using the HaploStats package adjusted for age and sex. A meta-analysis was performed using an inverse variance-weighted method assuming a random-effect.

Results: Three haplotypes were determined; Gly16Glu27, Arg16Gln27 and Gly16Gln27. Compared to the Gly16Glu27 haplotype, the Arg16Gln27 haplotype was significantly associated with an increased risk of asthma exacerbations (OR:1.37, 95% CI;1.03–1.81, $P = 0.028$, $I^2 = 0.0\%$).

Conclusions: We found that the Arg haplotype (Arg16Gln27) in the *ADRB2* gene increased the risk of exacerbations among asthmatic children using LABA and ICS. Whether or not this argues against prescription of LABA in patients with this haplotype needs to be considered.

906 | Prevalence of KRAS, NRAS, and BRAF gene mutations in metastatic colorectal cancer (mCRC) patients: a systematic literature review and meta-analysis

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Background: A systematic literature review and meta-analysis was conducted to summarize the prevalence of *KRAS*, *NRAS*, and *BRAF* mutations in mCRC patients. These mutations have substantial implications for treatment decisions among mCRC patients.

Objectives: The objectives of this study were to provide a comprehensive assessment of *KRAS*, *NRAS*, and *BRAF* mutation prevalence among mCRC patients as reported in the scientific literature and to identify potential sources of heterogeneity in mutation prevalence by conducting pre-specified subgroup analyses.

Methods: Multiple databases were searched to identify observational studies and clinical trials (standard of care arms only) that reported mutation status among mCRC patients. Random effects meta-analysis models were used to estimate summary prevalence estimates for each of the mutations. Subgroup and sensitivity analyses were conducted to identify potential sources of heterogeneity in mutation prevalence.

Results: The meta-analyses included 275 studies comprising over 77,000 mCRC patients. The summary prevalence estimate was 35.9% for *KRAS* mutations, 7.1% for *BRAF* mutations, and 4.1% for *NRAS* mutations. Female patients had significantly more *KRAS* and *BRAF* mutations than males (*KRAS*: 42.2% vs. 37.3%, $p = 0.011$; *BRAF*: 11.0% vs. 7.9%, $p = 0.018$), and significant variation by study location was observed for both *KRAS* ($p = 0.025$) and *BRAF* ($p = 0.002$) mutation prevalence.

Conclusions: The prevalence of *KRAS*, *BRAF*, or *NRAS* mutations in mCRC patients varies significantly by gender and study location. Compared to patients with wild-type tumors. The results of these analyses are informative for clinicians, patients, and researchers.

907 | The role of ABCG1 gene DNA methylations in lipid profiles and therapeutic efficacy of simvastatin in Chinese patients with hyperlipidemia

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Background: ATP-binding cassette transporter G1 (*ABCG1*) plays a critical role in lipid homeostasis by controlling the efflux of cellular cholesterol to HDL. DNA methylation is involved in lipid metabolism.

Objectives: The aim of this study was to estimate associations between DNA methylations in the *ABCG1* gene and serum lipids as well as their effect on the therapeutic efficacy of simvastatin in Chinese patients with hyperlipidemia.

Methods: We selected 211 subjects with extreme high ($n = 104$) and low response ($n = 107$) to simvastatin treatment from a total of 734 hyperlipidemic patients, who were treated orally with 20 mg/d simvastatin for eight consecutive weeks. The definition of treatment response was based on adjusted regression residuals for lipid-lowering response to simvastatin. Pretreatment DNA methylation levels at promoter of the *ABCG1* gene were measured by MethylTarget, a next generation Bisulfite sequencing-based multiple targeted CpG methylation analysis method.

Results: In the high response group, higher *ABCG1*_A and *ABCG1*_C mean methylation levels were positively associated with higher TG ($r = 0.225$, $p = 0.0286$; $r = 0.337$, $p < 0.001$, respectively). *ABCG1*_A DNA mean methylation levels were inversely associated with baseline HDL-C level ($r = -0.295$, $p = 0.00307$) and inversely with magnitude of change ($r = -0.294$, $p = 0.00304$) in HDL-C response to simvastatin (ΔHDL-C) after adjustment for age, sex, BMI, and baseline lipids. Similar patterns were also observed in the low response group. There was significantly inverse association between *ABCG1*_A methylation and the lipid-lowering response (ΔTC: $r = -0.295$, $p = 0.00272$; ΔHDL_C: $r = -0.33$, $p < 0.001$). Higher *ABCG1*_C methylation was relevant to lower ΔTG and ΔHDL-C ($r = -0.25$, $p = 0.0151$; $r = -0.394$, $p < 0.001$, respectively). Multivariable linear regression analysis of epigenetic predictors alone showed that *ABCG1*_A_mean methylation can significantly contribute to the inter-individual ΔHDL-C level variability (Adjusted $R^2 = 8.9\%$). *ABCG1*_C_mean methylation can explain up to 17.5% of the inter-individual ΔHDL-C level variability. Additionally, interaction on the ratio scale of the *ABCG1* gene DNA mean methylation and the SNP rs4148114 was significant in association with the lipid-lowering effect of simvastatin therapy.

Conclusions: The DNA methylation levels at the *ABCG1* gene are importantly epigenetic determinants of lipid levels and the lipid-lowering effect of simvastatin therapy. Further functional studies will contribute to a better strategy to stratify patients for a personalized lipid-lowering therapy.

908 | Identifying two gene clusters that may serve as a gene signature and biomarker of atopic dermatitis and can predict pimecrolimus efficacy and pharmacoepidemiology

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Background: Calcineurin antagonists (pimecrolimus) treat atopic dermatitis (AD) with different effectiveness and adverse events.
Objectives: The current report is to characterize and build a network to serve as a gene signature for Atopic Dermatitis (AD) and to predict pimecrolimus efficacy and pharmacoepidemiology.
Methods: Gene expression data are taken from GSE32473 gene expression profile of patients' skin suffering from an AD from the Gene Expression Omnibus (GEO) publically available web tool. The samples were ten baseline AD patients, and ten AD patients after topical treatment with either pimecrolimus. A total of 73 genes were found with unique expressions patterns in contrast between the AD patient's baseline and patients receiving pimecrolimus. geneMANIA, online tools were deployed to find the relevant network and subnetwork clusters.
Results: geneMANIA database search yielded 49% in co-expression pattern. 27% overlaps in pathway networks between the submitted genes. Four genes distinctly involved in regulation of receptor activity. Another four were in regulation in IkappaB kinase signaling. Differentially expressed after administration of pimecrolimus.
Conclusions: Analysis of differentially expressed genes after pimecrolimus reveals two significant gene clusters that are involved in receptor and Kappa kinase signaling pathways. These two important networks and their genes might serve as biomarkers for AD and a predictor gene signature for pimecrolimus medicine activity and adverse effects. Pathways related to gene clusters have been identified as a genetic signature to comprehend the underlying biology causing the AD clinical presentations. *LRRC4*, *OPRM1*, *MFHAS1*, *OPTC*, *P2RY1*, and *AVPR1A* all clustered around *GNB4* core gene. *GNB4* core gene was also found to be is among the under-expressed inflammatory genes after three weeks of treatment by pimecrolimus.

909 | Assessment of stakeholder perspectives of the clinical utility of pharmacogenomics in solid organ transplantation

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Background: Pharmacogenomics (PGx) is a component of precision medicine, with the goal of using an individual's genetic information to guide drug selection and dosing. In solid organ transplantation (SOT), several actionable PGx drug-gene pairs exist (e.g., tacrolimus-*CYP3A5*, azathioprine-*TMPT*, voriconazole-*CYP2C19*); however, few are routinely implemented in the clinical setting. A major obstacle impeding the translation of PGx in the transplant clinic is the lack of stakeholders' perspectives on its clinical utility.
Objectives: Assess patient and provider perspectives regarding the clinical utility of PGx testing following kidney, liver, and heart transplantation.
Methods: We conducted individual semi-structured interviews and focus groups with kidney, liver, and heart transplant patients and providers [i.e., physicians, pharmacists, and nurse practitioners (NPs)] from the University of Colorado and University of California San Diego. Audio-recorded focus groups and interviews were transcribed verbatim, coded using data management software, and thematically analyzed to identify salient themes in transplant patient and provider perspectives.
Results: The study enrolled 60 patients and providers. The patient cohort consisted of 36 kidney, liver, and heart transplant recipients who participated in 24 interviews or two patient focus groups (72% white; 72% men; mean age 55 ± 13 years). The provider cohort consisted of 24 kidney (33%), liver (33%), and heart (33%) transplant clinician interviews (50% physicians, 25% pharmacists, 25% NPs; 79% white; 58% men; mean age 44 ± 10 years). Qualitative analysis revealed that patients lacked an understanding about principles of PGx, but thought it sounded interesting and useful, and maintained trust in their providers to deliver the best possible care. Providers expressed willingness to use PGx testing in their transplant clinic when appropriate, but reported barriers to implementation of PGx, including lack of knowledge about ordering a PGx test and applying the results, lack of evidence demonstrating clinical utility in the transplant population, and patient financial burden.
Conclusions: The gap between patients' expectations and providers' level of knowledge about PGx indicates a need for provider education and ongoing support for successful translation of PGx into the transplant clinic. These results will be used to inform the development and administration of a national survey of medical directors of SOT programs to assess the perceived clinical utility of PGx in this population.

910 | Hormone replacement therapy and the risk of melanoma in post-menopausal women

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Background: There has been much speculation as to whether hormonal factors may affect malignant melanoma incidence; however, studies to date investigating the risk of melanoma associated with hormone replacement therapy (HRT) use have produced conflicting results.

Objectives: This study aimed to investigate if HRT was i) associated with an increased risk of melanoma ii) associated with an increased rate of secondary melanoma or all-cause mortality in patients diagnosed with malignant melanoma.

Methods: We conducted a nationwide case–control study (n = 8,279 incident melanoma cases; 2000–2015) using Danish healthcare registries. Conditional logistic regression was used to calculate odds ratios (ORs) for melanoma according to HRT use, adjusting for potential confounders. To investigate survival and secondary melanoma a cohort of all Danish women diagnosed with melanoma 2000–2013 (n = 6,575) was identified and followed through 2015. Cox proportional hazards models was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for second melanoma and all-cause mortality associated with HRT use compared to non-use.

Results: High use (≥1000 defined daily doses) of HRT was associated with an OR of 1.21 (95%CI 1.13 to 1.29) for melanoma risk, with no evidence of a dose–response pattern. Results were most pronounced among recent high users (OR, 1.28 95%CI 1.17 to 1.41) and for localized disease (OR, 1.25 95%CI 1.15 to 1.36). Similar estimates were obtained for intravaginal estrogen therapy (OR, 1.38 95%CI 1.13 to 1.68). Regarding secondary melanoma, no association was observed for post-diagnostic new-use of HRT (fully adjusted HR, 1.56 95%CI 0.64 to 3.80) nor continuous HRT use (fully adjusted HR, 1.26 95%CI 0.89 to 1.78). Similar associations were observed for all-cause mortality.

Conclusions: While we found evidence of an association between use of HRT and risk of melanoma, the increase in relative risk was limited. Further, the lack of dose–response, associations observed with recent use, localized disease and similar associations for intravaginal estrogen use suggests this is a non-causal association.

911 | First-line treatment of breast cancer and the risk of hematologic malignant neoplasms

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Background: Survival after early stage Breast Cancer (BC) has improved with the introduction of new therapeutic agents. At the same time, secondary malignant neoplasms, including hematologic malignant neoplasms (HMN), have become an increasing concern among BC survivors. However, the role of the various BC treatment modalities in explaining these secondary malignancies remains uncertain.

Objectives: To identify the treatment modalities of BC that are associated with the subsequent development of HMN.

Methods: A population-based cohort study was conducted using national data of the French National Health Data System. All women aged 20–85 years, diagnosed with an incident primary breast cancer between 2007 and 2015, who underwent surgery as first-line treatment for BC and who survived at least one year without developing any HMN or other secondary cancer were included and followed until December 2017. The risk of various types of HMN over time was compared according to BC first-line treatment modalities (surgery only or along with chemotherapy/radiotherapy/hormonal therapy/G-CSF [supportive granulocyte colony-stimulating factors]) using Cox models adjusted for sociodemographic characteristics and risk factors.

Results: Among a total of 324 056 BC survivors, 80.2% received radiotherapy, 37.8% received chemotherapy, 69.5% received hormone therapy and 23.7% received G-CSF. Overall, 2 291 cases of HMN occurred during a median follow up time of 4.9 years. Chemotherapy was associated with an increased risk of acute myeloid leukemia (AML) (N = 436, HR, 1.9, 95%CI, 1.5 to 2.6) and of Myelodysplastic syndrome (MDS) (N = 552, HR, 1.4, 95%CI, 1.0 to 1.9). Radiotherapy was associated with an increased risk of AML (HR, 1.5, 95%CI, 1.1 to 2.0). G-CSF was associated with an increased risk of acute lymphoblastic leukemia or lymphocytic lymphoma (ALL/LL) (N = 76, HR, 2.4, 95%CI, 1.1 to 5.3).

Conclusions: In our study, we found that certain types of HMN increased after treatment by chemotherapy, radiotherapy and/or G-CSF. Those risks should be taken into account in the initial management of BC.

912 | Corticosteroids and risk of hospitalization for infection among cancer patients treated with programmed cell death receptor/ligand 1 (PD-1/PD-L1) inhibitors

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Background: Corticosteroids are often used to manage immune-related adverse events after administration of PD-1/PD-L1 immune checkpoint inhibitors. Corticosteroid use has been previously associated with increased risk of serious infection in metastatic melanoma patients treated with immune checkpoint inhibitors (mainly targeting cytotoxic T-lymphocyte antigen 4); there is no information on this risk among other cancer types.

Objectives: To evaluate whether receipt of corticosteroids is associated with increased rate of hospitalization for infection in renal, urothelial, and lung cancer patients treated with PD-1/PD-L1 inhibitors.

Methods: We included all patients in the Danish Cancer Registry with a diagnosis of AJCC stage III or IV renal cell carcinoma (RCC), stage III

or IV non-small cell lung cancer (NSCLC), or stage II, III, or IV urothelial transitional cell carcinoma between 2013 and 2016. We further selected those who received treatment with PD-1/PD-L1 inhibitors as recorded in the Danish National Patient Registry (DNPR) between January 1, 2013 and March 1, 2018. We followed patients from the first date of treatment with PD-1/PD-L1 inhibitors (index date) until one year after the last treatment, death, emigration, or end of study period (September 1, 2018), whichever came first. Patients were considered exposed to corticosteroids from the first date of redemption of corticoid for systemic use (ATC codes H02AB or H02BX01) identified in the Danish National Prescription Registry after the index date. We used Cox regression to estimate age- and sex-adjusted hazard ratios (HRs) and associated 95% confidence intervals (95%CI) of hospitalization for infections based on ICD-10 codes in the DNPR.

Results: The cohort included 634 patients treated with PD-1/PD-L1 inhibitors (*n* = 55 RCC, *n* = 41 urothelial transitional cell carcinoma, and *n* = 538 NSCLC). Median age at initiation of PD-1/PD-L1 inhibitor treatment was 68.2 years (interquartile range (IQR), 61.4–73.4); 56% were men. During follow-up, 345 patients (54%) received corticosteroids at a median of 3.2 months after PD-1/PD-L1 inhibitor initiation (IQR, 1.4–5.9). During 561 person-years of follow-up, 422 hospitalizations for infection occurred (incidence rate, 113.1 per 100 person-years if exposed to corticosteroids and 57.1 if unexposed). The adjusted HR for hospitalization for infection was 2.38 (95%CI, 1.89–2.99).

Conclusions: Risk of hospitalization for infection doubled after corticosteroid treatment initiation in cancer patients treated with PD-1/PD-L1 inhibitors.

913 | Comparative safety and healthcare expenditures associated with frontline therapy for chronic myeloid leukemia

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Background: Tyrosine kinase inhibitors (TKIs) have dramatically improved survival for patients with chronic myeloid leukemia (CML). No overall survival differences have been observed between patients initiating frontline imatinib, nilotinib, or dasatinib; however, real-world safety and cost outcomes have not been well-studied.

Objectives: To evaluate the comparative safety and healthcare expenditures among CML patients initiating frontline imatinib, nilotinib, or dasatinib.

Methods: Eligible patients had 1+ fills for imatinib, nilotinib, or dasatinib between 1/1/2011–12/31/2016 (earliest fill = index date), 6+ months pre-index continuous enrollment, CML diagnosis, and no TKI use in the pre-index period. Safety events (defined as a hospitalization or emergency department [ED] visit) were compared across treatments using 1-year propensity score weighted relative risks (RR) and subdistribution hazard ratios (HR). Inflation-adjusted 1-year all-cause healthcare expenditures and out-of-pocket costs were compared across treatment groups using median regression.

Results: Eligible patients included 1417 imatinib, 647 nilotinib, and 1067 dasatinib patients. The 1-year risk of a safety event was high across treatment groups (risk [95% CI]: imatinib 37% [35%, 40%]; nilotinib 40% [36%, 45%]; dasatinib 44% [41%, 47%]), with higher risks among nilotinib (RR: 1.07 95% CI: 0.93, 1.23) or dasatinib (RR: 1.17 95% CI: 1.06, 1.30) patients, compared to imatinib. Over a median follow-up of 1.7 years (IQR: 0.8, 3.0), the cumulative incidence was higher among nilotinib (HR: 1.08 95% CI: 0.95, 1.24) or dasatinib (HR: 1.23 95% CI: 1.10, 1.38) patients, compared to imatinib. All-cause healthcare expenditures were high across treatment groups (median: $125,987) and were significantly higher among nilotinib and dasatinib patients, compared to imatinib (difference in medians [95% CI]: dasatinib vs imatinib: $22,393 [$17,068, $27,718]; nilotinib vs imatinib: $19,463 [$14,689, $24,236]). Median 1-year out-of-pocket costs were more similar across groups ($2,382), but higher among nilotinib patients, compared to imatinib patients.

Conclusions: Patients who received frontline imatinib had the lowest risk of hospitalization/ED visit and the lowest healthcare expenditures in the year following treatment initiation. Given a lack of significant differences in overall survival, imatinib may represent the preferred frontline therapy for most patients.

914 | Safety and cost-effectiveness analysis of Ponatinib versus other tyrosine kinase inhibitors in patients with chronic myeloid leukemia in the United States

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Background: Chronic myeloid leukemia (CML) is a malignant disease and the third most common type of leukemia. Tyrosine kinase inhibitors (TKIs) with similar spectrum of adverse effects are approved for CML therapy.

Objectives: To evaluate the cost-effectiveness of ponatinib compared to other second-line TKIs, including dasatinib, nilotinib, and bosutinib, in the treatment of patients with CML who failed or were intolerant to first-line TKIs in the United States.

Methods: A Markov state transition model was conducted to compare cost-effectiveness of second-line TKI for treatment practice of target patients using a US payer perspective over a life-long time horizon. Model transition, adverse-effect probabilities, and utility data were obtained from clinical trials and literature. Medical costs on CML treatment was estimated using the Medical Expenditure Panel Survey data between 2013 and 2016. Resource utilization included study drugs, monitoring, follow-up, adverse events and allogeneic stem cell transplantation. Primary outcomes were patient quality-adjusted life years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs)

per QALY gained with discount rate 3% per annum. Univariate sensitivity analyses and Bayesian multivariable probabilistic sensitivity analyses were conducted using Monte Carlo simulations.

Results: Total lifetime medical costs including follow-up care after allogeneic stem cell transplantation per CML patient were estimated at $2,226,616, $2,272,596, $2,362,797, and $2,457,005 for nilotinib, dasatinib, bosutinib and ponatinib, respectively. In the economic evaluation, dasatinib resulted in an ICER of $79,086/QALY compared to nilotinib. Ponatinib yielded an ICER of $176,278/QALY compared to dasatinib. Sensitivity analyses showed the model was robust to plausible changes in input parameters and had good face validity. Findings were sensitive to price and response rate of TKIs, and cost of adverse events management. The acceptability curve showed that dasatinib was the optimal therapy at a willingness-to-pay (WTP) threshold of $100,000/QALY. Between WTP thresholds of $160,000/QALY and $180,000/QALY, the probability that ponatinib or dasatinib was the optimal therapy was between 36% and 40%, indicating considerable uncertainty in the choice of optimal therapy.

Conclusions: Based on current treatment guidelines, this analysis indicates that dasatinib and ponatinib can be considered cost-effective options and provide clinical benefit compared to other TKIs for treating patients with CML in US.

915 | Use of antibiotics against urinary tract infections and risk of bladder cancer: a Danish nationwide case–control study

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Background: While bladder cancer mainly comprises urothelial carcinomas, squamous cell carcinomas are more prevalent in areas with high rates of Schistosoma haematobicum infections. Furthermore, some studies have demonstrated associations between frequent urinary tract infections (UTIs) and risk of squamous cell carcinomas specifically.

Objectives: To investigate the association between frequent UTIs, reflected by use of specific antibiotics, and risk of bladder cancer by histological subtype.

Methods: We conducted a nationwide case–control study using the Danish health registries. From the Danish Cancer Registry, we identified patients with a first-time diagnosis of histologically verified bladder cancer (non-invasive or invasive tumors) between 2000 and 2015. For each case, we age- and sex-matched 50 population controls free of bladder tumors. Use of antibiotics used against UTIs in Denmark (sulfamethizole, trimethoprim, pivmecillinam, and nitrofurantoin) was ascertained using the Danish Prescription Registry and categorized as no use (0–1 prescriptions), low (≥2), intermediate (2–9) and high-use (≥10), while applying a 2-year lag-period. We estimated the odds ratio (OR) associating high use of antibiotics against UTIs with squamous cell carcinoma bladder cancer, using conditional logistic regression. For comparison, similar analyses were performed for other bladder cancer histologies and for other antibiotics.

Results: We identified 333 squamous cell carcinomas of the bladder (2.7% of all cases). High-use of antibiotics used against UTIs was associated with squamous carcinomas with an overall OR of 11.4 (95%CI 7.6–17.0) and a clear dose–response pattern with ORs increasing from 2.5 (95%CI 1.7–3.6) with 2–4 prescriptions to 11.8 (95%CI, 6.2–22.4) with 20+ prescriptions ($p_{trend} < 0.001$). Similar associations were seen for the specific types of antibiotics used against UTIs (ORs ranging from 5.9–16.8). A weak association was observed for methoxyphenylpenicillin and squamous carcinomas (OR 2.4; 95%CI 1.3–4.7), but additional adjustment for antibiotics used against UTIs removed this association (OR 0.5; 95%CI 0.1–2.2). Urothelial carcinomas (90%; n = 11,029) were not associated with antibiotics used against UTIs (OR 1.1; 95%CI 0.97–1.3). Excluding patients with known urogenital disease did not influence the estimates for squamous cell carcinoma (overall OR 10.7; 95%CI 6.1–18.7).

Conclusions: UTIs, measured by use of specific antibiotics, are strongly, dose-dependently, and specifically associated with risk of squamous carcinomas of the bladder.

916 | Association between concomitant hydrochlorothiazide and cyclophosphamide use, and chemotherapy regimen discontinuation in breast cancer patients

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Background: Excluding some skin cancers, breast cancer is the most common cancer of women in the United States, and cyclophosphamide is a preferred agent in breast cancer treatment regimens. Hypertension is the most common chronic condition among older adults in the United States, with 55% of Medicare beneficiaries in 2015 having been diagnosed with hypertension. Hydrochlorothiazide, an antihypertensive, is one of the top ten most commonly used medications in the United States. Pharmacy reference databases (e.g. Micromedex) list cyclophosphamide and hydrocholorothiazide as a major drug–drug-interaction (DDI) due to myelossuppresion risk. However, the only study we found supporting this claim was an observational study conducted in 1981 with 14 breast cancer patients. No studies to date have evaluated clinical outcomes of this potential DDI in a large population of breast cancer patients.

Objectives: Estimate the association between concomitant cyclophosphamide and hydrochlorothiazide use (potential DDI) and treatment regimen discontinuation.

Methods: Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we included women 65 years and older with a first primary stage I-III breast cancer treated with cyclophosphamide. Potential confounders included colony stimulating factor (CSF) prior to treatment (for myelosuppression prevention), age at diagnosis, stage at diagnosis, race, treatment regimen, and Charlson comorbidity score. The association between concomitant hydrochlorothiazide use and treatment regimen discontinuation was assessed using modified Poisson regression with robust variance. Treatment discontinuation was defined as no treatment dose over 90 days after the expected time for the regimen.

Results: Among 2,213 women receiving cyclophosphamide adjuvant chemotherapy for first primary stage I-III breast cancer, 602 (27%) had concomitant hydrochlorothiazide and cyclophosphamide use and 1,740 (79%) completed their chemotherapy treatment regimen. The adjusted risk of treatment regimen discontinuation was similar between those receiving concomitant cyclophosphamide and hydrochlorothiazide vs. those unexposed to the potential DDI (risk ratio (RR) = 0.96, 95% confidence interval (CI): 0.81, 1.14).

Conclusions: These results indicate lack of association between the potential DDI and treatment regimen discontinuation. Results from this study support re-assessing and potentially lowering the severity of the noted interaction in drug reference databases.

917 | Early-life antibiotics use increases the risk of asthma and eczema: a discordant twin study

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Background: Epidemiological studies have shown that early-life exposure of antibiotics in children increases risk of asthma and eczema. However, causal relationships were difficult to assess in these studies (1,2).

Objectives: We aim to investigate evidence for causality in the relationship between early-life antibiotic use and development of asthma and eczema in a Dutch twin cohort.

Methods: We investigated 7,386 children (age: 3–10 years) from the Netherlands Twin Register prospectively followed by questionnaires (3). Outcome was defined as parental-reported asthma at age 3, 5, 7 or 10 years. Early-life antibiotic exposure was defined as parental-reported use of antibiotics between 0–2 years. Individuals derived from twin pairs were included in unmatched case–control analyses, using generalized estimating equation models. Conditional logistic regressions were performed in twin pairs using a co-twin control analysis. This design includes disease discordant twin pairs. Affected twins were matched to their healthy co-twin. It takes advantage of the fact that MZ and DZ twin pairs share different degrees of genetic relatedness and share their environment, while exposure to antibiotics can differ within twin pairs (4).

Results: Early-life antibiotic use was associated with an increased risk of asthma (OR: 1.28, 95% CI: 1.18–1.45; *n* = 7,386) and eczema (OR: 1.17, 95% CI: 1.08–1.27; n = 7,038) in affected twins with unrelated controls. After controlling for shared environmental factors by analyzing disease discordant MZ and DZ twin pairs (healthy co-twin as control), the risk of developing asthma was significantly increased (OR: 1.84, 95% CI: 1.05–3.22, *n* = 536), but non-significant for eczema (1.21, 95%CI: 0.81–1,80; *n* = 946). After controlling for both shared environmental and genetic factors in disease discordant MZ pairs, increased risk remained, but not statistically significant for developing asthma (OR: 3.33, 95% CI: 0.92–12.11; *n* = 138) and eczema (OR: 2.00, 95% CI: 0.90–4.45; *n* = 306). Lack of statistical power may be a reason for reaching this borderline significant finding. We could not correct for prescription of antibiotics caused by viral infections, which may be a confounder.

Conclusions: Our results suggest that the association between early-life antibiotic use and asthma or eczema is not confounded by environmental or genetic factors, and might be causal. The risks and benefits of using antibiotic therapy in young children should be considered before the start of therapy.

918 | Patterns of prescription opioid use among commercially insured United States youth and young adults with co-morbid chronic pain and mental health conditions

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Background: Approximately 30% of youth and young adults experience chronic non-cancer pain (CNCP) conditions. In adults, those with CNCP and mental health conditions are more likely to use opioids and to remain on opioid treatment. Among youth and young adults with CNCP little is known about the patterns of prescription opioid use and whether concurrent mental health conditions increase opioid use.

Objectives: Our goal was to examine the association between chronic non-cancer pain (CNCP), mental health disorders (MHD) and patterns of opioid use among commercially insured youth and young adults 10–25 years.

Methods: We conducted a retrospective cohort study derived from a 10% random sample of enrollees within the IQVIA™ PharMetrics Plus adjudicated claims database during January 1, 2006 to December 31,

2015. CNCP was defined as the earliest diagnosis of back, head, neck, arthritis or chronic pain (index date). MHD were assessed in the 6-months prior to the index pain diagnosis and included: mood disorders, anxiety, depression, personality disorders, adjustment disorders, and attention deficit hyperactivity disorders. Based on days supply we developed a 3-categorical level measure of opioid use (none, acute [<90 days], chronic [>90 days]). Among youth with CNCP we estimated the prevalence of opioid use among those with and without MHD. Multinomial logistic regression (AOR; 95% CI) was used to estimate the association of MHD with opioid receipt, controlling for demographic and clinical factors.

Results: Among 151,587 youth and adults diagnosed with CNCP, 25,449 (16.8%) had a co-morbid MHD. Both acute and chronic use of opioids were more common among those with CNCP and MHD (16.9% and 1.0%) compared to those with only CNCP (12.8% and 0.2%.) Youth with co-morbid CNCP and MHD were more likely to be prescribed opioids compared to those with only CNCP. The odds were lower for acute (1.07; 1.02,1.12) versus chronic (1.81; 1.46,2.25) use after opioid initiation.

Conclusions: Although the overall prevalence of opioid use is low, youth with CNCP and MHD are almost twice as likely than those without MHD to be chronically treated with opioids. These findings suggest potential adverse selection of youth with CNCP, where those at highest risk for dependence or adverse outcomes, are more likely to receive chronic opioid treatment.

919 | Outcomes associated with antidepressant augmentation: a group-based trajectory modeling with propensity score approach

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Background: Limited efficacy of antidepressant (ATD) in treating Major Depressive Disorder (MDD) in youth often leads to psychotropic augmentation soon after ATD initiation in community practice. However, there is insufficient evidence to support this practice.

Objectives: To estimate the odds of hospitalization and emergency department (ED) visits in youth with MDD who augment ATDs with another psychotropic medication.

Methods: A new user design identified US youth ≤18 (n = 3,055) diagnosed with MDD who initiated an ATD anytime from January 2007–June 2014 using IQVIA™ PharMetrics Plus claims data. New users had no ATD nor other psychotropic use 1-year prior (baseline) to the index ATD. Youth were followed for 1-year post the index ATD. We identified dose trajectories and augmentation (>15 days overlap of ATD with another psychotropic) in the first 6 months post index ATD. Outcomes (hospitalization and ED visits) were identified in months 7–12 post index ATD. Latent class growth analysis defined subgroups of youth with similar ATD dose trajectories. Within each dose trajectory group, we estimated the predicted probability of ATD augmentation, using baseline characteristics. Logistic regression with inverse probability of treatment weighting, compared the odds of hospitalization or ED visits among youth with ATD augmentation versus those without, within each trajectory subgroup.

Results: The four dose trajectories were slow downward titration (*n* = 287; 9%), sustained minimum (10 mg/d per FDA) dose (*n* = 982; 33%), sustained maximum (20 mg/d per FDA) dose (*n* = 1,361; 44%) and high dose titration (*n* = 425; 14%). ATD augmentation was most prevalent in the slow downward titration group (*n* = 90; 31%), followed by high dose titration (*n* = 112; 26%), sustained maximum dose (*n* = 292; 21%), and sustained minimum dose (*n* = 190; 19%). The proportion of youth who had a hospitalization or ED visit ranged from 21% - 26% across subgroups; the lowest in the sustained maximum dose and the highest in the high dose titration. The odds of hospitalization or ED visits among youth who augmented versus those who did not was 0.96 (95% CI: 0.48–1.92) for slow downward titration, 1.69 (95% CI: 0.84–3.39) for sustained minimum dose, 0.76 (95% CI: 0.42–1.37) for sustained maximum dose and 2.2 (95% CI: 0.70–6.9) for high dose titration.

Conclusions: ATD augmentation was not associated with a reduction in hospitalization or ED visits among youth with MDD. Exposure to concomitant psychotropic medications may carry safety risks that outweigh the potential benefits.

920 | A latent class growth analysis of antidepressant dose trajectories and treatment augmentation in youth

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Background: More than 40% of youth diagnosed with major depressive disorder (MDD) will not achieve complete response to treatment with an antidepressant (ATD). In community outpatient care, this is translated to either psychotropic augmentation, switching, or discontinuation of an ATD soon after starting treatment. Little is known regarding the relationship between ATD dosing and these therapeutic changes in community settings.

Objectives: This study aims are to a) determine if comorbid diagnoses are associated with ATD dose trajectory and b) identify ATD dose trajectories associated with augmentation, switch, or discontinuation during the 6 months after ATD initiation.

Methods: A retrospective new user design identified 5,725 US youth ≤18 diagnosed with MDD who initiated an ATD anytime from January 2007–June 2015 using the IQVIA™ PharMetrics Plus claims data. New users had no ATD nor other psychotropic use 1-year prior to the index ATD. Latent class growth analysis identified ATD fluoxetine equivalent dose trajectories 6 months post-index ATD and multinomial logistic regression identified factors associated with each dose trajectory. A Cox proportional hazard model compared the adjusted

hazard of the first event of augmentation (ATD overlap with another psychotropic for >15 days), switch (change to another psychotropic for >15 days), or discontinuation (no medication for ≥30 days) across dose trajectories.

Results: The five ATD dose trajectories identified were rapid (926; 16%) and slow downward titration (1,049; 18%), sustained minimum (10 mg/d per FDA) dose (1,406; 25%), sustained maximum (20 mg/d per FDA) dose (1,794; 31%) and high dose titration (550; 10%). Anxiety and/or PTSD was more likely in high dose titration (OR: 1.26; 95%CI: 1.01–1.39) and sustained maximum dose (OR: 1.18; 95%CI: 1.01–1.71), than the sustained minimum dose group. Severe mental illness (bipolar, schizophrenia) was more likely in the rapid (OR: 1.57; 95% CI: 1.23–1.99) and slow downward titration (OR: 1.71; 95% CI: 1.36–2.15) groups than the sustained minimum dose group. The groups most likely to augment were sustained maximum dose (HR: 1.41; 95% CI: 1.15–1.71) and high dose titration (HR: 1.97; 95% CI: 1.56–1.71). Nearly all (97%) of the rapid downward titration group discontinued or switched. A discontinuation or switch was also more likely in the slow (HR: 2.99; 95% CI: 2.70–3.33) downward titration group.

Conclusions: Comorbid psychiatric conditions may explain the therapeutic changes observed in each dose trajectory, however, further research is needed to inform optimal therapeutic management of MDD in youth.

921 | Selective serotonin reuptake inhibitors and type 2 diabetes in adolescents and youths

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Background: There is recent evidence suggesting that antidepressant use increases the risk of type 2 diabetes (T2DM) in adolescents and youths. However, selective serotonin reuptake inhibitors (SSRIs), the most widely used antidepressants in this age group, have minimal metabolic side effects questioning the biological plausibility of this finding.

Objectives: To examine the potential association between SSRIs and the development of T2DM in adolescents and youths.

Methods: Using nationwide US claims data from the Medicaid Analytic eXtract (2000–2014), we identified a cohort of adolescents and youths (age 10–24 years) with a medical diagnosis for an SSRI treatment indication. Within this cohort, new users of SSRIs were compared to new users of bupropion, an antidepressant that is known to not result in metabolic side effects. To increase the likelihood that the patient truly took the drug and to minimize exposure misclassification, we required 1+ additional dispensing of the respective therapy within 180 days after initiation. Additionally, to inform within-class treatment choices, we compared individual drugs within the SSRI class, using fluoxetine as the reference. Cox proportional hazards regression was used to estimate the association between SSRIs and T2DM, using propensity score (PS) stratification (based on 160+ variables) to control for potential confounding. As a secondary analysis, the high-dimensional propensity score (hdPS) was used to account for proxies of unmeasured confounding.

Results: Patients who initiated SSRIs (*n* = 366,225) were more likely to be female and had fewer co-occurring psychiatric conditions and prescriptions compared to bupropion initiators (*n* = 39,468). After propensity score stratification, all patient characteristics were well balanced between SSRI and bupropion initiators (absolute standardized difference < 0.05). During follow up (mean: 2.8 years), the incidence rate of T2DM was 2.4 and 2.3 cases per 1,000 person-years, respectively, among SSRI and bupropion initiators (crude HR = 1.04, 95% CI: 0.91–1.19). The association remained not substantial after PS stratification and hdPS stratification (adjusted HR = 1.11, 95% CI: 0.96–1.27 in both analyses). In the within-class comparison vs. fluoxetine, paroxetine (adjusted HR = 0.83, 95% CI: 0.68–1.01) and sertraline (adjusted HR = 0.90, 95% CI: 0.79–1.01) were associated with a decreased hazard of T2DM, and none of the hazard ratios were significantly increased.

Conclusions: In a large nationwide cohort of publicly-insured adolescents and youths, we found no substantial increase in the risk of T2DM among new initiators of SSRIs.

922 | Trends in antidepressant use among children and adolescents: a Scandinavian drug utilization study

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Background: The use of antidepressants in children and adolescents is controversial and serious adverse effects have been reported. A black-box warning in 2004 led to changes in medication guidelines and for now, selective serotonin reuptake inhibitors (SSRI) are the only antidepressants indicated for treatment in this age group.

Objectives: We aimed to describe and compare the use of antidepressants in Scandinavian children and adolescents throughout the last decade.

Methods: A population-based study design including all individuals aged 5–19 years in the study period of 2007–2017. Aggregate-level data on antidepressant use (ATC code N06A*) in Denmark, Norway and Sweden was extracted from publicly available data sources.

Results: Throughout the study period, the number of young antidepressant users increased markedly in Sweden (from 9.3 to 18.0/1000), whereas it increased slightly in Norway (5.1 to 7.6/1,000) and

decreased in Denmark (9.3 to 7.5/1,000, after a 2010 peak of 12.9/1,000). Hence, the percentage of Swedish children and adolescents who filled at least one antidepressant prescription in 2017 (1.80%) was more than twice as high compared to Denmark (0.75%) and Norway (0.76%). Antidepressants were most frequently used in the age group of 15–19 years and girls were more likely to receive treatment. The ratio between girls and boys treated per 1,000 was similar in the three countries (Sweden: 67.8/28.4 = 2.39, Denmark: 27.0/11.1 = 2.44, Norway: 30.2/11.5 = 2.63).SSRI were the antidepressants most commonly used in all three countries. The defined daily dose (DDD) of SSRI in the year 2017 was 5,611 per 1,000 inhabitants in Sweden, 2,709/1,000 in Denmark and 1,848/1,000 in Norway. The use of 'other antidepressants' (ATC code N06AX) also increased in Sweden, with a significantly higher use in 2017 (497/1,000) compared to Denmark (225/1,000) and Norway (170/1,000). The use of tricyclic antidepressants (TCA) in 2017 was generally low in all countries (Sweden: 30DDD/1,000, Denmark 38DDD/1,000, and Norway 42DDD/1,000).

Conclusions: Although the Scandinavian countries are considered comparable in regard to health care systems and medication guidelines, the trends of antidepressant use for children and adolescents differ profoundly. Swedish children and adolescents are more likely to receive treatment with antidepressants and the divergence to the use in Denmark and Norway is expanding throughout the last decade. The prevalence rates of childhood depression and anxiety disorders are not believed to vary between the Scandinavian countries, and obvious explanations for this finding are therefore lacking.

923 | Oral glucocorticoids and venous thromboembolism in children

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Background: Systemic glucocorticoid (GC) use is associated with many toxicities. Nonetheless, risks of GC-associated venous thromboembolism (VTE) in children are poorly understood.

Objectives: To quantify rates of new-onset VTE associated with GC exposure in a large pediatric population.

Methods: Using Medicaid claims data (2000–2010), we studied children age 1–18 with autoimmune disease (inflammatory bowel disease [IBD], juvenile idiopathic arthritis [JIA], or psoriasis [PSO]) or a comparator condition (attention-deficit/hyperactivity disorder [ADHD]) based on diagnoses ± pharmacy claims, excluding those with prior VTE or anticoagulant use. We studied time-varying oral GC use after a $\geq$ 6-month GC-free baseline, classifying dose as low, medium, or high based on prescribed prednisone-equivalent dosage and age−/sex-imputed weights. Outcomes were the first use of oral or injectable venous anticoagulants (primary) and VTE hospitalization plus anticoagulant within 4 months (secondary). We used Cox regression and weighted cumulative exposure (WCE) models to estimate adjusted hazard ratios (aHRs) and number needed to harm (NNH).

Results: Among 924,786 children (21.3% GC-exposed), 224 unexposed children (0.18/1000 person-years) and 58 currently exposed children (5.68/1000 person-years) were prescribed new VTE treatment. Among the unexposed, VTE rates were higher in children with IBD and JIA than in children with ADHD or PSO. After adjusting for age, sex, race/ethnicity, year, comorbidities, other medications, and healthcare usage, we found strong dose- and time-dependent relationships between GCs and newly treated VTE (>180d ago: aHR 1.1 (95% CI 0.8, 1.5); 1–180d ago: aHR 2.2 [95% CI 1.6, 3.0]; current low dose: aHR 6.1 [95% CI 3.4, 10.8]; current high dose: aHR 16.2 [95% CI 8.9, 29.2]). Associations using the secondary outcome were similar. Effect sizes increased with longer exposure duration and declined within 6 months after stopping GCs. Based on WCE models, sustained low-dose GCs (e.g., 0.1 mg/kg/day) appeared relatively safe (aHR < 1.2), but risks increased even with brief high-dose exposures (2 mg/kg/day x7 days: aHR 1.7). Risk differences were ~10-folder higher for children with IBD and JIA (NNH: ~55,000 for 2 mg/kg/day x7 days; ~2,000 for 2 mg/kg/day x30 days) than for those with ADHD or PSO (NNH: ~500,000–600,000 for 2 mg/kg/day x7 days; ~20,000 for 2 mg/kg/day x30 days).

Conclusions: In children with chronic conditions, current oral GC use is strongly associated with incident VTE in a dose- and duration-dependent fashion. VTE is a more common complication in pediatric IBD and JIA, but in absolute terms, this toxicity is rare in children.

924 | Psychotropic drug prescribing to children with attention deficit/hyperactivity disorder in the United States, 2002–2016

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Background: Use of ADHD drugs has been increasing in many countries, and prior studies of antidepressant and antipsychotic drugs have identified ADHD as a common reason for off-label usage. However, few comprehensive studies of psychotropic drug use have been performed for children with ADHD.

Objectives: To describe the extent and trends of prescribed non-ADHD psychotropic drugs for children with ADHD in the US and to evaluate how conduct disorder (CD) affects prescribing.

Methods: We used the National Ambulatory Medical Care Surveys (2002–2016) and outpatient National Hospital Ambulatory Medical Care Surveys (2002–2011), which provide nationally representative cross-sectional, visit-level data on demographics, diagnoses, and drugs ordered in outpatient clinics in the US. The study included all survey visits for children <18 excluding those for diagnoses or reported symptoms of anxiety, autism, bipolar disorder, depression, epilepsy/seizures, psychosis, or substance misuse/abuse. We identified visits

for ADHD using ICD-9-CM codes and visits for CD based on ICD-9-CM and reported symptoms. Antidepressants (AD), antiepileptics, antipsychotics (AP), and anxiolytics were grouped as non-ADHD psychotropic drugs. We compared rates of prescribing among groups with and without ADHD and/or CD using chi-square tests, accounting for the complex survey design. Trends were evaluated through logistic regression of elapsed time ([survey year-2002]/15) on drug class, adjusted for age, sex, race, ethnicity, insurance, setting of care, and presence of CD.

Results: Physicians prescribed non-ADHD psychotropic drugs at 9.8% of visits for ADHD alone and 28.3% of visits for ADHD + CD, compared to 7.7% of visits for CD alone and 1.2% of visits without ADHD or CD. Including ADHD drugs, ≥2 psychotropic drugs were prescribed at 19.1% of visits for ADHD and 32.8% of visits for ADHD + CD. Among non-ADHD psychotropic drugs, antidepressants were most commonly prescribed at visits for ADHD alone (5.9%), while antipsychotics were most commonly prescribed at visits for ADHD + CD (14.7%). Analyses suggested trends of increasing AD use (OR 1.8, 95% CI 0.7, 4.9) and decreasing AP use (OR 0.5, 95% CI 0.2, 1.5) over time.

Conclusions: US physicians frequently prescribe non-ADHD psychotropic drugs off-label to children with ADHD even in the absence of documented neuropsychiatric diagnoses or symptoms. Prescribing rates of these drugs are substantially higher for children with documented comorbid CD. More research is needed to understand the reasons for these prescribing patterns and their impact on outcomes.

925 | Variations in seasonal influenza vaccine effectiveness: a systematic review and meta-analysis of test-negative design studies

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Background: Test-negative design study using routine influenza surveillance data can avoid or minimize bias associated with confounding by health-care-seeking behaviour and misclassification of cases. In this design, patients presenting with influenza-like illness and testing positive for influenza virus are defined as cases and those testing negative are defined as comparators.

Objectives: To summarize and compare seasonal influenza vaccine effectiveness (VE) from test-negative design studies according to study region, influenza season characteristic, respiratory specimen swab collection time, and target age group.

Methods: We systematically searched appropriate bibliographic databases and relevant websites from January 2011 to July 2018 for full-text articles from test-negative design studies of seasonal influenza VE against laboratory-confirmed (PCR or culture) influenza conducted in outpatient primary care settings during the 2010/11 to 2017/18 influenza seasons. Two reviewers independently screened retrieved citations against the eligibility criteria using a two-stage sifting approach (screening of titles/abstracts and full-text articles) and extracted data from all included studies. Disagreements were resolved by consensus or by involving a third reviewer. We included only final seasonal influenza VE estimates. Pooled VE was calculated using inverse variance, random-effects model for all influenza, H1N1, H3N2, influenza A, and influenza B.

Results: Seventy full-text articles met our eligibility criteria and are included in the meta-analysis. Pooled VE was higher in the Southern hemisphere compared with the Northern hemisphere: 55% (CI: 49–60%; I^2 = 0%) compared with 40% (CI: 34–46%; I^2 = 78.8%) for all influenza, 66% (CI: 53–75%; I^2 = 0%) compared with 51% (CI: 45–56%; I^2 = 55.1%) for H1N1, 40% (CI: 26–51%; I^2 = 0%) compared with 25% (CI: 18–31%; I^2 = 61.7%) for H3N2, 53% (CI: 29–69%) compared with 40% (CI: 28–50%; I^2 = 71%) for influenza A, 58% (CI: 48–66%; I^2 = 0%) compared with 43% (CI: 36–50%; I^2 = 68.1%) for influenza B. Pooled VE across all influenza, influenza types and subtypes differed by vaccine antigenic similarity with circulating viruses (VE highest in antigenically similar), respiratory specimen swab time (higher VE with swab time of <8 days compared with swab time of ≤4 days), and age group (a reduction in VE with increasing age).

Conclusions: The available evidence suggests that study region, seasonal influenza vaccine antigenic similarity with circulating viruses, specimen swab time, and age influence seasonal influenza vaccine effectiveness.

926 | The risk of Arthus reaction following Tdap vaccination: vaccine adverse event reporting system and a review of literature

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Background: Repeated administration of tetanus toxoid-containing vaccines has been known in the past to result in an immune-complex reaction in hyper-immunized individuals, also known as Arthus phenomenon. Since 2013, the US Centers for Disease Control and Prevention (CDC) has recommended administration of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines Adsorbed vaccine (Tdap) during each pregnancy and recently, one Tdap (Adacel®, Sanofi Pasteur) was approved for repeat administration in adults.

Objectives: The objectives of this review were 1) to describe trends in spontaneously reported Arthus reactions following administration of any vaccine or Tdap in the US, and 2) to assess the risk of this phenomenon in persons receiving Tdap repeatedly.

Methods: We retrieved and reviewed "Type III immune complex mediated reaction" reports submitted to the US Vaccine Adverse Events Reporting System (VAERS) between 1990 and 2018. Reporting rates were estimated using Tdap doses distributed in the US from CDC and IQVIA's Drug Distribution Data. A systematic

literature review was conducted in PubMed to identify and review literature reports of Arthus reaction following any vaccination. Published manuscripts of clinical trials and observational studies that included safety outcomes after repeat Tdap vaccination were reviewed for any mention of Arthus-type reactions.

Results: A total of 192 suspected Arthus reaction reports were submitted to VAERS during the review period. Of these, 36 were reported after Tdap administered alone or concomitantly with other vaccines between 2008 and 2018. Vaccinee ages ranged between 11 and 64 years. There were more females (64%) among identified cases. Between 2013 and 2017, 14 suspected Arthus-type reaction cases were reported after Tdap administration among approximately 104 million doses of Tdap vaccines distributed in the US; the estimated conservative reporting rate was 0.1 cases per million doses distributed. The PubMed search did not identify any case reports of Arthus reaction published during the period of time when Tdap vaccines were licensed in the US or other countries. Similarly, no Arthus reaction cases were mentioned in published clinical trials and observational studies of repeat Tdap administration.

Conclusions: Arthus-type reactions following vaccination, including Tdap, are extremely rare. Increasing frequency of repeat Tdap administration in adults in the past several years did not result in detectable increases in the reporting rates of those events, confirming the favorable safety profile of the vaccine.

927 | Skin necrosis following 23-valent pneumococcal polysaccharide vaccination

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Background: Skin necrosis after vaccination is a rare local adverse event (AE) that can result in serious complications.

Objectives: Describe the characteristics of skin necrosis cases after administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Methods: A case series was conducted in the Vaccine Adverse Event Reporting System (VAERS). PPSV23 reports submitted from 1990 (VAERS inception) through January 9, 2019 associated with AEs of "injection site necrosis," "necrosis," "skin necrosis," or "vaccination site necrosis" were ascertained. A case of vaccination-site skin necrosis was defined as an individual whose report included a description of skin necrosis at or near the PPSV23 injection site. Empirical Bayesian data mining analyses were conducted to determine if skin necrosis was disproportionally associated with PPSV23 vaccine compared to other vaccine-AE pairs reported to VAERS.

Results: A total of 71 reports were ascertained, of which 44 (62%) met the case definition for vaccination-site skin necrosis. The median age of cases was 66 years (range = 51–96 years), and most were female (86%). The median time to onset of symptoms was one day (range = 0–18 days). Thirty (68%) cases received PPSV23 without concomitant vaccinations. The route of vaccine administration was noted for 29 (66%) cases, of which 21 (48%) received PPSV23 intramuscularly and 8 (18%) subcutaneously. Almost all cases (n = 42, 95%) were reported to have cellulitis or were described as having a cellulitis-like reaction in conjunction with skin necrosis. Blood or wound cultures were obtained in 10 (23%) cases, and in all but one case, culture results were negative. Fifteen cases (34%) were hospitalized, 19 (43%) required wound debridement, and 2 (5%) required a skin graft. No patterns were identified by onset date, reporting source, or product lot number. Data mining did not reveal disproportional reporting values for PPSV23 and skin necrosis.

Conclusions: Review of 28 years of US and international VAERS data revealed skin necrosis as a rare AE following PPSV23 vaccination. Most cases were associated with cellulitis or cellulitis-like reactions, not known to be of infectious origin, with some cases requiring hospitalization, wound debridement, and/or skin grafting. In addition to ensuring proper injection technique (optimizing injection site location, correct needle size), early recognition of skin necrosis and prompt evaluation and management are warranted.

928 | Safety surveillance of the four-component meningococcal group B vaccine (Bexsero®): vaccine adverse event reporting system (VAERS), January 2015–June 2018

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Background: Bexsero® (GlaxoSmithKline) is a four-component *Neisseria meningitidis* serogroup B vaccine (MenB-4C). It was licensed in the United States in 2015 under accelerated approval regulations for use among individuals ages 10–25 years. The Advisory Committee on Immunization Practices recommends MenB-4C for persons ages ≥10 years at high risk for meningococcal B disease; adolescents and young adults ages 16–23 years may also be vaccinated.

Objectives: To assess the post-licensure safety profile of MenB-4C by analyzing reports to the Vaccine Adverse Event Reporting System (VAERS).

Methods: VAERS is a national passive surveillance system for adverse events (AE) following immunization that uses the Medical Dictionary for Regulatory Activities (MedDRA) to code reported adverse events (AEs) and the Code of Federal Regulations to classify reports by seriousness. We analyzed U.S. reports involving MenB-4C received through June 30, 2018. We used Empirical Bayesian data mining to identify MenB-4C/AE combinations reported at least twice as often as expected.

Results: VAERS received 1,470 reports following MenB-4C vaccination (39% described concurrent administration of other vaccines). Most reports were among females (59%), with a median age of 17 years (interquartile range: 16–18 years). The most commonly reported AEs included injection site pain (23%), pyrexia (15%), and headache (15%). Median time from vaccination to AE onset was 0 days

(interquartile range: 0–1 days). There were 64 (4.4%) serious non-fatal and two (0.1%) death reports (none attributed to MenB-4C). Data mining identified disproportionate reporting for "injected limb mobility decreased" (secondary to injection site reactions including extensive swelling of the vaccinated limb and injection site pain).

Conclusions: The reported AEs for MenB-4C are consistent with the safety experience described in clinical studies and the product's package insert. We did not identify new safety concerns.

929 | Bacille Calmette Guerin vaccine safety surveillance in the Korea adverse event reporting system using tree-based scan statistics and traditional data mining methods

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Background: Comparable efficacy among Bacille Calmette-Guérin (BCG) vaccine with different strains or administration routes has been thoroughly documented. However, Substantial variations in the safety profile of different types of BCG vaccine have been reported.

Objectives: To conduct a data mining analyses using the tree-based scan statistic and traditional data mining methods to detect potential adverse events (AEs) following BCG vaccine, and explore the difference in the AE reporting rates of BCG vaccine for intradermal injection (BCG-ID) and BCG vaccine for percutaneous injection (BCG-PC) in the Korea Adverse Event Reporting System (KAERS) database.

Methods: We conducted vaccine safety surveillance study on the reported AEs of BCG vaccine from the Korea Institute of Drug Safety and Risk Management KAERS Database (KIDS-KD). We compared all vaccine-related AE pairs with AE pairs reported from the following BCG vaccines between 1 January 2005 and 31 December 2016: BCG-ID Danish (strain 1331; Statens Serum Institute), BCG-ID Tokyo (strain 172; Japan BCG Laboratory) and BCG-PC Tokyo (strain 172; Japan BCG Laboratory). Signal detection using the following three different data mining methods were compared: tree-scan statistic, Gamma-Possion shrinker Empirical Bayes Geometric Mean (EBGM), and traditional data mining method using reporting odd ratios, proportional reporting ratios and Bayesian confidence propagation neural networks of information components. Tree-scan statistic was employed to identify statistical associations (signals) of AE following BCG vaccines at a 0.05 level of significance.

Results: Among 19,448 all vaccine-related AE pairs, 620 AE pairs and 32 types of AE related to BCG vaccines were identified. A total of 4 signals were detected using traditional method, in which 3 signals were also detected by both tree-scan statistic and EBGM. The most predominant detected AE was lymphadenopathy (362/620; 58.4%), with higher reporting rate noted with intradermal injection (79.3%).

Conclusions: Tree scan statistic data mining method was successfully applied for signal detection of AEs following BCG vaccine in the KAERS database. Although BCG-ID was associated with higher AE reporting rate, caution should be taken when interpreting the results due to inherent limitations of data obtained from a spontaneous adverse event reporting system.

930 | Signal detection for vaccine safety in the vaccine adverse event reporting system using change point models

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Background: The Vaccine Adverse Event Reporting System (VAERS) have been a major data source for detecting signals of potential adverse effects (AEs) and monitoring vaccine safety. One of the main goals of VAERS is to monitor increases in reporting rate of AEs, as such signals can suggest safety issues caused by updates of vaccines or change in vaccine practices. Current disproportionality methods were largely developed for FDA Adverse Event Reporting System and ignore the temporal tends of reported adverse events. Thus, they cannot detect such temporal trends. The change point model has proven to be a powerful tool in detection of change over time in a sequence of observations in multiple research fields. In this study, we proposed a change point method to detect changes in AE reporting rates after flu vaccination.

Objectives: To examine temporal tends of reported AEs after flu vaccination using change point models.

Methods: We developed a change point model to detect the time points at which the reporting rate of a given AE changes. To capture the sparsity of events in VAERS data, we used zero-inflated Poisson model to characterize the number of reported events for a given AE during each year. We adapted the standard change model through composite likelihood-based inference to address a unique challenge of VAERS as a passive reporting system in which the study population varies across years. We demonstrate the proposed method using seasonal trivalent influenza virus vaccine (FLU3) in VAERS data (1990–2013).

Results: We extracted 6813 VAERS reports with at least one of the following serious outcomes: death, life-threatening illness, hospitalization, prolonged hospitalization, or permanent disability, which contained 3784 unique preferred terms (PTs). We applied the proposed method to the data and identified 2 PTs ("nuclear magnetic resonance imaging spinal abnormal" and "blood product transfusion") with increased reporting rates between 1990 and 2013, after adjusting for multiple comparison. Currently, most studies focused on general clinical AEs after vaccination. Imaging diagnosed AEs and hemolytic transfusion reactions after flu vaccine are understudied, although a few case reports were published. As VAERS is the front line

for vaccine safety, the signals detected using change point models in this study could provide early warning signals for further investigation.
Conclusions: As a complimentary tool to current signal detection methods for monitoring vaccine safety using VAERS, the change point model can be a useful method to detect potentially important changes in reporting rate of adverse events over time.

931 | A simulation study of the statistical power and signaling characteristics of an early season sequential test for influenza vaccine safety

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Background: The U.S. Food and Drug Administration (FDA) monitors the risk of Guillain-Barré syndrome (GBS) following influenza vaccination in a multilayered approach using Medicare and other data sources. In the 2017–18 season, we modified our near real-time surveillance in Medicare to detect early increases in GBS risk while avoiding false positives.
Objectives: To assess the ability of the Updating Sequential Probability Ratio Test (USPRT) to detect elevated risk in the 8–21 days post-vaccination compared to a historical rate early in an influenza season and the probability that signals accurately identify high GBS risk when high-risk seasons are uncommon.
Methods: We conducted a simulation study using a retrospective cohort design. We used Medicare Parts A and B claims data from the 2012–13 through 2016–17 influenza seasons to identify outpatient influenza vaccinations and primary-coded GBS hospitalized cases in days 8–21 post-vaccination. We simulated 20 different testing schedules using these inputs by varying the USPRT parameters, including the first testing week (between weeks 5–8) and the null hypothesis (1x-3x the historical rate). All testing schedules ended at week 11 as majority of vaccinations are administered by this date, after which regulatory action would have reduced impact. We then assessed the USPRT's power to detect elevated risk of GBS versus a fixed alternative rate (5x-30x the historical rate) and estimated the signal probability and the risk ratio (RR) after signaling when simulations were a mixture of low and high-risk seasons.
Results: We found >80% power to detect a risk 30x the historical rate in week 5 for the 1x null, and in week 6 for the 1.5x-3x null. Nearly all testing schedules had >80% power for a 5x risk by week 11. In simulations with 1% high-risk seasons, for the 1x null 10% of seasons signaled by week 11, which decreased to ~1% with the ≥2.5x null. The distribution of RRs after signaling was concentrated at high values (RR ~16.0 under the 2.5x null versus ~1.4 under the 1x null).
Conclusions: In the 2017–18 season, we specified the USPRT to test continuously from weeks 7–11 using the null hypothesis that the observed GBS rate was 2.5x the historical rate. This testing schedule allows the USPRT to detect a high GBS risk early in an influenza season or a pandemic. The selection of 2.5x the historical GBS rate as the null hypothesis reduces the number of statistically significant results when the risk is unlikely to be high, while maintaining adequate power to detect risk increases that may warrant further investigation.

932 | Adherence to controller therapy in chronic obstructive pulmonary disease: real life setting

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Background: Adherence to controller therapy in Chronic Obstructive Pulmonary Disease (COPD) is low. Insight into the different adherence trajectories and patient characteristics of each trajectory is important to develop target tools to improve adherence to COPD controller therapy.
Objectives: To investigate different patterns of adherence to COPD controller therapy and compare patients characteristics of the identified trajectories.
Methods: A retrospective cohort study (2007–2016) was conducted using electronic primary care data from IPCI (NL) and THIN (UK). COPD was defined as ≥1 disease code and ≥ 2 prescriptions of respiratory drugs in one year. Prescriptions of controller therapy were retrieved by ATC code from patient records. COPD controller therapy consisted of long-acting beta$_2$-agonists (LABA), long-acting muscarinic receptor antagonists (LAMA), corticosteroids (ICS), LABA+ICS fixed dose combination or LABA+LAMA fixed dose combination. Adherence was assessed per month and good adherence was defined as ≥80% of days covered by a prescription. A group-based trajectory modeling (GBTM) technique was applied to model 4 trajectories of adherence to controller therapy in the 2 years following diagnosis of incident COPD. Patient characteristics at baseline were compared between trajectory groups.
Results: In total, 6,022 incident COPD patients (mean age of 66.15 years) in IPCI and 37,315 incident COPD patients in THIN (mean age 67.12 years) were identified. In both databases, adherence to COPD controller therapy were categorized into 4 trajectories namely patients with; a good adherence (26.8% in IPCI; 29.8% in THIN), a poor adherence (34.5% in IPCI; 31.2% in THIN) and an adherence which either decreased (23.9% in IPCI; 25.5% in THIN) or increased (14.8% in IPCI; 13.5% in THIN) during follow-up. Compared to good adherent patients, poor adherent ones were younger, more

frequently smokers, had less severe COPD and suffered more often from depression and gastroesophageal reflux disease.

Conclusions: We identified distinctive adherence trajectories as well as patient characteristics related to these trajectories. Whether knowledge of risk factors of poor treatment adherence will result in improved COPD control needs to be investigated in further research.

933 | Are patients adherent to benzodiazepine treatment? Results of a retrospective cohort study in primary care in Spain

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Background: Data on primary non-adherence to psychotropic medications is still sparse and, in Spain, where the prevalence of use of benzodiazepines is among the highest within the Western countries, it is a matter of particular relevance.

Objectives: To assess primary non-adherence to benzodiazepines or related drugs in a primary care database in Spain, the time elapsing from prescription issue date until first dispensing and factors associated with primary non-adherence.

Methods: A cohort of individuals 18 years or older between 2011 and 2015 were identified from The Spanish Primary Care Database For Pharmacoepidemiological Research (BIFAP) and followed until a first ever e-prescription (written electronically by the primary care physician -PCP- and linked with dispensing data from the pharmacy) for a benzodiazepine or related drug [ATC: N05BA, N05CD or N05CD], death, end of available data or study period. We assessed the proportion of primary non-adherence, defined as failing to fill the new prescription within one year of the issue date (index date), as well as time until first-fill using Kaplan–Meier analysis. We also estimated the proportion of dispensations out of the total number of potential refills calculated based to the PCP's instructions (i.e. duration, dosage and pack size). Multiple logistic regression was used to estimate predictors of primary-non adherence compared with primary adherent patients.

Results: Out of 65,419 patients who received a fist ever benzodiazepine e-prescription, 10,910 (16.7%) were primary non-adherent. Among primary adherent patients (n = 54,509), 95.2% first filled their prescription within 10 days from the issue date and almost 80% were fully compliers (filled all the potential refills). Factors associated with an increased likelihood of primary non-adherence were: young age (18–35 years), high use of healthcare services (within 6 months prior to index date, ≥ 10 PCP visits: OR 1.64; 95%CI 1.51–1.79), benzodiazepine indicated for psychiatric conditions other than depression, anxiety, or sleep disorders, having socio-economic problems, duration of treatment prescribed by the PCP (≥1 year: OR 3.06; 95%CI 2.89–3.23) and not using any other drug concomitantly (OR 1.93; 95%CI 1.83–2.03).

Conclusions: The majority of benzodiazepines' new users in primary care in Spain were early initiators and comply with the whole treatment. Given special attention to individuals with the identified predictors, particularly to the prescribed length of treatment, may help improve primary adherence to benzodiazepines.

934 | Drug refill patterns of suvorexant and other insomnia medications: a US administrative claims database study

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Background: Suvorexant is the first marketed drug in a new category of insomnia medications known as orexin receptor antagonists. Limited data exist regarding refill patterns for suvorexant and other hypnotics.

Objectives: To describe refill patterns and time to discontinuation for new users of suvorexant and other insomnia drugs including zolpidem, temazepam, ramelteon, and low dose doxepin.

Methods: A new user cohort study was conducted using the Optum Research Database with patients having ≥2 prescriptions between January 2015 and September 2017, with ≥12 months continuous enrollment before and after the index date. The primary utilization measure was a drug refill ratio (RR) defined as days' supply/time between prescriptions. Initial and overall RR were defined using time between the index date and dates of first and last prescription, respectively. Baseline characteristics for suvorexant users with a high (≥0.8) RR and low (<0.8) RR were summarized. For the entire sample and for consistent users (with overall RR ≥ 0.8), time to discontinuation was described as the time between the first and last refill date, plus days' supply of the last prescription.

Results: The entire sample included 4,182 suvorexant, 46,400 zolpidem, 15,217 temazepam, 1,144 ramelteon and 183 doxepin new users, with a mean age of 65 years, 59 years, 65 years, 68 years and 58 years, respectively. Compared with zolpidem, suvorexant new users had a higher median (IQR) initial and overall RR of 0.9 (1.1–0.6) vs 0.6 (1.0–0.3) and 0.6 (0.84–0.4) vs 0.3 (0.6–0.2), respectively. The initial RR for suvorexant was comparable to other drugs including temazepam (0.6 [0.8–0.3]), ramelteon (0.7 [0.9–0.4]), and doxepin (0.6 [0.9–0.4]), with similar patterns also seen for the overall RR. For suvorexant new users, those with a higher overall RR were more likely female (70% vs 60%) and had more prevalent psychiatric disorders (e.g. bipolar/mania 14% vs 9%) compared to those with a lower RR. The median (IQR) time to discontinuation was 81.0 (153.3–36.1) days for the entire sample. For those with a high RR (≥0.8), the median (IQR) time to discontinuation was 31.0 (60.9–

25.7), 31.1 (57.7–24.8), 32.4 (65.3–26.1), 29.7 (63.9–23.0) and 28.5 (59.9–22.2) for suvorexant, zolpidem, temazepam, ramelteon, and doxepin, respectively.

Conclusions: Among new users of insomnia medications, the data trend towards more consistent use of suvorexant and other hypnotics compared with zolpidem, with higher median refill patterns for all new users during the initial refill and less frequent use over time. Time to discontinuation was shorter for more consistent users.

935 | Comparative persistence of non-vitamin-K Oral anticoagulants and phenprocoumon in patients with non-valvular atrial fibrillation - results from the reloaded study

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Background: Data on the persistence of factor-Xa non-vitamin-K oral anticoagulants (NOACs) for patients with non-valvular atrial fibrillation in the real-world setting is limited.

Objectives: We aimed to compare the risk of treatment discontinuation of individual NOACs vs. phenprocoumon in Germany.

Methods: We conducted a new user cohort study in patients with non-valvular atrial fibrillation (NAVF) based on German claims data between January 1st, 2013 and June 30th, 2017. A multiple Cox-regression was performed to calculate confounder-adjusted hazard ratios (HRs) for the risk of treatment discontinuation in new users of NOACs (rivaroxaban, apixaban and edoxaban) vs. new users of phenprocoumon. Subgroup analyses were conducted in patients with renal disease, frailty, by age group (<80 vs. 80+ years) and diabetes. As a sensitivity analysis, we assessed the consistency of our results following a stockpiling approach.

Results: The study population with NVAF comprised 22,339 initiators of rivaroxaban, 16,201 of apixaban, 2,828 of edoxaban and 23,552 of phenprocoumon. In the confounder-adjusted analysis, a comparable risk of treatment discontinuation was found for rivaroxaban (HR: 1.04; 95%-confidence interval (CI): 1.02–1.07), and apixaban (HR: 1.00; 0.96–1.03) and a lower risk for edoxaban (HR: 0.81; 0.76–0.86). In patients with renal disease, the risk was decreased for rivaroxaban (HR: 0.82; 0.78–0.87), apixaban (HR: 0.77; 0.73–0.82) and edoxaban (HR: 0.61; 0.53–0.70). Strong risk reductions for NOACs were also observed in frail, older and diabetes patients ranging from 57% to 20%. After allowing for stockpiling, a reduced risk of treatment discontinuation compared to phenprocoumon was also found in the overall population with similar risk estimates for rivaroxaban (HR: 0.82; 0.80–0.85), apixaban (HR: 0.86; 0.83–0.90) and edoxaban (HR: 0.77; 0.70–0.84).

Conclusions: Our study indicates a favorable treatment persistence of NOACs compared to phenprocoumon in NAVF patients with similar effects across individual NOACs. Beneficial effects were most pronounced in patients with renal disease and diabetes, as well as in older and frail patients. In addition, our results highlight the importance of also considering stockpiling in comparative safety and effectiveness studies assessing treatment persistence of NOACs and phenprocoumon as different intake schemes might have an influence on the prescribing patterns.

936 | Reality check: the mismatch of time to bisphosphonate benefit and real world persistence

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Background: Bisphosphonates are used to prevent osteoporosis-related fractures in older persons. Treatment persistence is essential for clinical benefit, with a minimum of 1 year for any benefit to be obtained. Clinical trials of bisphosphonate effectiveness have followed fracture outcomes for up to 3 years. Canadian osteoporosis guidelines suggest a course of at least 5 years of continuous therapy.

Objectives: 1) To characterize long-term persistence with bisphosphonate treatment in the Province of Manitoba, Canada. 2) To examine the relationship between risk factors for osteoporotic fractures and persistence with treatment.

Methods: A longitudinal observational study was conducted using population based administrative health care data from the Manitoba Population Research Data Repository from April 1st, 1998 to March 31st, 2014 to examine persistence with bisphosphonate treatment. Incident users over the age of 40 of alendronate, risedronate, or etidronate were followed until treatment discontinuation. Persons with Paget's disease, renal disease, or cancer were excluded. The primary outcome of treatment persistence was measured using Kaplan–Meier (KM) methods. Cox proportional hazard models were used to examine the association between risk factors for osteoporotic fractures and treatment persistence.

Results: There were 39,251 incident users of bisphosphonates identified. Median age at initiation was 71 years (IQR 62, 80), 89% were female, and 10.7% of users had a history of osteoporotic fractures. Despite treatment with bisphosphonates, only 53% of users had diagnostic codes for osteoporosis in their medical records prior to treatment. KM estimates of persistence at 1, 3 and 5 years were 51%, 30% and 19%. Cox regression found that a diagnosis of osteoporosis was associated with a lower likelihood to discontinue treatment (hazard ratio (HR) = 0.81, $p < 0.0001$), as was being female (HR = 0.84 $p < 0.0001$), while a prior history of osteoporotic fracture was not significant (HR = 1.00 $P = 0.9$).

Conclusions: In order for bisphosphonates to be effective in reducing rates of osteoporotic fracture, 1 year of treatment is necessary

for a small, but statistically significant benefit to be seen. Approximately ½ of users discontinue bisphosphonates with less than a year of therapy. Less than 20% of users meet the current guideline recommendation for 5 years of bisphosphonate treatment. Initial assessments suggest that risk (previous fracture) was not related to persistence. The results suggest greater support and patient-driven commitment may be required to ensure optimal drug duration with bisphosphonates.

937 | The unintended consequences of cost-related medication nonadherence: cancer survivors may substitute less expensive care with more costly services

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Background: Increasing evidence shows that good medication adherence can improve patients' health and reduce health care utilization. However, medication adherence among cancer survivors may decrease for economic reasons, and its impact on health care utilization remains unknown.

Objectives: This study aimed to evaluate the impact of cost-related medication nonadherence on primary care and inpatient/emergency department (ED) services among cancer survivors.

Methods: A retrospective pooled cross-sectional study was conducted using data from the National Health Interview Survey (NHIS) between 2011 and 2017. The measurement of cost-related medication nonadherence was based on a "yes" response of respondents to any of the following survey prompts: "skipped medication doses to save money in past 12 months", "took less medication to save money in past 12 months" or "delayed refilling prescription to save money in past 12 months". Multivariable logistic regressions were used to assess the impact of a self-reported cost-related medication nonadherence on primary care (home health care visits, office visits) and inpatient care or emergency department visits in past 12 months, controlling for demographics, income, health status and insurance related information.

Results: A total of 18,305 cancer survivors were identified out of 705,669 respondents during 2011–2017. Cancer survivors who responded "yes" to the survey prompt, indicating worse cost-related medication nonadherence, had a 6% decrease in home health care visits (OR = 0.94, 95% CI: 0.78–1.13, P = 0.485), and 5% decrease in physician office visits (OR = 0.95, 95% CI: 0.79–1.14, P = 0.567). More importantly, the same patients increased emergency department visits by 75% (OR = 1.75, 95% CI: 1.58–1.95, P = 0.000), and hospitalizations by 20% (OR = 1.20, 95% CI: 1.07–1.35, P = 0.003).

Conclusions: Cost-related medication nonadherence may induce cancer survivors to reduce use of primary care services such as home care visits or physician office visits to save money. Unintended consequences of this response may be poorer health outcomes, and increased use of more costly services such as hospitalizations or emergency department visits.

938 | Patient adherence and persistence to oral targeted therapies for hematologic malignancies: a retrospective cohort study among managed care enrollees

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Background: Existing studies evaluating patient adherence to oral targeted therapies such as tyrosine kinase inhibitors focus on small populations with single malignancies.

Objectives: To evaluate the patterns of use of oral agents in a large population across multiple hematologic malignancies.

Methods: Adult patients diagnosed with a hematologic malignancy and prescribed oral targeted therapy between 2011 and 2016 (N = 18,976) were identified from the MarketScan Commercial Claims and Encounters, and Medicare Supplemental databases. Eligible patients were enrolled in monthly prescription plans 6 months before and 12 months after index date (date of first prescription claim) (n = 2,442). Multivariable logistic regressions were used to determine predictors of adherence using the medication possession ratio (MPR), and persistence through prescription refill gaps.

Results: In total, 2,442 patients were included in the overall cohort, 1,757 in the once-daily (QD) group and 685 in the twice-daily (BID) group. The overall median adherence was 0.9 (MPR $\geq$ 80%) and was comparable between QD and BID groups. In the overall cohort and the QD and BID groups, 59% of patients were persistent at 12 months (gap = 60 days). Patients on QD and BID products did not have significant differences in adherence (fixed interval MPR, odds ratio [OR], 0.94; 95% CI, 0.75 to 1.18) or persistence (OR, 0.93; 95% CI, 0.75 to 1.17) 12 months from index. Significant predictors of adherence and persistence included patient age (18–50 years vs 51–64 years: adherence OR 1.99, 95% CI 1.52 to 2.61; persistence OR 1.54, 95% CI 1.18 to 2.03), total inpatient admissions (0 vs 3+ admissions: adherence OR 0.26, 95% CI 0.13 to 0.47; persistence OR 0.24, 95% CI 0.12 to 0.45), number of adverse events (continuous: adherence OR 0.81, 95% CI 0.76 to 0.87; persistence OR 0.79, 95% CI 0.74 to 0.84) and total hospital visits (0–20 visits vs 41+ visits:

adherence OR 0.49, 95% CI 0.37 to 0.67; persistence OR 0.50, 95% CI 0.37 to 0.67).

Conclusions: Patient-specific clinical factors, rather than regimen-specific factors, were the main predictors of oral targeted therapy adherence and persistence. Adherence to oral targeted therapies appears to be similar for patients on QD and BID regimens in the real-world setting.

939 | Assessment of impact of knowledge attitude & practice on patient medication adherence in asthma patients

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Background: Asthma is a chronic inflammatory reversible disorder which occurs at any age and requires special attention to the management of drug therapy. Assessment of medication adherence is crucial for understanding the patient need and also to assist them with overcoming any non-adherence for the better therapeutic outcome. Hence this study was designed to assess the KAP of asthmatic patients to understand its role in patient medication adherence.

Objectives: Assessment of the impact of KAP on patient medication adherence in asthma patients.

Methods: A randomized, interventional study was conducted in a tertiary care teaching hospital among asthma patients during the period of 10 months. Data were collected using data collection form. Patient's KAP towards their disease was evaluated using a validated questionnaire. GINA scale and ACT questionnaire were used to assess severity and symptoms control. Similarly, medication adherence was assessed using the canister weight method, the pill count method. A checklist was provided to measure the correct inhaler technique. A patient's diary and the education was provided to ensure the adherence and to correct the inhaler technique.

Results: A total of 80 patients out of 90 enrolled patients completed the study. Among them 40% were using Rota-haler in both groups and inhaler with spacer were used by 40% and 37% in test and control group respectively. KAP questionnaire was validated as good by all parameters. A statistically significant P-value (<0.005) was observed in KAP score from baseline to end visit in the test group. Whereas in the control group KAP score was not statistically significant. The similar result was observed with ACT in Test (P-value <0.005) as well as in Control group (P-value = 0.010). The questionnaire of GINA and ACT for assessing the level of asthma symptoms were the same. There was an improvement in Test group in terms of the level of asthma symptoms according to ACT and GINA (33%) with the baseline of 4.4% and end visit of 37.7% of patients, compared to the control group (11.42%). The difference in canister weight was observed more in test group in each follow-up as compared to control group. Whereas in pill count method average number of capsule left was less in test group as compared to control in each follow-up. Average requirement of emergency medication was more in Control as compared to test group.

Conclusions: the study findings concluded that KAP of asthmatics patient has a greater impact on their medication adherence and better treatment outcomes. So, there is a high need for providing the best education to every asthmatic.

940 | Racioethnic and provider specialty differences in adherence trajectories among Medicaid insured children with attention deficit hyperactivity disorder

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Background: Medication adherence among children with attention deficit hyperactivity disorder (ADHD) is known to be strongly associated with patients' race/ethnicity.

Objectives: To examine the racioethnic disparities in adherence trajectories among children with ADHD (6–12 years) and to assess the role of providers' specialty in explaining the disparities.

Methods: A retrospective longitudinal observational study was conducted using 2013–2016 data from a large pediatric Managed Care Plan in Texas that covered more than 400,000 Medicaid enrolled children and adolescents. Children aged 6–12 years with an ADHD diagnosis (ICD-9-CM code 314.XX or ICD-10-CM code F90.9) and a prescription for ADHD were first identified, and of which, those who met the initiation follow-up criteria of the Healthcare Effectiveness Data Information Set (HEDIS) were included in the analysis. The adherence pattern for 300 days after receiving the first ADHD prescription, was examined using group-based trajectory modeling. A multivariable multinomial logistic regression was performed to evaluate the association of race/ethnicity and provider specialty with the adherence trajectory group.

Results: The 3,083 patients who met the inclusion criteria were modeled into 3 different adherence trajectory groups (Complete adherers-4.12%, Rapid decliners/discontinuers-76.35%, and Slow decliners-19.53%). Racial differences across the 3 trajectories were noted. Compared to Caucasians, Hispanics were 3.51 times more likely to be rapid decliners/discontinuers (Odds ratio [OR] 3.51, 95% Confidence Interval [CI] 2.28–5.40); whereas African Americans were 6.41 times (OR 6.41, 95% CI 6.41–11.72) more likely to be rapid decliners/discontinuers and 3.2 times (OR 3.2, 95% CI 1.74–5.91) more likely to be slow decliners, respectively. Further, children who consulted by psychiatrists were 41% (OR 0.58, 95% CI 0.39–0.87) less likely to be rapid decliners/

discontinuers than those who consulted by primary care physicians or others. Children who received combination therapy compared to monotherapy were 94% (OR 0.06, 95% CI 0.04–0.09) less likely to be rapid decliners/discontinuers and 36% (OR 0.64, 95% CI 0.41–0.99) less likely to be slow decliners. There was no interaction effect between race/ethnicity with physician specialty.

Conclusions: There were significant racioethnic and provider specialty differences across patients in different ADHD medication adherence trajectories. However, the racioethnic differences were not associated with the access to mental health specialists.

941 | Adherence trajectories in asthmatic patients

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Background: Adherence to asthma medication is often suboptimal, leading to suboptimal control of the disease. Insight in adherence patterns in real life is important to improve asthma management.

Objectives: To study adherence patterns of inhaled corticosteroids (ICS) using group-based trajectory models and investigate risk factors for poor adherence in asthmatic patients.

Methods: A retrospective cohort study (2007–2016) in asthmatic patients, ≥5 years old in 2 primary care databases: IPCI (NL) and THIN (UK). Asthma was defined as ≥1 asthma disease code in combination with ≥2 prescriptions of respiratory drugs in one year. Prescriptions were retrieved by ATC code from patient records. We used group-based trajectory analysis to model 4 adherence trajectories of ICS within 2 years after asthma diagnosis, for children (5–17 years) and adults (≥18 years) separately. Good adherence was defined as ≥80% of days covered by a prescription. Patient characteristics at baseline were compared between trajectory groups.

Results: In total, 12,524 adults and 3,152 children from the IPCI database and 47,700 adults and 22,807 children from the THIN database were included. In all databases a trajectory of 'high adherent', 'decreasing adherent', 'increasing adherent' and 'poor adherent' patients were observed. In children, 'high adherent' patients were significantly younger and had more often eczema and rhinitis or nasal polyposis than 'poor adherent' patients. In adults, 'high adherent' patients were significantly older, had more often diabetes and GERD, less often rhinitis and were less often smokers than 'poor adherent' patients.

Conclusions: Conclusion: We observed different adherence trajectories with distinct patient characteristics. Targeting patients at risk for poor adherence is important to improve asthma management.

942 | Factors associated with inhaled corticosteroid non-adherence in pregnant women with asthma: a cross-sectional analysis

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Background: Among women prescribed inhaled corticosteroids (ICS) for asthma during pregnancy, non-adherence is common and may have serious consequences for both mother and baby. However, no previous studies have determined specific indicators of ICS non-adherence in this vulnerable group.

Objectives: To identify factors associated with ICS non-adherence in pregnant women with asthma.

Methods: Data utilized comes from three cohort studies (2004–2018, Eastern Australia) involving pregnant women with asthma recruited before 22 weeks of gestation (N = 1443). Demographics, asthma history and current symptoms were assessed and spirometry was performed. Women reported current medication use and number of ICS doses missed in the past week were recorded. Factors associated to ICS non-adherence (20% or more doses missed) were examined using backward step wise logistic regression.

Results: Of the 582 women prescribed ICS, 219 women (38%) were classified as non-adherent. Both adherent and non-adherent women were prescribed a dose of 500 μg [400, 800] a day; yet the actual daily dose in the past week was lower among non-adherent women (180 μg [0, 400] vs 500 μg [343, 800], $p < 0.01$). Non-adherent women were more likely to report season ($p = 0.04$) and work environment ($p = 0.02$) as asthma triggers. Adherent women had better lung function expressed in forced expiratory volume in one second, (FEV_1%) compared to non-adherent women (92.3% [81.4, 99.6] vs 87.9% [77.7, 97.5] p = 0.04). In multivariate analysis, non-Caucasian (OR 2.14, 95%CI 1.12–4.12, p = 0.02) and Indigenous ethnicity (OR 2.53, 95%CI 1.10–5.83, $p = 0.03$) and currently smoking (OR 2.19, 95%CI 1.28–3.74, p < 0.01) were associated with higher odds of being non-adherent.

Conclusions: In order to target ICS non-adherence during pregnancy, strategies that are culturally appropriate and target current smokers are needed.

943 | Patterns of adherence to prescribed opioids: the differential between opioid naïve and opioid existing patients of different age groups

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Background: Opioid prescribing has increased tremendously in the last two decades which concomitantly increased the unwanted consequences such as opioid abuse, misuse and overdose death. Poor adherence to opioid therapy is one of the factors contributing to these problems which are associated with increased healthcare cost. Limited data are available on opioid adherence and whether different age groups play a role in adherence is unknown.

Objectives: This study examined the adherence to opioid therapy in opioid naïve and opioid existing patients of different age groups.

Methods: This retrospective cohort study was conducted using pharmacy databases of tertiary hospital settings in Malaysia from 2011 to 2016. Adult patients aged ≥18 years old receiving at least two opioid prescriptions (buprenorphine, morphine, oxycodone, fentanyl, dihydrocodeine and tramadol) during the study period were included and stratified into opioid naïve and opioid existing pain patient groups. They were followed either until end of study period, discontinuation of therapy or death and were stratified into five age groups (18–40, 41–50, 51–60, 61–80 and ≥ 81 years old). Proportion of days covered (PDC) was used to estimate the adherence to opioid therapy which was calculated by dividing the total number of days covered with any opioids by the number of days in the follow-up period. Patients were considered adherent to opioid therapy if PDC was ≥80%. Factors associated with PDC were examined using the generalized linear modeling. The covariates used were age, sex, type of opioids and opioid daily dose.

Results: A total of 10569 patients with prescribing episodes of 36650 were included in the study. Of these, 91.7% (n = 9696) were opioid naïve patients and 8.3% (n = 873) were opioid existing patients. Adherence to opioid therapy (PDC ≥ 80%) was achieved in 24.5% of naive patients and 19.5% of existing patients. The median therapy of PDC in naïve patients was 35.5% (IQR 10.3–78.7) and 26.8% (IQR 8.8–69.5) in opioid existing patients. Among different age groups, patients in older age group of ≥81 years old (28.1%) were the highest to achieve ≥80% PDC among naïve patients while patients of ages 41 to 50 years old (24.0%) were the highest in the opioid existing patients.

Conclusions: Adherence to opioid therapy was shown in a small group of pain patients. Opioid naïve patients were more likely to adhere to opioid therapy compared to opioid existing patients. Close monitoring is required in opioid existing patients who use opioids for long term as poor adherence may contribute to adverse events of opioids.

944 | Statin adherence and risk of diabetes among the United States Department of Veterans Affairs Hospital Patient Population

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Background: There have been several reports that statin use may increase the risk of developing diabetes mellitus. Since statin therapy is recommended based on cardiovascular risk, confounding by indication is suspected. However, few studies adjusted for pre-statin lab values, or considered objective adherence to statin therapy based on post statin changes in low density lipoprotein.

Objectives: To investigate confounding by indication and non-adherence on the association between statin use and incident diabetes.

Methods: From a random sample of Veterans visiting James A Haley VA hospital In Tampa, FL, between 2007 and 2011 with at least two years of pharmacy records, we selected exposed patients (E) with an incident statin record; or unexposed patients (U) with no statin records. We then restricted patients to those with (1) no ICD code for diabetes mellitus prior to their baseline prescription or with 180 days after; (2) low density lipoprotein (LDL) and glucose measurements within 425 both before and after the baseline prescription. The glucose had to be from a chemistry panel accompanying a lipid panel. Since statins are known to reduce LDL by 30 to 50%, we estimated "statin adherence" by the post minus pre change in LDL and defined Group 1 (non-adherent: decrease less than 10% or an increase); Group 2 (low adherence: LDL decrease 10 to 39.99%) and Group 3 (adherent: LDL decrease by 40% or more) Follow-up data for incident type 2 diabetes mellitus was available through 2014. Risk ratios were estimated by Proc Genmod.

Results: Our final sample consisted of 1587 statin patients (E) and 2170 unexposed patients (U). Mean age was 61.2 and 59.0 and body mass index kg/m2 was 28.9 and 28.5 in E and U respectively. Risk of new type 2 DM after 180 days post baseline prescription was 13.9% and 6.8% in E and U respectively (RR =2.03, p < 0.001). Adjustment for age, BMI and baseline levels of LDL, triglycerides, glucose and creatinine reduced the overall RR slightly (RR = 1.82 [95% CI = 1.44, 2.31]). However, when groups based on LDL change were each compared to U, adjusted RR's were 2.07 (95% CI = 1.57, 2.72) for Group 1 (<10% LDL reduction or increase in LDL); 1.76 (95% CI = 1.32, 2.34) for Group 2; and 0.98 (95% CI = 0.57, 1.69) for Group 3 (≥40%reduction in LDL).

Conclusions: Since statin users with the greatest reduction in LDL have no increased risk of diabetes compared with non-users, it seems unlikely that statin use is responsible for the observed increase in diabetes risk. The increased risk is more likely to be due to unknown or inadequately measured confounders.

945 | Impacts of multi-dimensional interventions on medication adherence among type 2 diabetes mellitus patients in a Nigerian black population

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Background: The mortality and morbidity associated with Type 2 Diabetes Mellitus remains high in Nigeria owing to poor glycemic control. Non-adherence to medication is identified as an important contributing factor. There is a need to explore means of improving medication adherence among this population of patients.
Objectives: To determine the prevalence of medication non-adherence in a population of Type 2 Diabetes Mellitus patients seen in a tertiary health institution in Nigeria.
Methods: A cross-sectional survey over a 2-months period (November and December 2015) of Type 2 Diabetes Mellitus patients attending diabetic outpatient clinic of Lagos State University Teaching Hospital, Lagos, Nigeria who have been on medication for at least one year was done to assess adherence to medication using Modified Morisky Scale (MMAS-8) and Glycosylated hemoglobin (HbA1c). Patients with MMAS-8 score of <80% and HbA1c > 6.5% were considered non-adherent and interventions namely: patient education, counseling and regular medication reminder messages and phone calls were done over a 6 months period. Post interventions adherence evaluation was done. The results were summarized with descriptive statistics and the mean HbA1c compared with Student's Paired T Test using SPSS 20.
Results: A total of 291 patients were studied, 73.2% were female and 77% of the population were above 60 years. 60% of the total respondents were found to be non-adherent. The six months interventions brought about a significant reduction in the mean HbA1c of the non-adherent group (8.1 ± 1.6 vrs 7.1 ± 1.5, $p < 0.01$).
Conclusions: Non-Adherence to medication was high among the studied population and interventions such as patient education, counseling and regular medication reminder messages and phone calls improved adherence and glycemic controls.

946 | Impact of intensity of statin therapy on patients' persistence to treatment: a Scottish population-based study

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Background: Current UK treatment guidelines recommend high-intensity statin therapy (atorvastatin 80 mg) for secondary prevention of cardiovascular disease (CVD). However, information about treatment persistence with this high statin dose is limited.
Objectives: To evaluate persistence with high intensity statin therapy in comparison to moderate and low intensity in patients in Scotland.
Methods: Retrospective cohort study using the Scottish prescribing dataset in linkage with hospitalization records, including patients (≥ 18 years) who initiated statin treatment between January 2010 and December 2015 (index date); statin intensity was defined as high, moderate and low based on current National Institutes for Health and Care Excellence classifications. Persistence was calculated using the anniversary method; logistic regression models, adjusted for age, sex, comorbidity, type of prescribed statin and whether statins were indicated for primary or secondary prevention, were used to determine differences in persistence.
Results: A total of 73,716 patients (mean age 61.4 years, SD 12.6) were identified; the majority of them (n = 65,125, 88.3%) received moderate intensity statin therapy, while 7,163 (9.7%) received high intensity statins. Overall crude 1, 2 and 3-year persistence rates were 69.9%, 63.7%, and 59.2%, respectively; rates differed significantly between intensity levels, being consistently highest among high intensity patients (1 year: 74.7%, 2 years: 68.0%, 3 years: 63.3%). Patients with a diagnosis of ischaemic heart disease, angina, myocardial infarction or stroke during the one-year period prior to the index date (secondary prevention) had considerably higher rates of persistence than patients without recent prior CVD (primary prevention) (high intensity: 1 year 85.5% CVD vs 71.0% no CVD; 2 years: 78.0% vs 64.8%; 3 years: 73.5% vs 60.0%). Adjusted odds ratios for 1 year persistence when comparing high to moderate intensity were 2.94 (95% confidence interval (CI) 1.97–4.34) and 1.41 (95% CI 1.24–1.60) among patients with and without recent CVD, respectively.
Conclusions: High intensity statin therapy was associated with better persistence compared to moderate or low intensity, with almost two thirds of patients in Scotland still on treatment three years after initiation. However, whether this higher persistence translates into better clinical outcomes needs further research.

947 | Post option B+ Programme in Nigeria: schedule adherence among pregnant women with HIV

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Background: Nigeria is responsible for one-third of the global burden of mother to child transmission of HIV (MTCT). Hence, Nigeria is a crucial target in the global effort towards the elimination of MTCT. Adherence to Antiretroviral Therapy (ART) is a primary determinant of treatment success of HIV. In 2013, the World Health Organization (WHO) endorsed Option B+ as the preferred approach for prevention of MTCT in developing countries. Nigeria was the last country to implement Option B+ in 2017.

Objectives: We assessed schedule adherence and the predictors of schedule adherence in pregnant women with HIV under the Option B+ programme in Nigeria.

Methods: A cross sectional approach was adopted that involved dissemination of a standardized survey to obtain information about health behaviors and practices associated with the use of ART among pregnant women in four high-volume HIV treatment sites in Nigeria. Participants were asked how often they had missed taking the medication at the prescribed time. A participant was considered adherent if she had always taken her ART at the prescribed time over the four-day period. Not taking ART at least once at the prescribed time over the four-day period prior to the day of a survey was considered as non-adherent. The ART schedule adherence prevalence proportion was calculated and the bootstrap technique was used to calculate prevalence at 95% confidence intervals (CI). Multivariable logistic regression was used to identify factors independently associated with the primary outcome (ART schedule adherence), using a forward elimination variable selection strategy with $p < 0.10$ inclusion and $p < 0.05$ retention criteria. Model adjusted odds ratios (adjusted OR) and 95% CI were reported.

Results: The survey had a response rate of 92.6%.Of the 275 participants, 29.5% (95% CI: 24.0 to 34.2) self-reported taking ART at the prescribed time in the past 96 hours all of the time. In the multivariable logistic regression analyses, there were positive associations between travel time to the treatment site (OR = 0.5, 95% CI: [0.3 to 1.0], $p = 0.04$) and WHO clinical staging (OR = 0.3, 95% CI: [0.1 to 1.0], $p = 0.05$) with ART schedule adherence. The odds of non-adherence to ART schedule were 2.5 times lower in participants who were diagnosed as a HIV positive before getting pregnant compared with participants who were diagnosed as a HIV positive in their current pregnancy (OR = 2.5, 95% CI: [0.3 to 0.7], $p = 0.002$).

Conclusions: The proportion of women who were adherent to ART schedule was low. In order for Nigeria to be well positioned for elimination of MTCT of HIV, it is crucial that medication adherence is improved during pregnancy.

948 | Antiretroviral treatment non-adherence and virological failure in Côte d'Ivoire: a cross-sectional study

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Background: For people living with HIV (PLHIV), antiretroviral treatment (ART) adherence is essential for achieving an undetectable viral load. However, in West Africa both ART adherence and access to viral load measurement are ongoing challenges.

Objectives: The aims of this study were to describe ART non-adherence and virological failure and to identify factors associated with them in adults living with HIV in Côte d'Ivoire.

Methods: Participants who were ≥ 18 years of age and had been on ART for ≥1 year were enrolled from six HIV clinics. Trained social workers interviewed participants using a standardized questionnaire. Non-adherence to ART in the preceding 30 days was assessed using a visual analog scale. We defined virological failure as a viral load ≥1000 copies/ml. We identified associated factors using multivariate Poisson regressions.

Results: Among the 1,458 participants, 445 (31%) were non-adherent to ART. Participants who were younger, had disease at an advanced WHO stage, with ≥5 ARV pills, living with many people, who consumed alcohol, or had received professional health advice were more likely to be non-adherent. Among participants with viral load measurement available, 268 (18.5%) had virological failure. Participants who were younger, attended a hinterland HIV clinic, not working or working in informal sector, with ≥2 ARV pi**lls**, had a monthly income ≥60,000 FCFA, were hospitalized in the year before the interview, or were non-adherent to ART had a higher risk to have virological failure.

Conclusions: In our study, no ART adherence and virological failure were optimal in PLHIV on ART at least one year and more. In the African context of access limited to ART therapeutic options, innovative strategies should be implemented to improve adherence to treatment and regular monitoring of viral load.

949 | Associations between refill and guideline adherence to lipid-lowering medications and risk of cardiovascular event and mortality among patients with type 2 diabetes in Sweden

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Background: High refill adherence to lipid-lowering medications have been shown associated with lower risk of cardiovascular (CV) event and mortality among patients with type 2 diabetes (T2D). The impact of guideline adherence on patients' risk of CV event and mortality is unclear.
Objectives: To analyze risk of CV events and mortality in patients with T2D i relation to patients' refill adherence to lipid-lowering medications and the treating healthcare centers' adherence to lipid-lowering prescription guidelines.
Methods: Design: Register-based cohort study.
Setting: Swedish adults with T2D who initiated lipid-lowering medication use in 2006–2012.
Exposures: Patients' refill adherence to lipid-lowering medications and the treating healthcare centers' adherence to lipid-lowering prescription guidelines were considered the exposures. Refill adherence was measured using the medication possession ratio (MPR) and was categorized as high or low based on an 80% cut-off. Guideline adherence represented the annual prescription prevalence of lipid-lowering medications in T2D patients with LDL cholesterol above recommended target levels, and was categorized as high or low based on the median, 48% for primary prevention and 78% for secondary prevention.
Main outcome measures: Risk of CV events and mortality was considered the main outcomes.
Statistical analysis: Risk of CV events and mortality was analyzed by refill and guidelines adherence levels for primary and secondary prevention patients separately using Cox proportional hazard regression adjusted for age, sex, socioeconomic status and concurrent medication use as well as clinical- and health-related characteristics.
Results: Compared to high-adherent patients (MPR > 80%), low-adherent patients (MPR $\leq$ 80%) showed higher risk of all outcomes. Among primary prevention patient the increased risk was 44–51% for CV events, 79–90% for CV mortality and doubled risk for all-cause mortality. Corresponding risk for secondary prevention patients were 17–19% for CV events, 66–79% for CV mortality and 88–97% for all-cause mortality. Furthermore, primary prevention patients treated by low-adherent healthcare centers (guideline adherence <48%) showed higher risk of CV events and CV mortality. Otherwise, guideline adherence level showed no impact on risk of CV events or mortality.
Conclusions: Our results demonstrate the importance of high refill adherence to lipid-lowering medications in patients with T2D.

950 | Early discontinuation of antidepressant use by Dutch soldiers

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Background: Soldiers have a higher risk for developing psychiatric disorders that require treatment; often with antidepressants. However, antidepressants as well as the psychiatric disorder, may influence military readiness in several ways. In the general population, early discontinuation of antidepressant treatment is often seen. It is yet unknown whether this occurs to a similar extent in soldiers.
Objectives: to evaluate discontinuation of antidepressant use by Dutch soldiers in the first 12 months after start and determinants thereof.
Methods: Data was obtained from the military pharmacy. All Dutch soldiers who started using an antidepressant between 2000 and 2014 were included. Kaplan Meier curves were constructed to estimate the discontinuation rate over time and the influence of each determinant on discontinuation rate was estimated using Cox regression.
Results: 25.9% of the 2479 starters had discontinued their antidepressant use after one month; after three and six months this number increased to 52.7% and 70.3% respectively. Early discontinuation was higher in soldiers who received their first prescription from a neurologist or rehabilitation specialist (HR 1.85, 95% CI 1.55–2.21, HR 2.66 95% CI 1.97–3.58). In addition, early discontinuation was lower in soldiers who were prescribed serotonin reuptake inhibitors and other antidepressants (HR 0.57, 95% CI 0.51–0.60, HR 0.63, 95% CI 0.55–0.73), in soldiers between 40 and 50 years of age (HR 0.79, 95% CI 0.70–0.89) and when the antidepressants was prescribed by a psychiatrist (HR 0.84, 95% CI 0.77–0.92).
Conclusions: More than half of the soldiers discontinued their prescribed antidepressant within 6 months.

951 | Risk minimization effectiveness for Mirabegron in the Netherlands, Spain, UK and Finland

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Background: In September 2015, a Direct Healthcare Professional Communication (DHPC) letter was disseminated as a risk minimisation measure for mirabegron in the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency. Mirabegron is contraindicated in patients with "Severe uncontrolled hypertension defined as systolic blood pressure $\geq$ 180 mm Hg and/or diastolic blood pressure $\geq$ 110 mm Hg".
Objectives: To assess the effectiveness of the DHPC as a risk minimization measure by quantifying the proportions of mirabegron initiators with documented hypertension (severe or non-severe, uncontrolled or controlled hypertension) and the

frequency of blood pressure recordings before and during mirabegron treatment, relative to DHPC dissemination.

Methods: An observational cohort study using real-world data from the PHARMO Database Network (Netherlands), SIDIAP database (Spain), CPRD (United Kingdom, UK) and the national healthcare registers and electronic medical records from Finland. Data sources were selected based on uptake of mirabegron and availability of linked prescription and blood pressure data. Mirabegron initiators were identified from December 2012 until December 2016. Hypertension status was assessed at initiation based on hypertension diagnoses or treatment and blood pressure records.

Results: The study population comprised 52,291 patients. Severe uncontrolled hypertension was uncommon in all data sources: pre-DHPC overall proportion was 0.49% (145/29,799). Post-DHPC proportions were lower than pre-DHPC in the Netherlands (0.61% pre-DHPC, 0.26% post-DHPC, $p = 0.053$), similar in Spain and UK and higher in Finland (1.05% pre-DHPC, 1.60% post-DHPC, $p = 0.022$). For non-severe uncontrolled hypertension, post-DHPC proportions were lower in the Netherlands (15.84% pre-DHPC, 13.80% post-DHPC, $p = 0.038$), tended to be lower in Spain (12.54% pre-DHPC, 11.38% post-DHPC, ($p = 0.071$), and did not differ in the UK or Finland. Blood pressure values at mirabegron initiation were available for 29%–56% of patients across data sources. More frequent monitoring was observed in mirabegron users with hypertension than with normal blood pressure, whereas no difference was observed between post-DHPC and pre-DHPC.

Conclusions: Severe uncontrolled hypertension is uncommon among mirabegron initiators, reflecting the low population prevalence and suggesting that current labelling works well with respect to minimizing risks in this population. This study did not suggest further risk reduction or evidence of improved blood pressure monitoring following DHPC dissemination.

952 | Considerations when applying a structured benefit–risk assessment to drug delivery combination products

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Background: Structured benefit–risk assessments (BRA) using frameworks such as the CIRS-BRAT or PROACT-URL have been evaluated for use primarily with drugs. Applying the BRA to drug delivery combination products (DDCP) can lead to different challenges than when used for a drug alone.

Objectives: To identify specific considerations when applying the CIRS-BRAT framework to a DDCP compared with a drug alone using a triptan example.

Methods: The CIRS-BRAT framework includes defining a decision frame (including population, timeframe, and choice of comparator), identifying key benefits and risks, gathering and assimilating relevant data, and generating visualizations to communicate the results of the assessment. Unique considerations for each step in the application of the framework were identified to determine whether modification would be needed when applied to DDCP.

Results: The published drug-only triptan example used an active comparator and timeframe within 24 hours. Key benefits were reduced pain, decreased sensitivity to light, reduction in functional disability, and reduction in nausea and vomiting. Key risks included transient triptan sensations, central nervous system adverse events, and chest-related adverse events. When considering BRA for iontophoresis as DDCP with a triptan, the decision frame remained the same, although special consideration should be given in population and comparator selection. Improved quality of life due to the convenience of DDCP was identified as a new benefit outcome, and skin burn was identified as a new risk outcome. In this instance, where DDCP impacts patient convenience, patient preference data could be important to include in a BRA.

No differences in the framework were necessary for identification and extraction of source data nor for customization of the framework, though device-specific regulatory documentation could be useful when considering new benefits and/or risks associated with a device. Additionally, weighting via patient preferences could be applied. Display and interpretation are no different.

Conclusions: The CIRS-BRAT framework can be followed for DDCP, as noted in this triptan example, although additional considerations related to comparator, population, patient preferences, and timing may be more challenging to resolve compared with conduct of a BRA with a drug alone.

953 | Effectively communicating small probability drug risks to patients, a systematic review

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Background: Adequate patient understanding of the benefits and risks of drug treatments is vital for informed decision-making. Many patients, however, have a limited grasp of probabilistic concepts and hence are unable to accurately make such an appraisal. This challenge is especially acute in instances where the risks are severe but of low probability (<5.0%).

Objectives: The aim of this study was to review the research literature on different approaches to conveying small risk probabilities to patients to determine which methods have been found empirically to be most effective.

Methods: This review was conducted according to PRISMA guidelines. Pubmed, PsychINFO, Cinahl, and Embase databases were searched systematically for drug risk communication studies that assessed approaches to conveying drug risk probabilities to lay audiences. Studies which focused on small probabilities, or both small and large probabilities, were eligible for inclusion. The systematic review covered scientific research published between 1998 and 2018. The following keywords (and its variations) were used in the search: risk perception, risk communication, risk–benefit communication, benefit–risk communication, risk literacy, risk assessment, absolute risk, decision making, decision model, numeracy, natural frequency, icon array. Two reviewers independently reviewed the studies identified in the resulting literature search and identified those which involved testing of approaches to conveying small, or small and large, drug risk probabilities.

Results: Forty-four studies meeting inclusion criteria were identified and reviewed. Of these, 5 (11%) involved small probability risks. A combination of numerical information and visual aids was shown to improve patient risk understanding as compared to numerical information or visual aids alone. However, study findings were limited by the fact that majority of studies reviewed had small sample sizes and involved demographically homogeneous populations. Though there were 39 studies that included both small and large probability risks, these did not specifically evaluate small probabilities as different entities and did not specify how risk/benefit communication differed between the two probability types.

Conclusions: A combination of both numeric and visual formats are the most effective for conveying small probability risks to patients and other lay audiences. However, further research is needed and how best practices might differ from that of large risk drug probabilities.

954 | Are the risk minimization measures for diclofenac effective? A pre-post comparison based on German claims data

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Background: Since 2013—after a review of non-steroidal anti-inflammatory drugs by the European Medicines Agency—systemic diclofenac has been contraindicated in persons with certain cardiovascular diseases such as ischemic heart disease, peripheral arterial disease, and cerebrovascular disease throughout Europe. To date, the impact of these risk minimization measures has not been investigated.

Objectives: To compare diclofenac use before (2011) and after (2014) implementation of risk minimization measures, focusing on diclofenac initiators and the prevalence of ischemic heart disease, peripheral arterial disease, and cerebrovascular disease (i.e., new absolute contraindications [new CIs]) in these patients.

Methods: Using the German Pharmacoepidemiological Research Database (GePaRD) containing claims data of ~17% of the German population, we included all individuals aged ≥18 years with health insurance coverage on January 1, 2011 (cohort 2011) or January 1, 2014 (cohort 2014) and during a one-year pre-observation period for each cohort. Within each cohort, we identified diclofenac initiators, defined as persons with an outpatient prescription of systemic diclofenac in 2011 (cohort 2011) or 2014 (cohort 2014) but without any dispensation of diclofenac in the preceding year. We also identified persons with ≥1 new CI during the respective pre-observation periods. For each cohort, we calculated age-standardized proportions of persons initiating diclofenac in the entire cohort and among persons with new CIs and we determined the proportion of diclofenac initiators with ≥1 new CI.

Results: Each cohort comprised >10 million persons. Between 2011 and 2014, the proportion of persons initiating diclofenac decreased by 29% (from 8.2% to 5.8%) among females and by 26% (from 8.5% to 6.3%) among males. Among persons with ≥1 new CI, the decline between 2011 and 2014 was higher compared to the entire respective cohorts, but the difference was less than 5 percentage points (decline by 33% in women and by 30% in men). The proportion of diclofenac initiators with ≥1 new CI did not change between 2011 (11.7%) and 2014 (11.5%).

Conclusions: While our study found an overall decline of about 30% in diclofenac initiation between 2011 and 2014, this trend was largely independent of the presence or absence of new CIs, suggesting that physicians are unaware of new absolute CIs. The proportion of diclofenac initiators with a new CI remained at a high level (at least one in ten patients), demonstrating the need for research at the prescriber level (e.g., interventional studies) and further measures to improve patient safety.

955 | Differences among parents when weighing benefits and risks of potential treatments to delay insulin dependence in Type-1 diabetes in children

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Background: Type-1 Diabetes (T1D) onset can be predicted based on the presence of autoimmune biomarkers identified via screening. Treatments under development may offer a delay in T1D insulin

dependence; however, little is understood about patient or parent perspectives about the acceptability of these treatments.

Objectives: To investigate parent preferences, and preference heterogeneity, for treatments that delay the onset of T1D insulin dependence in children at risk of disease progression.

Methods: A discrete choice experiment survey using an online research panel assessed the preferences of U.S. parents told to assume one of their children (<18 years) would become insulin dependent within 2 years. Respondents were offered a series of 8 choices between 2 hypothetical treatments that would delay insulin dependence or no treatment (monitoring only). Treatments were defined by 6 attributes with varying levels (years until insulin dependence, reductions in the risks of long-term health complications, diabetic ketoacidosis, serious infection, injection site reaction, and nausea). Random parameters logit analysis provided the relative importance of benefits and risks. Latent class analysis was used to assess preference heterogeneity.

Results: For parents of children without T1D (n = 901), delaying insulin dependence, reducing risk of long-term health complications, and serious infection were the most important treatment attributes. These were also the 3 most important for parents of children with T1D (n = 600), in addition to reducing the risk of diabetic ketoacidosis. However, there was preference heterogeneity and 3 distinct classes of preferences. Class 1 (57% of sample) valued the benefits most highly, traded off among all treatment benefits and risks. Class members were more likely to have a college education, higher self-reported numeracy, and a child without T1D. Class 2 (23%) favored monitoring only and placed higher importance on avoiding treatment risks. Class 3 (20%) had disordered preferences, with membership predicted by Medicaid or no insurance, male gender, having a child with T1D, and failing comprehension questions.

Conclusions: Parents' preferences for treatments to delay T1D insulin dependence were heterogeneous, with some focusing on benefits and others on risks, while a third group answered inconsistently. Heterogeneity of preferences expressed over the benefits and harms in this survey provide guidance on what benefit–risk tradeoffs may be acceptable, and to whom, in future treatments to delay T1D insulin dependence.

956 | Assessment of colobreathe risk minimisation measures in the European Union: a cross-sectional study

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Background: Due to the potential safety concern of cough associated with the Colobreathe® (colistimethate sodium (CMS)) and Turbospin inhaler and potential medication errors due to inappropriate handling of the device, the product was approved with a requirement for additional risk minimisation measures (aRMM). Following reports of throat irritation or coughing as a result of capsule breakage in 2014, the instructions for inhaler use were revised and enhanced.

Objectives: The objective of this study was to assess the effectiveness of the aRMM, including the knowledge, receipt, and utilization of CMS educational materials by HCPs and patients/caregivers, knowledge regarding common side effects, and correct use of CMS and Turbospin inhaler.

Methods: A cross-sectional study was conducted using survey questionnaires for HCPs and patients/caregivers. The pre-tested questionnaires were designed to assess the knowledge, receipt, and utilization of CMS educational materials. Knowledge of common side effects and correct use by HCPs and patients/caregivers was also assessed.

Results: Of 124 HCPs surveyed, the majority of HCPs acknowledged awareness (86%; 95% CI 78.6–91.9%), receipt (91%; 95% CI 83.6–95.8%), and utilization (82%; 95% CI 71.9–89.1%) of the CMS educational materials and had knowledge of the 4 common side effects associated with CMS (93%; 95% CI 87.0–97.0%). Most HCPs correctly answered questions regarding the proper use of CMS (>90%),yet, awareness of the potential for capsule breakage was moderate (68%; 95% CI 58.1–76.0%). Of the 29 patients surveyed, almost half of patients/caregivers surveyed were aware of the educational materials (48%; 95% CI 28.7–68.1%); of those, 69.2% received the materials and they all utilized them. Most patients/caregivers had knowledge of common side effects associated with CMS (82%; 95% CI 61.9–93.7%); however, awareness of the potential for capsule breakage was low (48%; 95% CI 28.7–68.1%).

Conclusions: The majority of HCPs had a high level of awareness regarding the minimization of the potentials risks of CMS by proper use. While the sample size was small, patient/caregiver's knowledge of potential risks associated with CMS use and proper use of the Turbospin inhaler appeared high.

957 | Prevalence of antibiotic use, knowledge and attitudes towards antibiotic-free meat, Pennsylvania — 2016

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Background: Antimicrobial resistance is a major threat to human health worldwide. Inappropriate use of antibiotics in humans and agriculture fuels emergence of resistance. Understanding public's knowledge and attitudes can inform interventions to promote judicious use of antibiotics.

Objectives: Assess public knowledge about antibiotics, prevalence of prescriptions and attitudes towards antibiotic-free meat.

Methods: In 2016, a weighted probability sample (n = 6,810) of Pennsylvania adults was asked questions about antibiotic prescriptions and attitudes towards antibiotic-free meat as part of state-specific module in the national Behavioral Risk Factor Surveillance System (BRFSS).

Results: Among Pennsylvania adults, 40.9% (95% confidence interval [CI], 39.2%–42.6%) responded that they had been prescribed antibiotics in the previous 12 months and 6.2% (95% CI, 5.0%–7.7%) of these adults reported that they had persuaded their providers to prescribe these drugs. Asthmatic adults were significantly more likely to report receiving antibiotics (59.0% (95% CI, 53.6% - 64.3%)) than non-asthmatic adults (38.6% (95% CI, 36.8%–40.4%)) as were diabetic (55.1% (95% CI, 50.2%–60.0%)) versus non-diabetic (39.1% (95% CI, 37.3%–40.9%)) adults. Females were more like than males to have been prescribed antibiotics (45.1% of females (95% CI, 42.7% - 47.4%) vs. 36.3% of males (95% CI, 33.8% -38.8%)). Of respondents, 25.2% (95% CI, 23.6%–26.9%) thought that antibiotics are always appropriate to treat non-bacterial illnesses (e.g., cough or cold). Although knowledge varied by demographic characteristics, it increased with education and income and was lowest among adults with chronic illnesses (e.g., asthma, diabetes). Additionally, among males, younger adults (18–29), 32% (95% CI, 27.8%–37.1%) also thought that antibiotics should be used to treat viral illnesses as did 27.7% (95% CI, 21.1%–35.5%) of uninsured Pennsylvanians. Overall 42% (95% CI, 40–44%) of the survey participants reported that that they try to purchase antibiotic-free meat. This preference was higher among females (48.8% (95% CI, 46.0%–51.5%)) than males (34.8% (95% CI, 32.1%–37.7%)).

Conclusions: Inappropriate prescriptions in ambulatory care settings and deficiencies in the public's knowledge about ineffectiveness of antibiotics to treat viral infections call for simultaneous interventions among clinicians and patients. To promote judicious use of antibiotics in food animals, additional One Health measures are needed to engage consumers and to address their expectations and preferences.

958 | Assessment of the effectiveness of risk evaluation and mitigation strategies for Dulaglutide: 18- and 36-month prescriber surveys

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Background: The anti-diabetes medication dulaglutide (Trulicity®) had a Risk Evaluation and Mitigation Strategy (REMS) in the U.S. to ensure the benefits of the drug outweigh the risk of pancreatitis and the potential risk of medullary thyroid carcinoma (MTC). The REMS consisted of a communication plan whose elements included a healthcare provider (HCP) letter, an HCP factsheet, and a website.

Objectives: To assess the effectiveness of dulaglutide REMS at 18- and 36-months post-launch.

Methods: Validated web-based surveys were administered to 401 HCPs who have prescribed dulaglutide to at least one patient in the U. S. Two waves of surveys were initiated at 18 months (n = 201) and 36 months (n = 200) after product launch to evaluate HCP awareness of REMS key safety messages of informing HCPs about the risk of pancreatitis and the potential risk of MTC; appropriate patient counseling; discontinuing dulaglutide and ordering confirmatory tests when pancreatitis is suspected; and further evaluating dulaglutide users upon physical, imaging, or laboratory findings pertaining to the thyroid. Survey instruments collected information regarding demographics, clinical practice setting, and the safety messages above. Descriptive univariate analyses were performed. The REMS program is considered effective if the majority of HCPs demonstrated awareness of the key safety messages communicated.

Results: Participants were a reasonable representative sample of dulaglutide prescribers in the U.S. (50% endocrinologists, 40% primary care physicians; 7% nurse practitioners; and 3% physician assistants). Overall, about 27% of HCPs were aware of dulaglutide REMS program (30% in the 18-month survey and 24% in the 36-month survey), which is consistent with most REMS programs. Awareness of dulaglutide prescribing information and medication guide was higher than awareness of REMS components (88% and 62%, respectively). Majority of HCPs who received the REMS letter or REMS factsheet reported they have read all or some of them. Approximately 97% of HCPs were familiar with dulaglutide indications and limitations of use. Most of HCPs were aware of the risk of pancreatitis and the potential risk of MTC with dulaglutide (93% and 88%, respectively). HCP knowledge scores of corresponding risks by survey wave were 95% and 86% for the 18-month survey, and 91% and 90% for the 36-month survey.

Conclusions: The surveys showed that dulaglutide REMS program was effective in communicating the key safety messages, and as a result, the U.S. Food and Drug Administration has determined a REMS is no longer required for dulaglutide.

959 | Characteristics of risk evaluation and mitigation strategies (REMS) assessment plans: a review of REMS with ETASU (2014–2018) using RE-AIM

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Background: The recently published FDA draft guidance for industry on REMS assessments (2019) "encourages applicants and the research community to develop novel methods for assessing REMS ⋯ [to] help advance the science of post-market assessment of effectiveness of risk mitigation strategies." One such method is RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance), an implementation science framework that has been widely applied to evaluate health interventions (Glasgow, et al 2013) and is a recognized standard used by the National Institutes of Health.
Objectives: To characterize REMS assessment plans using RE-AIM and identify areas for advancing methods for evaluating REMS programs.
Methods: A review of REMS assessment plans was conducted for REMS programs approved by the FDA between 1/1/2014–12/31/2018. REMS assessment plans were eligible if they were: (1) for a new drug application (NDA) or a biologic license application (BLA), (2) included elements to assure safe use (ETASU), and (3) were not part of a shared system. Publicly-available approval letters through REMS@FDA were the source of information. Three reviewers calibrated the application of RE-AIM dimensions to each REMS assessment item using three randomly-selected assessment plans (Agreement = 75%). Discrepancies were discussed and resolved. Each assessment plan was adjudicated and assessed for gaps in RE-AIM dimensions.
Results: The median number of assessment items per REMS was 31 (IQR: 21–36). The distribution of items per RE-AIM criteria per REMS was: Reach (median = 2 (IQR: 2–4); Effectiveness (median = 2.5 (IQR: 1–4); Adoption (median = 3.5 (IQR: 2–5); Implementation (median = 18 (IQR: 14–24); Maintenance (median = 0 (IQR: 0–1). Adoption (among prescriber, health system agents of implementation) was often more commonly assessed than Reach (population-attributable number of patients affected). Assessment of heterogeneity of Adoption and Reach was generally absent. Implementation assessment items were most prevalent for drugs required to only dispense or administer the drug with evidence of safe-use conditions (ETASU D). Effectiveness (patient-level) and Maintenance assessments were most common among drugs that required patient monitoring (ETASU E).
Conclusions: Implementation science frameworks, such as RE-AIM, can be applied to characterize REMS assessment measures and identify opportunities for standardizing and strengthening their evaluation. Methods to measure Maintenance are needed to provide real-world evidence of their integration into the healthcare system.

960 | Evaluation of the effectiveness of risk minimisation measures targeting physicians on prescribing practices of thiocolchicoside containing medicinal products for systemic use

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Background: In 2014, risk minimisation measures (RMMs) concerning thiocolchicoside (TCC) for systemic use were requested to be implemented in all European countries marketing the product following an Article 31 Referral procedure. A direct healthcare professional communication (DHPC) and educational materials (EMs), were distributed to health care professionals to increase awareness related to genotoxicity risk.
Objectives: This study aimed to measure the effectiveness of RMMs, by ascertaining the proportion of targeted physicians who understood and implemented the latest prescribing conditions and safety information about systemic thiocolchicoside provided in the DHPC and EMs.
Methods: A cross-sectional web-based survey of prescribers of systemic thiocolchicoside was conducted in France, Greece, Italy and Portugal in 2017. Sampling targets for responding physicians were determined based on country specific prescribing patterns. Frequency of correct responses was calculated for six knowledge questions and information related to recent patients' prescriptions of TCC was analyzed. Results were provided overall, by country and by physician type (general practitioners, rheumatologists, orthopaedists-orthopedic surgeons).
Results: The recruitment rate (completers/eligible) was 71.4%. Among 651 responding physicians, 68.6% remembered having received either the DHPC or the EM or both. Knowledge was the highest for contra-indications to the use of systemic thiocolchicoside, related to patients' age (85.0%), pregnancy (87.6%), and lactation (80.3%) and was lower (49.1%) regarding restriction of use in women of childbearing potential not using contraception. Overall, knowledge of the right indication for use of systemic thiocolchicoside was 63.2%, while knowledge of dose and duration of treatment was higher for the oral form (78.9%) than for the injectable form (55.4%). These results were confirmed by the analysis of recent patients' prescriptions. Knowledge varied by physician specialty and country and was higher for physicians who reported receiving either the DHPC or the EM or both (p = 0.002).
Conclusions: This study revealed geographical as well as across prescribers' specialty contrasts in the knowledge of TCC RMMs. In addition, the results showed that when risk minimisation materials (DHPC and EM) receipt was acknowledged by physicians, it significantly improved their knowledge and attitude towards appropriate systemic TCC prescribing to patients.

961 | Patient registries - has the European medicines agency patient registry initiative had an impact on post-authorisation mandates?

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Background: In 2015, the European Medicines Agency (EMA) put forward an initiative on using data from patient registries to support the benefit–risk evaluation of medicinal products pre- and post-authorisation. One of the main aims of this initiative is to foster collaboration between potential users of registry data such as between pharmaceutical companies and registry holders within healthcare professional and patient associations, academia and other institutions.

Objectives: This research will describe the current situation of industry-funded registry studies and to what extend industry is collaborating already with academia or other institutions. This research will also explore trends in collaboration between the industry and registry holders for EMA mandated post-authorisation studies associated with the roll-out of the EMA patient registry initiative.

Methods: Clinicaltrials.gov was searched for registry studies funded by pharmaceutical companies and conducted in collaboration with regulators, academia, or other organizations. A study was considered a company-funded registry when it was classified as a patient registry within the database, contained the term "registry" in the study records or in the study title, had a prospective time perspective and was labeled as industry-funded. All registries first posted between 2014 and 2018 were included. The EU PAS register was searched for EMA requested studies with the term "registry" in the title and reviewed for collaborations.

Results: Clinicaltrials.gov lists 146 (36%) industry funded registries which are conducted in collaboration with academia or other organizations. Most of the studies are single-country studies of which 58% are conducted in Europe. 95 (65%) were first posted after 2015. 53 industry funded registries requested by the EMA are currently registered on the EU PAS register. 13 of those studies are conducted in collaboration with national or regional registries or registry networks of which 7 started after 2015.

Conclusions: There is a close collaboration between industry and academia on a country basis in conducting registries for a specific product or disease. Collaboration of industry with registry holders in order to reduce the initiation of new studies is only seen sporadically, and there is only little impact on post-authorisation mandates so far. As one of the results of the patient registry initiative, specific collaborations are being established for rare diseases and new therapies such as cell-based therapies.

962 | Medical benefit–risk assessment: Creating the value-tree an experience from six case studies

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Background: In the past decade, there has been an increased focus on structured benefit–risk (BR) assessment approaches and methods to facilitate regulatory decision making on medicines. The medical BR decision-making problem typically involves multiple conflicting objectives. A key consideration is establishing a sound set of criteria to evaluate the decision problem. A useful tool when identifying and visualizing the criteria for BR assessment is using a value-tree.

Objectives: To identify challenges related to creating the benefit–risk value-tree and to propose ways to address these challenges.

Methods: This study is based on six case studies from the IMI PROTECT project work package 5 - Benefit–risk integration and representation (PROTECT BR group). Data on value-tree creation in relation to the BR methods BRAT, MCDA and/or SMAA, were extracted from case study reports, associated supplemental material and peer-reviewed publications. A data extraction form was developed to retrieve information on the value-tree creation in the source material. The value-trees iterations were compared in terms of; changes in criteria, sub-criteria and outcome definition, together with the reasons for these changes. In addition, the final value-trees were assessed in relation to the basic properties; completeness, operationality, non-redundancy, and minimisation.

Results: Case study teams include medical specialists, statisticians and decision scientists. All six case studies were retrospective. Five case studies used a bottom-up approach in creating the value tree. For all case studies, value tree creation was an iterative process, where definitions of objectives were strongly informed by available data. Across all six case studies, three major challenges were identified: issues with double counting, completeness, and preference inconsistency. The issues often arose due to problems with data availability.

Conclusions: Regardless of the actual benefit–risk assessment methodology that was used, the main challenges in the value tree creation, in all six case studies, relates to data availability and accessibility. These challenges should be addressed before implementation in daily regulatory practice.

963 | Direct healthcare professional communications: Awareness, effectiveness and distribution preferences in Saudi Arabia

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Background: Direct Healthcare Professional Communication (DHPC) is one of the risk minimization measures that is used to inform healthcare professionals (HCPs) about the newly identified risks of approved medicinal products. Measuring the effectiveness of DHPCs is important to ensure that this tool is successful in mitigating certain risks.

Objectives: To measure the awareness, effectiveness and distribution preferences regarding DHPCs among HCPs in Saudi Arabia.

Methods: A descriptive cross-sectional study was conducted in Saudi Arabia in 2017. It employs a short online survey that is distributed randomly to practicing HCPs.

Results: A total of 166 HCPs participated in the survey; 46% physicians, 44% pharmacists and 10% Nurses. The majority of HCPs (86% physicians, 71% pharmacists and 88% nurses) have never heard of DHPC letters previously. Most physicians who read the letters agreed that DHPCs' content has influenced their practice (75%). In assessing preferences, 83% of respondents showed interest in receiving future DHPC letters. Furthermore, the most preferred channel of communicating DHPC letters among healthcare professionals was through e-mail (67%) and from the Saudi Food and Drug Authority (45%).

Conclusions: HCPs in Saudi Arabia have limited knowledge about DHPCs. On the other hand, HCPs who had received DHPC letters acknowledged the importance and impact of this risk minimization tool on their knowledge and practice. Further research to elucidate reasons for lack of access to DHPC letters is warranted.

964 | Applying CIRS-BRAT framework in a regulatory setting: Updated benefit risk assessment for fibrinogen concentrate in the setting of complex cardiac surgery

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Background: Fibrinogen concentrate (FCH) has been successfully used in perioperative bleeding in complex cardiac surgery (CCS), as reported in several single center trials; a global, multicenter randomized clinical trial did not show efficacy superiority over placebo, while the safety endpoints were favorable to FCH. As part of the 2015 periodic safety update report (PSUR) submitted to the European Medicines Agency (EMA), the sponsor conducted a benefit–risk assessment (BRA) using the CIRS-BRAT framework, to evaluate the evidence for the use of FCH in cardiac surgery. The EMA agreed that the benefit–risk profile was favorable and requested an update of the BRA for the 2018 PSUR.

Objectives: To update the benefit–risk profile of FCH in the clinical setting of CCS taking into account all published evidence and completed clinical trials as of April 2018.

Methods: The CIRS-BRAT framework was followed to establish the decision frame, identify key benefits and risks and gather and interpret data. and produce visualizations to display the results. An updated systematic literature review was conducted to identify new studies published since the original BRA. Forest plots were generated to show the benefits and risks of FCH compared to placebo or standard of care in randomized and observational studies by key benefits and risks, by study, and by crude pooled analyses of identified placebo-controlled clinical trials.

Results: The original BRA included 6 studies and the updated literature search identified 1 new randomized clinical trial and 1 new observational study that met criteria included in the decision frame. The updated BRA showed that the evaluated benefits (avoidance of allogeneic blood product transfusion within 24 hours, survival at 30 days and avoidance of re-operation due to bleeding) favored FCH in most studies. For the risk outcomes, in all studies the point estimates for TEEs and anaphylactic and hypersensitivity reactions were similar in the FCH and comparator groups. The benefit–risk profile of FCH in the setting of complex cardiac surgery was determined to still be favorable.

Conclusions: The use of a structured approach (CIRS-BRAT framework) facilitated assessment of a large volume of information in a complex setting, including both randomized trials and observational studies. The favorable benefit–risk profile of FCH in the setting of complex cardiac surgery was reconfirmed.

965 | Impact of European benefit–risk reassessment procedures on drug prescribing practices in Denmark

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Background: Since the implementation of the new Pharmacovigilance legislation (2012), the Pharmacovigilance Risk Assessment Committee (PRAC) became responsible for the assessment of safety-related referrals (i.e. reassessments of the Benefit–Risk balance of a (class of) medicine(s) in the EU.

Objectives: To determine the public health impact of safety referral assessments performed by PRAC in terms of intended and unintended consequences on drug utilization.

Methods: We created a cohort of PRAC safety referrals (Jul 2012-Sep 2017), and collected from information published on the EMA website: type, urgent (y/n), start date, ATC, authorisation pathway. Procedures were followed up until PRAC recommendation, which was categorized as suspension/revocation, general warning, drug–drug interactions

(DDI), restricted population, monitoring, safety confirmed (not mutually exclusive). Quarterly rates (Q1–2013 to Q3–2018) of drug utilization per 10000 inhabitants in Denmark were calculated (DDDs from the DK Health Statistics/population size from Statistics DK), and by consensus it was determined whether prescribing decreased (y/n). Multivariate logistic regression was used to determine the factors associated with decreased use.

Results: 45 safety referrals were started, of which 4 had not received PRAC recommendation by Sep 2017 and 1 concerned a broad class referral of RAS-acting agents, leaving 40 procedures for inclusion. Most referrals concerned nervous system products (17.5%), followed by products for blood and blood forming organs, musculoskeletal disease, respiratory disease and genito-urinary disease (all 12.5%). Average time to PRAC recommendation was 247 days. 20 products were excluded for impact analyses, as they were not marketed in DK, hospital use only, OTC products, or use was too low (<1/10000). For the 2 referrals, where all products were recommended to be withdrawn from the market, drug use decreased just for one; in the other case, the recommendation was not endorsed by CHMP. Of the remaining 18 referrals, drug use decreased for 9 (50%). None of the studied indicators was significantly associated with decrease in use. Recommendations to avoid DDI and those to monitor patients showed a slight trend towards decreased used after the referral.

Conclusions: For half of the referrals drug utilization of the products under investigation decreased. However, for a subset of referrals this was not in line with the PRAC recommendations and can be regarded as an unintended consequence. For those where usage decreased it is also uncertain whether it were the right patients that stopped using the drug.

966 | Do conflicts of interest predict interpretation of drug safety research? An analysis of Authors' opinions on venous thromboembolic risks of oral contraceptives

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Background: Oral contraceptives (OCs) are used by large populations of mainly young, healthy women. Therefore, tolerance for rare, serious harm is lower than for medicines used to treat or prevent serious disease. Epidemiological research has found higher risks of venous thromboembolism (VTE) with specific progestins in OCs: desogestrel and gestodene, from 1995, and drospirenone, from 2009. In both cases older, less costly levonorgestrel or norethindrone containing ('second generation') OCs had lower risks. European Medicines Agency and the US Food and Drug Administration reviews supported these risk differences; nevertheless, controversy persists.

Objectives: This study examines whether an association exists between financial conflicts of interests of authors of secondary literature on VTE risks of OCs and interpretation of the research evidence.

Methods: *Design:* retrospective analysis of articles citing epidemiological studies comparing drospirenone-containing OCs with second generation OCs from Jan 1, 2010 to Dec 31 2016. *Setting:* Web of Science search for articles citing at least 1 of 13 observational studies on VTE risks of drospirenone-containing OCs vs. second generation OCs. Articles were included if OC VTE risks were mentioned in the title or abstract or accounted for >50% of content. *Outcome measure:* Authors' opinions on VTE risks of drospirenone- containing OCs and/or desogestrel/gestodene- containing OCs vs. second generation OCs (higher, equivalent, or neutral) vs. pharmaceutical industry funding (present, absent, or no disclosure). Secondly, key stated rationales are examined. *Statistical analysis:* Relative risks and 95% confidence intervals calculated using SPSS 22.

Results: Of 481 citations, 148 met inclusion criteria, and 137/148 (93%) stated a position on VTE risks. In 60/137 (44%), authors declared financial conflicts, 59/137 (43%) declared none, and 18 (13%) did not disclose. Among those with conflicts, 37/60 (62%) judged drospirenone's VTE risks as equivalent to second generation OCs vs. 5/59 (9%) with no conflicts, RR = 7.3 (95% CI 3.1 to 17.2). In 109 both drospirenone and desogestrel/gestodene VTE risks were discussed; opinions were similar in 104 (95%). The most commonly cited reasons for judgments of equivalence were methodological limitations of administrative data.

Conclusions: There was a strong association between financial conflicts of interest and authors' positions. These findings raise questions about commercial influence on this ongoing scientific debate.

967 | Post market safety communications for sodium glucose co-transporter 2 inhibitors. An international case study of regulatory decision-making

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Background: Regulators use post-market alerts to warn prescribers of unexpected safety issues. However the US Food and Drug Administration (FDA), Health Canada (HC), Australia's Therapeutic Goods Administration (TGA), and the European Medicines Agency (EMA) differ considerably in these alerts. The reasons for this divergence are unclear.

Objectives: To compare decision-making about post-market safety communications for SGLT2 inhibitors (SGLT2s) by the FDA, HC, TGA, and EMA.

Methods: We conducted an in-depth process-tracing case study of post-market safety communications for SGLT2s, for which marketing approval occurred after major pharmacovigilance changes in all jurisdictions except Canada. Information was taken from publicly available regulatory documents in each jurisdiction from marketing approval to July 2018. Analysis focused on regulatory interventions for five safety issues: diabetic ketoacidosis (DKA), amputation, serious genitourinary

infections, acute kidney injury (AKI) and bone effects. Data sources, decision-making processes, actions, and their timing were assessed.

Results: The FDA communicated all five safety concerns, HC four, and the TGA and EMA two each. All regulators warned about DKA and amputation and added warnings to labels. The three discordant safety issues led to label changes for 16/21 (76%) drugs but only 10/21 (47%) were subject to advisories. Regulators warned less often or more slowly if they had reviewed the risk at approval, even for more serious events (amputation [HC], AKI (EMA) and fractures [EMA, TGA]. Lags from first to last regulator on the same safety issue ranged from 3 to 13 months. After the first advisory from another regulator, the longest time to respond by HC was 402 days (bone effects), FDA 242 days (AKI), TGA 90 days (DKA), EMA 42 days (DKA). EMA label changes without advisories were prompted by routine periodic safety reports or company-submitted label changes, and were product-focused. Accordingly, FDA warned of serious genitourinary infections in all SGLT2s, whereas EMA did so in only one (canagliflozin). The TGA provided the least information about decision-making; EMA the most.

Conclusions: The FDA communicated most but was not always the fastest. A lack of EMA advisories reflected a more product-focused approach; this may relate to EMA policy regarding centralized communication for only certain label changes. Little information was provided on the triggers for warnings; though TGA and HC tended to follow larger regulators. The impact of communication practices on prescribing merits further study.

968 | Risk assessment (RA) in pulmonary arterial hypertension (PAH) - overview and comparison

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Background: PAH is a rare, life-threatening disease. RA based on patient and clinical characteristics is essential in treatment decisions, but few publications have compared different RA strategies.

Objectives: To provide an overview and compare main RA strategies in PAH.

Methods: A literature review was performed to identify RA strategies in PAH. Key elements e.g. development, variables, assessment algorithms and implementation were extracted and compared.

Results: We identified 4 main strategies: REVEAL risk score (RRS) and strategies from French (FS), German (DS) and Swedish (SS) experts. All strategies assessed 1 yr mortality risk. RRS was developed based on Cox regression models using data from 2716 incident and prevalent patients in the REVEAL registry. Variables independently associated with survival were included in RRS. FS, DS and SS were developed based on European PH guidelines and abbreviated by expert opinion. RRS, DS and SS assigned patients into 5, 3 and 3 risk levels using up to 13, 6 and 8 variables, respectively. Each variable and risk level were assigned a score. In RRS, the sum of all scores represented overall risk. In DS and SS, average score of all variables was rounded to assess overall risk. In FS, patients with $\geq$3 of 4 variables in the low risk category were considered low risk. All strategies except FS allowed missing data, but impact of missing data on prediction accuracy has not been thoroughly examined. All strategies included exercise performance and right atrial pressure (RAP). Cardiac index (CI) was included in all but RRS. RRS also included PAH etiology, age, gender, comorbidity and vital signs. RA strategies were implemented in incident patients from various registries started between 2006–2009 using data at baseline (RRS N = 504; FS N = 1017; DS N = 1588; SS N = 530) and 1 yr follow-up (FS N = 1017; DS N = 1094; SS N = 383; RRS: not studied). For all strategies, low risk patients had 1 yr survival of $\geq$95% (Kaplan–Meier estimate). In an exploratory analysis (N = 603), replacing invasive (RAP, CI) with non-invasive variables (BNP/NT-proBNP) in FS had similar 1 yr survival in low risk patients. RRS had a c-index of 0.724. For FS, DS and SS, survival for all risk levels was significantly different (log-rank test $p < 0.001$).

Conclusions: Despite differences, all strategies identified patients who achieved low risk status. Several new therapies were approved in recent years; therefore, prediction accuracy of RA strategies in current datasets should be evaluated. Replacing invasive clinical variables with non-invasive ones in RA reduces disease burden. Trade-off between invasiveness and model accuracy remains to be examined.

969 | What's the harm? Exploring evidence of risk, seriousness of harm and prescriber advice in medicine safety advisories

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Background: Safety advisories are used by national medicines regulators to communicate risks associated with the prescribing and use of medicines. These advisories may also contain recommendations for safer prescribing. It is currently unknown how the strength of the evidence cited and the seriousness of the observed or theoretical harm relate to the type of risk minimisation advice provided, or whether different regulators communicate different advice about the same safety issue. These potential disparities could lead to national differences in information available to prescribers to make informed choices.

Objectives: First, to determine the characteristics of and the relationship between the strength of evidence cited, the seriousness of the harm and regulators' recommendations to prescribers. Second, to determine whether there are variations in the information provided to prescribers and patients in medicine safety advisories about the same harm released by regulators in the United States, Canada, the United Kingdom and Australia.

Methods: This retrospective study analyses the content of safety advisories issued by the US Food and Drug Administration (FDA),

Health Canada (HC), the Australian Therapeutic Goods Administration (TGA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) from 01 January 2007 until 31 December 2016. We will assess safety issues for which all included regulators had issued an advisory about an approved medicine or medicine class. Evidence cited, seriousness of the harm, and the actions recommended to prescribers (e.g. monitoring patients or using alternative medicines) will be extracted. Frequency counts and regression analysis will be used to identify associations between regulators, the strength of evidence, seriousness of the harms and the risk mitigation actions recommended.

Results: We identified 1441 advisories (FDA = 382 MHRA = 469 HC = 370 and TGA = 220), grouped into 680 drug safety concerns. Of these, 70/680 (10.3%) were eligible for inclusion as all the regulators that had approved the medicine or class had also issued an advisory on the specific safety concern. Prescribing advice, of any kind, was provided most often by the FDA: in 47/53 (88.7%) of included advisories, followed by the MHRA in 55/66 (83.3%) advisories. The TGA and HC included prescribing advice less often, in 42/53 (79.3%) and 39/50 (78.0%) respectively.

Conclusions: We hypothesize that the individual regulatory authority and the seriousness of the harm identified are the major explanatory variables for action(s) recommended by the regulator.

970 | Risk communication in community pharmacies - impact on self-medication

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Background: Self-medication is defined as the selection and use of medicines by individuals (or a member of the individuals' family) to treat self-recognized or self-diagnosed conditions or symptoms. Appropriate self-medication has many benefits but it is also linked to potential risks such as incorrect diagnosis, delays in seeking medical advice when needed, infrequent but severe adverse reactions, dangerous drug interactions, incorrect manner of administration, incorrect dosage, incorrect choice of therapy, masking of a severe disease and risk of dependence and abuse.

Objectives: The aim of the study was to assess pharmacists' attitudes and previous experience with risk communication on self-medication in community pharmacies in Bulgaria.

Methods: An anonymous, questionnaire-based, descriptive study was performed. A prevalidated close-ended questionnaire was distributed among random sample of community pharmacists in Bulgaria. Data was analyzed using SPSS v.19.

Results: A total of 99 questionnaires were collected. 60.6% of the responders claim that patients very often consult them about their self-medication practices but rarely about possible adverse drug reactions and other drug-related problems such as drug interactions. 51.5% of pharmacists consider presenting information about risks as a mandatory part of the pharmaceutical consultation and the majority of them (87.9%) believe that it could affect patients' decisions. According to 18.2% of the responders up to 80% of self-medicating patients do not use their over-the-counter medicines as recommended in the patient leaflet. 63.6% of the responders believe that over-the-counter medical products have high potential for drug misuse and abuse and 12.1% consider them with a substantial potential for drug interactions.

Conclusions: Data suggests that patients consider over-the-counter medicines safe and rarely seek information about possible risks. The conducted pilot study showed that pharmacists should be the primary and pro-active source of information about risks of self-medication products.

971 | Efficacy and safety of tyrosine-kinase inhibitors as first-line therapy in EGFR mutant-harboring advanced non-small cell lung cancer patients: A network meta-analysis

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Background: Epidermal growth factor (EGFR) mutation is presented in about 10–15% of all Non-Small cell lung cancer (NSCLC) cases in the US. Five tyrosine kinases (TKIs) are approved as first-line treatments for NSCLC patients with positive EGFR mutation in the US; erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib. Most randomized clinical trials (RCTs) compare one of these drugs with platinum-based chemotherapy (PBCT) and there is limited head-to-head trials that directly compared EGFR-TKI's. Clinicians needs to make a choice among multiple treatment options and a network meta-analysis (NMA) enables the comparison of EGFR-TKI's simultaneously, even if some were never compared directly.

Objectives: To compare the efficacy and safety of EGFR-TKI's as first-line treatment in patients with locally advanced, metastatic NSCLC with positive EGFR mutation.

Methods: We searched the following databases; PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for relevant articles up to December 2018. We selected RCTs comparing at least 2 TKIs or a TKI with PBCT. We performed a frequentist random-effects NMA using the multivariate meta-analysis approach. The surface under the cumulative ranking curve (SUCRA) was used to determine the probability that a given TKI would be the best for efficacy and safety. Using SUCRA values, we created a cluster ranking plot to visualize both efficacy and safety ranks as a guide for clinicians in decision making.

Results: Fifteen eligible trials (3750 patients) were included. There were statistically significant differences between some TKIs and PBCT for overall survival (OS), progression-free survival (PFS) and grade 3 or higher adverse events. PFS results suggests that dacomitinib had highest probability of being the most effective (SUCRA, 75.9%), followed by, osimertinib (SUCRA, 69.5%), erlotinib (SUCRA, 59.9%),

afatinib (SUCRA, 55.9%), gefitinib (SUCRA, 36.1%), PBCT (SUCRA, 2.7%). We observed a similar ranking trend for OS except for the fact that dacomitinib and osimertinib has no OS data. Adverse events results suggest that osimertinib (SUCRA, 84.3%) and gefitinib (SUCRA, 78.9%) has the highest probability of being the safest. Upon simultaneously visualizing efficacy and safety in cluster plots, osimertinib, gefitinib, and erlotinib formed a cluster for the most effective and safe TKIs while dacomitinib and afatinib formed a cluster for lesser safety and effective TKIs.

Conclusions: This NMA suggests that osimertinib, gefitinib, and erlotinib might be the most efficacious and safest TKIs.

972 | Use of postapproval safety studies in the evaluation of safety concerns listed in the European risk management plan of two mature TNF inhibitors

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Background: In March 2017, revision 2 of Good pharmacovigilance practice (GVP) Module V regulating the European risk management plan (EU-RMP) came into effect. Consequently, Janssen as the Marketing Authorization holder (MAH) of two mature TNF inhibitors (TNFi) was requested to re-evaluate the safety concerns included in the EU-RMP and provide justification for keeping, removing or re-classifying each of them.

Objectives: To develop a scientifically-robust and consistent approach that could be used for the evaluation of the EU-RMP safety concerns for the two TNFi (REMICADE [originator infliximab] and SIMPONI [originator golimumab]), but also for other Janssen products.

Methods: Three independent algorithms informing the decision making were developed for each risk category within the EU-RMP. These algorithms were composed of a set of questions to determine whether the safety concerns were sufficiently characterized or needed further analysis; whether risk minimization measures were in place and adequate; and whether ongoing pharmacovigilance activities were likely to support further characterization of the risk. A wide range of data were analyzed: regulatory history, clinical data, post-approval safety study data, product information, trending analyses from the MAH's global safety database and the availability/need for risk minimization measures.

Results: A total of 13 and 7 post-approval safety studies (ongoing and completed) for originator infliximab and originator golimumab, respectively, were included in the analysis. Studies were scrutinized in terms of strength of evidence, length of follow-up, incidence and indicators of potential causality. Studies were also analyzed as to their potential to further characterize these outcomes. Based on this comprehensive evaluation, using the algorithms as a guidance, and taking all available data sources and opportunities for risk minimization measures into account, about 75% of the safety concerns were concluded to qualify for removal without jeopardizing the effectiveness of the RMP.

Conclusions: Well-designed post-approval studies, along with other data sources and risk minimization tools, are important to help characterize a medicine's safety profile, thereby allowing to keep its EU-RMP contemporary while minimizing unnecessary burden to stakeholders.

973 | Use of immune checkpoint inhibitors and risk of immune-related adverse events among patients with advanced melanoma: A systematic review and network meta-analysis

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Background: Immune checkpoint inhibitors (ICIs) have emerged as effective treatment options with increasing overall survival for advanced melanoma. Immune-related adverse events (AEs) are an increasing safety concern of ICIs, but little is known about the risk of immune-related AEs varies by ICI.

Objectives: We conducted a network meta-analysis comparing the risk of immune-related AEs among different therapies for advanced melanoma.

Methods: We systematically searched for phase II and III randomized controlled trials (RCTs) of advanced melanoma from PubMed/MEDLINE, EMBASE, Web of Science, and Scopus (01/01/2010–06/30/2018). RCTs were included if they reported any immune-related AEs (e.g., pruritus, colitis, hypothyroidism, and hepatitis) comparing ICIs (i.e., ipilimumab, nivolumab, pembrolizumab) with chemotherapies (e.g., dacarbazine), different ICIs, or different doses of the same ICI. Bayesian network meta-analysis with Markov Chain Monte Carlo simulation was used to compare therapies simultaneously. We applied non-informative prior distribution, and random-effect generalized linear models. Based on the pooled odds ratios (ORs) and 95% credible intervals (95% CrI; Bayesian equivalent of confidence intervals), we estimated the probability for immune-related AEs for each treatment.

Results: Ten RCTs were included (n = 5,349 participants). Four RCTs compared ICIs to chemotherapy. Six RCTs compared different ICIs and/or different doses. Compared to chemotherapies, none of the ICIs were associated with any increased immune-related AE risk (point estimates of the pooled ORs ranged from 0.41 to 3.20, all p-values >0.05). Within ICIs, compared to ipilimumab 10 mg/kg, a decreased risk of immune-related AEs was observed for ipilimumab 0.3 mg/kg (OR = 0.13, 95% CrI = 0.02–0.77) and nivolumab 3 mg/kg (OR = 0.26, 95% CrI = 0.09–0.78). Except comparing to ipilimumab 0.3 mg/kg, pembrolizumab 2 mg/kg was associated with a decreased risk compared to other ICIs (point estimates of the pooled ORs ranged from 0.19 to 0.72, all p-values <0.05). No association was found among other ICI comparisons. The top three therapies with the lowest probabilities for immune-related AEs were ipilimumab 0.3 mg/kg, pembrolizumab 2 mg/kg, and nivolumab 3 mg/kg.

Conclusions: The risk of immune-related AEs of ICIs was not different from chemotherapies. Among ICIs, ipilimumab 0.3 mg/kg, pembrolizumab 2 mg/kg, and nivolumab 3 mg/kg may be preferred options for patients with advanced melanoma at high risk of immune-related AEs.

974 | Utilization of PCSK9 inhibitors in an Italian region during the first year of access to National Healthcare Service reimbursement

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Background: Italy has a single-payer universal healthcare system. Evolocumab and alirocumab (PCSK9i) were approved in Italy in 2017 for the treatment of hyperlipidemia. Due to their high cost, reimbursement was restricted to very high-risk patients in primary or secondary cardiovascular prevention who had no benefit from, or were intolerant to, oral lipid lowering therapies (LLT).

Objectives: To characterize patients treated with PCSK9i in Tuscany (Italy) and describe the pattern of use during the first year of reimbursement.

Methods: Patients claiming at least one PCSK9i in Tuscany (3.7 million inhabitants) from July 1st 2017 to June 30th 2018 were selected from health administrative databases (HAD). Use of LLT and persistence (no gap ≥60 days between subsequent prescriptions) in the previous six months, as well as comorbidities since 1996, were described. In the subpopulation starting PCSK9i in 2017, adherence (proportion of days covered≥75%), persistence (no gap ≥30 days) and concomitant LLT during the first six months of treatment were evaluated.

Results: Two hundred sixty-nine PCSK9i new users (7.2 per 100,000 inhabitants) were included in the cohort: 176 used evolocumab and 93 alirocumab. Patients were mainly male (71.0%), ≥51 years old (63.2%), in secondary prevention (70.2%) and affected by FH (53.5%). In the cohort, 66 patients (24.5%) had diabetes and 12 (4.5%) chronic renal failure. Among secondary prevention patients, the first PCSK9i prescription occurred on average 4.9 years after the last cardiovascular event. During the six months before PCSK9i initiation, 165 patients (61.3%) received high potency LLTs (HPLLT), and 78% of them were persistent; 24 additional patients (7.0%) were persistent to non-high potency LLT. During the first six months of treatment (data available for 105 PCSK9i users), 83 patients (79.0%) were adherent, 78 (74.3%) were persistent. 53 patients (50.5%) used PCSK9i in monotherapy, whereas 36 (34.3%) received a concomitant HPLLT.

Conclusions: Utilization of PCSK9i, in the first year of reimbursement, was low. Patients were mainly in secondary prevention and persistent to previous LLT, consistently with reimbursement access criteria. Patients previously non-persistent to LLT might have been involved in clinical trials with no treatment records in HAD. During the first six months, PCSK9i were mainly used in monotherapy and with high adherence and persistence. This timely work sets the stage for future longer-term studies useful to improve appropriateness of use, drug access and public healthcare assistance sustainability.

975 | Trends in biologic utilization for the Management of Juvenile idiopathic arthritis in the United States, 1997–2018

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatological disease in pediatrics and associated with significant morbidity and health care spending. Despite many new biologic therapies, little is known regarding how JIA treatment has changed over time.

Objectives: To describe annual volume of biologic prescriptions for oligoarticular and polyarticular JIA in the United States (US) from 1997, the year the first biologic of interest was approved, through 2018.

Methods: We used the OptumLabs® Data Warehouse, a large database with de-identified administrative claims for the privately insured, between November 1997 and October 2018. We focused on individuals with a diagnosis of JIA (ICD-9 714.3, ICD-10 M08); we also included persons with a rheumatoid arthritis code under age 20 (ICD-9 714.X, ICD-10 M06). We quantified use of tumor necrosis factor inhibitors (TNFi), abatacept, rituximab and tocilizumab, and reviewed product approval dates and changes in major US clinical treatment guidelines to provide qualitative context.

Results: Among the products of interest, a total of 29,537 unique prescriptions were identified, with prescription volume increasingly steadily over the years examined. Approximately three-fifths (59%) of prescriptions were for females, and the median age of biologic recipients was 16 years (interquartile range 13–18 years). Etanercept accounted for approximately 41% of total prescriptions and increased relatively steadily between 1998 and 2018, whereas adalimumab accounted for more than half (54%) of total prescriptions and increased gradually between 2002 and 2007, moderate between 2007 and 2014 and sharply between 2014 and 2018. Certolizumab pegol, while not approved for use in JIA in the US, comprised approximately 3% of all biologic prescriptions, while other biologics accounted for less than 1% of total volume observed.

Conclusions: To our knowledge, this study is one of the first to examine long-term trends in the biologic treatment of JIA in the US. Despite the advent of novel inhibitors of interleukins, B-cells and T-cells, the market remained dominated by two TNFi during the period we examined. Further analyses will examine patient-level factors associated with biologic initiation, adherence and persistence in children and adolescents with JIA, as well as the effect that utilization management strategies, clinician and patient preferences may have on the patterns observed.

976 | Rates of major adverse cardiovascular events (MACE) and revascularization among patients with psoriasis or psoriatic arthritis treated with apremilast, biologics, DMARDs, and corticosteroids in the US MarketScan database

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Background: Patients with psoriasis or psoriatic arthritis (Psor/PsA) are at increased risk of cardiovascular events.

Objectives: To compare rates of MACE and revascularization by treatment type in patients with Psor/PsA.

Methods: We conducted a population-based cohort study of treated Psor/PsA patients in the MarketScan database in 2014–2016. The cohort entry was the date of the first prescription for a study drug (apremilast only or in combination, anti-tumor necrosis factor-α (anti-TNF-α) biologics only, other biologics and disease-modifying antirheumatic drugs (OBDs) only, corticosteroids only, OBDs + corticosteroids, and anti-TNF-α biologics with OBDs and/or corticosteroids) after March 21, 2014. Patients were followed from cohort entry through censor date (first of date patient became a case, end of record, or Dec 31, 2016). MACE was defined as inpatient myocardial infarction, stroke or cardiac arrest; revascularization was a revascularization procedure without MACE; all ≥7 days after cohort entry. A patient was considered currently exposed from prescription date through prescription duration +30 days. We calculated incidence rates (IRs) and 95% confidence intervals per 100 patient-years. We compared IRs to OBDs only using Poisson regression.

Results: The study population included 124,714 patients (median age: 51 years, 51% female, 3.9% serious cardiovascular disease (CVD) history). IRs were low for both outcomes, and few differences between treatments reached statistical significance. Among the 569 MACE cases, IRs were as follows: for apremilast only (0.22 [0.11, 0.39]), anti-TNF-α biologics only (0.22 [0.18, 0.26], $p < 0.001$ vs. OBDs only), OBDs only (0.36 [0.29, 0.43]), anti-TNF-α biologics with OBDs and/or corticosteroids (0.39 [0.30, 0.51]), corticosteroids only (0.41 [0.32, 0.52]), apremilast in combination (0.56 [0.29, 0.98]), and OBDs + corticosteroids (0.64 [0.43, 0.91], $p = 0.005$ vs. OBDs only). Among the 580 revascularization cases, IRs were as follows: for apremilast only (0.22 [0.11, 0.39], $p = 0.047$ vs. OBDs only), anti-TNF-α biologics only (0.28 [0.23, 0.33], p = 0.005 vs. OBDs only), and OBDs only (0.40 [0.33, 0.49]). IRs for other exposures were between 0.36 and 0.43. Among patients with no serious CVD history, IRs were generally lower but relative effects between study drugs were consistent with the main analyses.

Conclusions: Rates of MACE and revascularization were low for treated Psor/PsA patients and generally were similar across treatments.

977 | Biosimilar safety dashboard to assess switching in veterans

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Background: Biosimilar interchangeability has not been established for biosimilars used in the US. Due to the rising cost of biologics, healthcare systems will continue to use newly marketed biosimilars. It is important to monitor the safety and effectiveness of switching patients to biosimilars. The Department of Veterans Affairs (VA) developed a prototype dashboard to allow for real-time tracking and safety monitoring of biosimilar switchers.

Objectives: To describe the real-time biosimilar prototype dashboard developed to assess biosimilar utilization, switching patterns, and outcomes temporally associated with switching in Veteran patients.

Methods: This was a descriptive analysis of outpatients given infliximab from 1/1/16–1/31/19 and switched to/from the originator infliximab or a biosimilar (DYYB or ABDA). A real-time infliximab safety dashboard was developed using prescription, diagnosis and procedure data obtained from the corporate data warehouse. Patients were identified as single switchers (only 1 switched product) or multiple switchers (more than one product switch). Patient characteristics, utilization, switching patterns, and outcomes such as adverse drug events (ADE) were assessed. ADEs included anaphylaxis, angioedema, angina, fatigue, headache, jaundice, myalgia, rash, and weight loss.

Results: A total of 4,814 infliximab patients (88% male) were identified during the evaluation period. Of those, 1,690 (35%) patients had at least one switch, and 1,024 (61%) were single switchers only. Of the remaining 666 (39%) multiple switchers, 105 (16%) switched back to the originator product after any biosimilar administration. Among all switchers, 930 (55%) patients switched from originator to biosimilar, 607 (36%) had a biosimilar to biosimilar switch, and 153 (9%) switched to an originator product from a biosimilar. Of single switchers, 335 (33%) and 69 (7%) patients had at least one ADE or hospitalization respectively. For multiple switchers, 172 (26%) and 38 (6%) patients

had at least one ADE or hospitalization respectively after the most recent switch. Among recent biosimilar to biosimilar switchers, 138 (23%) had at least one ADE and 22 (4%) had at least one hospitalization.

Conclusions: The biosimilar dashboard allows for real-time assessment of biosimilar utilization, switching patterns, and monitoring of safety outcomes such as ADEs and hospitalization. This provides timely and valuable information to providers and decision makers. In this early assessment it appears that more switches do not correlate to increased ADEs or hospitalizations. Future assessments will also include outcomes for non-switchers.

978 | Biosimilar use in the United States: An analysis of filgrastim and infliximab

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Background: The Biologics Price Competition and Innovation Act of 2009 created an approval pathway for biosimilars in the U.S. As more biosimilars are approved, accurate identification of biologics and biosimilars in claims data and understanding use patterns and patient characteristics are fundamental needs for conducting future post-marketing studies.

Objectives: To identify users of filgrastim and infliximab biologics and biosimilars in 17 Data Partners in the Sentinel System, and describe their use patterns and patient characteristics.

Methods: Filgrastim biologic and biosimilar products (Neupogen, Zarxio, Granix) and infliximab biologic and biosimilar products (Remicade, Inflectra, Renflexis) were included. Product use was assessed monthly from 1/1/2015–1/31/2018 via administrations in healthcare encounters (HCPCS codes) and dispensings from outpatient pharmacies (NDCs). Among those with >1 administration, we calculated the gap, in days, between the first and second administration. Lastly, we described demographics and indication (gastrointestinal (GI) vs. non-GI) based on a diagnosis in the prior year for users of infliximab.

Results: We identified 39,329 and 9,118 users of Neupogen and Zarxio (filgrastim-sndz), respectively, based on administrations, and 16,696 and 7,735 users, based on dispensings. The proportion of filgrastim administrations for Neupogen declined from 85% in 1/2015 to 30% in 10/2017, while Zarxio administrations increased to 53% in 10/2017 after market introduction in 9/2015. The proportion of administrations for Granix (tbo-filgrastim) remained stable over the study period, ranging from 15%–23%. We identified 76,654 and 1,093 users of Remicade and a biosimilar to infliximab, respectively, based on administrations. Dispensings identified 5,743 Remicade users compared with 157 and 0 users of Inflectra and Renflexis, respectively. Inflectra users tended to be older, more often female, and more likely to have baseline diagnoses for non-GI indications compared with Remicade users. The median gap between administrations was 12, 11, and 11 days for Neupogen, Zarxio, and Granix, respectively, and was 48 and 41 days for Remicade and biosimilars to infliximab, respectively.

Conclusions: More users of filgrastim and infliximab biologic and biosimilar products were identified from administrations in healthcare encounters than dispensings. Data on observed gaps between administrations can be used when creating exposure definitions in future studies on biosimilars. Additional analyses should assess whether reference biologics and biosimilars are given to different patient populations.

979 | Post-market safety outcomes for original therapeutic biologics approved by the Food and Drug Administration between 2002 and 2014

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Background: Biologics comprise a large and growing market in the USA. Patterns of post-market safety outcomes, and their association with assignment to pre-market expedited programs have not been systematically described.

Objectives: This study was conducted to examine the association between 3 expedited programs developed by the FDA to reduce pre-market review or development time (fast track designation, priority review designation, and accelerated approval with a surrogate endpoint) and post-market safety outcomes for original therapeutic biologics (OTBs) approved between October 1, 2002 and December 31, 2014.

Methods: Post-market safety outcomes, defined as a safety-related withdrawal or a safety-related update to the *Boxed Warning* (BW), *Contraindications* (C), *Warnings and Precautions* (WP), *Adverse Reactions* (AR) or *Drug Interactions* (DI) sections of the label from the OTB's approval through December 31, 2015, were recorded following a review of label updates posted on 2 public FDA websites: Drug Safety-related Labeling Changes database and Drugs@FDA. Wilcoxon rank-sum, chi-squared, and Fisher's exact tests, and logistic regression were utilized to examine bivariate associations. Kaplan–Meier analysis with Wilcoxon tests were done to examine association with time to first safety outcome.

Results: A total of 61 OTBs were approved during the study period. Follow-up was 1–13.2 years (median, 5.9 years). 30 (49.2%), 42 (68.9%) and 9 (14.8%) OTBs, respectively, were assigned fast track designation, priority review designation, and accelerated approval with a surrogate endpoint. Two OTBs were withdrawn from the market due to safety reasons while 49 (80.3%) had at least one safety-related label update. There were 158 individual label updates addressing 935 safety-related issues. There was a total of 26, 19, 101, 106 and 7

individual label updates, respectively, for the BW, C, WP, AR, and DI sections. 96, 31, 355, 537 and 13 safety issues were added to the BW, C, WP, AR and DI sections, respectively. OTBs with a priority review designation were less likely to have a safety outcome compared to those without (100% vs 62%; $P = 0.01$). The other 2 expedited review programs were not associated with the occurrence of a safety outcome (fast track designation: OR = 1.3, 95% CI 0.3–4.8; accelerated approval with a surrogate endpoint: OR = 0.5, 95% CI 0.1–4.7). None of the 3 expedited review programs were significantly associated with time to the first safety outcome.

Conclusions: The 3 expedited programs examined were not associated with an increase in post-market safety outcomes.

980 | Social media data analysis with population-based methods: A pilot investigation of mild hypersensitivity among users of subcutaneously administered monoclonal antibodies

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Background: Patients may turn to social media to express thoughts about their use of medicines and the resulting data may comprise a useful resource for pharmacovigilance (PV). Using the Brandwatch® Inc. platform, we assessed social media data with a pilot drug and event pair: subcutaneously administered monoclonal antibodies (SA mAbs) and symptoms indicative of mild hypersensitivity reactions (mild HRs).

Objectives: To identify and assess mentions of symptoms associated with mild HRs among self-reported users of SA mAbs and trends in these mentions over time in Brandwatch data.

Methods: *Design:* Cross-sectional monthly social media data was searched for symptoms of mild HRs and self-reported SA mAbs use.

Setting: Brandwatch has collected social media data from a variety of Internet sources including social networks (eg. Facebook, Twitter), news services, and industry websites; English language data from 2015 to 2019 were used.

Exposures: The exposure was patients' self-reported use of a mAb where SA is listed as the route of administration in the US Product Insert.

Outcome: Outcomes included patients' mentions of symptoms associated with mild HS in the social media report that contained the reference to the use of a SA mAb. Mild HS was defined by symptoms previously described in publications on hypersensitivity or social media such as rash, fever, or hives.

Statistical Analysis: We conducted descriptive univariate analysis and examination for temporal trends.

Results: Among all mentions of SA mAb use ($n = 134263$), 9622 (7.17%) included a mention of a symptom of a mild HR. Mentions of mild HS increased over the study period among users of mAbs that were introduced in the study period, but mentions of mild HR among those who used mAbs introduced before the study period remained stable. Mentions of all mild HRs regardless of drug use increased over the observation period.

Conclusions: The observed large counts and proportions of mild HRs mentioned among self-reported users of SA mAbs over time suggest the Brandwatch data may be useful for PV. Limitations of the analysis included an inability to validate the social media mentions and the non specificity of the reported events. Additionally, we focused on mild HS because it is associated with SA drugs and potentially amenable to self-diagnosis and discussion on social media. In the future, we will test new drug and event pairs, including severe events, in the context of signal detection and compare those results to analyses from traditional PV data sources such as spontaneous reports and healthcare databases.

981 | A survey among health care professionals to assess their knowledge and understanding on Darzalex® (daratumumab) educational materials regarding the risk of interference for blood typing in 12 European countries

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Background: Darzalex® is a human IgG monoclonal antibody immunotherapy indicated for the treatment of adult patients with multiple myeloma. Daratumumab in the serum binds to red blood cells (RBCs) resulting in pan-agglutination in indirect Coombs tests and induce the risk of masking the presence of antibodies to minor antigens and may persist for up to 6 months after the last daratumumab infusion. As risk minimization measures (RMMs)Educational materials (EM) were developed in 2016 and aimed to inform about the associated blood compatibility risk and provide guidance for risk management activities. The EM were distributed in 2016 and 2017 in European countries where the drug was commercially available.

Objectives: This post-authorization safety study (PASS) is designed to evaluate whether the health care professionals (HCPs), and blood transfusion management department personnel (BTMDP) received and understood the EM.

Methods: This study was conducted in 12 European countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Norway, Spain, Slovakia, Sweden, Switzerland) by using an anonymous, cross sectional and non-interventional survey. The recruitment target was 400 participants. Questionnaires were distributed via a web-based platform. The criteria for considering the EM as effective were correct answers from ≥80% of respondents for key questions of relevance to the RMMs. The questions assessed understanding of

daratumumab and its mode of action to interfere with blood typing, and knowledge of the potential for daratumumab to cause this interference and the relevant mitigation methods for this.

Results: A total of 408 participants completed the questionnaires with 254 HCPs (62.3%) and 154 BTMDP (37.7%). As preliminary results, overall, between 95% and 100% of participants were aware of the EM and between 80% and 100% have correctly answered key questions about the knowledge of the risk associated with the interference of daratumumab and blood testing except the question relative to the type of testing concerned (ABO typing, RhD typing or detection of regular antibodies) with a result <65%. The responses were consistent between HCPs and BTMDP.

Conclusions: The preliminary survey results suggest that the participants knew EM and were aware of the risk associated with the interference of daratumumab and blood testing which suggests an overall satisfactory effectiveness of the risk minimization measures. The final results will become available in July 2019.

982 | Effectiveness and safety of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria: Systematic review and meta-analysis

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic hemolytic anemia caused by a defect in the red blood cell membrane mediated by the complement system. Eculizumab, is the first drug indicated for this condition, with a high economic impact, specially for countries that provide publicly-funded drugs.

Objectives: To evaluate the effectiveness and safety of eculizumab in PNH treatment.

Methods: A systematic review (SR) and meta-analysis of cohort studies evaluating the effectiveness and safety of eculizumab in PNH treatment was conducted in January 2019, through PUBMED, EMBASE, LILACS and Cochrane Library databases, manual search and gray literature. The selection of the studies was performed by two independent reviewers and, in cases that were disagreements, they were solved by a third reviewer. The meta-analysis was conducted in Review Manager® 5.3 software. The effectiveness outcomes evaluated were: reduction of hemolysis, increase in hemoglobin level, reduction of transfusions; and safety: thromboembolic events and mortality. The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale.

Results: A total of 1854 studies were found, of which eight were included in SR. All the studies had low methodological quality, since most of them have not presented comparator group (non-exposed). For the outcome reduction in hemolysis, a change in LDH levels (lactate dehydrogenase) was observed, which showed a statistically significant decrease in patients using eculizumab. No statistically significant difference was observed in the increase in hemoglobin level (median 1.53, 95% CI 0.55–4.39). Patients in the eculizumab group had a greater chance of achieving transfusional independence (RR 2.77, 95%CI, 1.9–4.05), those who did not become independent required fewer red cell bags. Regarding safety, eculizumab reduced the risk of thromboembolic events (RR 0.13, 95% CI 0.07–0.25) and about the mortality, it was observed that only after 36 months of treatment, eculizumab had a protective effect with a statistically significant difference.

Conclusions: Eculizumab is an innovative drug that has been shown to be effective and safe for the treatment of patients with PNH. However, since it presents a high cost, it can compromise the population's access to the treatment.

983 | Switching from infliximab-originator to infliximab-biosimilar in rheumatologic patients: The clinical impact in Tuscan Region, Italy

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Background: In 2015, Tuscan Health Authority recommended to physicians the prescription of biosimilar infliximab (BI), thus promoting the switching from originator infliximab (OI) to BI.

Objectives: To assess the clinical impact of the recommendation for the use of BI in Tuscan rheumatoid arthritis (RA) patients.

Methods: We conducted two interrupted time series analyses on RA patients in the Tuscan healthcare administrative databases. The analysis 1 included naïve patients who started infliximab between January 1st, 2012 and December 31st, 2016. We followed patients up to 1 year. The analysis 2 included prevalent infliximab users recorded from January 1st to December 31st, 2013 (group 1) and from January 1st to December 31st, 2015 (group 2). Both groups were followed for 2 years. In both analyses, we described the patterns of treatment as well as the occurrence of rheumatologic visits, emergency department visits (EDV) and hospitalizations for any causes.

Results: In the analysis 1, 214 patients were included (52 in 2012, 64 in 2013, 31 in 2014, 29 in 2015 and 38 in 2016). Patients starting with BI were 18 (62.1%) in 2015 and 33 (86.8%) in 2016. Switching from OI to BI occurred since 2014, and no switch from BI to OI was recorded. We observed neither relevant differences in the pattern of treatment

(frequency of treatment persistence, switching to another anti-TNF or swapping to another non-anti TNF) nor in the frequency of the rheumatologic visits, EDV and hospitalizations over the observation years. In the analysis 2, 354 patients were included in group 1 and 334 in group 2. All patients started with OI. In the group 2, we observed that: 96 (28.7%) patients switched to BI; 66 patients (19.8%) switched to another anti-TNF drug, versus 55 patients (15.5%) of group 1; 7 patients (2.1%) swapped to other non-anti-TNF drugs versus 6 patients (1.7%) in group 1. The mean number of rheumatologic visits per patient increased from 2.8 (group 1) to 3.9 (group 2). The proportion of patients with at least one EDV increased from 35.9% (group 1) to 45.5% (group 2). The proportion of hospitalized patients increased from 34.5% to 37.4%; the mean number of hospitalizations per patient did not vary.

Conclusions: Over the study period, the recommendation of Tuscan Health Authority was associated with an increased utilization of BI in RA patients. In naïve users, no impact was observed on the patterns of use and outcomes. Likewise, in prevalent users, no major changes in the patterns of use were observed. The increase in EDV and rheumatologic visits could be explained with a cautious approach to BI by both physicians and patients.

984 | The incidence of infusion reactions associated with monoclonal antibody drugs targeting the epidermal growth factor receptor in metastatic colorectal cancer patients: A systematic literature review and meta-analysis

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Background: Infusion reactions have been reported in studies of metastatic colorectal cancer (mCRC) patients treated with anti-EGFR therapies, including cetuximab and panitumumab, with incidences ranging from 0–33%.

Objectives: A systematic literature review and meta-analysis were conducted to estimate the incidence of infusion reactions in this population and identify variations in this incidence by patient and study characteristics.

Methods: Multiple scientific databases were searched to identify observational studies or clinical trials of mCRC patients treated with anti-EGFR therapies that reported rates of infusion reactions, hypersensitivity, or allergy/anaphylaxis. Random effects models were used to meta-analyze the incidence of infusion reactions overall and stratified by therapy, study design, geographic location, *KRAS* mutation status, and grade of reaction severity.

Results: Among 48 studies included in this meta-analysis, the pooled estimate for infusion reaction incidence was 0.049 (95% CI: 0.036–0.065), or nearly 5%. Reactions of grades 1 or 2 were more common than reactions of grades 3–5 (0.089 vs. 0.028) No significant variations in infusion reaction incidence were observed by study design, KRAS status, or study location.

Conclusions: Infusion reactions occur in approximately 5% of mCRC patients treated with anti-EGFR therapies and the incidence varies significantly by grade and severity. Future studies should consider investigating survival outcomes for only those patients with infusion reactions to determine its prognostic relevance.

985 | Prescribing patterns from medical chart abstraction of patients administered lipegfilgrastim: A pilot study in Europe

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Background: In the context of the regulatory approval for market authorization of lipegfilgrastim in the European Union, the European Medicines Agency requested a drug utilization study as part of the pharmacovigilance plan to characterize the extent of off-label use of lipegfilgrastim. To address the challenges of implementing a study of off-label use in multiple countries with diverse healthcare systems and clinical practices, a pilot study was designed.

Objectives: The objective of this pilot study was to explore the feasibility of conducting a drug utilization study of lipegfilgrastim in Europe using medical records and to examine the pattern of lipegfilgrastim on-label and off-label use.

Methods: Data on lipegfilgrastim use between September 2014 and April 2017 were abstracted from medical records by two independent medical abstractors. Lipegfilgrastim indication was categorized either as on-label or as one of four types of off-label (I-IV) according to pre-defined criteria. An inter-rater reliability analysis was conducted to measure the degree of abstractor agreement for on-label and off-label use.

Results: Information from 46 medical records was abstracted. Lipegfilgrastim use during the first chemotherapy treatment cycle was mostly indicated for prevention of neutropenia (82.6% of patients). On-label use was documented in 42 patients (91.3%), while off-label use was documented in two patients (4.3%); all events of off-label use were attributed to use with non-cytotoxic drugs. The remaining two patients (4.3%) had missing data. Overall agreement between the abstractors was high (91.6%). For three types (Types I-III) of off-label use, the kappa values suggested a perfect agreement ($\kappa = 1$). For Type IV off-label use (use in patients treated with non-cytotoxic drugs), $\kappa = 0$, suggesting a poor agreement.

Conclusions: While recruitment was challenging, the results of this pilot study confirm the feasibility and availability of medical records and the use of pharmacists as abstractors to assess on- and off-label use of lipegfilgrastim. Lipegfilgrastim was mainly prescribed according to the approved indications.

986 | Prescribing practices associated with biologic therapies for psoriasis

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Background: After a physician writes a prescription, several things can happen: a patient can choose not to take the medication, it may not be covered by insurance, or they may start it and discontinue because of side effects or lack of efficacy. There is little information describing physician prescribing practices associated with biologic therapies for psoriasis.

Objectives: To investigate the physician prescribing practices associated with biologic therapies used to treat psoriasis in the United States.

Methods: A cohort study was performed using data from OptumInSight's electronic health records database, a de-identified dataset containing information from over 81 million individuals in the United States with a diagnosis of psoriasis between 1/1/2007–6/30/2017. Patients were classified as having psoriasis if they had 2 diagnosis codes for psoriasis, on 2 separate days or 1 diagnosis for psoriasis and a prescription for a systemic psoriasis therapy/phototherapy on a separate day. Time began at the second qualifying event and was continued until the patient left the database or died. Only patients with at least 1 prescription for a biologic medication (adalimumab, etanercept, infliximab, secukinumab and ustekinumab) were included in the analysis. Time between first and last prescription was used as a measure of drug survival in this dataset; at least 1 prescription every 180 days was required for continuous therapy.

Results: There were 34,714 patients included in the analysis. Between 27.7% - 53.1% of patients received a single prescription for the drug. The median number of prescriptions written for each drug was 2 for infliximab, secukinumab and ustekinumab and 3 for adalimumab and etanercept. Patients prescribed infliximab had the longest median time between first and last prescription (7.0 mos, IQR: 2.9–20.8 mos) and patients prescribed secukinumab had the shortest time (3.4 mos, IQR: 1.3–7.3 mos). A subset of patients (N = 12,857) on the same biologic medication for at least 12 months was identified. Again patients on infliximab had the longest median time between first and last prescription (median: 34.7 mos, IQR: 21.5–54.2 mos) and those on secukinumab had the shortest median time (15.4 mos, IQR: 13.3–19.5 mos).

Conclusions: Up to 50% of patients who received a first prescription for a biologic did not receive a second prescription for the same medication. The median time between first and last prescriptions was less than 12 months. Understanding prescribing patterns for biologic medications, helps to understand some of the difficulty physicians have selecting appropriate systemic treatments for psoriasis.

987 | Vemurafenib associated drug reaction with eosinophilia and systemic symptoms: Exploration of novel adverse effect using disproportionality analysis

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Background: Signal detection is one of the most advanced and emerging field in pharmacovigilance. It facilitates early adverse drug reaction detection that may not have been identified in pre-marketing clinical trials. Vemurafenib is a BRAF inhibitor approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of metastatic melanoma.

Objectives: This study aims in the identification of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with vemurafenib using disproportionality analysis of the FDA Adverse Event Reporting System (FAERS).

Methods: Data were obtained from the public release of data in FAERS. Case/non-case method was adopted for the analysis of association between vemurafenib use and DRESS. The data mining algorithm used for the analysis was Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR). A value of ROR-1.96SE > 1, PRR $\geq$ 2 were considered as positive signal.

Results: A total of 7,869 reports for DRESS have been reported in the FDA database as on December 2018. Among which 101 reports were associated with vemurafenib. DRESS ranked 49th among 900 vemurafenib associated adverse drug events. A positive signal was obtained with ROR: 13.10 and PRR: 13.12. Four deaths were reported and the non-death serious reports included hospitalization, life-threatening, disability, and other serious events with 61, 11, 2 and 39 reports respectively.

Conclusions: A positive signal was observed for vemurafenib associated DRESS, although a causal relation cannot be definitively proved. Health care professionals should be cautious about the possibility of encountering serious adverse events associated with vemurafenib and should be reported to the regulatory authorities.

988 | Evaluation of thrombocytopenia and hemorrhage associated with secukinumab

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Background: Secukinumab is a human monoclonal antibody works by inhibiting the action of interleukin (IL)-17 involved in inflammatory and immune responses. It is an immunosuppressant agent used in many

autoimmune diseases: plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.

Objectives: The aim of this review is to evaluate the risk of blood adverse events: thrombocytopenia and hemorrhage associated with the administration of secukinumab.

Methods: A systematic search was conducted using PubMed, Ovid, Cochrane and Google scholar of relevant studies for each adverse event. The search terms include the following in different combinations: Secukinumab, Cosentyx®, Interleukin-17 inhibitor, thrombocytopenia, low platelet count, thrombopenia bleeding hemorrhage and hemorrhage. Cases of thrombocytopenia and hemorrhage suspected with secukinumab reported to World Health Organization (WHO) until the 9th of Jan 2019, were reviewed. The association was assessed using WHO-Uppsala Monitoring Centre causality system.

Results: We Identified 27 serious cases of thrombocytopenia reported to WHO database. Most of the cases were unassessable 14 (51.85%) due to insufficient information. However, two cases of severe and intense reduction in platelet counts during treatment with secukinumab have been reported, and evaluated to be possibly related to therapy with secukinumab. There were 41 serious cases of hemorrhage reported to the WHO database with secukinumab. Hemorrhage was assessed unlikely to be related to secukinumab use.

Conclusions: There is a probable risk of thrombocytopenia associated with secukinumab use. Platelet counts monitoring is recommended before and during treatment. Skin monitoring is also recommended for any discoloration that could indicate a reduction in platelet counts in high-risk patients. These risks need further close monitoring.

989 | Younger age is the main determinant for first-line biological treatment in rheumatoid arthritis

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Background: The EULAR guidelines for the treatment of rheumatoid arthritis (RA) recommend the use of conventional synthetic anti-rheumatic drugs (cs-DMARDs) at the onset of the disease and only in the case of therapeutic failure the addition of a biological drug (b-DMARD) is suggested. The use of biological treatment as first-line therapy is a critical issue.

Objectives: To evaluate in clinical practice determinants for first-line biological treatment in patients with RA.

Methods: A cohort of patients with RA, resident in a central Italian Region (Lazio: about 6 million of inhabitants) and with at least one DMARD prescription between 2010–2016 was selected using Health Information Systems. Only new users (1 year wash-out) were included and the first-line treatment was identified: cs-DMARD or b-DMARD. Through multivariate logistic regression models (OR; IC95%) determinants of therapy such as age, comorbidity and co-medication were investigated. The analysis was carried out for the whole population and separately for sex. Moreover, among patients with cs-DMARDs as first-line treatment, the switching versus a b-DMARD in the first year was analyzed.

Results: The DMARD-new users with RA, between 2010–2016, were 5,391; 5.5% (N = 296) of them with b-DMARD as first-line treatment (11.0% in combination with a cs-DMARD). Considering the year of dispensing, this percentage ranged from 3.6% (2015) to 7.4% (2011). Among the cs-DMARDs the most prescribed active ingredient was metrotrexate (59.1%), while among the b-DMARDs was etarnecept (32.4%), followed by adalimumab (22%). The average age of the cohort was 51 years with 77% of women; the prevalence of diseases such as hypertension, diabetes, hypothyroidism and cardiovascular diseases was 43.4%, 18.7%, 16.8% and 12.1% respectively. In the 6 months preceding the start of therapy, 61.3% used NSAIDs and 62.1% corticosteroids. Determinants of first-line b-DMARD use were: age ($OR_{<30 vs\ <65}$ = 5.9; 3.9–8.9), cancer (OR = 2.8; 1.5–5.2), cardiovascular diseases (OR = 1.8; 1.2–2.6), use of NSAIDs (OR = 0.6; 0.4–0.7) and corticosteroids (OR = 0.6; 0.5–0.7). The association pattern was similar between males and females. Finally, among the new users of cs-DMARDs, 7.5% of the patients started a b-DMARD in the first year of treatment.

Conclusions: In clinical practice, about 6% of patients with RA have a b-DMARD as first-line treatment. This therapeutic option, even if not supported by scientific evidence, is mostly link to younger age and clinical profile of the patients. Further analyses on real world data are necessary to investigate appropriateness and to promote a better use of these drugs.

990 | Racial disparities associated with risks of erythropoiesis-stimulating agents in cancer patients after Medicare reimbursement policy change

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Background: Due to risks of cardiovascular and thrombovascular events, Centers for Medicare and Medicaid Services (CMS) issued a Medicare reimbursement policy change for erythropoiesis-stimulating agents (ESAs) in cancer patients. Given different utilization patterns in different racial groups, racial disparities are significant policy concerns.

Objectives: To examine racial disparities associated with the risks of myocardial infarction (MI), stroke, and venous thromboembolism (VTE) events of ESAs after Medicare.

Methods: This study applied a retrospective incident user cohort design using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The index date was the date of the first ESA prescription. Incident users of ESAs were followed up to one year since the index date for a diagnosis of MI, stroke, or VTE. Individuals who were aged 66 years or older, were eligible for Medicare because

of age, had a primary diagnosis of breast cancer, colorectal cancer, lung cancer, lymphomas, ovarian cancer, or prostate cancer, received chemotherapy after cancer diagnosis, and initiated ESAs after chemotherapy were included in this study. We excluded individuals who had a diagnosis of MI, stroke, or VTE one year before the index date. ESAs use was measured based on Medicare Part B and D claims. The diagnoses of MI, stroke, and VTE were measured from Medicare Part A and B claims. Logistic regression models were used to examine racial disparities associated with Medicare reimbursement policy change on the risks of MI, stroke, and VTE among incident users of ESAs. Racial disparities were measured based on odds ratios (OR) of adverse events between Caucasians and African Americans.

Results: This study identified 17,236, 16,250, and 14,224 incident users of ESAs free of MI, stroke, and VTE, respectively. In the adjusted logistic regression analyses, Medicare reimbursement policy change was not associated with the future development of MI (OR: 1.01; 95% CI: 0.74–1.39), stroke (OR: 0.99; 95% CI: 0.84–1.15), and VTE (OR: 0.93; 95% CI: 0.84–1.03). Compared to Caucasians, African Americans had similar risks of MI (OR: 1.20; 95% CI: 0.68–2.10) and stroke (OR: 1.22; 95% CI: 0.94–1.59). African Americans, however, had an increased risk of VTE (OR: 1.34; 95% CI: 1.12–1.61) than Caucasians.

Conclusions: Medicare reimbursement policy change was associated with racial disparities in the risk of VTE in cancer patients using ESAs. Future Medicare policy changes should consider the potential unintended consequences on racial minorities.

991 | Incidence rate of serious infections in patients with ulcerative colitis with or without systemic therapy in the United States

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Background: Patients with ulcerative colitis (UC) are at a higher risk of developing serious infections. Information on serious infections risk is lacking in patients with UC on systemic therapies.

Objectives: To determine the incidence rate of serious infections in patients with UC treated with and without systemic therapy.

Methods: A retrospective cohort study was conducted in the Optum™ Clinformatics™ Data Mart (CDM) in the US by including adults who had at least two diagnoses of UC on medical claims ≥7 days apart in 2008–2018, and ≥ 1 year of continuous health plan enrollment before the index date, defined as the first treatment after the first UC diagnosis. Patients were classified into those treated with biologics, non-biologic systemic therapy, and no systemic therapy based on UC treatment. Descriptive statistics were generated for patient demographics and clinical characteristics. A standardized difference of greater than 0.1 was used to indicate meaningful difference between treatment groups. Crude and age and sex-standardized incidence rate and 95% confidence intervals (CIs) were estimated for serious infections by treatment.

Results: A total of 75,611 adults (45.3% male) with UC were eligible for the study. Among them, 7,394 (9.8%), 39,618 (52.4%) and 28,599 (37.8%) received biologics, non-biologic systemic therapy, and no systemic therapy, with mean age 45.2, 55.2 and 57.5 years, respectively. Patients who received no systemic therapy had higher proportion of hypertension, hyperlipidemia, diabetes, COPD, and chronic kidney disease than those on biologics and non-biologic systemic therapies, whereas those on biologics had the highest proportion of extra-intestinal manifestations and autoimmune diseases compared with those on non-biologic systemic therapy and not on systemic therapy. A total of 6,609 serious infections occurred during 180,331.1 patient-years, resulting in an overall incidence rate of 3.66 (95% CI 3.58–3.75) per 100 patient-years. The incidence rate (per 100 patient-years) was 4.86 (4.52–5.21), 1.87 (1.79–1.96) and 6.1 (5.91–6.29), with age- and sex-standardized rate being 5.21 (4.81–5.60), 1.65 (1.57–1.74) and 4.15 (3.99–4.30) among those who received biologics, non-biologic systemic, and no systemic therapy, respectively.

Conclusions: Among patients with UC, the incidence rate was highest in biologic users, followed by those not on a systemic therapy and those on non-biologic systemic therapy. These discrepancies may partially be attributed to differences in the proportion of patients with higher UC disease severity in the biologic users.

992 | Safety profile of two TNF-a inhibitors adalimumab and golimumab: An analysis of FAERS database 2012–2018

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Background: Both adalimumab (Humira) and golimumab (Simponi) are tumor necrosis alpha inhibitors that are indicated for the treatment of rheumatoid arthritis. Adalimumab contains a black box warning for an elevated risk of lymphoma and other fatal malignancies.

Objectives: The purpose of the study was to analyze the safety profile and adverse events associated with adalimumab and golimumab.

Methods: A retrospective descriptive study was conducted for two study drugs, adalimumab and golimumab, that were introduced into the market in 2002 and 2009 respectively. The data source was the FDA Adverse Events Reporting System (FAERS) from quarter 1 of 2012 to quarter 2 of 2018. Both brand names and bioequivalent names were used to extract and analyze the adverse event (AE) data. The frequently reported AEs were analyzed and categorized using the MedDRA preferred terminology. Numbers of AE reports, case profiles and malignancies were also compared between Humira and Simponi and grouped by age, sex, and year. Trendlines, histograms, and pie charts were used to present the descriptive data.

Results: There were approximately one million AEs reported for brand-name Humira, and 11,582 AEs reported for its bioequivalent form adalimumab. There were 84,069 for brand-name Simponi and 3,274 for golimumab. The most commonly reported AEs were nausea,

headache, pneumonia, vomiting, diarrhea, pyrexia, tuberculosis, lower respiratory tract infection, urinary tract infection, nasopharyngitis, influenza, and malaise. For malignancies, there were 8,884 (0.87%) cases reported for Humira and 1501 (2%) cases reported for Simponi. The most commonly reported malignancies were Lymphoma with 1146 (12%) cases for Humira, and 198 (13%) cases of breast cancer for Simponi. Average age was 51.2 for Humira and 58.3 for Simponi. AE cases were more commonly reported in females for Humira (46%) and Simponi (63%). The most commonly reported outcome was a severe medical event for Humira (82,875; 8%) and Simponi (13,934; 16.5%).

Conclusions: Both Simponi and Humira have serious safety profiles. Simponi seems to have more cases of malignancies and severe medical events than Humira. More post-marketing surveillance study is warranted for Simponi.

993 | Trends in the utilization of short-acting filgrastim following the United States market launch of the first biosimilar

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Background: In September 2015, filgrastim-sndz became the first Food and Drug Administration approved biosimilar available in the United States. Research suggests initial uptake of 32% in Medicare Part B; however, the adoption of filgrastim-sndz among Part D patients remains unknown.

Objectives: To identify and compare trends in Medicare Part B and Part D utilization of short-acting filgrastim products following biosimilar market entry.

Methods: We used 2015–2016 Part D Prescriber files and Physician and Other Supplier files from the Centers for Medicare and Medicaid Services Providers Utilization and Payment Data. We used the product's brand-name or Healthcare Common Procedure Coding System codes to identify Medicare Part D prescriptions (≥11) or Medicare Part B non-institutional claims for filgrastim products indicated for febrile neutropenia: filgrastim (originator biologic), tbo-filgrastim (follow-on biologic approved prior to the implementation of the US biosimilar licensure pathway) or filgrastim-sndz (biosimilar).

Results: Prior to biosimilar entry, 146,559 Medicare claims were filed for filgrastim products, of which Medicare Part B and D represented 91% and 9%, respectively. Originator filgrastim accounted for the majority of all filgrastim product use (95% and 98% of Part B and Part D claims, respectively). Following biosimilar entry of filgrastim-sndz, utilization of originator filgrastim declined to 60% of Part B and 74% of Part D claims; the follow-on biologic tbo-filgrastim increased to 7% of Part B and 2% of Part D claims; and the biosimilar filgrastim-sndz made up the remaining 33% of Part B and 24% of Part D claims.

Conclusions: Our findings are consistent with prior research and suggest that market entry of filgrastim-sndz likely contributed to the decreased use of originator filgrastim across Medicare beneficiaries; and that increased market competition may have prompted providers to switch to or increase the use of cheaper alternatives.

994 | Oral kinase inhibitors, biologics and serious infection in rheumatoid arthritis

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Background: Higher rates of serious infections have been reported in rheumatoid arthritis (RA) patients using biologics. Tofacitinib is the first of a unique class of oral kinase inhibitors that acts intrinsically against the JAK_STAT pathway, thereby modulating lymphocyte development and function. Studies have reported elevated risk of varicella zoster virus (VZV) infection in tofacitinib users but the risk of other serious bacterial infections are not well examined.

Objectives: To estimate the risk of hospitalized infections in RA patients started on tofacitinib (TOFA), abatacept (ABA), or tumor necrosis factor inhibitors (TNFi).

Methods: We identified RA patients defined as ≥1 RA diagnosis followed by biologic or tofacitinib use in the MarketScan® commercial database (2008–2017). We identified TNFi, ABA and TOFA users and followed them until the first occurrence of serious hospitalized infections (sepsis, pneumonia [PNA], meningitis, encephalitis, endocarditis, pyelonephritis, septic arthritis, osteomyelitis and VZV, defined using an inpatient primary diagnosis) or discontinuation of the drug. We described patient's characteristics and calculated incidence rates (IRs) of each infection endpoint and their 95% confidence intervals (CIs).

Results: Among 40,370 patients (mean age 50 years, 79% female), 6,117, 20,131, and 9,340 were TOF, TNFi, and ABA users, respectively. TNFi users were slightly younger and more likely to be male compared to ABA and TOFA users. TOFA users were more likely to be on steroids in the last year and less likely to have a diagnosis of hepatitis C. During a total follow-up of 24,688 person-years, we observed 1,478 events. The crude IR (95% CIs) of hospitalized VZV infection for TOFA, TNFi, ABA was 40 (32–48), 19 (17–21) and 22 (18–26), respectively. The RI for hospitalized PNA was 25 (19–31), 15 (13–17), and 12 (9–15) for TOFA, TNFi, and ABA, respectfully. The crude IR of other infectious outcomes were much lower and similar among the three groups.

Conclusions: The crude risk for VZV and PNA were significantly higher in TOFA users compared to TNFi and ABA users. The VZV finding was consistent with previous studies and the risk of other serious bacterial infections were similar among three groups except for PNA. Nonetheless, our current analyses are purely descriptive, as they do not fully consider the differences in measured patient characteristics. Also, we were not able to differentiate bacterial vs. viral PNA. Further studies are needed to better understand the risk of serious bacterial and viral infections among these novel DMARDs.

995 | Premedication and the risk for infusion related reactions among patients receiving monoclonal antibody therapy: A systematic review and meta-analysis

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Background: Premedication before the infusion of monoclonal antibodies have become standard of practice for many institutions; however, limited research has examined the efficacy and safety of premedication.
Objectives: The purpose of this study was to determine whether the use of premedication influences the risk of infusion related reactions (IRR) among patients receiving intravenous monoclonal antibody therapies.
Methods: Study design: Systematic review and meta-analysis of randomized controlled trials (RCT) and observational studies on premedication and risk of IRR among adult patients receiving intravenous monoclonal antibody therapy. **Data sources:** Ovid MEDLINE, Embase and EBM Reviews databases were searched from 1980 through January 2018 using a combination of various MESH terms and keywords. **Statistical analysis:** Random effects model was used as the primary analysis.
Results: A total of 14 studies including 11 observational studies and 3 RCT met inclusion criteria and were included in the review. Overall, meta-analysis of the observational studies showed no significant association between the use of any premedication regimen and the risk for IRR (OR = 0.88; 95%CI = 0.48–1.64) with significant heterogeneity among the studies (I^2 = 90%). Similarly, meta-analysis of the RCT also found no significant association between the use of any premedication regimen and the risk for IRR (RR = 0.93; 95%CI = 0.51–2.83) with significant heterogeneity among the studies (I^2 = 71%). Regarding specific premedication regimens, the use of antihistamines (OR = 1.86; 95%CI = 1.53–2.26; I^2 = 1%) or a combination of corticosteroids and antihistamines (OR = 2.85; 95%CI = 1.40–5.67); I^2 = 39%) as premedication were associated with an increased risk for IRR. There was no significant associations between the use corticosteroids (OR = 1.06; 95%CI = 0.57–2.14; I^2 = 51%) as premedication and the risk for IRR.
Conclusions: Limited research has examined whether premedication influences the risk of IRR among patients receiving intravenous monoclonal antibody therapy and it indicates lack of consistent evidence for the effectiveness of premedication on the risk for IRR among patients receiving intravenous monoclonal antibody therapy. Further research is recommended.

996 | Medication persistence in the first line of biological drugs in rheumatoid arthritis

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Background: The majority of studies report that there are no differences between biological drugs for the efficacy in rheumatoid arthritis (RA), but several factors may influence their persistence.
Objectives: To evaluate the persistence of biological drugs in the first line of biological treatment in RA.
Methods: We evaluated a historical cohort composed of RA patients of the Brazilian National Health System, who started the first line of biological treatment in the period between 2013 June to 2014 December. A national database was developed, using three administrative databases of the Brazilian National Health System Computing Department: The Outpatient Information System, the Mortality Information System, and the Hospital Information System. The endpoint was the medication persistence at 12 months. Kaplan–Meier survival curves were traced to verify the time up to treatment discontinuation, that is, the loss of biological drugs persistence at 12 months. Log-rank test was used to verify if differences between the groups have occurred for the persistence endpoint.
Results: A population composed of 16,518 individuals started the first line of biological drug. Out of such individuals, 8,622 (52.20%) persisted in the treatment at 12 months. Abatacept was the drug that presented higher persistence (300.32 days; Confidence Interval [CI] 95% 289.99–310.65), followed by golimumab (290.17 days; CI 95% 285.61–294.74), tocilizumab (286.61 days; CI 95% 274.75–298.48), etanercept (278.63 days; CI 95% 275.35–281.92), and adalimumab (274.20 days; CI 95% 271.37–271.37) and, with lower persistence certolizumab (262.9 days; CI 95% 251.41–274.39) and infliximab (245.18 days; CI 95% 238.64–251.71).
Conclusions: The medication persistence was different between biological drugs. The rigorous follow-up of patients, by a multidisciplinary team, is important to enable the development of strategies for the adequate use of such drugs.

997 | Antimicrobial resistance in non-typhoidal salmonella from retail poultry meat by antibiotic usage-related production claims - United States, 2005–2015

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Background: Antimicrobial resistance (AMR) to non-typhoidal *Salmonella* from contaminated poultry is a public health concern. Antibiotic-resistant *Salmonella* infections can be associated with severe illness and prolonged hospitalization. Injudicious use of antibiotics in humans and agriculture fuels emergence of resistance. The National Antimicrobial Resistance Monitoring System (NARMS) tracks AMR in *Salmonella* isolated from humans, animals and food sources.
Objectives: Characterize antimicrobial resistance in *Salmonella* recovered from retail poultry sold in the United States by antibiotic usage-related production claims.

Methods: We reviewed antimicrobial susceptibility and whole genome sequencing data from 3,793 *Salmonella* isolates collected from 2005–2015 through the NARMS retail meat program. These were recovered from 32,911 poultry meat samples purchased from randomly selected retail outlets across 14 states. Antibiotic usage claims on the poultry packaging were used to categorize the sample as conventionally raised or labeled as antibiotic-free. Pearson's chi-square tests and Student t-tests were used to compare drug resistance classes between isolates from poultry meat with and without antibiotic-related claims. Genetic mechanisms for resistance to selected antibiotics were investigated in a subset of isolates.

Results: The prevalence of *Salmonella* in conventional poultry meat was 11.8% (3,494/29,522) versus 8.8% (299/3,389) in poultry meat labeled as antibiotic-free ($p < 0.0001$). *Salmonella* from conventional poultry meat was more likely to be resistant to 3 or more drug classes (27.3%, 954/3,494) as was poultry meat labeled as antibiotic-free (10.0%, 30/299) [$p < 0.0001$]. Salmonella from conventional poultry exhibited significantly higher resistance in 5/9 drug classes including tetracycline ($p = 0.0379$) and penicillin ($p < 0.0001$). Beta-lactam resistance genes including bla_{CMY-2} were higher in isolates from conventional meat compared with isolates from samples labeled as antibiotic-free, 16.1% (215/1328) versus 5.2% (11/209) [$p < 0.0001$].

Conclusions: Conventionally-raised poultry meat was more likely to be contaminated with multi-drug resistant *Salmonella*. The presence of genes that decrease the power of antibiotics to treat patients with severe salmonellosis is concerning. These findings, from a decade-long collaborative national surveillance effort, highlight importance of judicious use of antibiotics in food-producing animals.

998 | Respiratory viral testing and antimicrobial de-escalation among hospitalized patients at a tertiary care facility, 2015–2016: A matched cohort study series

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Background: The use of multiplex respiratory viral panel (RVP) tests is increasing. Although costly, they enable identification of pathogens that would otherwise be clinically undetectable. These tests have the potential to limit unnecessary antibiotic use, but data are limited on their clinical effectiveness.

Objectives: To estimate risk differences (RD) for the relation between positive (+) and negative (−) inpatient respiratory viral tests (RVP *vs* rapid polymerase chain reaction, PCR, tests for influenza with or without respiratory syncytial virus) and subsequent antimicrobial de-escalation (discontinuation, intravenous to oral, or spectrum narrowing).

Methods: We reviewed electronic health record data on adults (age ≥ 18 years) who were admitted to an inpatient floor or stepdown unit at University of North Carolina Hospitals and had a respiratory viral test collected within 48 hours of admission between September 2015–April 2016 ($n = 1342$). We estimated 3-day RDs for the relation between respiratory viral testing and antimicrobial de-escalation. To control confounding and account for the 37-hour mean lag between PCR (faster) and RVP (slower) tests resulting, we leveraged the treatment decision design over a series of 1:1 matched cohort studies. Each study targeted a clinically relevant scenario: 1) ordering RVP test (*vs* no RVP order) after learning PCR- status; 2) learning RVP+ result (*vs* no RVP result) after knowing PCR- status; 3) learning RVP+ result (*vs* RVP-) after knowing PCR- status; and 4) learning RVP+ result (*vs* RVP-) given no prior PCR. For each subcohort, referent patients were matched to index patients by self-reported race, self-reported gender, respiratory viral test in prior month (y/n), age (+/−10 years), and season (+/−1.7 months).

Results: The overall cohort was 61% White, 29% African-American, 51% female, and median age was 56 years (IQR 39–69). Across all matched subcohorts, the matching success rate ranged 79–88% and referent 3-day risk of antimicrobial de-escalation ranged 0.6%–1.9%. In scenario 1, ordering RVP results was associated with higher de-escalation (3-day RD 7.6%; 95% confidence limits [CL] 3.2%, 12.1%). In scenarios 2–4, learning RVP+ results was associated with even higher de-escalation (3-day RDs 14.8%, 13.8%, and 15.4%, respectively; largest 95% CL difference was 21.9%).

Conclusions: RVP testing and positive RVP results were associated with increased antimicrobial de-escalation. Future research should evaluate potential effect modification across patient subgroups and cost-effectiveness of these tests.

999 | Comparing hospital and primary care physicians' attitudes to antibiotic resistance

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Background: Misuse of antibiotics either in primary care and hospital setting has been identified as one of the main causes of bacterial resistance.

Objectives: To identify attitudes of hospital and primary care physicians about antibiotic resistances.

Methods: The study was conducted in Portugal's Central Regional Health Administration and included 480 physicians working in primary care and 125 in working in hospitals setting, all in the National Health Service (NHS). A self-administered questionnaire with 17 statements regarding knowledge and attitudes towards antibiotic prescribing, antibiotic use and antimicrobial resistance was sent to the physicians. The statements were followed by a continuous visual analog scale (VAS) for respondents to mark with a cross, accordingly to their agreement with the sentence (from 0 to 20).

Results: Both primary care and hospital physicians report high agreement with the importance antibiotic resistances in their own setting, and that the dispensing antibiotics without a prescription should be more closely controlled. Primary care physicians are more convicted that new antibiotics will be developed to solve the problem of resistance [Percentile 75: 16, 11; $p < 0{,}001$], and that the prescription of an antibiotic to a patient does not influence the possible appearance of resistance [Percentile 75: 10, 3; p < 0,001]. They also have higher accordance with the use of a broad-spectrum antibiotic, in case of doubt, to ensure that the patient is cured of an infection [Percentile 75: 16, 13; $p = 0{,}013$]. Physicians working in hospital setting have higher accordance that in a primary-care context, one should wait for the microbiology results before treating an infectious disease [Percentile 75: 15, 11; p = 0,012].

Conclusions: This study revealed some differences between primary care and physicians' attitudes and perceptions about antibiotics use and bacterial resistances. A project to improve antibiotics use, the eHealthResp Project [FCT (PTDC/SAU-SER/31678/2017)] was approved to evaluate the effectiveness of e-Health tools in supporting clinical decision-making and empowerment of patients in the management of upper respiratory tract infections. *Acknowledgements:* Project PTDC/SAU-SER/31678/2017, supported by the operational program of competitiveness and internationalization (POCI), in its FEDER/FNR component POCI-01-0145-FEDER-031678, and the Foundation for Science and Technology, in its state budget component (OE) and Institute for Biomedicine - iBiMED (UID/BIM/04501/2013 and POCI-01-0145-FEDER-007628).

1000 | The role of comorbidities, infections, and treatments in sepsis: A retrospective analysis of a large United States electronic health record database

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Background: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, affecting more than one million patients per year in the United States. Chronic comorbid conditions that alter the immune system could also lead to sepsis.

Objectives: The objective of the present study was to examine comorbidities, complications, common pathogens, infections, and treatments of sepsis.

Methods: This retrospective study examined data from a U.S. electronic health record database (Cerner Health Facts®). All inpatient visits (age $\geq$ 18 years) between 2012–2016 with a principal ICD9/10 diagnosis of sepsis were included in the analysis. Chronic comorbid medical conditions, complications, and infections were characterized by corresponding ICD9/10 diagnosis codes. Laboratory test results and medications were examined to analyze treatment patterns.

Results: The study included 510,720 sepsis-related visits (50.2% female), with 49.7% of the cohort over 65 years old. Septic shock was present in 16.2% of visits, while 14.2% were in severe stage. The most prevalent comorbid conditions were chronic obstructive pulmonary disease (33.9%) and diabetes (33.5%). Organ failure was a major complication seen in 59.5% of visits. Urinary tract infection (31.4%) and pneumonia (31.2%) were observed to be the most common infections. The top pathogen identified was gram-negative rod/bacillus (13.7%), followed by *E. coli* (12.3%). During susceptibility testing for gram-negative rod/bacillus, aminoglycosides were the most commonly tested (2,816 tests). Gram-negative rod/bacillus was highly susceptible to quinolones (96.6%; 1,792 of 1,856 tests) and was most resistant to aminopenicillins (54.4%; 992 of 1,824 tests). IV hydration/fluid challenges (79.5%) and antibiotics (73.2%) were most commonly used for the treatment of sepsis. Within antibiotics, vancomycin (28.1%), levofloxacin (21.6%), and ceftriaxone (20.9%) were prescribed often.

Conclusions: This large database analysis provides insights on the pathogenesis, comorbidities and most often employed diagnosis/treatment strategies for sepsis.

1001 | Single nucleotide polymorphisms of Pfdhfr and Pfdhps: Implications on prophylactic malaria control measures in Maiduguri, Northeast Nigeria

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Background: Prophylactic malaria control measures with Intermittent Prophylactic Treatment in Pregnancy (IPTp), Intermittent Prophylactic Treatment in Infancy (IPTi) and Seasonal Malaria Chemoprevention (SMC) largely depend on efficacy of sulphadoxine-pyrimethamine (SP).

Objectives: The present study assessed Single Nucleotide Polymorphisms (SNPs) of *Pfdhfr* and *Pfdhps* in Maiduguri, Northeast Nigeria in other to ascertain the efficacy of SP in the region.

Methods: Dried blood-spot (DBS), Giemsa-stained thick and thin blood smears were collected from 63 randomly selected subjects of both sexes, aged <1–80 years with malaria parasitaemia at three study

sites in Maiduguri between May and October, 2018 following an informed consent. *Plasmodium specie* was determined and parasite density (PD) was estimated using the smears. Genomic DNA (gDNA) of *P. falciparum* was extracted from the DBS using QIAamp DNA Mini Kit. The gDNA was subjected to Nested Polymerase Chain Reaction (PCR) followed by Restriction Fragment Length Polymorphism (RFLP) to determine SNPs at codons N51I, C59R and S108 N of *Pfdhfr* and codons S436A/F, A437G and K540E of *Pfdhps*. The data were subjected to statistical analysis using appropriate tools.

Results: The geometric mean PD of the 63 subjects was 8845 (2100–13,400) asexual parasites/μl blood. The PD was neither influenced by study sites ($p > 0.05$), age ($p > 0.05$) nor sex ($p > 0.05$) of the subjects. The prevalence of triple *Pfdhfr* mutant alleles (51I, 59R and 108 N) was 60.3% (38/63) and was significantly higher ($p < 0.05$) than triple wild alleles (N51, C59 and S108) with 17.5% (11/63). The prevalence of the triple mutation was significantly higher ($p < 0.05$) among female (68.4%; 26/38) than male (48.0%; 12/25) subjects. Mutant allele 108 N had significantly highest ($p < 0.05$) prevalence (82.5%; 52/63) than 51I (60.3%; 38/63) and 59R (66.7%; 42/63). Double mutation of *Pfdhps* at codons S436A and A437G was recorded in 4.8% (3/63) of the samples with individual prevalence of 28.6% (18/63) and 27.0% (17/63) for 436A and 437G mutants, respectively ($p > 0.05$). No mutation was recorded at codon K540E.

Conclusions: The detection of mutant alleles of *Pfdhfr* and *Pfdhps* in the present study could be an indication of compromised efficacy of SP in Maiduguri, hence, the need for caution in the implementation of IPTp, IPTi and SMC in the region. These findings could contribute to success of malaria prophylaxis. However, urgent clinical and robust molecular studies may be required to ascertain the efficacy of the drugs prior to introduction of other prophylactic measures.

1002 | Association between phosphate disturbance and mortality among critically ill patients with sepsis and septic shock

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Background: Phosphate disturbance is one of the most common electrolyte disturbances encountered in the intensive care unit (ICU). There are limited studies linked it with increased ICU mortality. However, results still controversial.

Objectives: The aim of this study is to examine the association between hypophosphatemia, hyperphosphatemia on day one of the ICU admission and the ICU and hospital mortality in critically ill patients with septic and septic shock.

Methods: This is a retrospective cohort study that include adult patient with age ≥ 18 years old, critically ill with septic or septic shock, and admitted in either surgical, trauma or medical intensive care unit between January 2014 to September 2017. The patients divided into three groups based on their serum phosphate level during the first 24 hours of ICU admission. The hypophosphatemia less than 0.73 mmol/L, and hyperphosphatemia more than 1.52 mmol/L. The primary endpoints were all-cause ICU and hospital mortality. Secondary endpoints were ICU, hospital length of stay, and mechanical ventilation duration. Baseline characteristics and outcomes were reported as numbers and percentages for categorical variables and were compared among groups using Chi-square test. While continuous variables reported as means and standard deviations using ANOVA test. Multivariate logistic regression analysis was used to determine if phosphate level was an independent predictor for ICU or hospital mortality. Results were presented as adjusted odds ratio (OR) and 95% confidence intervals.

Results: Of the 1422 patients enrolled in the study, 188 (13%) were categorized as hypophosphatemia, 369 (26%) as hyperphosphatemia, and 865 (61%) as normophosphatemia at day one of their ICU admission. There were significant association between hyperphosphatemia and ICU mortality (adjusted OR 1.5, 95% CI 1.0–2.1, $P = 0.04$), and hospital mortality (adjusted OR 1.7, 95% CI 1.2–2.3, $P = 0.002$). However, there was a reduction on mortality between hypophosphatemia and ICU mortality (adjusted OR 0.5, 95% CI 0.27–0.9, $P = 0.02$), but was not significant with hospital mortality (adjusted OR 0.8, 95% CI 0.54–1.32, $P = 0.46$). Furthermore, there were no significant differences in ICU and hospital length of stay or mechanical ventilation duration between the groups.

Conclusions: Hyperphosphatemia is associated with increased ICU and hospital mortality in critically ill septic and septic shock patients. It serves as a strong independent risk factor for mortality. Future interventional studies are required to define the causal relationship between phosphate level and mortality.

1003 | CD4+ count and antiretroviral therapy contributing to patterns of prolonged amenorrhea among women with or at-risk of the human immunodeficiency virus

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Background: Recent studies have shown that one-third of HIV-infected women experience 12 months or more of prolonged amenorrhea (PA). This occurs more commonly in HIV-infected women relative to the general population. Research to date has not fully explored the association between CD4+ and antiretroviral therapy (ART) and intermittent PA.

Objectives: To assess the association between baseline sociodemographic, clinical, and treatment characteristics and intermittent PA.

Methods: Our study included 1,374 HIV+ and at-risk HIV- women age ≥ 18 years in the Women's Interagency HIV Study longitudinal cohort with at least one episode of PA, defined as 12 months of self-reported amenorrhea. We excluded women with hysterectomy

and double oophorectomy at any point, and women lost to follow-up after the first episode of PA. Patterns of amenorrhea were classified as: 1) single PA episode without resumption of menses, 2) single PA episode with resumption of menses, and 3) intermittent PA episodes. Baseline characteristics include: age at first PA (<45 years; ≥45 years), ART use, HIV status, race/ethnicity, BMI (underweight, normal, overweight/obese), current smoker, alcohol use (≥3 drinks/day), diabetes, hepatitis, and CD4+ count. We conducted bivariate chi-square analysis, and multinomial logistic regression in a subset of HIV+ women (*n* = 773) to examine the association between baseline ART and CD4+ with PA group (reference = single PA episode without resumption of menses), adjusting for all other baseline characteristics.

Results: Of our total sample, 66% (*n* = 910) had a single PA episode without resumption of menses, 7% (*n* = 90) had a single PA episode with resumption of menses, and 27% (*n* = 374) had intermittent PA episodes. Age at first PA, current smoker, alcohol use, BMI, race/ethnicity, and Hepatitis C coinfection were significantly associated with PA group. Baseline ART was not significantly different between women with a single PA episode with resumption of menses (OR: 0.68; 95% CI: 0.24–1.91) or intermittent PA (OR:1.54; 95% CI: 0.84–2.84) compared to women with a single PA episode who did not resume menses. Relative to women with a single PA without resumption of menses, women with a single PA episode and resumption of menses were less likely to have low CD4+ between 200–500 cells/mm^3 (OR: 0.44; 95% CI: 0.20–0.98) and Hepatitis C coinfection (OR: 0.27; 95% CI: 0.09–0.82).

Conclusions: Low CD4+ count was associated with decreased likelihood of resumed menses. Future research is warranted to see if time-varying CD4+ and ART, which alters CD4+, are associated with PA group.

1004 | Bacteriological study and antibacterial susceptibility of Ludwig's angina

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Background: The knowledge of the local pattern of infection and antibacterial sensitivity in Ludwig's angina is essential to enable efficacious treatment for it. However, no previous studies in Bangladesh have investigated the pattern of bacteria responsible for developing Ludwig's angina and antibiotic sensitivity.

Objectives: We aimed to evaluate the association between microorganisms responsible for Ludwig's angina and antibiotic sensitivity.

Methods: A prospective observational cohort study carried out from April 2016 to September 2016 in the Department of Otolaryngology & Head Neck Surgery (Dhaka Medical College Hospital, Bangladesh) and Department of Clinical Microbiology (International Centre for Diarrhoeal Disease Research, Bangladesh). A total of 100 patients with Ludwig's angina were included in the study. The responsible microorganisms and antibiotics sensitivity test were performed for all patients. Data were analyzed using a logistic regression through SPSS.

Results: The most frequently isolated organism in Ludwig's angina was Streptococcus (40%) followed bt *Staphylococcus aureus* (23%). The aerobic bacteria were found to be 60% resistant to doxycycline, 59% to penicillin-G and 59%% to ampicillin, whereas they were found to be 65% susceptible to ceftriaxone, 58% to ceftazidime and 56% to ciprofloxacin. The vancomycin was sensitive to 70% patients for Streptococcus, odds ratios (OR) = 2.19 [95% confidence interval (CI): 0.90–5.42] and to 65% patients for staphylococcus aureas, (OR) = 1.63 [(CI): 0.65–5.44].

Conclusions: Early diagnosis and treatment is essential to prevent complications. All patients must be treated initially with intravenous antibiotics, with treatment subsequently updated based on a culture and sensitivity report to reduce the mortality and morbidity.

1005 | Epidemiology of respiratory syncytial virus-associated illnesses in young children

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Background: RSV-associated illness (RSV-AI) is a primary cause of morbidity and hospitalization of young children and infants, most often presenting as bronchiolitis or other types of lower respiratory tract infection.

Objectives: To determine clinical and demographic factors of RSV-AI cases and explore epidemiologic patterns of RSV-AI in a cohort of young children in the U. S to inform RSV product development.

Methods: This retrospective cohort analysis used claims data obtained from 16 Data Partners contributing to the FDA's Sentinel System. We identified RSV-AI cases in children 1 month to 5 years from Jan. 2008 through June 2016. An RSV-AI case was defined as an RSV diagnosis code in the child's claims data during the study period. Baseline characteristics examined included care setting of RSV-AI diagnosis and three RSV risk factors: prematurity, chronic lung disease (CLD), and congenital heart disease (CHD). Risk factors were identified by occurrence of a relevant diagnosis code in the child's claims history from birth through the RSV-AI index date for prematurity, and through 2 months post RSV-AI index date for CLD and CHD. RSV diagnoses were classified by care setting: inpatient hospital stays or outpatient encounters (emergency department and ambulatory care). We calculated the proportion of RSV-AI cases with the risk factors of interest and other demographic characteristics by care setting.

Results: Our analysis identified 138,669 cases of RSV-AI among children 1–6 months of age and 179,259 cases among children 7 to 60 months of age. Outpatient encounters predominated in both age groups (1–6 months: *N* = 24,192 inpatient, *N* = 119,363 outpatient; 7–60 months: *N* = 20,002 inpatient, *N* = 156,019 outpatient). Children

with documented risk factors for RSV-AI comprised a small proportion of total cases [CLD lt3%, CHD lt6%, extremely preterm (lt29 weeks) lt5% for both groups].

Conclusions: It is well acknowledged that RSV-AI is a significant concern in children with CLD, CHD, or prematurity. However, using the Sentinel System, we found that most children with RSV-AI did not have these risk factors. Future development of new RSV prophylactics and therapeutics will need to consider these findings.

1006 | Identification of ordinal endpoints indicating influenza complications: A feasibility study relevant to the study of medical countermeasures

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Background: Medical countermeasures (MCMs) are FDA-regulated products used in the event of a public health emergency. "Ordinal endpoints" (categorical outcomes evaluated on an ordered scale, e.g. increasing severity) of influenza complications may be useful in evaluating the utilization, safety, and/or effectiveness of influenza-related MCMs.

Objectives: To determine whether ordinal endpoints can be identified for patients with influenza in the Sentinel System.

Methods: Using the Truven Health MarketScan® Databases in the Sentinel Common Data Model, we identified health plan members over 6 months of age with influenza-like illness (ILI). ILI was identified using ICD-9-CM and ICD-10-CM diagnosis codes (without lab confirmation) in the outpatient and emergency department settings in two periods (July 2014–June 2015 and July 2015–June 2016). Starting on the day of ILI diagnosis through 30 days after, we identified inpatient admissions; using diagnosis and procedure codes, we identified use of critical care, supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). We calculated the rate of these endpoints per 10,000 ILI diagnoses by period and age group. We also calculated the proportion of the cohorts with influenza vaccination (183-day lookback) and influenza testing (days 0 through 30).

Results: We identified 551,777 ILI diagnoses in 2014–15. The endpoint rates ordered from least to most severe were: 111/10,000 ILI diagnoses for inpatient care, 84/10,000 for critical care, 3/10,000 for supplemental oxygen, 6/10,000 for mechanical ventilation, and 0.14/10,000 for ECMO. Members over 65 years had the highest rate of hospitalization following ILI diagnosis (836/10,000) as well as all other endpoints, but they had the lowest rate of influenza testing (3,747/10,000 compared to 6,999/10,000 among all other ages). One-quarter (25%) of patients with ILI had evidence of influenza vaccination. We identified 267,314 diagnoses of ILI in the 2015–16 period and endpoints were captured at somewhat higher rates compared to the prior period. Influenza vaccination was observed among 17% of those with ILI in the 2015–16 period; influenza testing occurred among 66%.

Conclusions: We demonstrated the feasibility of identifying complications among individuals diagnosed with ILI, via ordinal endpoints, in a large claims database. However, mechanical ventilation and supplemental oxygen may not be well captured due to the nature of billing practices. Next steps include conducting this analysis in the Sentinel System.

1007 | Hospitalizations due to *Klebsiella pneumoniae* pneumonia in the United States

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Background: *Klebsiella pneumoniae* are an important source of community-acquired pneumonia. The prevalence of pneumonia infections associated with *K. pneumoniae* has not been explored in the United States (US) recently.

Objectives: To determine the rates of *K. pneumoniae* in the (US) using National Inpatient Sample (NIS) Data and compare results with existing literature.

Methods: Pneumonia associated with *K. pneumoniae* infections were identified for 2012–2014 using the ICD-9-CM code 482.0 (*K. pneumoniae* pneumonia) in the NIS, which provides data on inpatient visits from a sample of US hospitals. Age- and gender-specific hospitalization rates were calculated by dividing the number of hospitalizations for each gender & age group by the US population and then averaging the rates. Two targeted literature searches were conducted using PUBMED to estimate rates of *K. pneumoniae* pneumonia in the US: the first to identify the proportion of pneumonia cases due to *K. pneumoniae*, and the second to identify studies describing the total prevalence of pneumonia. The proportion of pneumonia associated with *K. pneumoniae* was then applied to the rate of pneumonia to determine the literature-based rate of *K. pneumoniae* pneumonia. Rates calculated from the NIS data and the literature estimates were applied to the US 2017 population to determine the prevalence of *K. pneumoniae*.

Results: From 2012–2014, 66,065 hospitalizations were identified with *K. pneumoniae* pneumonia in the NIS. There were 7.1 hospitalizations per 100,000 people per year on average. Higher rates of hospitalizations were consistently found among males (8.7 vs 5.5) and the elderly (≥65: 28.7 vs <65: 3.6). Using the proportion of pneumonia comprised by *K. pneumoniae* and the total prevalence of pneumonia identified in the literature, the rate was estimated at 29.26 cases per 100,000 people per year; substantially more than the overall NIS estimate, though similar to the NIS rate observed in the elderly. This may be explained by the population included in the study used as the

prevalence estimate for *K. pneumoniae* pneumonia, which had a median age of 57.

Conclusions: NIS data is a conservative, population-based estimate and may be more robust than the literature-based estimates, which literature are often determined from smaller subsets of specific populations and may not be an accurate representation of the true disease burden. It is important to assess the representativeness of the patient population before making national estimates of disease burden.

1009 | A conceptual model to evaluate disease-related stigma and access to healthcare among patients with hepatitis C virus infection

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Background: The number of individuals with hepatitis C virus (HCV) infections has tripled since 2010, due to increasing injection opioid use, and HCV now causes more deaths each year than any other infectious disease. Despite curative medications, most patients remain undiagnosed, are not linked into care, and do not receive antiviral treatment. Disease-related stigma, a social process linking individual attributes to medical diagnoses, is associated with poor health outcomes and decreased quality of life. Disease-related stigma may be intensifiedamong patients experiencing multiple forms of stigma, such as due to racism or substance use. Several studies have called for conceptual models to assess the impact of stigma on access to healthcare and aid the development and testing of interventions.

Objectives: This paper proposes a conceptual model of the determinants and consequences of HCV-related stigma in access to healthcare, treatment initiation, and antiretroviral adherence.

Methods: We conducted semi-structured interviews among 20 patients with a history of HCV infection who presented to care at five academic and community-based outpatient clinics across Philadelphia. We collected narrative data on patient experiences with HCV and situations within which perceptions of stigma arise and influence engagement with healthcare.

Results: We identified multiple intersecting stigmatized attributes, such as injection drug use, HIV coinfection, race, and poor HCV-related knowledge, which may amplify experiences of stigma among patients with HCV. As a result of HCV-related stigma, patients described social distancing by family and friends, often choose not to disclose their HCV status, and/or felt socially and emotionally isolated.

Conclusions: Using an iterative approach, we developed a conceptual model that links HCV-stigma, stigmas of other attributes, and the social effects on the patient's access to HCV testing, linkage to care, and HCV treatment adherence. This model can be used to guide research and interventions to improve patient engagement in care and health-related quality of life.

1010 | Geospatial analysis of gonorrhea incidence, antibiotic resistance and internet usage

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Background: A geospatial analysis was performed to further understand the relationship between gonorrhea incidence, antibiotic resistance and internet usage has been performed.

Objectives: To investigate the purported relationship between the increase in gonorrhea incidence and antibiotic resistance reported at the country level in Europe and the use of hookup apps.

Methods: Gonorrhea incidence and resistance to the commonly prescribed antibiotics, Ciprofloxacin, Azithromycin, Cefixime and Penicillin G were obtained from the European Center for Disease Control (ECDC) Surveillance Report 2014. Additional country level data that represent general population characteristics and demographics were obtained from the World Bank and Social Progress Index. Maps were created in ArcGIS by combining the aforementioned data sources with World boundary shapefiles, missing data were modeled using an Inverse Distance Weighted (IDW) algorithm. Statistical analysis by Principle Component Analysis (PCA) and Partial Least Squares (PLS) as implemented in Simca 13.0 was combined with visual data exploration performed in Spotfire.

Results: The PLS model obtained was moderately predictive of gonorrhea incidence across the full dataset, with ciprofloxacin resistance and internet usage being among the most important variable descriptors. Countries with the highest ciprofloxacin resistance were visually selected from a box plot where the European region was divided geographically. The relationship between gonorrhea incidence and internet usage was updated on a scatter plot to reflect the selected countries, whereupon a strong correlation was observed. This was not the case when all countries where included in the analysis.

Conclusions: A subset of European countries with high ciprofloxacin resistance, predominantly situated through the center of the continent, demonstrated a strong relationship between gonorrhea incidence and internet usage. This study may support the notion that an increasing trend in gonorrhea incidence in certain countries could be related to the use of internet-based dating apps.

1011 | Describing the epidemiology of cold and flu in hypertensive patients in the US by analyzing with novel observational health data sciences and informatics (OHDSI) tools

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Background: With recent changes to guidelines published by the American College of Cardiology/American Heart Association (ACC/AHA), nearly half of all adult Americans are classified as having hypertension (HBP). Oral decongestants, commonly taken by patients to relieve nasal congestion due to cold or influenza (flu), may cause an increase in blood pressure. The AHA therefore advises that hypertensive patients be cautious in choosing cold/flu products.

Objectives: The aim of this study is to describe the characteristics and incidence of patients in the United States (US) who are hypertensive and have had at least one diagnosis of cold or flu.

Methods: The US Truven Market Scan Medicare Supplemental beneficiaries (MDCR) and Commercial Claims and Encounters (CCAE) databases converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) were used as data sources in this study. MDCR includes elderly patients who are 65 or older. The exposure of interest was a diagnosis of HBP whilst the primary outcome was incidence rates of cold or flu annually from 2007–2016. The secondary outcomes included identifying any seasonal trends in incidence rates by looking at the monthly incidence rates as well as describing patient characteristics such as comorbidities and co-medications. ATLAS tool within OHDSI platform was used to create cohorts and calculate the incidence rates.

Results: The majority of HBP patients with at least one diagnosis of cold or flu were aged 40 and over. The most common comorbidities in this patient population were inflammation, pain and hyperlipidaemia. The average incidence rates of HBP patients with at least one diagnosis of cold or flu between 2007 and 2016 were 1.07 and 1.75 per 1000 person years in CCAE, respectively, and 0.70 and 0.85 in MDCR, respectively. Incidence rates were lowest in 2007 for both cold and flu. The incidence of flu peaked (4.05) in 2009, dropped in 2010, before gently increasing until 2014 when the rate decreased again. In contrast, the incidence rates of cold remained fairly stable over time. Seasonally, the incidence rates were generally highest in December and March each year for both cold and flu. The study results also shows a peak for flu in 2009 when the pandemic flu occurred in US.

Conclusions: The results from this retrospective observational study show that cold and flu are frequent events in patients diagnosed with HBP. The incidence rates for HBP patients with at least one diagnosis of cold or flu have been shown to fluctuate over time but typically increase between the months of December and March.

1012 | Aerobic micro-organisms and antibiotic sensitivity: A study on head and neck space infection

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Background: Antibiotics are extensively used in daily clinical practice in many developing countries including Bangladesh. However, no previous studies in Bangladesh have investigated in the association between aerobic micro-organisms and antibiotic sensitivity of head and neck space infection.

Objectives: We aimed to evaluate the association between aerobic microorganisms and antibiotic sensitivity for infections and antimicrobial susceptibility in head and neck (single and multiple) abscesses.

Methods: A prospective observational cohort study carried out from January 2016 to July 2016 in the Department of Otolaryngology & Head Neck Surgery (Dhaka Medical College Hospital, Bangladesh) and Department of Clinical Microbiology (International Centre for Diarrhoeal Disease Research, Bangladesh). After considering inclusion and exclusion criteria, a total of 100 patients in both sex with deep neck infections were included. The aerobic micro-organisms and antibiotics sensitivity test were performed for all patients. Data were analyzed using a logistic regression through SPSS.

Results: The highly common bacteria were *Staphylococcus aureus* (23%) and acinetobacter species (16%). The aerobic bacteria were found to be 82% resistant to cefixim, 79% to azithromycin and 65% to ampicillin. The antibiotic Ceftriaxone was most (89% patients) sensitive for acinetobacter species, odds ratios (OR) = 2.67 [95% confidence interval (CI): 0.75–9.42] and to 79% patients for staphylococcus aureas, (OR) = 2.32 [(CI): 0.65–8.33].

Conclusions: Although there is a big signal for antibiotics sensitivity, because of low power, we did not identify any significant associations between aerobic microorganisms and antibiotic sensitivity. We recommend to treated patients initially with intravenous antibiotics using proper guidelines to reduce the antibiotic resistance.

1013 | Patient characteristics and current management of systemic lupus erythematosus patients in a large, representative US-based real world registry cohort

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Background: Systemic lupus erythematosus (SLE) is a heterogeneous, multifactorial disease with a debilitating and highly variable clinical course. Real world data are critical to better understand these patients and their unmet clinical needs, as clinical trials are by design highly restrictive and typically not representative of the overall SLE population.

Objectives: To assess clinical, laboratory, symptomatic and disease activity information in SLE patients.

Methods: The OM1 SLE Registry (OM1, Boston), an ongoing, continually enrolling, representative sample of patients with SLE in the U.S. who are followed prospectively by specialists was used to characterize patient characteristics, disease manifestations, and treatments. SLE Registry patient data and linked administrative claims data from January 2013–December 2018 were utilized.

Results: The average age of the 35,484 SLE Registry patients was 49.9 years (standard deviation = 15.1), and consistent with the epidemiology of lupus, 92% of patients were female. Nearly 20% had evidence of lupus nephritis, while 2% had lupus endocarditis or pericarditis. While 8.5% of patients were treated with the disease-modifying therapy (DMT) Benlysta (belimumab), 75% were treated with anti-malarials and many with other 'off label' therapies. Nearly one-third of patients had at least a one Multi-Dimensional Health Assessment Questionnaire score (MDHAQ). Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores were reported for over 1,400 patients. and 20% showed high or very high disease activity.

Conclusions: Use of a representative, real-world cohort of SLE patients followed by rheumatologists provides unique information on treatment patterns and outcomes. Disease activity scores may be useful to identify patients for trials, but are not routinely collected in clinical practice. Treatment options are currently limited to a single DMT and more typically a combination of off-label immunosuppressants and steroids, demonstrating an unmet clinical need for patients with this debilitating condition.

1014 | Predictors for poor drug-resistant tuberculosis treatment outcomes in the Netherlands: A retrospective cohort study

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Background: Population migration and complex treatment of drug-resistant tuberculosis (DR-TB) patients are major issues in low incidence TB countries.

Objectives: We aimed to analyze patient risk factors for poor outcome of TB treatment among DR-TB patients in the Netherlands.

Methods: This retrospective cohort study included adult patients with confirmed DR-TB treated from 2005 to 2015. We obtained data from a nationwide exhaustive registry of tuberculosis patients in the Netherlands. Predictors for unsuccessful TB treatment (defaulted and failed treatment) and TB-associated mortality were analyzed using multivariate logistic regression.

Results: Among 10,303 registered TB patients, 545 patients with DR-TB (5%) were included. The majority of patients were foreign-born (86%) and newly diagnosed TB (89%) patients. The cumulative incidence for unsuccessful treatment and mortality were 5% and 1%, respectively. Among all DR-TB cases, having Multidrug-resistant TB (MDR-TB) (OR 4.43; 95%CI 1.70–11.60), being homeless (OR 9.10; 95%CI 2.32–35.74), and drug addiction (OR 6.66; 95%CI 1.72–25.82) were predictors for unsuccessful treatment, while miliary and central nervous system TB (OR 15.60; 95%CI 2.18–111.52) were predictors for TB mortality. Furthermore, males (OR 9.80; 95%CI 1.18–81.68) and drug addicts (OR 7.50; 95%CI 1.07–52.37) were identified as independent predictors for poor treatment outcomes (unsuccessful treatment or TB-associated mortality) in the subgroup of MDR-TB cases.

Conclusions: The majority of cases were primary drug-resistant and foreign-born. To further improve treatment outcome, special attention should be given to the high-risk DR-TB patients.

1015 | Risk of venous thromboembolic events in adult patients with systemic lupus erythematosus: Systematic review and meta-analysis

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Background: Although observational studies suggest people with systemic lupus erythematosus (SLE) have a heightened risk of venous thromboembolic events (VTEs), meta-analyses that integrate evidence across studies to estimate the pooled risk have not been performed.

Objectives: To conduct a systematic review and meta-analysis to estimate risk of VTE, including pulmonary embolism (PE) and deep vein thrombosis (DVT), in patients with SLE.

Methods: We conducted a systematic review using MEDLINE and EMBASE from inception to March 2018 to identify observational studies (cohort and cross-sectional) that evaluated risk of several major cardiovascular outcomes in patients with SLE compared with a general population or healthy controls (protocol published in PROSPERO 2018 CRD42018098690). Here, we report the results for venous thromboembolic outcomes. Studies were included that provided effect estimates (relative risks or hazard ratios) for the calculation of pooled effect estimates. Random effects models were used to calculate pooled risk ratios (RRs) and 95% confidence intervals (CIs) separately for VTE, PE, and DVT. Visualization of funnel plots and the Egger's test were used to evaluate publication bias. Robustness of the results was tested using the leave-one-out function. Sensitivity analysis was used to assess the impact of removing studies with high risk of bias (ie, cross-sectional).

Results: A total of 9 studies were identified for inclusion in the meta-analysis: 7 for VTE (including 2 cross-sectional studies), 3 for DVT, and 4 for PE. Meta-analysis of the VTE studies showed a significantly increased RR of 3.67 (95% CI: 2.10 to 6.42) for patients with SLE compared with a general population. Removing the 2 cross-sectional studies did not impact the results (RR 4.06 [95% CI: 3.12 to 5.28]). The pooled RRs for PE and DVT were 4.47 (95% CI: 1.79 to 11.15) and 5.51 (95% CI: 2.27 to 13.39), respectively. The statistical

heterogeneity was high, with an I^2 ranging between 92% and 99%. Visual examination of the funnel plots showed evidence of publication bias; however, this was not supported by the Egger's test results. The leave-one-out function confirmed the robustness of the results.

Conclusions: Overall, risk of VTE was found to be significantly higher, >3–6-fold higher, among patients with SLE compared with the general population. Future research should focus on assessing the impact of traditional and SLE-specific modifiable risk factors on VTE to further identify patients with SLE most at risk to support targeting prevention and treatment strategies.

1016 | Bariatric surgery increases the risk of major osteoporotic fracture: A self-controlled case series patients from the CPRD GOLD database linked to HES

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Background: The number of people undergoing bariatric surgery is likely to increase due to the obesity epidemic. Evidence suggests that bariatric surgery may increase the risk of fracture, however it is unclear whether this is due to the differences in characteristics between patients with and without surgery.

Objectives: To assess the association between bariatric surgery and fracture risk using a within person design.

Methods: A self-controlled case series analysis was undertaken on patients undergoing bariatric surgery and experiencing a fracture within 5 years either side of surgery date in the clinical practice research datalink (CPRD) GOLD dataset linked to hospital episode statistics (HES). The primary outcome was any fracture (except skull or digits), secondary outcomes were major (hip, vertebrae, forearm and humerus) and peripheral (forearm and lower leg) fractures. A Poisson model, producing incidence rate ratios (IRR), compared the 5-year post-operative fracture incidence to the 5-year pre fracture window. A post hoc analysis separated the two post-operative time windows into 0–2 years and 2.01–5 years. All models are adjusted for time varying bisphosphonate use.

Results: Of 5,492 patients undergoing bariatric surgery, 252 patients had 272 fractures at any site, 75 had 80 major osteoporotic fractures and 126 had 135 peripheral fractures. Only major fracture risk was found to be increased, with a near three fold excess risk (IRR (95% CI), 2.70 (1.31, 5.57)). Other results were 1.17 (0.86, 1.60) and 0.92 (0.60, 1.42) for any and peripheral fractures respectively. The post hoc analysis identified statistically significant increases to risk in the 3rd to 5th year post surgery for both any and major fractures 1.73 (1.08, 2.77) and 4.98 (1.94, 12.78) respectively. Major osteoporotic fractures also showed an increase risk in the first two years IRR 2.49 (1.17, 5.30). No increase in risk of peripheral fractures was observed.

Conclusions: Although only 75 patients had major osteoporotic fracture/s, risk post-surgery increased 2.5 times for the first two years before further increasing to 5-fold for the next three years. Further research is needed to understand the underlying mechanisms and potential therapy.

1017 | Characteristics and symptom severity of 21,101 patients reporting systemic lupus erythematosus in the PatientsLikeMe online health community

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Background: Online health communities and research networks such as PatientsLikeMe (PLM) may provide important insight into understanding chronic diseases, including systemic lupus erythematous (SLE).

Objectives: To describe the characteristics of patients with SLE in PLM.

Methods: Retrospective observational study in PLM online health network database. Inclusion criteria were registration with PLM between 2011–2017, aged over 18 years at registration, and reported both SLE and treatment with one or more SLE medications (anti-malarials, immunosuppressives, corticosteroids, calcineurin inhibitors and biologics). Information reported within 30 days of registration was used to assess eligibility and characterize demographics and clinical characteristics, comorbidities, treatment, and severity of symptoms they reported, both general (included in symptom panel for all PLM patients) and additional SLE symptoms.

Results: 21,101 patients met the inclusion criteria. The median age at registration was 46 years (IQR 38–53), the majority were female (96.8%, *N* = 21 050), and 94.8% (18,491/19,502) patients who reported country were US residents. The 17,994 patients who recorded race were predominately Caucasian (67.8%) and African-American (22.4%). In the 6 489 patients who reported when they had first experienced SLE symptoms the median age of onset was 30 years (IQR 21–39) and age at first diagnosis was 36 years (IQR 27–44) (*N* = 6 936). The most commonly reported comorbidities were fibromyalgia 7.9%, discoid lupus 6.8%, lupus nephritis 6.3%, rheumatoid arthritis 4.8%, subacute cutaneous lupus 4.7%, Sjogren's Syndrome 3.9%, CNS lupus 3.9%, and lupus pneumonitis 3.1%. At registration patients reported having tried an average of 2.2 SLE medications, most commonly; anti-malarials 83.8%, corticosteroids 78.8%, immunosuppressive 32.3%, and biologic treatment 9.4%. Around 31% of patients (N = 6,448) entered any symptom report at registration. Of those who reported specific symptoms these were rated as moderate

or severe by >80% for fatigue, pain, and joint pain and > 50% for insomnia, brain fog, muscle pain, joint swelling, sun sensitivity and muscle weakness.

Conclusions: The age, gender and race of SLE patients in the PLM community are broadly consistent with the general US SLE population. The PLM SLE population provides a unique source of real world information on the patient experience of symptoms of SLE beyond the clinical environment that can be utilized to improve understanding of SLE.

1018 | Systemic lupus erythematosus (SLE) disease characteristics associated with the type I interferon gene signature: Baseline data of the SLE prospective observational cohort study (SPOCS)

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Background: Despite accumulating data on the role of type I interferons (IFNs) in the pathogenesis of SLE, real-world, longitudinal clinical data on the type I IFN gene signature (IFNGS) collected from patients with SLE are limited.

Objectives: This initial analysis of the SLE Prospective Observational Cohort Study (SPOCS; NCT03189875) examined the prevalence of the type I IFNGS (high vs low) and its association with baseline SLE disease characteristics in patients with moderately to severely active SLE receiving standard-of-care treatment.

Methods: SPOCS is an international, multicenter, prospective observational cohort study of patients enrolled with moderately to severely active SLE (SLEDAI-2 K $\geq$ 6 at entry) from Australia, Canada, France, Germany, Italy, Spain, the United Kingdom, and the United States; a completion date of 2022 is planned. Patients are evaluated biannually during a 3-year follow-up period. At each visit, data are collected on disease activity and damage, treatment received, type I IFNGS (stratified high or low IFNGS based on a predefined cutoff), and several patient-reported outcomes.

Results: As of November 15, 2018, a total of 307 patients were enrolled in SPOCS (North America, *n* = 184; Europe, *n* = 123), of whom 96.1% (*n* = 295) were female, with a median age of 46 years (range: 18–88). At study entry, the prevalence of high type I IFNGS was 70.5% (*n* = 210) vs 27.9% (*n* = 83) for low type I IFNGS, with 1.7% (*n* = 5) unknown (9 missing data). IFNGS-high patients were younger than IFNGS-low patients (median: 42.5 years [range: 18–82] vs 50 years [19–88], *P* < 0.0001) and diagnosed with SLE at an earlier age (*P* < 0.0001). SLEDAI-2 K scores were greater for IFNGS-high patients vs IFNGS-low patients (*P* = 0.0002), whereas SDI scores were similar between the 2 groups. Fewer comorbidities were reported for IFNGS-high patients than for IFNGS-low patients (79.5% [*n* = 167] vs 91.6% [*n* = 76], *P* = 0.0136). Lower complement C3 and C4 levels were observed in IFNGS-high vs -low patients. At study entry, antinuclear antibodies and ribonucleoprotein antibodies were more frequent in the IFNGS-high vs IFNGS-low subset of patients. A greater percentage of IFNGS-high patients were dsDNA antibody positive vs IFNGS-low patients (*P* = 0.0411).

Conclusions: The profile of patients with a baseline high type I IFNGS differed from those with low type I IFNGS, in that those with high type I IFNGS comprised a group that on average was younger, had greater SLEDAI-2 K scores, was more serologically active, and seemed to have fewer comorbidities.

1019 | Prevalence and incidence of venous thromboembolism among patients with rheumatoid arthritis in Japan

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Background: While there is an accumulating evidence on the relationship between rheumatoid arthritis (RA) and thromboembolism, epidemiological studies evaluating prevalence and incidence rates of venous thrombotic events (VTE) among Japanese patients with RA are sparse.

Objectives: To estimate prevalence and incidence rates of VTE among patients with RA in Japan.

Methods: The Medical Data Vision (MDV) administrative claims database was used to identify a cohort of adult (more than 18 years old) Japanese patients with RA between September 2012 and August 2017. Patients had more than 2 times RA diagnosis codes plus use of any disease-modifying anti-rheumatic drugs (DMARD) or Janus kinase (JAK) inhibitors within 31 days, and had at least 365 days of continuous enrollment prior to, and 365 days follow-up period after the index date (first prescription date of any conventional or biological DMARD (cDMARD and bDMARD, respectively). Patients who had prior history of VTE in the prior year and used another cDMARD or bDMARD in the same class in 365 days prior to index date were excluded. ICD-10-CM codes related to deep vein thrombosis or pulmonary embolism were used to identify VTE, combined with inpatient or outpatient drug claim for anticoagulant medications use within 31 days following the inpatient or outpatient VTE diagnosis. Additionally, the procedure code of ultrasound was exploratory added to VTE definition. Prevalence (%) and incidence rates per 100 person-years (PY) were estimated for the cohort, and reported overall and by DMARD class.

Results: A total of 15,095 patients with RA were identified (68.2% females, mean age 65.2 years). The prevalence and incidence rate of VTE were 1.1% and 0.44 per 100 PY, respectively. The corresponding rate decreased when the procedure code of ultrasound was included in VTE definition (prevalence, 0.3%; incidence, 0.11 per 100 PY). The prevalence and incidence of VTE was slightly higher among patients treated with bDMARD vs. cDMARD (1.3% vs. 1.1%; 0.47 vs. 0.43 per 100 PY).

Conclusions: The incidence of VTE among patients with RA in the MDV database is consistent with previous studies. However, the addition of a requirement for an ultrasound procedure code to the definition of VTE leads to a lower rate. Further studies are suggested to characterize VTE rates in Japanese patients with RA.

1020 | The effect of concomitant diabetes on RA-related outcomes: Results from the ACR's RISE registry

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Background: Some evidence has suggested that RA patients with diabetes might be more likely to have worse clinical outcomes and adverse events compared to RA patients without diabetes.

Objectives: We evaluated the effects of diabetes on HAQ (Health Assessment Questionnaire) change and infection in RA patients, comparing those with diabetes to those without diabetes.

Methods: Using the ACR's Rheumatology Informatics System for Effectiveness (RISE) EHR-based registry, we identified RA patients who had ≥1 rheumatologist visit with a valid HAQ measured (index visit) in 2016. Eligible patients were required to have ≥1 previous visit and a subsequent outcome visit with any HAQ measured at 12 months (± 3 months) after the index visit. We identified diabetes based on ≥1 ICD-9 or ICD-10 diagnosis code, any medication for diabetes, or elevated diabetes lab value (A1C, random glucose) using all available data prior to the index visit. Mean HAQ change between the index and outcome visit was calculated based on HAQ categories at the index visit (0–0.5, 0.5–1, and 1–3). Generalized linear models was used to calculate the adjusted mean HAQ change controlling for potential confounders, including demographics, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic use. First infection during the follow up was defined by diagnosis codes or anti-infective medications. We calculated the incidence rate (IR) of infections among patients with and without diabetes and compared hazard ratios (HR) using Cox regression adjusting for potential confounders.

Results: Among 457,950 patients included in the 2016 RISE registry, we identified 3,853 RA patients with diabetes and 18,487 without diabetes. Overall, the mean HAQ change between index and outcome visit among diabetes patients was 0.03 and among non-diabetic was 0.002 ($p < 0.01$). After stratifying on baseline HAQ and compared to patients without diabetes, diabetic RA patients worsened more and improved less, depending on their baseline HAQ. Among those with diabetes, we identified 761 infections, yielding an IR of 22.6 (95% CI: 21.0–24.2) per 100 person years. For non-diabetic patients, we identified 3,239 infections with an IR of 19.8 (19.1–20.5). After adjusting for potential confounders, the HR of infection among diabetes (HR 1.17, 95% CI 1.08–1.27) was not significantly different from non-diabetes patients.

Conclusions: RA patients with concomitant diabetes had greater worsening, or less improvement, in their functional status, suggesting additional interventions may be needed for RA patients with diabetes to optimize this and other comorbidities.

1021 | Temporal trends in the incidence of non-traumatic lower limb amputation in patients with type 1 diabetes mellitus in the United States from 2008 to 2016

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Background: A few studies reported a declining trend in the incidence of non-traumatic lower limb amputation (LLA) in patients with type 1 diabetes mellitus (T1DM). However, limited data exist on the temporal trends for the recent years, especially in the United States (US).

Objectives: To examine temporal trends in the incidence of non-traumatic LLA in patients with T1DM using a US claims database during the years 2008–2016.

Methods: Using a retrospective cohort study design, patients with T1DM were identified using a modified approach based on a validated algorithm published by Klompas et al during a study period from January 1, 2008 to June 30, 2017 from the Truven MarketScan database. The first event of non-traumatic LLA occurring from the date on which a criterion of the algorithm was met until the end of the study period was identified by the presence of ICD-9/ICD-10 procedure codes in any setting. The patients were followed until the occurrence of LLA, end of database enrollment, or study period. Temporal trends in incidence rates (IR) were examined by calculating overall and sex-specific IR per 100,000 person-years (PY) by calendar year, from 2008 to 2016, and mean annual percent change (±SD) in the IR.

Results: Mean age and length of follow-up was 43.1 years and 3.6 years in the 93,813 T1DM patients identified during the study period, respectively, and 500 non-traumatic LLA events occurred during the follow-up. For all non-traumatic LLA, IR per 100,000 PY decreased by 57.8%, from 240.0 in 2008 to 101.1 in 2016. The annual percent change in IR ranged from −15.6% to 30.2%, with a mean annual percent reduction of 9.0% (±15.9%). When stratified by type of LLA, the IR per 100,000 PY of minor LLA (below the ankle) decreased from 151.5 in 2008, to 71.6 in 2016. The annual percent change in IR ranged from −42.4% to 33.5%, with a mean annual

percent reduction of 6.0% (±26.0%). The IR of major LLA (at or above ankle) decreased from 88.5 in 2008 to 29.5 in 2016, per 100,000 PY. The annual percent change in IR ranged from −45.2% to 36.1%, with a mean annual percent reduction of 8.0% (±34.4%). Among males, IR per 100,000 PY of all LLA decreased from 317.8 in 2008 to 114.2 in 2016, with a mean annual percent reduction of 9.7% (±21.1%). Among females, the IR per 100,000 PY of all LLA decreased from 159.8 in 2008 to 87.2 in 2016, a mean annual percent reduction of 5.5% (±20.1%).

Conclusions: In line with the findings from prior literature, the incidence of non-traumatic LLA declined by 9% per year, on average, during the years 2008–2016 in the US, and the decline was comparable between the two sexes and the types of LLA.

1022 | Availability of disease activity measures from systemic lupus erythematosus patients in a large, representative US-based real world registry cohort

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Background: Systemic lupus erythematosus (SLE) is a heterogenous, multifactorial disease with a debilitating and highly variable clinical course. Measurement of disease activity is resource intensive but essential to monitoring of disease status. These scores can be used for diagnosis, prognosis, and evaluation of changes over long periods in routine clinical practice.

Objectives: To assess the availability of disease activity information in SLE patients and assess changes over time.

Methods: This study used the OM1 SLE Registry (OM1, Boston), an ongoing, continually enrolling, representative sample of patients with SLE in the U.S. who are followed prospectively. Deep clinical data, including patient-reported outcomes, electronic medical records (EMR) and administrative claims data were used to characterize patient characteristics, disease manifestations, treatments, and outcomes. Analyses included patients in the registry between January 2013 and December 2018.

Results: Within the SLE Registry (n = 35,484),the average age at cohort entry was 50 years (SD 15.1) and consistent with the epidemiology of SLE, 92% of patients were female. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, commonly used during clinical development, were reported for over 1,400 patients (4%). Based on the first observed score, 23% had no disease activity, 29% were classified as mild, 28% were classified as moderate, 12% were classified as high and 8% were classified as very high. With a mean of 3 months between scores, 66% of the 790 patients with 2 or more scores stayed in the same category while 23% showed improvement. Among those with at least one SLEDAI score, 35% were treated with Benlysta, and there was no discernable pattern of increasing proportion of users based on SLEDAI severity. Additional analyses of the timing of Benlysta and other medications relative to scoring will be pursued. Proportion of patients with non-specific to SLE health related scores included: the Multi-Dimensional Health Assessment Questionnaire (MDHAQ, 31%), patient global assessment score (30%), physician global assessment score (18%), and fatigue visual analogue scale (10%).

Conclusions: Although a variety of non-specific scores are recorded for patients with SLE, capturing changes in diseases status over time remains challenging in the absence of repeated measurements of disease-specific scores in routine practice.

1023 | Characterizing differences in pain score reporting among patients newly diagnosed with rheumatoid arthritis in the U. S. using Optum™ integrated claims-EHR data

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Background: Pain scores are a commonly used patient-reported outcome measure for rheumatoid arthritis (RA). However, there is limited knowledge of pain measures in electronic health record (EHR) data and systematic differences between those with and without pain scores.

Objectives: Our GSK-funded research measured differences in newly diagnosed RA patients with and without recorded pain scores with respect to demographic, insurance, and medication characteristics over 2 years of follow-up.

Methods: We used a retrospective cohort to evaluate our outcome (≥1 pain score recorded vs. no pain score recorded) among US adults with an initial RA diagnosis (index date) between 01 Jan 2013 and 30 Jun 2015 using EHR data from *Optum's de-identified Integrated Claims-EHR dataset (2007–2018)™*. We limited pain scores to those recorded the same day a patient received a RA diagnosis code. We assessed our outcome at index date (ID), index date to 6 months (ID-6mo), 6 months to 1 year (6mo-1 yr), and 1 year to 2 years of follow-up (1 yr–2 yr). Our sample included 40,543 RA patients after excluding patients with history of RA prior to ID or under 18 years of age at ID. We also required patients to be active in the database at least 12 months prior to and 2 years following their ID. We calculated odds ratios and 95% confidence intervals (OR [95% CI]) using logistic regression for each characteristic with respect to our outcome.

Results: Pain scores were recorded for 20.5% of RA patients at ID, 20.6% for ID-6mo, 17.3% for 6mo-1 yr, and 26.7% for 1 yr–2 yr. At ID, RA patients had a mean age of 58.6 years (SD = 14.4) and were: female (77.6%); Caucasian (79.9%) or African American (11.4%); and, not Hispanic (90.2%). Across all time intervals, the odds of having a pain score recorded were greater among African Americans (1.21 [1.12,1.30] to 1.29 [1.20,1.39]) and lower among Asians (0.61 [0.49,0.77] to 0.72 [0.59,0.87]) compared to Caucasians; lower among commercial insurance patients (Yes vs. No: 0.74 [0.71,0.78] to 0.83 [0.79,0.88]); higher among Medicaid patients (Yes vs. No: 1.41

[1.31,1.53] to 1.77 [1.65,1.91]); and; higher among patients using NSAIDS (Yes vs. No: 1.76 [1.64,1.90] to 2.07 [1.95,2.20]), corticosteroids (Yes vs. No: 1.81 [1.71,1.92] to 2.73 [2.58,2.87]), targeted therapies (Yes vs. No: 1.13 [1.06,1.20] to 3.02 [2.87,3.19]), and opioids (Yes vs. No: 3.28 [3.13,3.43] to 3.62 [3.40,3.85]).

Conclusions: There are several differences in newly diagnosed RA patients with and without EHR pain score data. Research using EHR pain score data should investigate potential bias due to missing data.

1024 | Pre-operative predictors of post-operative pain relief: Pain score modeling following spinal fusion surgery

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Background: Pain relief is a strong predictor of patient satisfaction after spinal fusion surgery. Despite the limitations in self-reported measures, specific pain performance assessments may provide health providers a more distinct impression of pain among spinal fusion population.

Objectives: To establish the average pattern of self-reported face-rating pain score using linear mixed modeling and to explore pre-operative predictors of post-operative pain following spinal fusion surgery.

Methods: Through data partnership with Mercy Technology Services, adult patients who underwent multilevel spinal fusion surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. Around 199, 108, 55, 37, and 25 out of 810 spinal fusion patients were with both baseline and follow up pain score at 2-week, 1-month, 3-months, 6-months and 12-months after surgery, respectively. Average pain relief curve was characterized using linear mixed regression modeling. Preoperative factors associated with no-pain-relief (no change or increased pain score) three months after surgery were investigated using multivariable logistic regression. Both prior literature knowledge and p value ($p < 0.05$) were used to obtain the final model.

Results: Although patients started with different levels of pain score, similar pain relief patterns were observed (age: mean 62y (SD: 15); 56% female; 45% Commercial). The study population ($N = 296$) started with an average pain score of 7.1 and changed by −0.2 per month one year after surgery. Both intercept and slope of time were statistically significant. Around 62.1% patients reported pain relief three months after surgery. Main preoperative variables statistically significantly associated with no-pain-relief were lower baseline pain level (aOR: 0.7, 95% CI:0.5–0.9), younger (10-year increment: aOR: 0.4, 95% CI: 0.2,0.6), higher ASA score (aOR: 8.1, 95% CI:2.3–36.1) and lower systolic pressure (aOR: 0.97, 95% CI:0.93–0.996). We did not observe statistically significant association between number of spine level fused and pain relief three months after surgery (aOR:1.02, 95% CI:0.86–1.21).

Conclusions: Over sixty percent of the study spinal fusion population reported pain relief three months after surgery. Improving general health status before surgery may increase the chance of pain relief after spinal fusion surgery. Studies with larger simple size are warranted.

1025 | Burden of illness in patients with systemic sclerosis in the United Kingdom

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Background: Systemic Sclerosis (SSc) is a rare heterogeneous autoimmune disease of connective tissue characterized by immune dysfunction, widespread vasculopathy and fibrosis, which is clinically manifested by multi-organ involvement. Patients with SSc often develop interstitial lung disease (ILD) which is currently the leading cause of death. The burden of disease and effect of SSc on healthcare costs in the UK is currently unknown.

Objectives: This study aimed to investigate patient characteristics and the burden of illness related to first SSc diagnosis.

Methods: We carried out a population-based cross-sectional study using data from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). All adult patients with a diagnosis of SSc were identified using International Classification of Diseases-10-Clinical Modification diagnosis codes in hospital records and READ codes in primary care electronic records combined with an adapted version of the EULAR algorithm for defining SSc over 2005–2016. Patients were classified into 3 groups: incident SSc, SSc with incident ILD (SSc-ILD), and SSc with other organ involvement (SSc-OOI). All-cause healthcare utilization costs (adjusted to 2016 GBP) were reported overall and by disease group. Because of the overlap between the 3 groups, statistical comparisons between the groups were not conducted.

Results: The study included 675 individuals with incident diagnosis of SSc, 19% of the cohort had SSc-ILD and 71% had SSc-OOI with an SSc-ILD&OOI overlap of 15%. 79% of the cohort were women and the average age at diagnosis was 61 years (SD = 17). Median healthcare costs were estimated at £2,601(IQR 962–6,885) per patient per year among patients with SSc and were higher among patients with SSc-ILD (£5,899, IQR £2,986 - £13,905) compared to patients with SSc-OOI (£3,449, IQR £1,271 - £8,717). The majority (42%) of the cost burden was attributed to inpatient hospital activity, where 52% of appointments were planned (elective day and day cases admission). The biggest driver of inpatient costs came from respiratory and musculoskeletal-related attendances.

Conclusions: Our results highlight the significant healthcare burden of patients diagnosed with SSc through UK primary care or secondary/tertiary care routes. These findings should inform the development of initiatives to improve management of SSc.

1026 | Evaluation of discriminative ability of commonly used indices to predict outcomes after spinal fusion surgery

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Background: American Society of Anesthesiologists (ASA) score, Charlson (CCI), Elixhauser (ECI) and Functional Comorbidity Index (FCI) have been used as risk-adjustment tools in quality and safety data. However, no study has compared the predictive performance of these indices particularly in spinal fusion patients across varied outcomes.

Objectives: To compare the discriminative ability of ASA, CCI, ECI, FCI, as well as provider's spinal fusion surgery volume (PV) for postoperative outcomes following spinal fusion surgery.

Methods: Through data partnership with Mercy Technology Services, adult patients who underwent spinal fusion surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. Postoperative outcomes assessed included: (1) infection within 3-months after surgery, (2) all-cause 3-months readmissions, (3) one-year all-cause mortality, and (4) self-reported pain relief 3-months after surgery. For each outcome, six multivariable logistic regression models were constructed. One base model that included age, gender and BMI and five models with the variables in the base model and an additional index, CCI, ECI, FCI, ASA or PV. The predictive performance was assessed using area under the curve analysis (AUC) derived from these models.

Results: A total of 810 spinal fusion patients were included in the analysis (age mean: 60, SD: 15, 52% female, 52% commercial insured). For infection, AUC (95% CI) of base and the two most predictive models (ECI and ASA) were 0.52 (0.47–0.57), 0.68 (0.63–0.73) and 0.67 (0.62–0.72), respectively. For all cause 3-months readmission, AUC (95% CI) of base and the two most predictive models (CCI and ECI) were 0.57 (0.507–0.63), 0.65 (0.60–0.71) and 0.65 (0.59–0.70), respectively. For one-year all-cause mortality, AUC (95% CI) of base and the two most predictive models (ASA and PV) were 0.70 (0.59–0.81), 0.82 (0.71–0.93) and 0.77 (0.67–0.87), respectively. For 3-months self-reported pain relief, AUC (95% CI) of base and the two most predictive models (ASA and PV) were 0.72 (0.62–0.82), 0.76 (0.66–0.86) and 0.74 (0.64–0.84), respectively.

Conclusions: ASA score and provider's volume outperformed other comorbidity indices in predicting mortality and pain relief. The discriminative ability of all indices for infection and readmission was poor (all AUC < 0.7). Future research developing comorbidity measures with improved predictivity for infection and readmission after spinal fusion surgery would be promising.

1027 | Evaluation of discriminative ability of commonly used indices to predict outcomes after fracture repair surgery

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Background: American Society of Anesthesiologists (ASA) score, Charlson (CCI), Elixhauser (ECI) and Functional Comorbidity Index (FCI) have been used as risk-adjustment tools in quality and safety data. However, no study has compared the predictive performance of these indices particularly in fracture repair patients across varied outcomes.

Objectives: To compare the discriminative ability of ASA, CCI, ECI, FCI, as well as provider's spinal fusion surgery volume (PV) for postoperative outcomes following adult fracture repair surgery.

Methods: Through data partnership with Mercy Technology Services, adult patients who underwent fracture repair surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. Postoperative outcomes assessed included: (1) infection within 3-months after surgery, (2) all-cause 3-months readmissions, (3) one-year all-cause mortality, and (4) extended length of stay (LOS) ($\geq$ 3 days). For each outcome, six multivariable logistic regression models were constructed. One base model that included age, gender and BMI and five models with the variables in the base model and an additional index, CCI, ECI, FCI, ASA or PV. The predictive performance was assessed using area under the curve analysis (AUC) derived from these models.

Results: A total of 14,044 fracture repair patients were included in the analysis (age median: 65, IQR, 47–81, 59% female). For infection, AUC (95%CI) of base and the two most predictive models (ECI and ASA) were 0.66 (0.65–0.68), 0.703 (0.69–0.71) and 0.698 (0.69–0.71) respectively. For all cause 3-months readmission, AUC (95%CI) of base and the two most predictive models (ECI and CCI) were 0.67 (0.66–0.68), 0.69(0.68–0.70) and 0.68 (0.67–0.69), respectively. For one-year all-cause mortality, AUC (95%CI) of base and the two most predictive models (CCI and ECI) were 0.79 (0.78–0.81), 0.84(0.83–0.85) and 0.83 (0.82–0.84), respectively. For extend LOS, AUC (95%CI) of base and the two most predictive models (ASA and ECI) were 0.72 (0.716–0.733), 0.76 (0.755–0.77) and 0.755 (0.747–0.763), respectively.

Conclusions: Of the model evaluated, Elixhauser Comorbidity Index had better discriminative ability across all outcomes assessed. The predictive ability of all indices for infection and readmission was poor (all AUC $\leq$ 0.7). Future research developing comorbidity measures with improved predictivity for infection and readmission after fracture repair surgery would be promising.

1028 | Ivabradine for the treatment of heart failure: A systematic review and meta-analysis

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Background: Ivabradine has a pure heart rate reduction through its selectivity to bind to I_f channels. However, the use of ivabradine remains limited due to the conflicting evidence of its safety and efficacy.

Objectives: To determine the efficacy and safety of ivabradine compared to control in subjects with heart failure (HF) on clinical and patient-reported outcome measures used in HF management.

Methods: We performed a systematic search in the following databases: Medline, Embase, Ovid and the Cochrane Central Register of Controlled Trials from inception through June 2018. Peer-reviewed, randomized controlled trials of ivabradine versus control group in patients with heart failure with or without low ejection fraction, were included. We adhered PRISMA checklist and flow diagram. Our primary outcomes were: all-cause mortality, cardiovascular mortality, or hospital readmission. Secondary outcomes include resting heart rate (HR)from baseline until the end of follow-up, left ventricular ejection fraction (LVEF), and adverse events. Two investigators independently extracted data from each eligible study and assessed risk of bias via Cochrane collaboration's risk of bias tool. We assessed the treatment effect on binary outcomes by using the risk ratio (RR) with the corresponding 95% confidence intervals (CIs). For continuous outcomes, we calculated the difference in mean changes from baseline between ivabradine and control group.

Results: Six trials with 17886 patients were included. There was no significant difference among ivabradine treated group versus control group in lowering all-cause mortality, cardiovascular mortality, or hospital readmission. There was no statistically significant difference between ivabradine and control group in the mean difference in change from baseline of heart rate. However, ivabradine had an increase in mean difference in percentage of ejection fraction (EF) by 3% as compared with control group (summary RR, 3.27 [95% CI, 2.08 to 4.45]; I^2 = 26%). The incidence of phosphenes, blurred vision and bradycardia as adverse events were significantly higher with ivabradine by 4 and 5 times as compared with control group (summary RR,4.08 [95% CI, 2.80 to 5.95]; I^2 = 0%) and (summary RR,5.04 [95% CI, 2.49 to 10.18]; I^2 = 85%) respectively.

Conclusions: Administration of ivabradine to adults with heart failure with or without low ejection fraction significantly improved the ejection fraction. However, the incidence of bradycardia was higher with ivabradine group.

1029 | Trends in ambulatory analgesic use over an 8 year period in patients after myocardial infarction using a Nationalwide claims database

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Background: Myocardial infarction (MI) is a leading cause of premature death; moreover, owing to global population growth and aging, it represents a major disease burden. The current guidelines on MI recommend caution in the use of COX-2 selective or non-selective NSAIDs.

Objectives: To explore the usage patterns of nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics in patients after myocardial infarction (MI) over a period of 8 years, focusing on the indications of analgesic use.

Methods: A nationwide cross-sectional study using the Korea National Health Insurance Service (NHIS) database was performed. We assessed ambulatory analgesics used at least 30 days after discharge from incident hospitalization with MI (ICD-10, I21). We assessed the prevalence of ambulatory analgesic medication, including NSAIDs, acetaminophen, and opioids, used in three indication categories: musculoskeletal (M00-M99), respiratory (J00-J99), and other diseases. Annual trends in the prescriptions of individual analgesic medications were also evaluated. For the prescriptions including analgesics as the unit of analysis, we compared the proportion of prescriptions with NSAIDs for each indication of the analgesic prescription, by using Chi-square test. we assessed the trends in individual analgesics between 2008 and 2015. All analyses were computed by using SAS version 9.4 (SAS Institute, Cary, NC).

Results: We identified 75,131 patients with a history of MI and an ambulatory prescription for analgesics. Frequently used analgesics differed between musculoskeletal diseases (tramadol injection (19.4%), aceclofenac (13.7%), and diclofenac injection (9.4%)) and respiratory diseases (acetaminophen (35.5%), tramadol injection (15.6%), and loxoprofen (15.3%)). During the study period, a significant increase in the use of aceclofenac, loxoprofen, and tramadol/acetaminophen fixed combination was observed, with a significant decrease in the use of tramadol and diclofenac injections.

Conclusions: Patterns of analgesic use differed according to indication. The importance of drug-disease interactions of NSAIDs used after MI needs to be studied further, especially for patients with musculoskeletal diseases. The high prevalence of aceclofenac and loxoprofen use suggests the necessity of safety evaluations and monitoring for medications for which a relatively small amount of evidence on safety is available.

1030 | The effects of initiation of secondary prevention pharmacotherapy on 1-year mortality after stroke

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Background: Combination pharmacotherapy is common in the initiation of secondary prevention of stroke. However, evidence of optimal combination therapy on mortality after stroke is limited.

Objectives: This study aimed to determine the effects of different numbers of combined cardiovascular drug classes on 1-year mortality in stroke patients.

Methods: Patients aged 45+ with the first record of stroke or transient ischemic attack were identified through The Health Improvement Network database, UK from Jan 2007 to Dec 2016. Exposure to different combined numbers of six cardiovascular drug classes (lipid-regulating drugs, antiplatelet drugs, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), calcium-channel blockers (CCBs), diuretics and β-blockers) were defined according to cardiovascular drugs prescribed during the first 90 days after the first diagnosis of stroke. The study outcome was 1-year all-cause mortality. A propensity score matched analysis was conducted using the Cox proportional hazards models.

Results: Of the 38,151 patients, 6,255 were with 1 class (16.4%), 10,235 with 2 classes (26.8%), 8,238 with 3 classes (21.6%), 4,694 with 4 classes (12.3%), 1,473 with 5 classes and 174 with 6 classes (0.5%). Compared with patients with 1 class, the hazard ratios of all-cause mortality were reduced with 2 classes (HR 0.80, 95% CI:0.67–0.97), 3 classes (HR 0.72, 95% CI:0.61–0.86), 4 classes (HR 0.62, 95% CI:0.50–0.75), 5 classes (HR 0.60, 95% CI:0.43–0.85) and all 6 classes (HR 0.29, 95% CI:0.09–0.99).

Conclusions: The results suggest an additive effect of cardiovascular drug classes on mortality in stroke patients. Increasing the number of cardiovascular drug classes appears to be positively associated with reduced risk of 1-year mortality after stoke.

1031 | Relationship between daily versus evening/bedtime statin dosing and changes in low-density lipoprotein cholesterol

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Background: The Food and Drug Administration recommends certain statins for evening/bedtime administration, whereas others are recommended for daily administration. However, little is known about how these different dosing instructions may impactlow-density lipoprotein cholesterol (LDL-c).

Objectives: To evaluate the association between daily versus evening/bedtime statin dosing and changes in LDL-camong new initiators.

Methods: This was a retrospective analysis of electronic health records (EHR) and pharmacy claims data from a healthcare delivery system in northern California between 2010 and 2016. The study cohort was composed of new users of statin therapy ≥35 years of age at the time of first electronic prescription, with EHR activity 12–36 months before and after the index statin prescription, and at least 12 months of follow-up. Statin administration was dichotomized as daily vs. evening/bedtime based on the medication order field. We excluded patients who had a change in instructions during follow-up and patients with all other dosing instructions (e.g., three times per week). The outcomes were mean change in LDL-c and likelihood of attaining LDL-c < 70 mg/dLbetween 12 and 24 months from baseline. We used regression models to assess differences in mean change in LDL-c and the likelihood of attaining LDL-c < 70 mg/dLfor patients with daily vs. evening/bedtime dosing. Adjusted mean differences and odds ratios (OR) with 95% confidence intervals (CI) were estimated before and after statistical adjustment for patient, prescription, and provider covariates, including statin adherence.

Results: Of 5099 eligible incident-statin users (mean age, 63 years), 53% were prescribed evening and 47% daily dosing instructions. No differences were observed in mean change in LDL-c (adjusted mean difference: 1.42 mg/dL; 95% CI: −1.02, 3.89) or likelihood of attaining LDL-c < 70 mg/dL (adjusted OR: 0.83; 95% CI: 0.67, 1.04) for evening vs. daily dosing over a mean of 19-months follow-up.

Conclusions: Among incident statin users from a real-world clinical setting, those with daily and evening dosing instructions had similar mean changes in LDL-c and likelihood of attaining an LDL-c < 70 mg/dL. Given potential clinical equipoise for evening and daily dosing, clinicians should consider patient-tailored statin dosing instructions to reduce potentially unnecessary regimen complexity.

1032 | Comparative effectiveness study of combined antihypertensive medications for Nigerians

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Background: In Nigeria, hypertension remains a preventable risk factor for cardiovascular (CV) diseases. Available data suggest that at least 75% of patients will need a combination antihypertensive therapy to achieve the therapeutic goal. In addition to risk reduction in CV events and BP control, cost-effectiveness has become an important consideration in antihypertensive drugs selection.

Objectives: To compare and contrast the clinical and economic effectiveness of antihypertensive drug combinations among Nigerian

hypertensive patients with compelling indication to receive combination therapy.

Methods: A double-blind randomized controlled trial of 4 groups of antihypertensive drug combinations, Telmisartan/Amlodipine/Chlorthalidone (TCA), TC, TA and CA was conducted among hypertensive patients. The choice of medications for this study was based on JNC-7 recommendation, also based on recent cost-utility analysis of antihypertensive medications for Nigerians. The participants were recruited from 3 private hospitals in Enugu Metropolis of Nigeria and randomly assigned to the study groups. The primary outcome of this study was BP control based on JNC-8 guideline while the secondary outcomes were cost-effectiveness per QALY, cost-effectiveness per control and patients' self-reported health status. Descriptive and inferential statistics were used for statistical analyses. $P < 0.005$ was considered statistically significant.

Results: Of 110 patients enrolled in the study, more than half were women (55.5%). The mean age of the patients was 54.93 ± 12.38. On average, the enrolled patients have had hypertension for over 9 years (9.17 ± 8.4). At least 77% of the patients in all the groups completed the study except for TA group (66.7%). The probability of BP control was highest in the TCA group (0.37 ± 0.00). The CA group showed the best cost-effectiveness per QALY. However, the group with the most favorable cost-effectiveness per control was TCA (59.30 ± 0.00) followed by CA (79.09 ± 0.00). Patients reported health status indices were highest for CA followed by TCA group.

Conclusions: The trial demonstrated no significant difference in BP control across the 4 different combinations of anti hypertensives. Although the highest probability of BP control was seen in TCA group. The CA and TCA groups demonstrated the most cost-effective per QALY and per control respectively. Health care providers should consider the use of TCA and CA in management of hypertension in Nigerians with compelling indication to use dual or triple therapy. Nonetheless, there is need to further validate the study findings using larger population.

1033 | Anti-hypertensive drugs and endothelial function: Results from the Brazilian longitudinal study of adult health (ELSA-Brasil)

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Background: The effects of different classes of antihypertensive drugs on endothelialfunction and inflammatory markers are not yet well established and may be relevant for therapeutic choices.

Objectives: To evaluate the association between the use of different classes of antihypertensive drugs with serum CRP levels and endothelial function (assessed by Peripheral Arterial Tonometry-PAT) in a sample of Brazilian adults.

Methods: This cross-sectional study was developed with a sample of ELSA-Brasilbaseline participants with medical diagnosis of hypertension, using at least one interest class of antihypertensive (ACEI, ARB, calcium channel blocker, β-blocker and diuretics) and without medical diagnosis of CVD or coronary disease. The inflammatory and endothelial function markers were, respectively, CRP levels and BPA and PAT ratio. Thus, 3,522 participants who had PCR information and 397 with BPA and PAT ratio information participated in this analysis. The associations between use of different classes of antihypertensive drugs (evaluated as binary variables; reference category was the use of other classes of antihypertensive drugs) with response variables, PCR and BPA and PAT ratio, were estimated using generalized linear models and linear regression.

Results: Regarding CRP and PAT ratio, no statistically significant association wasfound with the use of none classe of antihypertensive drug, even after adjusting for confounders. Participants using diuretics had lower levels of BPA (better endothelial function) compared to those not using diuretics [0.96 (0.93–0.99); $p < 0.05$] and participants using beta-blockers had a borderline association with higher levels of BPA (worse endothelial function) compared to those not using this class [1.03 (1.00–1.05); $p = 0.05$].

Conclusions: Our study contributes to the literature on effects of the different classes ofantihypertensive on systemic inflammation and endothelial function by providing evidence that endothelial function seems to be better among diuretic users and worse among users of beta-blockers. Further studies are needed to assess if these effects can, independently, provide a better prognosis for patients with arterial hypertension and whether they may in fact add greater benefits to clinical practice.

1034 | Does the comparative effectiveness of first line anti-hypertensive drugs differ according to age?

Sarah-Jo J. Sinnott; Ian J. Douglas; Elizabeth Williamson; Liam Smeeth; Laurie Tomlinson

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Background: Current clinical guidelines recommend different first-line anti-hypertensive drugs for hypertension based on whether the patient is aged </≥55 yrs. The evidence underpinning these recommendations is limited and not conclusive.

Objectives: To explore the comparative effectiveness of first-line anti-hypertensive drugs stratified by age </≥55 yrs.

Methods: We used UK primary care data from the Clinical Practice Research Datalink to establish a cohort study. We identified new initiators of Angiotensin Converting Enzyme-Inhibitor/Angiotensin Receptor Blocker (ACE-I/ARB), Calcium Channel Blocker (CCB) and thiazide diuretics and followed to investigate change in systolic blood pressure (BP) at 12 weeks post initiation. We also investigated changes in diastolic BP, along with additional timepoints of 26 and 52 weeks. We compared thiazides vs CCB, thiazides vs ACE-I/ARB and CCB vs

ACE-I/ARB. We used mixed linear models with a random intercept for each patient with interactions to model the effect of the exposure drug across age ≥ 55 yrs (yes or no). Models were adjusted with propensity scores to adjust for confounding.

Results: We identified 154,257 initiators of ACE-I/ARB, 115,931 initiators of CCB and 39,632 initiators of thiazides. The mean age was 55.5 yrs (SD 12.7), 63.4 yrs (SD 12.2) and 66.4 yrs (12.7). At 12 weeks after initiation, systolic BP was 2.46 mmHg (95% CI 0.56–1.31) higher in patients aged ≥55 yrs prescribed thiazides than those prescribed CCBs. This difference was larger than that seen for <55 yrs (+1.46 mmHg, 95% CI 1.22–1.71). Systolic BP after 12 weeks was higher in patients aged ≥55 yrs prescribed thiazides (+1.27 mmHg, 95% CI 1.07–1.46) than those prescribed ACE-I/ARB. This difference was larger than that seen for <55 yrs (+0.43 mmHg, 95% CI 0.09–0.75). Patients prescribed CCB vs ACE-I/ARB has lower systolic BPs at 12 weeks and the difference trended towards being more pronounced for those aged ≥55 yrs (−1.00, 95% CI -1.14 - -0.86) than those aged <55 yrs (−0.77, 95% CI -0.96 - -0.58). Trends for diastolic BP were similar.

Conclusions: In those aged ≥55 years CCB and ACE-I/ARB appear superior to thiazides. There was a trend towards CCB being superior to ACE-I/ARB in the older population, although the confidence limits overlapped indicating similar effectiveness.

1035 | Does the comparative effectiveness of first line anti-hypertensive drugs vary by gender?

Sarah-Jo Sinnott; Ian J. Douglas; Elizabeth Williamson; Liam Smeeth; Laurie A. Tomlinson

LSHTM, London, UK

Background: Previous drug utilization research indicates that thiazide diuretics are used more often in women than men. Current research on whether the effectiveness of anti-hypertensive drugs differs by gender is conflicting.

Objectives: To explore the comparative effectiveness of first-line anti-hypertensive drugs stratified by gender.

Methods: We used UK primary care data from the Clinical Practice Research Datalink to establish a cohort study. New initiators of Angiotensin Converting Enzyme-Inhibitor/Angiotensin Receptor Blocker (ACE-I/ARB), Calcium Channel Blockers (CCB) and thiazide diuretics with elevated blood pressure (BP) were identified and followed to investigate change in systolic BP at 12 weeks post initiation. We also investigated diastolic BP and additional timepoints 26 and 52 weeks. We compared thiazides vs CCB, thiazides vs ACE-I/ARB and CCB vs ACE-I/ARB. We used mixed linear models with a random intercept for each patient with interactions to model the effect of the exposure drug across gender (male or female). Models were adjusted with propensity scores to adjust for confounding.

Results: We identified 154,257 initiators of ACE-I/ARB, 115,931 initiators of CCB and 39,632 initiators of thiazides. The mean age was 55.5 yrs (SD 12.7), 63.4 yrs (SD 12.2) and 66.4 yrs (12.7) and the proportion of females was 42.5%, 50.0% and 64.2% in ACE-I/ARB, CCB, thiazides respectively. At 12 weeks, systolic BP was +2.47 mmHg higher (95% CI 2.25–2.68) in women prescribed thiazides than in women prescribed CCB. This difference was larger than the same drug comparison in men (+1.46 mmHg, 95% CI, 1.22–1.71). Similar results were observed for thiazides in comparison to ACE-I/ARB. Women prescribed CCB had lower systolic BP at 12 weeks than women prescribed ACE-I/ARB (−1.30 mmHg, 95% CI -1.45 - -1.14) and this difference was more substantial than the same drug comparison in men (−0.73 mmHg, 95% CI, −0.88 - -0.57).

Conclusions: Prior research suggests thiazides are used frequently in women, however our analyses indicate that thiazide diuretics are less effective at lowering systolic BP than CCB or ACE-I/ARB in women. CCB compared to ACE-I/ARB reduced systolic BP to a greater extent in women than men.

1036 | Risk factors of major bleeding in patients prescribed rivaroxaban in primary Care in England

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Background: The association between oral anticoagulant use and bleeding risk has been widely reported. However, patients may have underlying risk factors which predispose to bleeding. It is valuable to understand the predictors for major bleeding in patients prescribed rivaroxaban.

Objectives: Multivariable logistic regression analyses to explore potential risk factors for major bleeding within gastrointestinal, urogenital and intracranial sites.

Methods: A case/non-case design evaluated the association between clinical risk factors and major bleeding in rivaroxaban patients (N = 17546) enrolled to a 12-month cohort study in England (2012–2016). Clinical risk factors for bleeding and bleeding outcomes were collected from general practitioners via questionnaires sent at ≥3, and ≥ 12 months observation. Multivariable logistic regression analyses examined the association for each site and models were based on two approaches; clinical risk factors selection model and HAS-BLED model. The clinical risk factors selection model included all reported clinical risk factors for bleeding. The HAS-BLED model included HAS-BLED risk score categories (low, moderate, high) and gender. Statistically significant (p < 0.05) associations are presented in the results.

Results: Gastrointestinal major bleeds (n = 176) Clinical risk factors selection model Age 65–74 vs. <65 years OR 2.4 [95% CI 1.3, 4.6]; Age ≥ 75 vs. <65 years OR 4.2 [95% CI 2.3, 7.5]; Predisposition to/history of bleeding OR 4.8 [95% CI 3.1, 7.5] HAS-BLED model Moderate vs. low OR 4.0 [95% CI 2.1, 7.6]; High vs. low OR 8.9 [95% CI 4.0, 19.9] Urogenital major bleeds (n = 36) Clinical risk factors selection model Age 65–74 vs. <65 years OR 0.2 [95% CI 0.1, 0.7]; Female vs.

male OR 2.9 [95% CI 1.4, 6.1]; Malignancy OR 2.6 [95% CI 1.1, 6.3] HAS-BLED model Female vs. male OR 2.7 [95% CI 1.3, 5.6] Intracranial major bleeds (n = 57) Clinical risk factors selection model Age ≥ 75 vs. <65 years OR 2.8 [95% CI 1.1, 6.9]; History of cerebrovascular accident (including haemorrhagic)/transient ischaemic attack OR 2.2 [95% CI 1.3, 3.9]; Predisposition to/history of bleeding OR 2.6 [95% CI 1.0, 6.7] HAS-BLED model Moderate vs. low OR 3.3 [95% CI 1.2, 9.1]; High vs. low OR 9.0 [95% CI 2.5, 31.9].

Conclusions: Overall, findings from both models are in keeping with known clinical risk factors for bleeding. For urogenital major bleeds the higher risk in females and younger age group may be related to menstrual bleeding. In clinical practice it is recommended that a bleeding risk assessment, including individual patient characteristics, should be performed prior to anticoagulation.

1037 | Comparative effectiveness of first line anti-hypertensive drugs: Variation by ethnicity

Sarah-Jo J. Sinnott; Ian J. Douglas; Elizabeth Williamson; Liam Smeeth; Laurie A. Tomlinson

LSHTM, London, UK

Background: Current clinical guidelines recommend Calcium Channel Blockers (CCB) and thiazides for black patients newly initiating drug therapy for hypertension. The evidence underpinning these recommendations is not conclusive.

Objectives: To explore the comparative effectiveness of first-line anti-hypertensive drugs stratified by ethnicity; white, black and south Asian.

Methods: We used UK primary care data from the Clinical Practice Research Datalink to establish a cohort study. New initiators of Angiotensin Converting Enzyme-Inhibitor/Angiotensin Receptor Blocker (ACE-I/ARB), CCB and thiazide diuretics were identified and followed to investigate change in systolic blood pressure (BP) at 12 weeks post initiation. We also investigated diastolic BP and timepoints 26 and 52 weeks. We compared thiazides vs CCB, thiazides vs ACE-I/ARB and CCB vs ACE-I/ARB. We used mixed linear models with a random intercept for each patient with interactions to model the effect of the exposure drug across 3 levels of ethnicity; white, black and south Asian. Models were adjusted with propensity scores to adjust for confounding.

Results: We identified 154,257 initiators of ACE-I/ARB, 115,931 initiators of CCB and 39,632 initiators of thiazides. More than 95% of the population was white, 1.5% was black and 1.8% was south Asian. At 12 weeks, there was no evidence to suggest that black patients prescribed thiazides had higher or lower systolic BP than those prescribed CCB. In contrast, white patients and south Asian patients prescribed thiazides had higher systolic BP when compared to patients on CCB (+1.91 mmHg, 95% 1.72–2.10 and + 2.06 mmHg, 95% CI 0.82–3.30 respectively). Black patients prescribed thiazides had lower systolic BP than those prescribed ACE-I/ARB at 12 weeks (−2.57 mmHg, 95% CI -3.97 - -1.18). In contrast, white patients prescribed thiazides had slightly higher systolic BP (+0.52 mmHg, 95% CI 0.33–0.71) compared to white patients prescribed ACE-I/ARB. At 12 weeks post initiation, both black and south Asian patients had lower systolic BP on CCB compared to ACE-I/ARB (−2.31 mmHg, 95% CI -3.29 - -1.55 and − 2.04 mmHg, 95% CI -2.71-1.37 respectively). In white patients prescribed CCB, systolic BP decreased by 1.15 mmHg (95% CI -1.28 - -1.02) vs white patients prescribed ACE-I/ARB.

Conclusions: When compared to ACE-I/ARB, CCB were more effective at lowering systolic BP in black patients than in white patients. Similarly, when compared to ACE-I/ARB, thiazides were more effective at lowering systolic BP in black patients than in white patients.

1038 | Improvements in disease activity scores associated with bDMARD use by rheumatoid arthritis patients in a large US-based real world cohort

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Background: Disease activity scores (DAS) are specific clinical measures used to quantify abnormalities in patients with rheumatoid arthritis (RA). Changes in Routine Assessment of Patient Index Data 3 (RAPID3) scores, as well as swollen and tender joint counts and remission status are useful metrics to assess treatment effects of new and costly therapies such as biological disease modifying anti-rheumatic drugs (bDMARDs).

Objectives: To characterize the changes in RAPID3 scores, joint counts and remission status associated with bDMARD use.

Methods: The OM1 RA Registry (OM1, Boston, MA) follows more than 100,000 adult patients longitudinally with deep clinical data, including laboratory, symptom, patient-reported and disease activity information. The study period includes data from Jan 2013-Jan 2019. Differences in RAPID3 scores (range 0–10), joint counts (range 0–28) and disease status (remission/low/moderate/high) before and 6-months after the start of 9 specific bDMARDS were assessed. Disease remission is defined in accordance with the criteria described by American College of Rheumatology/European League Against Rheumatism.

Results: Overall, 88,424 patients had at least one DAS, 76.2% were women and mean age was 65 years. Across a series of 9 bDMARDs, baseline values of RAPID3 ranged from 4.14 to 4.69. After 6 months following bDMARD treatment, scores ranged from 3.68 to 4.29, with improvements seen for all bDMARD groups. Among the 16,467 patients with swollen joint measures, the range of improvement over 6 months was 1.23 to 2.03 joints. Among the 16,727 patients with swollen joint measures, the range of improvement over 6 months was 1.61 to 2.64 joints. The percent of patients transitioning from moderate/high to remission/low status ranged from 16.5% to 24.2%. Investigation of bDMARD-specific improvements for all metrics, adjusted for baseline factors is ongoing.

Conclusions: Within a real world cohort of RA patients, bDMARDS were associated with a range of improvements in disease scores and remission

status. Identification of the impact that bDMARDS have on these metrics provides insight into appropriate use of these costly medications.

1039 | Real-world effectiveness of methotrexate, ciclosporin, acitretin and fumaric acid esters for psoriasis: Does treatment history matter?

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Background: Real-world effectiveness of the systemic therapies methotrexate (MTX), ciclosporin (CsA), acitretin (ACI) and fumaric acid esters (FAE) prescribed to patients with moderate–severe psoriasis is poorly characterized.

Objectives: To determine whether systemic treatment history predicts the effectiveness of ACI, CsA, FAE and MTX.

Methods: The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) is a pharmacovigilance register investigating the long-term safety of systemic therapies prescribed to psoriasis patients. Established in 2007, over 15,500 patients have been recruited from 160 dermatology centres across the UK and Ireland. Patients registering on MTX, CsA, ACI or FAE with at least 6 months follow-up were analyzed. Exposure time for the registration therapy was calculated from initiation to censor at: discontinuation date; latest follow-up; or death. Effectiveness was defined as achieving Psoriasis Area and Severity Index (PASI) $\leq$3 using the first longitudinal PASI reported after initiating therapy. Treatment history was classified into incident (first systemic), prevalent (prescribed registration therapy previously), or previous systemic use (prescribed another systemic therapy previously). Multivariable logistic regression estimated the odds ratio (OR) of achieving PASI$\leq$3 with a priori baseline covariates included. Missing data were accounted for using a multiple imputation model of 20 datasets.

Results: In total, of 4113 patients analyzed, 1991 (48%) were prescribed MTX, 1022 (25%) CsA, 765 (19%) ACI and 335 (8%) FAE. The proportions of incident, prevalent and previous systemic users, respectively, were similar for MTX (41%; 18%; 41%), CsA (38%; 16%; 46%) and ACI (42%; 16%; 42%), but differed for FAE (19%; 15% 66%). The proportion of patients achieving PASI$\leq$3 were 31% MTX, 36% CsA, 22% ACI and 26% FAE. Prevalent users of ACI (OR 0.67, 95% confidence interval [CI] 0.45–0.99) and CsA (0.64, 0.47–0.87) were less likely to achieve PASI$\leq$3 compared with incident users. Prevalent users of MTX (0.81, 0.64–1.02) and FAE (0.66, 0.33–1.31), and previous systemic users did not differ significantly to incident users in achieving PASI$\leq$3.

Conclusions: The effectiveness of MTX and FAE does not appear to differ by treatment history categories and could be prescribed as first or subsequent lines of therapy. Prevalent users of CsA and ACI registering on those therapies were less likely to achieve PASI$\leq$3 compared to incident users. The findings for CsA may reflect the intermittent short-term use in clinical practice.

1040 | Comparative effectiveness of long-term lifestyle and pharmacological interventions for primary prevention of type 2 diabetes: A network meta-analysis of randomized controlled trials

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Background: Lifestyle modification and some pharmacological interventions have been proven effective in preventing or delaying type 2 diabetes (T2D); however, their comparative efficacy is unclear.

Objectives: We therefore undertook a network meta-analysis to integrate both direct and indirect evidence to estimate the relative effects of all interventions against each other for preventing T2D.

Methods: We searched electronic databases through October 2018 and identified long-term randomized trials (follow-up $\geq$1 year) that evaluated the interventions for T2D prevention in adults with prediabetes (IFG or IGT). A network meta-analysis was conducted to calculate the summary odds ratio (OR) and 95% confidence interval (CI) and rank the effectiveness of these interventions.

Results: We included thirty-three trials involving 54,910 individuals with prediabetes and 13,189 incident T2D cases during the median trial duration of 3 years. Our network meta-analysis showed that lifestyle modification (OR, 0.53; 95% CI, 0.42 to 0.66), insulin sensitizers (0.44; 0.31 to 0.62), alpha-glucosidase inhibitors (0.60; 0.42 to 0.87), and weight-loss drugs (0.39; 0.23 to 0.66) were significantly associated with decreased risk of developing T2D as compared with the controls. Lifestyle modification (0.57; 0.36 to 0.90), insulin sensitizers (0.48; 0.28 to 0.81), and weight-loss drugs (0.43; 0.22 to 0.82) were associated with lower risk than renin-angiotensin system blockage. Weight-loss drug was associated with lower risk of T2D than insulin secretagogues (0.49; 0.25 to 0.98). Ranking of these interventions suggested weight-loss drugs being the optimal intervention for preventing T2D (89.5%), followed by insulin sensitizers (84.1%), lifestyle modification (66.7%), and alpha-glucosidase inhibitors (54.4%).

Conclusions: Overall, four interventions (lifestyle modification, insulin sensitizers, alpha-glucosidase inhibitors, and weight-loss drugs) showed significant and comparable benefits on the primary prevention of T2D, although weight-loss drugs seemed to be the most effective.

1041 | Evaluation on therapeutic equivalence of generic and brand-name controlled-release doxazosin

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Background: It may not be feasible to assess the therapeutic equivalence between brand and generic drugs by comparing efficacy, safety and adherence as conducted in clinical trials. Instead, persistence, a global measure of efficacy, safety, and tolerability, can be employed as a surrogate outcome to examine therapeutic equivalence using a retrospective claims database.

Objectives: To evaluate the prescription persistence of generic and brand controlled-release doxazosin.

Methods: A retrospective cohort study with new user design was conducted by using two million random sampled database from Taiwan National Health Insurance Database (NHID). BPH patients who aged over 50 years and newly prescribed controlled-release doxazosin during 2009 to 2015 were enrolled. Patients were grouped to generic or brand doxazosin users. The non-persistence was defined as an event of treatment change, which included discontinuation, switching study drug or augmentation with another anti-BPH medications. We followed up patients who incurred treatment change, or up to one year, whichever came first. We also conducted sensitivity analysis based on patients' previous BPH medication history to eliminate confounding by BPH severity. Propensity score (PS) was performed and Cox proportional hazards regression was used to calculate hazard ratios and confidence interval.

Results: There were 8,596 brand and 1,472 generic users met study criteria. The mean age was 68 years old and hypertension was the most frequent comorbidity among two groups. Compared to brand users, the adjusted hazard ratio for treatment change in generic users was 1.01 [95% CI: 0.9–1.14]. The result from sensitivity analysis was consistent with primary result, implying no significant treatment change between generic and brand users (HR 0.92 [0.77–1.11], HR 1.11 [0.88–1.41], HR 0.95 [0.75–1.2] in mild, moderated and severe BPH, respectively.)

Conclusions: The findings indicate that generic and brand doxazosin are therapeutic equivalent.

1042 | Real-world safety and effectiveness of onabotulinumtoxina treatment of Crow's feet lines and glabellar lines: Results of a Korean 4-year postmarketing surveillance study

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Background: Based on results from pivotal trials in North America, Europe, and Asia, onabotulinumtoxinA was approved in the Republic of Korea for treatment of moderate to severe lateral canthal lines (ie, crow's feet lines [CFL]) and glabellar lines (GL), separately or in combination.

Objectives: To fulfill Korean regulatory requirements, a postmarketing surveillance (PMS) study was conducted to assess safety and effectiveness of onabotulinumtoxinA in real-world clinical practice over a 4-year period.

Methods: The study was conducted at 26 sites in the Republic of Korea from February 2014 to February 2018. Adult Korean subjects aged 18–75 years with moderate to severe CFL treated with onabotulinumtoxinA from a 50 U vial at the labeled CFL dose (24 U total) were enrolled; the target sample size was ≥600 subjects. Safety and effectiveness data were collected at all in-office visits within 3 months of the index treatment or before the subject received another onabotulinumtoxinA treatment, if it occurred within the 3-month period. All adverse events (AEs), including serious AEs (SAEs), were recorded, regardless of causal relationship or whether they were considered unexpected (ie, AEs not mentioned in the onabotulinumtoxinA Korean prescribing information). Investigators assessed effectiveness by rating the overall change in CFL since last treatment (improved, unchanged, or worsened). Data were summarized by descriptive statistics.

Results: A total of 695 subjects were included in the full analysis set. The safety population comprised 667 subjects (mean ± SD age, 40.9 ± 13.0 years; range, 20–75 years), 87.3% of whom were female. Most subjects (69.9%) were treated for moderate to severe CFL, with 30.1% treated for moderate to severe CFL and GL simultaneously. Fourteen AEs were reported in 11 subjects (1.7%). Most AEs were mild (12; 85.7%), 1 was moderate, and 1 was severe (both eyelid ptosis). The majority (11; 78.6%) of AEs resolved without sequelae. Two AEs (injection site pain) reported in 2 subjects were deemed possibly related to onabotulinumtoxinA. One unexpected SAE (acute renal failure) occurred in 1 subject (0.3%). All unexpected AEs (n = 4 [0.5%]) were mild and considered unlikely to be related to treatment. Of the 376 subjects in the effectiveness analysis set, overall change from baseline in CFL was rated as improved in 375 (99.7%) and as unchanged in 1 (0.3%).

Conclusions: OnabotulinumtoxinA was well tolerated and effective for treatment of CFL with or without GL in this Korean PMS study. No new safety concerns were identified.

1043 | Treatment patterns of systemic antifungal dispensation in hospitals in England: An analysis of the health treatment insights database

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Background: Systemic fungal infections are a growing public health challenge and are a major cause of morbidity and mortality in hospitalized or immunosuppressed patients. In the UK, the number of cases of fungal bloodstream infection reported to national surveillance systems increased 24% between 2013 and 2017 [1]. With antimicrobial

resistance becoming a growing concern, it is important to understand the reasons for antifungal use in hospital.

Objectives: To describe the indications for systemic antifungal therapy in a large linked database of pharmacy and hospital discharge data in England (The Hospital Treatment Insights (HTI) database) broken down by primary and secondary diagnoses.

Methods: A retrospective cohort study of inpatients dispensed oral or intravenous antifungal medications during a hospitalization occurring between January 2010 and January 2017, as recorded within HTI. Data on exposure were defined by molecule name and included: Amphotericin B, Anidulafungin, Caspofungin, Fluconazole, Flucytosine, Griseofulvin, Isavuconazole, Itraconazole, Ketoconazole, Micafungin, Miconazole, Posaconazole, Voriconazole. Indications were inferred using diagnostic codes (ICD-10) recorded in Hospital Episode Statistics and analyzed using descriptive statistics.

Results: The cohort comprised 101,151 patients with 155,194 hospitalisations from 2010 to 2017. The mean age was 58 years (SD 21.5). In 10-year age bands, the most common band for children was 0–9 years (n = 4,142 (2.7% of hospitalisations)) and 60–69 years for adults (*n* = 35,092 (22.6%)), closely followed by 70–79 years (*n* = 34,360 (22.1%)). The top 5 primary diagnoses were: acute myeloblastic leukemia (*n* = 8,806 (5.7% of hospitalisations)), multiple myeloma (n = 8,758 (5.6%)), unspecified sepsis (*n* = 7,108 (4.6%)), unspecified lobar pneumonia (*n* = 6,302 (4.1%)) and diffuse large B-cell lymphoma (*n* = 5,507 (3.6%)).

Conclusions: Our study shows that hematological malignancies are the leading diagnoses associated with dispensation of systemic antifungals in England. A limitation of this study includes the inferring of diagnostic coding. However, results are consistent with clinical practice. Linked pharmacy and hospital discharge data (HTI) can provide insights into the likely indications of systemic antifungal use and monitor treatment patterns for this important cause of healthcare associated infections.

[1]https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/691268/hpr1018_polymcrbls.pdf

1044 | Impact of fluoroquinolone pre-authorization on ceftriaxone use and resistance in a large academic Hospital in South East United States of America

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Background: Antimicrobial pre-authorization, a process that limits the use of specific antimicrobials, is a useful antimicrobial stewardship (AS) strategy that can improve antimicrobial prescribing and decrease bacterial resistance. The impact of pre-authorization on the use of other antibiotics and the subsequent emergence of bacterial resistance is important in understanding the complex effects of AS interventions.

Objectives: To examine the relationship between fluoroquinolone pre-authorization (FP) and 1) ceftriaxone utilization and 2) the emergence of bacteria resistant to ceftriaxone in a clinical setting.

Methods: In October 2005, the University of Alabama at Birmingham hospital began implementing FP. Using a retrospective ecological design, change in the days of ceftriaxone therapy per 1000 patient-days 5 years before (09/2000–08/2005) and 5 years after (12/2005–11/2010) FP implementation was evaluated and compared using a Poisson regression model. Logistic regression was used to estimate and compare the emergence of ceftriaxone non-susceptible (CTR-NS) isolates of *E. coli, K. pneumoniae, E. cloacae and A. baumannii* 3 years before (2003–2005) and 3 years after FP implementation (2006–2008). Non-susceptible isolates are either resistant or showed intermediate resistance to ceftriaxone.

Results: After FP implementation, the average days of ceftriaxone therapy per 1,000 patient-days was 5 times more than before FP implementation (RR: 5.03; 95% CI: 4.56, 5.53; p-value: < 0.0001). When compared to the period before FP implementation, there was a decrease in the odds of CTR-NS *E. coli* (OR: 0.58; 95% CI: 0.46, 0.72; p-value: < 0.0001) and CTR-NS *E. cloacae* (OR: 0.62; 95% CI: 0.53, 0.73; p-value: < 0.0001) isolates by 42% and 38% respectively after FP implementation. However, there was a statistically non-significant increase in the odds of CTR-NS *A. baumannii* (OR: 1.10; 95% CI: 0.88, 1.37; *p* = 0.39) and CTR-NS *K. pneumoniae* (OR: 1.02; 95% CI: 0.81, 1.29; *p* = 0.89) isolates after the implementation, when compared to the period before the implementation.

Conclusions: Antimicrobial pre-authorization may increase the use of another antibiotic, but the effect on emergence of bacterial resistance is unclear. In this retrospective evaluation, fluoroquinolone pre-authorization resulted in increased ceftriaxone use; however, this did not negatively affect ceftriaxone resistance among select gram-negative organisms. Large-scale studies in other settings are needed to confirm this finding.

1045 | National medication use evaluation of combination antibiotic-corticosteroid ophthalmic products for acute conjunctivitis

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Background: Antibiotic-corticosteroid combination ophthalmic products (COPs) are not indicated for treatment of acute conjunctivitis (AC), which is usually viral, and overuse increases the risk of adverse reactions, including antimicrobial resistance and glaucoma. Overprescribing of COPs among non-specialists (non-ophthalmologists/optometrists) is a potential medication safety concern, thus a

medication use evaluation (MUE) was conducted within the Veterans Health Administration (VA).

Objectives: This quality improvement initiative evaluated presence of documented reasons, screening, and follow-up care for COP use by non-specialist prescribers for Veterans with or without AC.

Methods: A retrospective, multi-centered MUE was conducted utilizing database evaluations and chart reviews. Diagnosis codes, clinic stop codes, and prescriptions were identified through corporate data warehouse (CDW) and prescription databases. Veterans who received outpatient prescriptions for COPs from April 1, 2017 to March 31, 2018 and visited a primary care (PCP), emergency department (ED) provider, or other non-specialists were identified. Two samples of Veterans, with AC diagnosis codes and without AC codes, were included. Veterans having chronic conjunctivitis over 4 weeks, COPs prescribed by non-VA providers, or ocular surgery were excluded. Chart reviews were conducted to evaluate appropriate COP use, including verifying documented reasons (AC and/or other diagnoses), screening of intraocular pressure (IOP) at baseline, and screening IOP at follow-up within 30 days. Descriptive statistics were used to compare demographics and COP use.

Results: Overall, 300 Veterans were included, 216 (72%) with AC and 84 (28%) without AC. Baseline characteristics were similar between groups. Most non-specialists who prescribed COPs were ED providers (41%), followed by PCPs (26%). Among non-specialist prescribers, 92% of patients with AC had that diagnosis alone documented as the reason for COP use. For those without AC, 24% had no documented reason for use. Screening rates of IOP were low at baseline (2.5% with AC, 6.7% without AC). Follow-up IOP screening rates was similarly low (12% with AC, 8.9% without AC).

Conclusions: Inappropriate use and monitoring of COPs for AC among non-specialist prescribers is a concern. This finding prompted a medication safety newsletter alert and ophthalmology partnership to educate PCP and ED providers to avoid using COPs for AC and to understand appropriate indications for use. Future evaluations will assess the impact of these interventions on COP use.

1046 | Trends in pharmacotherapy for uncomplicated urinary tract infections in the United States, 2007–2016

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Background: Concerns of multidrug resistance may be influencing pharmacotherapy for urinary tract infections (UTI), but our knowledge of recent trends is limited.

Objectives: To assess 10-year trends in prescription practices for uncomplicated UTI in a national adult population.

Methods: To assess trends among those aged 18–64 years (*N* = 2,690,547), we utilized the Optum© Clinformatics® Data Mart (CDM), a de-identified administrative claims database that includes 15–18 million individuals covered annually by commercial insurance in all 50 US states. For analyses among those aged 65+ years (*N* = 371,227), we utilized the Medicare 5% Sample from the Centers for Medicare and Medicaid Services. UTI was defined as an outpatient claim with a UTI-related diagnosis code followed by a pharmacy claim within 72 hours for an anti-infectious agent. We assessed temporal trends in the prevalence of UTI-related prescription fills from 2007 to 2016, overall and stratified by sociodemographic characteristics.

Results: Over the 10-year study period, quinolones were the most commonly used medications (CDM: 41.2%; Medicare: 41.5%), followed by urinary anti-infectives (CDM: 22.0%; Medicare: 17.2%), and sulfonamides (CDM: 17.4%; Medicare: 15.8%). Over time, quinolone use decreased among both CDM enrollees (46.8% in 2007 to 32.9% in 2016) and Medicare enrollees (49.0% in 2007 to 34.0% in 2016). Conversely, urinary anti-infective use increased from 18.8% in 2007 to 27.7% in 2016 among CDM enrollees, and from 15.4% in 2007 to 18.8% in 2016 among Medicare enrollees. Among CDM enrollees, quinolone use increased with increasing age (34.5% among those 18–24 *vs*. 46.4% among those 55–64), while urinary anti-infective use decreased (24.7% among those 18–24 *vs*. 19.7% among those 55–64). Medication use was more similar across age groups among Medicare enrollees. Quinolone use was more common among men (CDM: 58.4%; Medicare: 47.7%) compared to women (CDM: 39.5%; Medicare: 40.2%), while urinary anti-infective use was more common among women (CDM: 23.7%; Medicare: 18.8%) compared to men (CDM: 5.2%; Medicare: 9.8%). We also found differences by race/ethnicity and socioeconomic status, with non-Hispanic Black and low-income enrollees less likely to use a urinary anti-infective and more likely to use a sulfonamide.

Conclusions: Our study demonstrates shifting UTI treatment patterns over time and differences by age, gender, race/ethnicity, and income.

1047 | Regional variation in the potentially inappropriate first line use of fluoroquinolones in Canada: A key to antibiotic stewardship?

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Background: Systemic oral fluoroquinolones are among the most widely prescribed class of antibiotics and are associated with potential harmful side effects. Their use has been expanded to milder infections, such as urinary tract infections (UTI), acute bacterial sinusitis (ABS) and acute exacerbation of chronic obstructive pulmonary disease (AECOPD), with limited evidence of superiority to first line antibiotics.
Objectives: To determine the rates of initial antibiotic dispensations for uncomplicated UTI, ABS and AECOPD in the outpatient setting across Canada, and to describe the determinants of variation in the use of fluoroquinolones.
Methods: We formed three retrospective population-based cohorts, one for each infection type, in each of six Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan). We used administrative health data spanning January 1, 2005 to the latest date of data availability for each site. We identified ambulatory visits with a diagnosis for UTI in women, ABS or AECOPD, and determined antibiotic exposure by the first antibiotic dispensed within 5 days of the event. The proportions of fluoroquinolones among the initial antibiotic dispensations for uncomplicated UTI, ABS or AECOPD events were described by province and over the study period.
Results: Among 2,170,027 women, 4,303,144 uncomplicated UTI events were identified. The proportion of events treated with fluoroquinolones, mostly ciprofloxacin, varied by province and ranged from 19% in Saskatchewan to 52% in Alberta. We identified 3,467,678 ABS events among 2,087,934 patients. Between 2% (Nova Scotia) and 11% (Ontario) of events treated with an antibiotic were dispensed a fluoroquinolone. Among 598,347 patients, 1,319,128 AECOPD events were identified. Fluoroquinolone use, mostly levofloxacin and moxifloxacin, varied by province and ranged from 6% in Nova Scotia and 36% in Ontario. Differences in provincial formulary criteria and enforcement, local practice and marketing patterns may partly explain these large interprovincial variations in the use of fluoroquinolones.
Conclusions: Systemic oral fluoroquinolones were commonly used as first line therapies, particularly for uncomplicated UTI and AECOPD. However, first line fluoroquinolone use varied widely across provinces. Formulary criteria and enforcement may be a key to facilitating better antibiotic stewardship and limiting potentially inappropriate first line use of fluoroquinolones.

1048 | Dolutegravir exposure among women of child-bearing potential living with HIV and during early pregnancy - a drug utilization study

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Background: Dolutegravir (DTG) is an integrase strand transfer inhibitor indicated for the treatment of human immunodeficiency virus (HIV) type-1 infection. The U.S. Food and Drug Administration approved Tivicay (DTG) for use in combination with other antiretroviral drugs in August 2013; a fixed dose combination (FDC) containing abacavir/lamivudine/DTG was approved in August 2014; and a FDC containing rilpivirine/DTG was approved in November 2017. This drug utilization analysis was prompted by findings from the Tsepamo Study in Botswana, which identified a signal for neural tube defects (NTD) in the offspring of mothers exposed to DTG at conception. Labeling for DTG-containing drugs was subsequently updated to warn of NTD risk with DTG use at conception through the first trimester.
Objectives: To describe the prevalence of exposure to DTG-containing regimens among pregnant women and women of child-bearing potential living with HIV in the Sentinel System.
Methods: Using the Sentinel Distributed Database (SDD), we examined the prevalence of DTG use (using National Drug Codes) among women of childbearing age (15 to 49 years old) with an HIV diagnosis and women aged 15 to 49 years old with live birth deliveries, August 2013 through March 2018. Prevalence of DTG use during the first month of pregnancy and during the first trimester were specifically examined.
Results: The prevalence of DTG use was high among women with HIV, increasing from 304.1 users per 10,000 women (229 per 7,530) in the first year of approval, to 2,133.5 users per 10,000 women (719 per 3,370) in the nine-month period starting August 2017. Over 1.1 million pregnancy episodes were identified, 21 of which had DTG use during the first month of pregnancy and 25 during the first trimester of pregnancy. DTG use during the first trimester increased from 0 exposures out of 268,001 pregnancies in the year from August 2013–July 2014, to 5 exposures out of 77,227 pregnancies in the nine-month period starting August 2017.
Conclusions: Although prevalence of DTG use in the SDD among HIV-infected women of childbearing age was substantial, the absolute number of DTG-exposed pregnancies was observed to be low. Despite the inclusion of a diverse U.S. population in SDD, data used in this analysis primarily include individuals who receive employer-based health care benefits plus a small proportion of Medicaid recipients. Therefore, the study's findings may not generalize to certain populations such as Medicaid recipients.

1049 | Prevalence of isoniazid preventive therapy use and factors predicting its use among HIV-infected patients in a Nigerian teaching hospital

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Background: HIV/AIDS is a pandemic disease associated with opportunistic infection, especially tuberculosis, which may result in high morbidity and mortality. The burden of the disease is high in Nigeria,

which is ranked second among most prevalent HIV population in the world. Despite the benefit of Isoniazid Preventive Therapy (IPT) in reducing burden of HIV/TB co-infection, the uptake is generally limited in developing countries.

Objectives: The aim of this study was to determine the prevalence of IPT use and the limiting factors among HIV-infected patients at Lagos University Teaching Hospital (LUTH) in Nigeria.

Methods: This cross-sectional study involved 300 HIV-infected individuals attending APIN clinic at LUTH over a 3-month period. A pro forma was used to capture the socio-demographic data, patients' exposure to tuberculosis and IPT use. Clinical data of eligible patients were also extracted and include the baseline laboratory parameters such as CD4 count, Hemoglobin concentration and viral load. Main outcome measure was prevalence of IPT use and IPT non-use. We also predicted the factors that affected the use of IPT. Data were analyzed using SPSS version 20.0. The demographic and clinical variables among IPT users and IPT non-users were compared. Binary logistic regression was used to predict the demographic and clinical variables determined IPT use among the patients. Any p value <0.05 was considered to be statistically significantly.

Results: Of the 300 cohort evaluated (218;72.7%) were females; their mean age was 41.74 ± 10.46 years. Tuberculosis co-infection was most predominant (47;15.7%) among those with HIV-infected and majority (133; 44.3%) had a CD4 count in the range of 200–500 cells/ml. The uptake of IPT use was low (20;7.9%) among HIV-infected patients without TB co-infection. Among the factors affecting the uptake of IPT were: Lack of awareness of its benefit (23;7.7%), IPT not prescribed (263;87.6%) and fear of adverse drug reaction (5;1.6%) and affordability 2 (0.7%). Lack of awareness about IPT use was found to be independently associated with poor IPT uptake (18; 2, p = 0.00).

Conclusions: IPT uptake was found to be very low in this study. Increase awareness and policy implementation of IPT by healthcare provider is necessary.

1050 | Utilization of direct acting antivirals for the treatment of hepatitis C in he province of Manitoba, Canada

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Background: Direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C viral (HCV) infection have been approved by Health Canada in recent years. These agents are significantly more efficacious than previous interferon-based therapies providing sustained virologic responses (SVRs) as high as 100%. They also have better safety and tolerability profiles and have become first line therapy for HCV.

Objectives: To describe incident rates of HCV diagnosis, the characteristics of the HCV patient population, and the utilization of the DAAs in the province of Manitoba.

Methods: The administrative databases of the Manitoba Centre for Health Policy (MCHP) Repository were used to determine all HCV cases in the province between calendars years 1995 and 2017. Linkage of the population registry with the provincial laboratory database allowed for the construction of a cohort of HCV patients and the description of their demographic characteristics. Dispensations of the DAAs available on the Canadian market at the time of the study were counted using the DPIN databases. Analyses were conducted with SAS® statistical software.

Results: Incident rates of HCV diagnosis increased from 42 per 100,000 population in 1995 to 64 per 100,00 in 2001; subsequently, rate of HCV diagnosis decreased to a 21 per 100,000 in 2011. In 2017, the annual rate was 38 per 100,000. Over the 22-year period, 9,445 HCV cases were identified; mean age at diagnosis was 40.2 ± 13.7 years, 58% were males, 77% lived in urban areas and more than 65% belonged to the lowest income quintiles. Between 1999 and 2011 fiscal years, 100% of the market share for HCV therapies belonged to the peg-interferon + ribavirin regimen, by 2017 fiscal year 99.7% of market share was for DAAs in Manitoba. The most prescribed agent was the ledispavir/sofosbuvir combination product with more than 60% of all prescriptions.

Conclusions: Our preliminary results demonstrate a rapid uptake of the new DAAs which have taken the entire market of the medications for chronic HCV infection. The population treated was predominantly male and of low income. Further studies are warranted to investigate the effectiveness of DAAs in patients who had not responded to interferon-based therapies or had relapsed after treatment. **Acknowledgements** Results and conclusions are those of the authors; no official endorsement by Manitoba Health, Seniors and Healthy Living or MCHP is intended or should be inferred.

1051 | Ceftolozane-Tazobactam utilization in the national veterans affairs healthcare system

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Background: Treatment of Gram-negative infections is complex due to underlying patient conditions, pathogen characteristics, and high rates of resistance to antimicrobial treatments. Ceftolozane/tazobactam is approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections and has been assessed in a trial of nosocomial ventilated pneumonia.

Objectives: We aim to understand how this newer antibiotic has been used in clinical practice in the Veterans Affairs (VA) nationally.

Methods: This retrospective study included VA patients receiving ceftolozane/tazobactam between 1/1/15–4/30/18. The index date was defined as the first date of ceftolozane/tazobactam receipt, determined from either barcode medication administration or pharmacy dispensing records. Demographics and comorbidities were assessed at the time of ceftolozane/tazobactam initiation. Organisms, source of positive cultures, and antibiotic exposures were assessed before and after the index date.

Results: A total of 231 unique patients received ceftolozane/tazobactam. The mean age was 67.6 (±12.4), 98.7% were male, and 68.4% were white. The most common infections were pneumonia (*n* = 79, 34.2%), urinary tract infections (*n* = 73, 31.6%), and osteomyelitis (*n* = 46, 19%). Polymicrobial cultures were common (*n* = 107, 46.3%). Most patients had cultures positive for *P. aeruginosa* (*n* = 174, 75.3%), with the most common source being the lung (*n* = 62, 35.6%, sputum and bronchoalveolar lavage), followed by urine (*n* = 32, 18.4%), skin (*n* = 23, 13.2%), blood (*n* = 22, 12.6%), and bone/joint cultures (n = 22, 12.6%). Additionally, 32.9% (*n* = 76) of patients had a previous positive *P. aeruginosa* culture in the month prior to the index date. Patients were commonly treated with other antibiotics in the 30 days prior to initiating ceftolozane/tazobactam (*n* = 215, 92.1%), including piperacillin/tazobactam (*n* = 92, 39.8%), meropenem (*n* = 78, 33.8%), and cefepime (*n* = 71, 30.7%). Ceftolozane/tazobactam was used as monotherapy in 39.4% (*n* = 91) of patients from day 2 to day 7 after the start of ceftolozane/tazobactam. The median time to ceftolozane/tazobactam initiation was 4 days after culture, with a subsequent median 15-day hospital stay.

Conclusions: In the national VA healthcare system, ceftolozane/tazobactam is mostly being used for pneumonia, urinary tract infections, and osteomyelitis, with the most common infecting organism being *P. aeruginosa*. About one-third of patients had previous positive cultures for *P. aeruginosa* and the majority were treated with other antibiotics before ceftolozane/tazobactam was initiated.

1052 | Antibiotics utilization in Ghana using real world claims data

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Background: There is a global call to monitor the consumption patterns of antimicrobials because of the looming threat of antimicrobial resistance. In Ghana, most research on prescribing patterns of antimicrobials has been limited to just single centre studies and hence the real national picture has never been clear enough.

Objectives: To study antibiotic utilization in Ghana using nationwide claims data.

Methods: Using claims data from 1st January, 2015 to 31st December, 2015, we identified all antibiotics in the Medicines List of Ghana's National Health Insurance Scheme (NHIS) using the Anatomical Therapeutic Chemical (ATC) Classification System codes. We determined the prescription patterns according to in-patient and out-patient clinic attendance, and by age and sex categories. We also calculated the defined daily dose (DDD) of each prescribed antibiotic. Concentrating on the ten most prescribed antibiotics, we determined the types of morbidities they are used in treating. All diseases in the claims data are classified using ICD-10 codes.

Results: In all there were about 27 different types of antibiotics in the operational NHIS Medicines List. The most prescribed antibiotic was metronidazole with a DDD of 0.98 million, and was used predominantly for infectious gastroenteritis. This was followed by amoxicillin-clavulanic acid (DDD = 2.12 million) used most of the time to manage pneumonia, Ciprofloxacin (DDD = 1.19 million), amoxicillin (DDD = 1.70 million) and so on. Amoxicillin, cefaclor, azithromycin, amoxicillin-clavulanic acid, clarithromycin, cotrimoxazole, erythromycin, flucloxacillin, were prescribed mainly among out-patients, and ampicillin, benzyl penicillin, ceftriaxone, and gentamycin were more common among in-patients.

Conclusions: This study shows that the NHIS claims data can be of use in the study of treatment patterns for infectious diseases in Ghana. The national dimension of the data gives a good picture of antibiotics usage among out-patient and in-patients in the country.

1053 | Temporal trends in the dispensation of systemic antifungal therapy in hospitals in England: An analysis of the health treatment insights database

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Background: Systemic fungal infections are a leading cause of mortality and morbidity in hospitalisations and are increasingly recognized as an important cause of healthcare associated infection. As resistance is a growing concern, it is of interest to understand trends of antifungal use over time.

Objectives: The study aims to describe the trends of antifungal (Intravenous (IV) or oral) exposure in the Hospital Treatment Insights (HTI) database from 2011 to 2016. HTI is a linked database of pharmacy (Hospital Pharmacy Audit (HPA)) and hospital (Hospital Episode Statistics (HES)) data which covers ≈ 28% of English trusts.

Methods: A retrospective cohort study of hospitalized patients dispensed antifungal treatments in HTI between 2011 to 2016. Antifungal drugs included: Amphotericin B, Anidulafungin, Caspofungin, Fluconazole, Flucytosine, Griseofulvin, Isavuconazole, Itraconazole, Ketoconazole, Micafungin, Miconazole, Posaconazole, Voriconazole. Exposure was defined as the first antifungal dispensed during a hospitalization. Exposure over time was described and stratified by patient demographics and analyzed with Chi-Squared tests for trend.

Results: A cohort of 139,203 antifungal dispenses during a hospitalization were analyzed; the median duration of hospitalization was 11 (IQR: 3 to 28) days. IV's made up 16.6% (*n* = 22,647) of the cohort while 83.7% (*n* = 116,556) of the cohort was dispensed oral medications. There was no difference in the number of dispensations by sex: males (*n* = 69,466, 49.9%), females (n = 69,737, 50.1%); and the mean age was 61.1 (SD: 20.1) years. Within 1 year of antifungal treatment exposure from 2011 to 2015, 27,477 (23.9%) patients died in hospital with the median time to death of 42 (IQR: 11 to 141) days. In-hospital antifungal dispensation increased year on year from 21,203 in 2011 to 24,139 in 2016. There was a larger (50.3%) increase in IV antifungal dispenses from 2011 (*n* = 3,065) to 2016 (*n* = 4,607) (p for trend <0.01). While death in hospital within one year of antifungal exposure remained stable from 2011 to 2015 (23.9% to 24.7%, *p* = 0.22).

Conclusions: Our study shows increasing annual antifungal use in English hospitals from 2011 to 2016. Planned analyses will include stratification by drug class and proportion of all hospitalisations resulting in systemic antifungal dispensation. Overall, HTI can provide insights into the trends of antifungal use over time and monitor treatment patterns for this important cause of healthcare associated infections.

1054 | Antibiotics utilization review in a Nigerian tertiary hospital

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Background: Antibiotic resistance is a global problem and inappropriate use is a major cause. This situation is worse in developing countries like Nigeria where infectious disease burden is higher. Conducting antibiotics (AB) utilization reviews is key to identify problems with their use, evaluate causes and take remedial action. Most studies undertaken in Nigeria assessed AB use in outpatient settings, which could not address all factors/situations affecting AB use in hospitals. This study, however, assessed AB utilization among inpatient in a Nigerian University teaching hospital using 17 core inpatient AB use indicators.

Objectives: To assess AB use among inpatients in a Nigerian tertiary hospital.

Methods: A quantitative, cross-sectional survey was conducted for all patients admitted in medical, surgical, pediatrics, and obstetrics and gynecology wards from October 2015 to March 2016 using 17 core AB use indicators developed under the Rational-Pharmaceutical Management (RPM-Plus) program. It improved on the WHO outpatient indicators and serve as a simple tool for evaluation of critical aspects of AB use in health facilities. Also, 16 inpatient physicians were randomly surveyed from the wards studied using semi-structured interviews to understand the reason behind the prescribing practice observed. Interviews were audio-recorded, transcribed verbatim, and thematically analyzed.

Results: Complete case-notes of 2356 patients were surveyed. About 46.5% were females and 57.7% between ages 21–60 years (SD = 41.40). AB was prescribed in 68.8% of hospitalized patients. The overall AB prescription encounters were 4669, out of which,60.4% were injections and 39.9% were prescribed in generics. Each patient was prescribed an average of 2.8 antibiotics (SD = 0.89) at an average cost of ₦13,632 ($40) (SD = 42.73) per hospitalization. The proportion of prescribed AB actually administered was 87.4%, while 88.5% were empirically prescribed. Only 62.2% of essential antibiotics were available. There were no systems regulating AB use. Physicians reported factors such as; poor laboratory services, pressure from pharmaceutical companies, patients' AB abuse, among others to have influenced the AB utilization.

Conclusions: The study identified poor AB utilization in the facility, evidenced by over-prescribing, high empiric and non-generic AB prescribing, etc. This calls for urgent intervention. Establishment of systems regulating AB use in this facility could promote rational use; and curtail cost.

1055 | Abstract Withdrawn

1056 | Characteristics and timing of treatment among patients with influenza-like illness

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Background: Understanding the characteristics of those who do and do not receive treatment for influenza can aid in the design of future studies of medical countermeasure utilization, safety, and effectiveness.

Objectives: To examine baseline characteristics of individuals with outpatient influenza-like illness (ILI) across two influenza seasons, by treatment status and timing.

Methods: Using Truven Health MarketScan® Databases formatted to the Sentinel Common Data Model, we identified individuals ≥6 months of age with incident ILI (30-day washout) via influenza-specific diagnosis codes (without lab confirmation) in the outpatient and emergency department settings, in July 2014–June 2015 and July 2015–June 2016, separately. We identified incident treatment with influenza antivirals (oseltamivir, peramivir, zanamivir; 10-day washout) via dispensings and administrations. We assessed treatment on ILI diagnosis date and separately on days 1–5 after diagnosis. We assessed the presence of comorbidities in the 183 days preceding ILI diagnosis for asthma, diabetes, chronic obstructive pulmonary disease

(COPD), and obesity. Influenza vaccination in the 183 days prior to ILI and influenza testing ±7 days from diagnosis were examined.

Results: In the 2014–2015 period, of the 26,923 ILI patient diagnoses identified, there were 15,827 ILI diagnoses with treatment on the same day, 911 diagnoses with treatment in the 1–5 days after, and 9,866 with no evidence of treatment within 5 days. The mean age for each treatment group was 28.7, 33.1, and 29.8 respectively. Asthma was observed among 7.5% of those treated the same day, 10.3% of those treated days 1–5, and 7.8% of the untreated. Diabetes was observed in 5.0% of those treated the same day, 11.1% of those treated days 1–5 days, and 5.8% of the untreated. History of COPD and obesity also were higher among those treated days 1–5 compared to the those treated the same day as diagnosis as well as the untreated group. Prior influenza vaccination was 23–26% across groups; influenza testing was high in all groups but highest among those treated same day (75%). There were 51% fewer diagnoses of ILI in the 2015–2016 period, reflecting the mild nature of that season, but the trends were similar for comorbidities by treatment status.

Conclusions: For the 2014–2015 and 2015–2016 influenza seasons, many patients who met our definition of ILI were treated with an influenza antiviral. Individuals treated on days 1–5 were older and had more comorbidities than those treated on the same day or not treated at all. Future work will investigate additional stratifications of treatment days in the Sentinel System.

1057 | Use of non HIV medication among people receiving antiretroviral treatment in Côte d'Ivoire, a cross sectional study

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Background: In Côte d'Ivoire, people living with HIV (PLHIV) have free access to antiretroviral therapy (ART) and cotrimoxazole. Yet, they may use other medications to treat non-HIV diseases. Scarce data are available regarding the use of non-HIV medications in Africa. This study describes the use of non-HIV medications and identifies the factors associated with their use by PLHIV on ART in Côte d'Ivoire.

Objectives: This study describes the use of non-HIV medications and identifies the factors associated with their use by PLHIV on ART in Côte d'Ivoire.

Methods: A cross-sectional study was conducted in six HIV clinics in 2016. HIV-1-infected adults receiving ART for at least one year were eligible. A standardized questionnaire was used to collect demographics, HIV characteristics and medication use data. Associated factors were identified using a multivariate adjusted Poisson regression.

Results: A total of 1,458 participants (74% women) were enrolled. The median age was 44 years, and the median duration of ART was 81 months. A total of 696 (48%) participants reported having used at least one non-HIV medication. Among the 1,519 non-HIV medications used, 550 (36%) had not been prescribed and 397 (26%) were from the nervous system class. Individuals who were more likely to report the use of at least one non-HIV medication included those who had been treated in an Abidjan HIV clinic, had a high school education level, had a monthly income between 100,000 and 200,000 FCFA, had a poor perceived health status, had WHO advanced clinical stage, had used traditional medicine products and had not used cotrimoxazole.

Conclusions: Half of PLHIV on ART reported using non-HIV medication. Further research is needed to assess whether the use of non-HIV medication is appropriate iven the third of those medications are not being prescribed.

1058 | Strategy to improve hepatitis C treatment drug use in Colombia

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Background: The high cost of treatment for H-C can limit access and adherence to treatment. The governments need to balance the incentive to promote innovation and to provide access to treatment to the population. In 2017 The Colombian Health System decided to design a strategy to ensure the access and adequate drug utilization of Hepatitis C treatment. This strategy included centralized purchasing, design a law, develop clinical practice guidelines and clinical and logistic pathway, direct observe treatment, follow up to the cohort of patients, assess the clinical outcomes and economic results.

Objectives: Multi-criteria evaluation of the strategy to improve access to Hepatitis C treatment and health outcomes in Colombia.

Methods: • Design: Descriptive study, follow up a cohort, the population: patients with diagnostic of Hepatitis C in the contributory regime in Colombian Health System. The follow up was from October 2017 to October 31st, 2018. • The population was patients with a new diagnosis of Hepatitis C or Patients with a previous diagnosis of hepatitis C without treatment but whit indication to start treatment. All patients of the contributive regimen in Colombia with a confirmed diagnosis. • Exposures: Treatment Daclatasvir, Ledipasvir/Sofosbuvir, Sofosbuvir. • Outcomes: Cure of Hepatitis C defined how undetectability of viral levels 12 weeks after finish treatment,

treatment abandonment, serious adverse events, reduction in the cost of drugs. • Descriptive statistics.

Results: 74% (*n* = 792) of the reported patients met the criteria to take a treatment for hepatitis C. The number of patients that finished 12 weeks of treatment and the follow up to close the case and determined the curation to October 2018 was 417 cases (52%), of this 401 (73%) were cured, 2 patients suspended treatment by physician decision, 12 patients died, 2 patients were disaffiliated by the insurance. None of the patients abandoned treatment. Did not report serious adverse events. Centralized purchasing has reduced the drug prices in more than 60% in overall, before the multidimensional strategy the cost from 250, 250 and 720 treatment (Dacla, Sofos, Sofo/ledi respectively, 84 tablets each one) US $108.216.950, and after the strategy implementation the cost was US $ 11.043.300, 90% saving.

Conclusions: The strategy implemented in Colombia health system (contributory regime) improved the access to treatment through reduced prices and was possible to achieve the clinical outcomes, cure of the patients, improve the adherence of the patients and physicians. This strategy will be replicated in a subsidized regime. Currently the centralized purchasing it remains.

1059 | Indications for Otic quinolone use in South Korea

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Background: Otic quinolones are widely used for the treatment of acute otitis externa (OE) and otitis media (OM) with non-intact tympanic membranes. Because they are considered to be safe, use for unapproved indications may have become more common. Recent studies have linked otic quinolones with tympanic membrane perforations, making off-label use controversial.

Objectives: The aim of this study was to assess indications, which are recorded on Korean prescriptions, for otic quinolones to elucidate the prevalence and types of off-label use.

Methods: Subjects receiving otic quinolones in 2016 were identified from South Korean Health Insurance Review Agency data (HIRA-NPS). We considered only the first prescription fill within a given 30 day window designated as unique treatment episode, of otic quinolones including ofloxacin, ciprofloxacin plus hydrocortisone, ciprofloxacin plus fluocinolone, and ciprofloxacin plus dexamethasone. Indications for otic quinolones were reviewed and classified by a senior otologist.

Results: There were 1,468,033 patients in the 2016 HIRA-NPS and otic quinolones were prescribed for 18,568 patients (1.26%). We identified 22,888 unique quinolone treatment episodes, with 84.2% patients having one episodes and 10.8% having two. Only 22.6% of prescriptions were for patients less than 18 years old. 97.2% of indications were deemed appropriate (eg, OM and OE). Questionable uses included cerumen impaction, post-traumatic tympanic membrane perforation, and temporal bone fractures. Proportions of questionable uses of otic quinolones were similar between pediatric and adult patients.

Conclusions: Otic quinolones are seldom prescribed for unapproved indications in South Korea.

1060 | Trends of antibacterial-effect traditional Chinese medicine consumption in secondary and tertiary hospitals in China: An analysis of pharmaceutical sales data, 2011–2015

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Background: Antibiotic consumption is a major driver for antimicrobial resistance. China, a large consumer of antibiotics, has implemented substantial regulations towards antibiotic use in the past decade. However, there is little evidence regarding the consumption of antibacterial-effect traditional Chinese medicines (AeTCM), which is commonly used in China and may have potential connection with antibiotic usage.

Objectives: To describe the trends of AeTCM expenditure and consumption in secondary and tertiary hospitals in China, using pharmaceutical sales data for the study period of 2011–2015.

Methods: We retrospectively analyzed aggregated monthly surveillance data on AeTCM sales to 114 secondary hospitals and 468 tertiary hospitals from 28 provinces in China from January 2011 to December 2015. A total of 1294 drugs were identified in single or compound preparation following *Guideline for Clinical Application of Chinese Patent Medicine - Infectious Diseases*. Expenditure and population weighted consumption of AeTCM were analyzed. Compound annual growth rate (CAGR) of expenditure and consumption between 2011 and 2015 were calculated. Drug consumption was expressed in DDD per 1000 per inhabitants per day (DID). We further explored the consumption disparity between oral and injection of AeTCM over the five years. Data were managed and analyzed in Microsoft Excel 2016.

Results: Total AeTCM expenditure and consumption increased during study period ($0.79 billion in 2011 to $1.31 billion in 2015; 4.07 DID in 2011 to 6.82 DID in 2015). CAGR of expenditure and consumption was 13.43% and 13.75% respectively. At provincial level, CAGR of expenditure and consumption was the lowest in Fujian (−4.96%, −5.60%) and the highest in Guansu (31.04%, 35.10%). Compared with injective AeTCM, the expenditure and consumption of oral AeTCM increased ($0.37 billion in 2011 to $0.68 billion in 2015; 3.41 DID in 2011 to 5.77 DID in 2015). CAGR of expenditure and consumption of injective AeTCM were 9.49% and 5.35% and that of oral AeTCM were 16.58% and 14.03%.

Conclusions: Although major efforts had been made to reduce the risks of excessive antibiotic use in China and certain progress had been achieved, total AeTCM expenditure and consumption showed a significant upward trend during the study period. It showed that there was potential substitute effect between consumption of AeTCM and antibiotics. Despite literatures showed that AeTCM had anti-infection effect, further research on rationality of AeTCM use is still in great need to facilitate infection treatment.

1061 | Drug utilization evaluation of antimicrobial agents at a tertiary care hospital: Point prevalence survey

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Background: Antibiotics are considered as life-saving drugs, but their inappropriate and overuse is rendering them ineffective. The maximum use of antibiotics happen in hospitals, thus it is necessary to identify the shortcomings and address the same. Point Prevalence Surveys (PPS) have been found to be a feasible and efficient alternative to prospective surveillance.

Objectives: To evaluate the appropriateness and compare antibiotic utilization practices among medical and surgical departments.

Methods: At a tertiary care teaching hospital in south karnataka, prospectively, in-patients prescribed with one of the 10 selected antibiotics (amikacin, gentamicin, cefoperazone-sulbactam, piperacillin-tazobactam, meropenem, vancomycin, teicoplanin, linezolid, polymyxin B and polmyxin E) were included (n = 188). Residents in clinical microbiology were coordinated by clinical pharmacist for the training and collection of data. Individual case records forms were then evaluated by the Antimicrobial Stewardship team. Outcome measure was to assess the appropriateness of therapy and to evaluate variation in the practices of antibiotic use. Data was analyzed using IBM SPSS software (16.0) and chi-square test was used to identify the association.

Results: Median (IQR) age was 53.5(30.75) years with a male predominance of 63%(119). No Microbiological Test (MT) was performed in 17%(32) of patients. Indication was empirical in 66% whereas definitive in only 19%. Piperacillin-tazobactam was prescribed in 23%(44), followed by cefoperazone-sulbactam 21%(40) and meropenem 16%(31), with only 2%, 13% and 16% of them having a definitive indication, respectively. Inappropriate dosing in 27%(51), with under-dose in 13%(25) and overdose in 14%(26). Under-dosing was seen with gentamicin 67%, polymyxin 33% and amikacin 29% whereas overdosing with cefoperazone-sulbactam 40%, amikacin 18% and meropenem 13%. Statistically significant difference between medical and surgical departments was observed in use of over dose (p = 0.005) and the practice of requesting MT (p < 0.001).

Conclusions: The selected antibiotics are considered as reserved, but most of those were used empirically and a varied utilization practice was observed in medical versus surgical departments. The findings underscore the need to perform more elaborate drug utilization studies, perform strict surveillance, promote evidence based medicine and provide support for optimal antibiotic dosing.

1062 | Antimicrobial prescribing patterns and compliance with treatment guidelines in critical care unit at a National Referral Hospital in Kenya

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Background: Antimicrobial agents are among the commonly prescribed medicines in hospitals, including the Critical Care Unit. The inappropriate and unnecessary use of antimicrobial agents is a major contributor to the development of antimicrobial resistance which has substantial clinical and economic implications.

Objectives: To determine the patterns of antimicrobial prescribing and the level of compliance to antimicrobial prescribing guidelines in Critical Care Units at Kenyatta National Hospital (KNH), the largest referral hospital in Kenya.

Methods: This was a descriptive retrospective longitudinal study which involved extraction of data from medical records of patients aged ≥13 years, who were admitted to the Critical Care Units in 2017. Data extracted included medication history, including the use of antimicrobials agents, diagnosis, and any documented review of the prescribed antimicrobials. Data was abstracted using a predesigned standardized data collection tool, entered in Epi Info and analyzed using STATA version 13.0.

Results: A total of 309 patients' records were included in this study. The prevalence of antimicrobial prescribing was 98.4%. The antimicrobial agents commonly prescribed were Ceftriaxone (36.8%), Metronidazole (16.9%) and Meropenem (12.4%). Only 40.9% of the prescribed antimicrobials were compliant to the hospital's treatment guidelines. Only 35% of the participants were on a single antimicrobial agent while 36% (n = 111) were on two. Less than 2% (n = 5) of the participants had more than five antimicrobial agents. The proportion of patients who had a review or stopping of antimicrobial therapy documented in their medical records was 11.7% (n = 36).

Conclusions: There was a high prevalence of antimicrobial prescribing in the Critical Care Unit with sub-optimal compliance to the available

guideline affecting patient clinical outcomes. The documentation of antimicrobial indication, stoppage or review was sub-optimal as well. These findings highlight the need for antimicrobial stewardship programme to improve the rationale use of antimicrobials at this referral hospital.

1063 | Visualizing drug treatment pathways in type 2 diabetes

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Background: ADA/AACE treatment guidelines recommend metformin as first line pharmacotherapy in T2DM for patients with A1C less than 9%. For patients requiring progression to dual therapy, recommended 2nd line treatments include SGLT2s, DPP4s, GLP1 receptor agonists, sulfonylureas (SU), thiazolidinediones, and insulin, with treatment choice based on drug-specific effects, including cardiovascular benefit, and patient factors, including presence of atherosclerotic cardiovascular disease (ASCVD).

Objectives: To explore real-world drug treatment patterns among commercially-insured adults with type 2 diabetes initiating metformin monotherapy during April 2014 to March 2016, including variation by presence of ASCVD.

Methods: Patients were identified from the de-identified Optum® Clinformatics® Data Mart database. Patients entered the cohort on metformin initiation and were required to have a diagnosis of type 2 diabetes in the preceding 180 days and no prior use of any oral or injectable antidiabetic medications. Patients were followed for treatment changes until disenrollment or the end of available data. Data were analyzed using the Aetion Evidence Platform™.

Results: During the study period, 48,702 patients initiated metformin monotherapy. Patients had a mean age of 60.5 (± 13.4) years and 51.5% were male. Patients had prevalent co-morbidities and complications, including ASCVD (31.9%), neuropathy (12.7%), and nephropathy (9.6%). Following metformin initiation, 38.2% remained on metformin monotherapy to the end of follow-up, 27.8% had a 90 + −day gap in treatment followed by re-initiation or treatment change, 17.6% discontinued treatment entirely, and 16.4% progressed to another therapy with no gap. For the 7,996 patients progressing, the most common pattern was dual therapy with metformin (98.0%), followed be triple therapy with metformin (1.0%), and a switch to another agent (0.5%). There were 29 different treatment patterns observed among patients progressing to dual or triple therapy. The most frequent second-line drug combination with metformin were SU (48.9%), DPP4s (17.7%), insulin (12.3%), and SGLT2s (10.0%).

Conclusions: We observed a range of treatment patterns following metformin initiation in real-world data. While patterns appeared generally consistent with treatment guidelines, there were high rates of non-persistence. Given the complexity and variation in real-world treatment patterns, Sankey plots were a helpful visualization tool.

1064 | Utilization of dulaglutide in primary Care in England: Interim results from a post authorisation safety study

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Background: Dulaglutide is a once-weekly injectable long acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) authorized in England for the treatment of type 2 diabetes mellitus (T2DM).

Objectives: To assess the utilization of dulaglutide in real-world primary care practice in England.

Methods: A descriptive cohort study (Modified Prescription-Event Monitoring) identified dulaglutide users from dispensed primary care prescriptions of dulaglutide between 2015–2017 in England. Patient characteristics and drug utilization data were collected from prescribing general practitioners (GPs) via questionnaires sent ≥12 months after the 1st prescription issued for each patient. Summary descriptive statistics were calculated.

Results: 1467 evaluable dulaglutide users with T2DM diagnosis confirmed. Median age: 58 yrs (IQR 51, 66); 775 males (52.8%). Baseline obesity (Body Mass Index (BMI) ≥30 kg/m^2) was present in 45.9% of the cohort (89.9% where BMI specified), while poor T2DM control, indicated by Hemoglobin A1c ≥58 mmol/mol (7.5%) was observed in 60.1% of patients (93.1% where specified). Median duration of T2DM was 10.0 yrs (IQR 6.0, 14.1). The decision to initiate dulaglutide was most frequently made by a specialist nurse (*n* = 766, 52.2%) followed by the GP (*n* = 352, 24.0%), and hospital doctor (*n* = 299, 20.4%). Most patients were prescribed 0.75 mg once-weekly (*n* = 233, 15.9%) or 1.5 mg once-weekly (*n* = 762, 51.9%). There were a small number of reports (*n* = 14, 0.9%) of >once-weekly usage. In the majority of patients, dulaglutide was prescribed as either add-on dual therapy (*n* = 469, 32.0%) or add-on triple therapy (*n* = 908, 61.9%); the most frequently reported concomitant anti-diabetes medication (ADM) was metformin (*n* = 624, 42.5%). In sub-populations not previously studied in clinical trials, the most frequently reported usage was in patients ≥75 yrs (*n* = 80, 5.5%).

Conclusions: This interim analysis suggests that dulaglutide is largely being prescribed in accordance with prescribing recommendations and national T2DM management guidelines. Results suggest most frequent use in patients with poor diabetic control where existing treatment with alternative ADM may not have achieved optimum control. This preliminary analysis of baseline data will be updated in the final report.

1065 | European multi-country drug utilization study of dulaglutide

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Background: Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist approved in Europe for the treatment of type 2 diabetes mellitus.

Objectives: This study aimed to characterize dulaglutide utilization patterns in real-world conditions in subpopulations of patients for which little data exist.

Methods: Electronic medical record databases in France, Germany, and Spain were used to evaluate dulaglutide use in the following subpopulations of interest: patients with severe renal failure, heart failure, liver disease, and severe gastrointestinal disease; children and adolescents (<18 years); elderly (≥75 years); and pregnant and breastfeeding women. Eligible patients were those who initiated dulaglutide in 2017 with ≥6 months of continuous history before dulaglutide initiation. Subpopulations of interest were defined by ICD-10-CM diagnosis and procedure codes for respective conditions. Patients with a recorded diagnosis of severe renal failure or an estimated glomerular filtration rate of <30 ml/min/1.73 m^2 recorded closer to dulaglutide initiation date were considered having pre-existing severe renal failure.

Results: A total of 4,420 dulaglutide initiators were identified, corresponding to 1,309 in France; 1,891 in Germany; and 1,220 in Spain. Mean age was 60 years and 53% males across the 3 countries. All dulaglutide initiators in Germany, and vast majority of those in France (96%) and Spain (98%) were diagnosed with type 2 diabetes, with preponderance of patients using dulaglutide as add-on type 2 diabetes therapy (France 79%; Germany 80%; and Spain 88%). No children or adolescents were identified among initiators of dulaglutide during the analysis year. Slightly over one-third of dulaglutide initiators were elderly patients (≥65 years old); those aged ≥75 years comprised about 11% in France and Germany, and 8.3% in Spain. Among women treated with dulaglutide, only 3 (one in Germany and two in Spain) were pregnant or breast-feeding at the time of starting treatment with dulaglutide. Few to no patients had pre-existing severe renal failure (none in France; Germany 0.5%; and Spain 1.9%). The frequencies of other pre-existing conditions were: liver disease (France 0.6%; Germany 3.0%; and Spain 16.9%), heart failure (France 1.9%; Germany 10.5%; and Spain 5.7%), and severe gastrointestinal disease (France 5.8%; Germany 9.9%; and Spain 9.0%).

Conclusions: This study showed that in 2017, dulaglutide is not widely used by patient groups of interest and is used by the intended population as an add-on therapy rather than first-line type 2 diabetes mellitus therapy according to the labeled indication in these three European countries.

1066 | Utilization of exenatide once-weekly (Bydureon®) in primary Care in England: Results from a PASS

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Background: Exenatide extended-release (Bydureon®) is a glucagon-like peptide-1 receptor agonist administered once-weekly by subcutaneous injection. Approved in 2011, Bydureon® is licensed to improve glycaemic control in combination with other antidiabetes medications (ADMs) in patients (pts) with type 2 diabetes mellitus (T2DM) when current therapy, with diet and exercise, is inadequate. A Post Authorisation Safety Study (PASS) was conducted to monitor the use and safety of Bydureon® in primary (1°) care in England.

Objectives: To describe the utilization of Bydureon® in 1° care.

Methods: A cohort study identified pts from dispensed Bydureon® prescriptions in England (2012–2016). Pt characteristics and drug utilization data was collected from prescribing general practitioners (GPs) via questionnaires sent ≥12 months after the 1st Bydureon® prescription issued for each pt. Summary descriptive statistics were calculated.

Results: Questionnaire response rate = 37.2% (7752/20860). Evaluable cohort = 6294 pts prescribed Bydureon® for T2DM (median age 57 years [IQR 50, 65]; 55.2% male). 2 pts were < 18 years. 16 pts had an off-label indication of type 1 diabetes and were excluded from analyses. At baseline, where specified, 91.7% of pts (*n* = 2390) were obese (BMI ≥30 kg/m^2) and/or had an HbA1c ≥7.5% (*n* = 1986, 90.0%); of those pts with a raised HbA1c, 66.0% (*n* = 1311) had measurements of ≥9.0% indicating very poor diabetic control. Bydureon® was mostly prescribed in 1° care (*n* = 3269, 51.9%); 'specialist decision' was the overwhelming reason for prescribing (*n* = 3113, 49.5%). The majority of pts were exenatide naïve (*n* = 4556, 72.4%), whilst 25.9% (*n* = 1629) were previous Byetta® (exenatide twice-daily) users. For 109 pts (1.7%), prior exposure to Byetta® was unknown. Nearly all pts (*n* = 5948, 94.5%) were taking Bydureon® 2 mg once/week, in accordance with the product label. Pts predominantly started Bydureon® as triple therapy (*n* = 3876, 61.6%) or dual therapy (*n* = 1936, 30.8%); monotherapy use was lower (*n* = 161, 2.6%). Metformin (*n* = 5753, 81.5%) and sulphonylureas (*n* = 2382, 45.0%) were the most frequent concomitant ADMs at index.

Conclusions: Bydureon® was largely used in accordance with prescribing recommendations in 1° care in England, with most frequent use in pts with poor diabetic control where treatment with alternative ADMs may have been unsuccessful. In addition, characteristics of pts prescribed Bydureon® are in keeping with the T2DM pt profile. This study design allowed for the timely collection of drug utilization data directly from GPs and suggests shared Bydureon® T2DM treatment arrangements between 1° and 2° care.

1067 | Determinants for initial treatment choice in diabetic macular edema

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Background: While attention is often paid to the physician role in initiating therapy, less consideration is given to the role patient choices (out-of-pocket costs, insurance plan, geography) make in determining initiation of treatment.

Objectives: To assess the patient-related factors that may impact the choice for initial therapy for diabetic macular edema (DME), focusing on factors patient chose prior to diagnosis.

Methods: Setting: This is a retrospective cohort study using administrative medical claims data from a large, national insurer. **Participants:**All patients newly diagnosed with DME from 2013–2016 were observed for 90 days after diagnosis or until first treatment was received. **Exposures:**The different baseline demographic and patient-related factors when DME was diagnosed. **Outcome measures:** The primary outcome was the odds of receiving the different possible initial treatments for DME (anti-vascular endothelial growth factors (anti-VEGF), focal laser, steroids or observation), no treatment and not following up.

Results: Of 6220 new DME patients, 3010 did and 3210 did not have a follow up (fu) exam within 90 days of diagnosis. 1557(51.7% of patients who had fu) were seen, but had no treatment during the observation window. Of those treated, 617(20.5% of those who had follow up) received bevacizumab, 191(6.3%) ranibizumab or aflibercept (rani/aflib), 560(18.6%) focal laser, 38(1.3%) steroid injection and 50(1.7%) had an injection with no drug noted. Having any copay (vs. $0) lowered the odds of receiving any treatment (OR:0.60,95%CI:0.51–0.71, $p < 0.001$) and treatments individually (anti-VEGF treatment OR:0.72,95%CI:0.59–0.88; bevacizumab OR:0.73,95%CI:0.59–0.91; rani/aflib OR: 0.70; 95%CI:0.49–0.99, focal laser OR:0.44,95%CI:0.35–0.55, $p < 0.001$). Contrary to copays, having a high deductible and type of insurance plan were not associated with initiating treatment($p > 0.41$ for all comparisons). Patients in the Northeast had lower odds of initiating anti-VEGF treatment (OR:0.60, 95%CI: 0.44–0.82, $p < 0.001$) and were specifically bevacizumab (OR:0.47, 95%CI:0.33–0.67, $p < 0.001$). Furthermore, Northeast patients who were treated with anti-VEGF had a higher odds of receiving rani/aflib compared to bevacizumab (OR:2.39, 95%C:1.31–4.37, $p < 0.001$). Southern Midwest patients had a higher odds of treatment (anti-VEGF OR:1.35,95%:1.02–1.77,$p < 0.001$; bevacizumab (OR:1.40,95%:1.04–1.87; focal laser OR:1.39, 95%:1.01–1.89,$p < 0.001$).

Conclusions: Patient choices such as copays and where they live are important factors in determining the initial choice in the treatment of DME.

1068 | Gender differences in reported adverse drug reactions at different time periods after drug initiation

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Background: Females may have a higher risk for reporting adverse drug reactions (ADRs) than males. This has also been shown for drugs commonly prescribed among patients with type 2 diabetes, such as biguanides and sulfonylureas. It is unknown whether gender differences in ADRs are consistent at different time periods of exposure.

Objectives: To assess whether gender differences in reported ADRs for biguanides and sulfonylureas are consistent at different time periods of drug exposure after treatment initiation.

Methods: This study had a longitudinal design in which data of patients with type 2 diabetes participating in Lareb Intensive Monitoring (LIM) were used. LIM is a non-interventional prospective observational cohort study of the Netherlands Pharmacovigilance Centre Lareb in which patients initiating specific drugs were followed for a period of 12 months. During this period, patients were asked to complete a web-based survey about experienced ADRs at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months after drug initiation. We included patients initiating a biguanide (i.e metformin) or sulfonylurea (i.e tolbutamide, gliclazide, glimepiride). The outcome was the proportion of patients reporting any ADR versus no ADR. We assessed this proportion at each time point and per drug class. Differences in proportions between males and females were tested using Pearson Chi-Squared tests. P-values <0.05 were considered statistically significant.

Results: For the biguanides, 1,712 patients were included (41% females, average age 58 years), and 474 completed all surveys (37% females). Over time, the proportion of females and males reporting an ADR decreased from respectively 34% and 25% at 2 weeks after initiation to 17% for both females and males at 12 months after initiation. Differences between females and males were statistically significant for the measurement at 2 weeks, 6 weeks, and 3 months. For the sulfonylureas, 651 patients were included (41% females, average age 59 years), and 171 completed all surveys (36% females). The proportion of females and males reporting an ADR decreased from respectively 27% and 17% at 2 weeks after initiation to respectively 5% and 9% at 12 months after initiation. Statistically significant differences between females and males were observed for the measurement at 2 weeks and at 6 weeks.

Conclusions: Differences between females and males in the reporting of ADRs were only observed in the early phases after treatment initiation. Further studies are needed to assess explanations for this

pattern over time for instance by focusing on the somewhat larger dropout rate of females.

1069 | Drug-utilization study examining characteristics of patients prescribed add-on treatment to metformin

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Background: Despite availability of clinical guidelines, choosing which treatment to add-on for patients inadequately controlled on metformin for type 2 diabetes mellitus (T2DM) can be challenging for clinicians.

Objectives: To compare characteristics of patients prescribed different anti-diabetics as add-on to metformin including: sulphonylureas, gliptins, thiazols, sglt-2 inhibitors, GLP-1 analogues and insulins.

Methods: We compared characteristics of patients with T2DM at the time they were prescribed different add-on therapies to metformin using The Health Improvement Network, a UK primary care database, between 2007–2016. We examined demographics, risk factors and the history of comorbidities across the different groups. We fitted regression models to estimate prevalence ratios (PR) and identify those factors most strongly associated with prescribing of particular add-on treatments.

Results: From a cohort of T2DM patients, we identified 32,793 patients who commenced add-on therapy to metformin. Of this total, 20,905 were commenced on sulphonylureas, 7,488 on gliptins, 2,336 on thiazols, 984 on insulins, 605 on GLP-1 and 475 on SGLT-2 s. Patients prescribed sulphonylureas were on average older (59.8 ± 12.1 years). More women were prescribed insulin (57%) and more men thiazols (62%). Body weight was highest among GLP-1 users (120.2 ± 24.7 kg) and lowest for insulin users (89.9 ± 22.4 kg) at time of prescribing, while HbA1c was lowest for GLP-1 (69.9 ± 19 mmol/mol) and highest for sulphonylureas (75.5 ± 20 mmol/mol). Those with history of CVD (cardiovascular disease) at add-on initiation were 4% more likely to receive sulphonylureas (PR = 1.04, 95%CI: 1.02–1.07) and 22% less likely to receive insulin (PR = 0.78, 95%CI: 0.65–0.94). Patients with history of severe mental illness were 85% more likely to be prescribed insulins (PR = 1.85, 95%CI: 1.35–2.52), whereas patients with history of retinopathy were 20% more likely to be prescribed thiazols (PR = 1.20, 95%CI: 1.10–1.30). For each 1% increase in HbA1c, the probability of receiving sulphonylureas increased by 4% (PR = 1.04, 95%CI: 1.03–1.04). Conversely, for each unit increase in BMI, the probability of receiving sulphonylureas decreased by 2% (PR = 0.98, 95%CI: 0.98–0.98).

Conclusions: Characteristics of patients prescribed different add-on therapies after metformin for T2DM differed for several variables. Patients with a history of CVD or higher HbA1c at baseline were more likely to be prescribed sulphonylureas. A useful next step would be to compare prescribing patterns to national guidelines and identify deviations from recommended practice.

1070 | Utilization of prescription anti-obesity drugs in the U.S. Food and Drug Administration's (FDA) sentinel system, 2008–2017

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Background: Obesity is major public health concern affecting 40% of adults and is associated with $147 billion in medical costs in the United States. Despite the availability of pharmacotherapy options to augment diet and exercise lifestyle interventions, evidence of low adoption of anti-obesity medications (AOM) exists.

Objectives: To characterize the utilization patterns and treatment duration of AOM approved for use in adults included in the U.S. FDA's Sentinel System.

Methods: We conducted a descriptive drug utilization analysis in adults >18 years initiating AOMs in 17 Sentinel Data Partners from 2008–2017 (generally commercial insurers, but Medicare contributed fee for service enrollee data). We characterized new users (first dispensing in 183 days) of any AOM (lorcaserin, bupropion/naltrexone, liraglutide, phentermine/topiramate, orlistat, phentermine, benzphetamine, diethylpropion, phendimetrazine), and individual AOMs. Baseline patient characteristics, including Body Mass Index (BMI) and cardiovascular history were described in the 183 days prior to first dispensing. Treatment duration was depicted with Kaplan Meier survivor curves; persistence was assessed primarily with a 60 day gap between dispensings to account for inconsistent medication use.

Results: We identified 267,836 AOM new users, predominately female (82%) and less than 65 years of age (92%). Only 50% of AOM users had a diagnostic codes for obesity and only 14% had one for BMI; among AOM users with a BMI diagnosis code, 87% had a BMI $\geq$30 (obese). Hypertension (30%) and hyperlipidemia (28%) were common comorbidities among AOM users. Phentermine (n = 198,203) was the most common AOM, followed by bupropion/naltrexone (n = 29,106). Approximately 37% of phentermine users continued use beyond 90 days, despite labels recommending use for a "few weeks". Across AOM, duration of use was generally short (median, 62 days); at 1 month, 59% of AOM users remained in treatment and persistence declined substantially thereafter (2 months = 51%, 3 months = 37%). After 6 months, 17% of AOM users were still on treatment.

Conclusions: The most commonly used AOM was phentermine, followed by bupropion/naltrexone. Most AOM users were female and < 65 years of age. In the majority of AOM users, treatment duration was short.

1071 | Utilization pattern and adherence to novel anti-obesity medications: A retrospective study in a privately insured population

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Background: Obesity is an endemic medical condition in the United States while access to anti-obesity medications (AOM) has been limited due to safety and/or effectiveness issues. Sympathomimetic agents are approved as short-term AOM (SAOM) while five AOMs are available for long-term use (LAOM). The literature on utilization pattern and adherence to AOMs is limited.

Objectives: To evaluate the utilization pattern of AOMs and adherence to LAOMs (phentermine/topiramate, naltrexone/bupropion, lorcaserin, liraglutide, orlistat).

Methods: We used the IBM MarketScan Database for Commercial Claims data (2012–2017) to estimate AOM utilization among diagnosed obese/overweight patients. Patients with continuous enrollment in health plans were identified in each year and obesity/overweight was measured with appropriate diagnosis codes (ICD-9 and ICD-10) on medical encounters. AOM use was defined as having &ge 1 pharmacy claim during the year. To evaluate adherence to LAOMs, patients with 6 months of health plan enrollment before and after drug initiation were included. Patients with <2 LAOM claims and < 30 cumulative days' supply were excluded (early discontinuation). We calculated the proportion of days covered (PDC) during the 6-months period following initiation and used a threshold of 80% to define high adherence. Demographic and clinical characteristics including the Charlson Comorbidity index were measured during the 6-months baseline period. We also calculated the average out of pocket cost of LAOM for 30 days' supply. A multivariable generalized estimating equation model was used to compare adherence among the LAOMs.

Results: We identified 7.4 million prevalent obese/overweight patients. SAOM utilization was 2.1% in 2012 and decreased to 1.6% in 2017. In contrast, LAOM utilization increased from 0.1% in 2012 to 1.9% in 2017. We identified 63,337 eligible treatment episodes with LAOMs (79.9% among females, mean age 46.3). Adherence to LAOM was moderate (mean PDC: phentermine/topiramate (59.3%), naltrexone/bupropion (54.3%), lorcaserin (51.4%), liraglutide (62.3%), orlistat (51.9%)). In the adjusted model, liraglutide was weakly associated with high adherence compared to phentermine/topiramate (odds ratio: 1.14; 1.08, 1.20) and both drugs were significantly associated with high adherence compared to other LAOBs.

Conclusions: Utilization of AOMs appears to be low among insured patients, but lack of formulary coverage resulting in self-pay might produce underestimates. Adherence to LAOMs is moderate which require real-world safety and effectiveness evaluations.

1072 | Antidiabetic therapy De-intensification from a physician perspective and factors affecting their prescribing: A cross-sectional study

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Background: There are limited guidelines that address antidiabetic therapy de-intensification in order to decrease the burden of its associated hypoglycaemic events. The high prevalence of inappropriate intensive antidiabetic therapy has increased the importance of investigating physicians' perspectives towards this approach, including their decision to individualize their treatment goal, de-intensify antidiabetic therapy, and factors which affect their prescribing.

Objectives: This study aims to understand the physicians' perspective regarding antidiabetic therapy de-intensification and factors that affect their prescribing for patients with type 2 diabetes mellitus (DM).

Methods: A cross-sectional survey study was conducted using a self-administrated questionnaire from January 2018 to January 2019 in Saudi Arabia. Two previously validated questionnaires, one developed by Genere and the other by Grant, were adopted and used in this study. Univariate/multivariate logistic regression was used to assess the relationship between physicians' demographic and practice characteristics and their awareness of, agreement with and practice of HbA1c individualisation and their practice of antidiabetic therapy de-intensification.

Results: A total of 205 physicians have participated in the study. The findings of this study showed that the majority of the physicians reported that they were familiar with the principle of antidiabetic therapy de-intensification (89.3%, n = 183), and agreed with it (68.2%, n = 118). However, only 78.6% of them reported that they were applying it frequently. In addition, this study highlighted factors considered while prescribing antidiabetic medications and showed that physicians reported giving more importance to patients' medical profiles such as comorbidity, last measured HbA1c level, and physician's assessment of patient's health status rather than other variables like patients adherence, preference to delay or avoid therapy, or specific requests with regards to their therapy.

Conclusions: It is suggested that healthcare professionals should pay more attention to other non-clinical factors as they are associated with better adherence and disease control.

1073 | Are medication adherence and Total healthcare cost associated with generic and brand levothyroxine initiation

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Background: Although generic levothyroxine has been approved in the U.S. since 2004, its use and substitution remains suboptimal.
Objectives: To examine the difference in medication adherence and total healthcare cost between generic and brand levothyroxine new users.
Methods: This was a retrospective cohort study of new users of brand and generic levothyroxine identified in the fee-for-service 5% sample of 2013–2015 Medicare (n = 13,606) and 11 states' 2011–2012 Medicaid (n = 7,871) administrative claims data. Brand and generic levothyroxine use was identified with NDC codes in pharmacy claims files. Primary outcomes included: 1) medication adherence (defined by proportion of days covered (PDC) $\geq$ 80%) to levothyroxine treatment, and 2) total healthcare cost (including outpatient, inpatients, prescription) during 12 months after levothyroxine initiation (index date). Patient demographics (sex, age, race, region, urban/rural, comorbidity) and health service utilization factors were assessed at the 6-month washout period in both Medicare and Medicaid cohorts. Provider (sex, credential) and prescription (initial dosage) factors were also controlled in the Medicare cohort. Multivariable logistic regression and generalized linear models were used to assess the associations between generic vs. brand levothyroxine initiation with medication adherence and total healthcare cost, controlling for covariates, respectively.
Results: Among all levothyroxine new users, more Medicare beneficiaries were adhering to treatment than Medicaid beneficiaries (71.20% vs. 64.88%, respectively). However, there was no association between generic vs. brand product initiation and adherence to levothyroxine in either Medicare or Medicaid cohort (P > 0.05). Medicare new users also had higher total healthcare cost than Medicaid beneficiaries ($15,249 (standard deviation (SD) = 159.55) vs. $10,249 (SD = 104.45), respectively). After controlling for adherence and covariates, generic levothyroxine new users had lower total healthcare cost than brand new users in both cohorts (coefficient estimate (CE) with standard error (SE) = −0.59 (0.11) in Medicare; CE (SE) = −0.28 (0.03) in Medicaid).
Conclusions: This large, real-world analysis found no association between medication adherence and brand/generic levothyroxine initiation. However, generic levothyroxine new users had significant lower total healthcare cost than brand new users. Using generic levothyroxine did not reduce medication adherence, and it may help reduce total healthcare cost.

1074 | Proton pump inhibitor (PPI) use in Australia: Evaluating national quality use of medicines initiatives

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Background: Proton pump inhibitor (PPI) use has grown substantially, prompting widespread concerns about overuse, in particular the use of high dose PPIs for durations longer than clinically necessary. In response to these concerns, initiatives encouraging quality use of PPIs have been launched in many countries.
Objectives: To characterize recent trends of PPI use in Australia (2012–2017) and evaluate the impact of the two nationwide campaigns launched in 2015 targeting quality use of PPIs; one led by NPS MedicineWise (NPS), the other by Choosing Wisely Australia (CWA).
Methods: We used dispensing records from a nationally-representative 10% sample of Australians eligible for subsidized medicines through the Pharmaceutical Benefits Scheme (PBS). We estimated the annual prevalence, incidence and duration of PPI use among people 18 years and over. To assess the impact of both initiatives, we used interrupted time series (ITS) analysis of monthly PPI dispensings (stratified by tablet strength; high, standard, low), monthly rates of switching from higher to lower strength PPIs, and monthly rates of PPI discontinuation. We used statins as a comparator medicine for the ITS analyses.
Results: 523 092 people were dispensed at least one PPI between July 2012 and July 2017; their average age was 61 years (SD; 17 years) and 56% were female. Annual prevalence of PPI use increased from 14.6 to 15.7 per 100 persons. Annual incidence and prevalence increased with age, as did duration of use. Following the year-long NPS and CWA campaigns, we observed significant decreases in monthly PPI dispensings, particularly for standard tablet strengths (1.9% and 2.3% respectively). We found no significant changes in monthly rates of switching to lower strength PPIs or discontinuing PPI treatment. We did not observe changes in monthly dispensings or rates of discontinuation for our comparator medicine, statins.
Conclusions: Our findings demonstrate the decline in monthly PPI dispensing rates coincided with the roll out of national quality use of PPI campaigns. However, this may be due, at least in part, to the increased availability of over-the-counter PPIs from February 2016 onwards. Rates of discontinuation and switching to lower PPI strengths did not change, despite being the main target of these campaigns. Future interventions should attempt to better educate older users, where use is most common.

1075 | National Trends in proton pump inhibitors (PPIs) use and patient factors associated with PPIs use in the United States: 2002–2015

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Background: In the United States (U.S.), PPIs are among the highest-selling classes of drugs, but evidence in its utilization patterns among patient subgroups is limited.

Objectives: To examine the trends in PPIs use, overall and by patient subgroups, and identify patient factors associated with PPIs use among nationally representative, noninstitutionalized U.S. population.

Methods: A retrospective, serial cross-sectional analysis using the 2002–2015 Medical Expenditure Panel Survey (MEPS) data was conducted. PPIs use was identified by matching generic PPI names in the MEPS household prescribed medicines event files in each calendar year. Trends in annual proportion of participants with any PPI use, overall and by patient's self-reported age (<25, 25–39, 40–64, 65+), race/ethnicity (non-Hispanic white, black, Asian, other), sex (male, female), geographic region (Northeast, Midwest, West, South), income (poor, low, middle, high), health insurance status (public, private, uninsured), body mass index (BMI: underweight, normal, overweight, obese), marital status (married, widowed, never married, other), and esophageal disorder (presence, absence) were examined using simple linear regression models. Merging all data from 2002–2015, a multivariable model with generalized estimating equation was used to identify patient factors associated with PPIs use, controlling for year and self-reported health status. All the results were weighted to represent national estimates and $P < 0.05$ was set for statistical significance.

Results: Overall proportion of PPIs use in U.S. increased from 5.5% (standard error (SE) = 0.2) in 2002 to 8.8% (SE = 0.3) in 2015 ($P_{trend} < 0.001$). PPIs use trend increased significantly in different patient age (except 40–64), race/ethnicity, sex, region, income, and marital status subgroups ($P_{trend} < 0.05$). Trends also increased in participants with public health insurance and those who were obese. Among patients with esophageal disorders, PPIs use was 73.8% in 2002 and 78.8% in 2015 ($P_{trend} > 0.05$). Multivariable results found that participants who were older than age 25, female, non-Hispanic white, living in Northeast, with higher income, having public or private health insurance, obese, and married had higher likelihoods of using PPI.

Conclusions: PPIs use increased by 60% in 2002–2015 among the U. S. population. PPI use trends were similar across most patient factors but varied by the patient's health insurance and BMI. Understanding utilization patterns of PPI could inform practitioners to identify potential treatment disparities and suboptimal uptake.

1076 | Use of proton pump inhibitors and mortality among Icelandic prostate cancer patients

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Background: Proton pump inhibitors (PPIs) are commonly used drugs among cancer patients. While pre-treatment with PPIs has been reported to enhance the efficacy of chemotherapeutic agents, post-diagnosis PPI use has been associated with increased prostate cancer-specific and overall cancer mortality.

Objectives: To determine whether post-diagnosis PPI use is associated with mortality among prostate cancer patients.

Methods: In this population-based cohort study, we identified patients between 40–85 years of age with an incident diagnosis of prostate cancer in Iceland between 2007 and 2012 ($n = 1058$). Follow-up was from 12 months after diagnosis until death, emigration, or the end of December 31, 2015. We defined post-diagnosis use as ≥2 filled prescriptions following diagnosis and lagged the exposed person-time by 12 months. Pre-diagnosis use was defined as ≥2 filled prescriptions in 3 years prior to diagnosis. Post-diagnosis users where then further categorized as continuous (post- and pre-diagnosis use) and new users (post-diagnosis use only). We used time-dependent Cox proportional hazard regression models to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific and all-cause mortality associated with post-diagnosis use of PPIs. In secondary analyses we stratified PPI use by timing of use (continuous use, new use), clinical stage (localized, non-localized) and cumulative dose (1–365 DDDs, >365 DDDs).

Results: We identified 347 (32.8%) post-diagnosis PPI users and 711 (67.2%) non-users. Out of the 347 patients using PPIs after diagnosis, 59 patients (17.0%) died due to any cause and 22 patients (6.3%) due to prostate cancer, compared with 144 (20.3%) and 76 (10.7%) among non-users, respectively. Post-diagnosis PPI use was not statistically significantly associated with prostate cancer-specific mortality (HR 0.88; 95% CI: 0.52–1.48) or all-cause mortality (HR 1.02; 95% CI: 0.73–1.43). Stratification by timing of use and clinical stage did not reveal any statistically significant associations to the mortality outcomes of interest. Furthermore, we did not find any evidence of a significant dose–response association.

Conclusions: Our findings did not indicate an association between post-diagnosis PPI use and mortality among prostate cancer patients.

1077 | Utilization of linaclotide in United Kingdom

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Background: Linaclotide is used to treat moderate-to-severe irritable bowel syndrome (IBS) predominantly with constipation (IBS-C) in adults. Data on its use in routine clinical settings and specific subgroups are lacking.

Objectives: To describe the characteristics of patients prescribed linaclotide and the linaclotide treatment patterns.

Methods: Patients with a prescription of linaclotide between 05/2013–12/2017 in the Clinical Practice Research Datalink (CPRD), a population-based primary care database from the UK, were included. We defined sub-types of patients with IBS using an algorithm based on diagnostic codes, prescriptions and symptomatology. We describe patient characteristics, comorbidities, comedications and certain sub-groups. These included ≤17 years, patients with chronic constipation and no IBS, patients with gastrointestinal (GI) obstruction or inflammatory bowel disease (IBD) and abusive/excessive use (patients with medical record of obesity, eating disorder, anorexia, bulimia or most recent BMI ≥30 or < 20 during one year up to index date, and no IBS). We also describe treatment patterns i.e. persistence, switching and discontinuation in patients prescribed linaclotide.

Results: 1319 patients were prescribed linaclotide, of whom 0.9% were ≤ 17 years, 0.4% were patients with chronic constipation and no IBS, 3.5% had GI obstruction or IBD and 17.0% had potential for abusive/excessive use. 41% of patients had a missing IBS diagnosis in their records. Of the remaining 778 patients, 68.8% had IBS-C, 6.7% had IBS predominantly with diarrhea, 6.4% had mixed IBS and IBS sub-type could not be determined in 18.1% of patients. The mean age at linaclotide prescription was 46.7 years (SD: 16.7) and 86.3% were female. Around one-third of all linaclotide patients were overweight (30.6%), 22.9% were obese and 4.8% underweight. Hypertension (25.2%) and cardiovascular disease (19.2%) were the most common comorbidities in linaclotide users. Laxatives (71.9%), antibiotics (61.3%), proton-pump inhibitors (51.6%) and antispasmodics (47.1%) were the most common comedications. A total of 48.6% of patients switched from linaclotide; of these 41% switched to laxatives, while 36% discontinued without switching to another drug. The median duration of linaclotide treatment was 28 days (IQR 28–119 days). 15.3% of patients had a persistent use of linaclotide.

Conclusions: Linaclotide in the UK was largely prescribed in accordance with the EU label. Most patients with a linaclotide prescription had IBS-C. The median duration of treatment was around a month, and among the patients who switched, the largest group started on laxatives.

1078 | Bone mineral density testing after initiation of androgen deprivation therapy for prostate cancer

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Background: Androgen deprivation therapy (ADT) is a staple of advanced prostate cancer (PCa) treatment, however several side-effects are associated with its long-term use. Notably, loss of bone mineral density (BMD) is accelerated which increases fracture risk. Clinical guidelines recommend BMD testing when initiating ADT to properly assess baseline fracture risk.

Objectives: The objective was to examine the proportion of baseline BMD testing in men initiating long-term ADT in the province of Quebec, Canada.

Methods: The cohort consists of men extracted from a random sample from Quebec public healthcare insurance administrative databases who were diagnosed with PCa from 2004–2012 and treated by ADT. Only patients who received at least one year of continuous ADT treatment were included. The primary study outcome was the receipt of baseline BMD testing (defined as a BMD test identified from medical claims in the period from 6 months prior to or up to 12 months after ADT initiation). Multivariable logistic regression analysis was performed to identify variables associated with baseline BMD testing.

Results: We identified 3713 patients who initiated ADT at a mean age of 75 years old during the study period, of which 700 (18.9%) underwent baseline BMD testing. Rates of baseline BMD testing increased by year of ADT initiation, from 11.9% in 2004 to 19.7% in 2007 and to 24.1% in 2012. Following multivariable analyses, year of ADT initiation remained associated with higher odds of baseline BMD testing (odds ratio [OR] 1.09 for each increasing year, 95% confidence interval [CI] 1.05–1.13, $p < 0.001$), as did prior local radical treatment (OR 1.62, 95% CI 1.33–1.98, $p < 0.001$). Conversely, older patient age (OR 0.98, 95% CI, 0.97–0.99, $p = 0.001$) and rural residence (OR 0.60, 95%CI 0.48–0.75, $p < 0.001$) were associated with lower odds of baseline BMD testing.

Conclusions: In our study population, the rate of baseline BMD testing in men initiating ADT was low, although the rates were increasing over time. Lower rates in rural areas suggest potential healthcare access issues. Additional efforts emphasizing the importance of BMD testing in prostate cancer clinical guidelines may be needed.

1079 | Prestop: Patients perspective on discontinuation of CML TKI-treatment

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Background: Chronic myeloid leukemia (CML) is a malignant hematologic disease with recommended life-long treatment with tyrosine kinase inhibitors (TKIs). The results of several trials show that approximately half of CML patients with stable disease can discontinue TKI-treatment without loss of efficacy. However, little is known about patients' perspective and attitude on, and willingness to discontinue TKI treatment and influencing factors.

Objectives: To gain insight into patients' willingness and preferences regarding discontinuation of CML TKI-treatment and to identify factors that may influence this.

Methods: An observational, cross-sectional, multicenter study by means of an (electronic) questionnaire was conducted in the Netherlands. Adult CML patients were recruited through outpatient pharmacies and or hematology department of several Dutch hospitals, and through the national patient association for patients with hematological malignancies: Hematon. Patients were asked about their willingness and preferences regarding discontinuation of TKI-treatment. Logistic regression analysis was used to determine factors associated with patients' willingness to discontinue TKI-treatment.

Results: A total of 185 patients participated in this study: 59% aged ≥55 years, 54% female and most patients using imatinib (36%). Most Dutch CML patients on TKI-treatment (79.5%) were willing to discontinue treatment. Patients most frequently reported: no more side effects, being afraid of an aggressive relapse, and being frequently monitored as the most important advantage, disadvantage, and condition for discontinuing treatment respectively. Univariate logistic regression showed that young age (0.41 (0.18–0.92) P = 0.03), paid work (3.04 (1.44–6.41), P = 0.00), being informed about discontinuation studies (6.25 (2.36–16,52) P = 0.00), and severe adverse advents (2.64 (1.21–5.76), P = 0.01) were associated with patients' willingness to discontinue TKI-treatment.

Conclusions: Most patients were willing to discontinue TKI-treatment and reported advantages. However, patients also reported disadvantages and conditions to discontinue treatment. Moreover, several factors were associated with TKI- treatment discontinuation. These findings can be used to tailor the information provided to the patient during patient counseling. However, additional research is needed to get deeper information on patients who reported no willingness to discontinue TKI-treatment.

1080 | Design of a centrally aggregated medication use evaluation: Anticholinergics in dementia

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Background: Conducting medication use evaluations (MUEs) across a large integrated health care system (HCS) such as the Veterans Affairs (VA) HCS can be resource consuming and challenging to coordinate on a timeline. VA Center for Medication Safety (VAMedSAFE) designed a novel distributive approach termed centrally aggregated MUE (CAMUE) whereby a facility-provided toolkit allows for standardized chart review, analysis, and submission of results to VAMedSAFE for aggregation. We illustrate our CAMUE evaluating anticholinergic medication (AChM) use in dementia patients.

Objectives: A CAMUE was used to assess, among Veterans with dementia: (a) prescribing patterns of incident outpatient AChM; (b) if non-AChM alternatives were tried first; (c) whether risk–benefit analyses were documented; (d) harms associated with AChM.

Methods: A CAMUE toolkit, consisting of a list of target patients, protocol, operations manual, and Microsoft Access database (data collection form, table, pre-programmed report) was electronically provided to each site. The VA Pharmacy Benefits Management (PBM) outpatient prescription database and Corporate Data Warehouse were used to identify dementia patients with incident outpatient AChM prescriptions (> = 7 days) in CY2016. Hospice/palliative care patients were excluded. Reviewers verified eligibility, reviewed charts (6-month look-back and 30-day follow-up) per instructions, and transcribed de-identified summary measures generated by the Access Report into a Microsoft InfoPath form. VAMedSAFE combined site counts into grand totals, with descriptive statistics and measures of variability as appropriate.

Results: Nineteen sites submitted data on 1094 eligible patients for aggregation. Antihistamines were the most common class (31%, 28.6–34.1). Non-pharmacological alternatives to the indication for the index AChM were trialed in 18% (15.9–20.5); non-AChMs were trialed in 36% (32.9–38.5). A risk–benefit assessment of AChMs in dementia was documented in 13% (11.2–15.2) of cases. An untoward event (fall, delirium, worsening dementia) was reported in 15% (12.6–16.7). In these, 32% (25.3–39.7) had the AChM discontinued or dose reduced.

Conclusions: CAMUE is a novel approach offering a standardized, autonomous tool for efficiently conducting multi-site MUEs. The results suggest that the risk of AChM use in Veterans with dementia is underappreciated by prescribers, although under-documentation of risk/benefit assessment is also likely. VAMedSAFE recommended a prescribing tool or decisional support system to alert prescribers to the potential risk.

1081 | Retrospective interrupted time series examining hypertension and diabetes treatment affordability and government expenditures following changes in patient cost sharing in the "Farmácia Popular" Program in Brazil

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Background: Increasing medicines availability and affordability is a key goal of Brazilian health policy. "Farmácia Popular" (FP) Program is one of the government's key strategies to achieve this goal. Under FP, antihypertension (HTN) and antidiabetics (DM) medicines have been provided at subsidized prices in private retail settings under FP since 2006, with increase in patient copay in 2009 and free of charge since 2011.

Objectives: To analyze the affordability and government expenditures of HTN and DM treatment under FP, focusing in public financing mechanisms and sustainability.

Methods: Quasi-experimental, longitudinal, retrospective study using interrupted time series to analyze: HTN and DM treatment coverage; total and per capita expenditure; percentage paid by Ministry of Health (MoH); and patient cost sharing. Analyzes were conducted in the dispensing database of the FP program (from 2006 to 2012).

Results: FP has increased its coverage over time; by December 2012 FP covered on average 13% of DM and 11.5% of HTN utilization in Brazil, a growth of over 600% and 1500%, respectively. The overall cost per treatment to the MoH ranged from R$19.0 to R$ 25.0 for HTN and from R$16.8 to R$21.6 for diabetes over the period analyzed, representing a reduction in per capita cost of around 22%. The amount paid by patients for the medicines covered increased over time until 2011, especially following an increase in copayment in April 2009. Overall, considering all types of medicine, the average percentage of the sale price paid by patients ranged from 14% to 34% for HTN and 18% to 44% for DM.

Conclusions: FP rapidly increased its coverage during the period analyzed. Costs of HTN and DM treatment in FP were reduced after 2011 for both patients (free) and government (better negotiated prices). However, the overall FP expenditures by MoH increased due to markedly increased utilization, raising questions about the financial sustainability of the program over time.

1082 | Real-world impact on pharmacological management of Type 2 diabetes following a drug subsidy decision: A joinpoint regression on utilization data in Singapore, 2014–2017

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Background: Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor was recommended by Singapore's Drug Advisory Committee (DAC) for listing on the Medical Assistance Fund (MAF) in May 2017 as an add-on therapy for managing type 2 diabetes mellitus (T2DM) based on clinical and cost effectiveness.

Objectives: To examine the impact of MAF listing of dapagliflozin on the utilization pattern of available SGLT-2 inhibitors in both the public and private healthcare sectors.

Methods: A pre-post quasi-experimental study was conducted using commercially available sales data in Singapore between 2014q2 (when SGLT-2 drugs became available) and 2017q4. The public sector includes public hospitals and government-funded primary healthcare clinics (polyclinics). Private sector includes private hospitals, private clinics and retail pharmacies. The access to MAF is limited within the public sector to patients who qualify based on means testing. Temporal changes by channel (hospitals, polyclinics, retail pharmacies and private clinics) adjusted for background growth rate (1.4% per quarter) in the national expenditure of all oral T2DM drugs were examined using Joinpoint Regression analysis. The changes between slopes were examined using t-test at a significance level of 0.05.

Results: The total volume in defined daily doses (DDDs) of all SGLT-2 drugs amounted to 1 million in 2017q1 prior to MAF listing of dapagliflozin, with an average increase of 77,904 (95%CI: 72,429-83,379) per quarter since 2014q2. Following the MAF listing, the quarterly growth increased significantly ($p < 0.001$) to 354,250 (95%CI: 261,658-446,842). The total sales reached 1.8 million by 2017q4, of which 55% occurred in the public sector (32% pre-listing); and 46% was for dapagliflozin (29% pre-listing). The post-listing (2017q2-2017q4) sales of SGLT-2 drugs reached 792,163 (18% of all-channel sales) in polyclinics, where none of the SGLT-2 inhibitors were used previously. The sales in the private sector and hospitals continued to grow at similar rates to pre-listing.

Conclusions: The real-world impact of listing dapagliflozin on MAF has shown to be the largest in the primary care sector (polyclinics). This demonstrates the intended outcome of subsidy as a policy lever in improving access and shifting management of T2DM from acute to primary care, where care management is most appropriate. Further analysis is required to identify the underlying factors that contribute to differing utilization patterns of dapagliflozin across healthcare settings after MAF listing.

1083 | A rapid monitoring tool to provide near real-time evaluation after a new drug policy implementation

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Background: Rigorous outcome evaluations of drug policy changes are time consuming yet policymakers sometimes desire rapid feedback on policy impacts.

Objectives: To describe a method to rapidly monitor changes in health care utilization following the implementation of a change in drug coverage.

Methods: The rapid monitoring tool (RMT) was first designed and implemented in the Canadian province of British Columbia in 2014. The RMT analyzes historical patterns of health care utilization (drugs, physician services, and hospitalizations), and compares those historical patterns against post-policy data repeatedly and within weeks of policy implementation. Historical data are drawn from 3 to 5 pre-policy years and consist of several cohorts of patients who used the policy-related medications on the historical anniversaries of the policy implementation date. The historical cohorts are then followed for one year during which the incidence of several health care outcomes are measured. When the historical utilization patterns are stable they are used as a basis for predicting expected utilization after the policy change, assuming the policy had no effect. Departures from a historical pattern are then recorded as possible policy-related impacts, and post-policy reports are generated.

Results: For the drugs policies so far examined, historical utilization patterns typically provided reasonably precise and stable utilization patterns against which post-policy data could be compared. In one scenario, comparisons of post-policy data with historical patterns in the first year of a policy implementation showed no effect of the policy on health care utilization, with post-policy trends that overlapped or averaged the historical trends. RTM was easy to implement and provided rapid ongoing monitoring of the effects of the policy.

Conclusions: Implementation of a data-driven pattern detection algorithm successfully provided rapid detection of unexpected changes in health care utilization after new policy implementation.

1084 | To study the impact of educational intervention on drug utilization of reserve antibiotics

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Background: Emergence of antimicrobial resistance is shrinking the pool of antibiotics and healthcare practitioners across the globe are facing challenges even for the treatment of minor infections. Various strategies have been suggested to promote rational use of antibiotics, of which, interventional approach is found to be the most efficient one.

Objectives: To perform drug utilization evaluation and assess the impact of educational intervention on the use of reserve antibiotics.

Methods: Retrospectively, at a 2000 bedded tertiary care teaching hospital, data pertaining to use of antibiotics was obtained from the pharmacy sales department. An educational intervention in the form of a full-day workshop was conducted for about 100 in-house health care practitioners. This was followed by post intervention collection of antibiotics usage data. Data was collected for a span of 7 months in pre and post intervention groups during the same months. IBM's SPSS Software (16.0) was used for statistical analysis and comparison was done using paired sample t-test.

Results: Over a period of 7 months pre and post intervention, about 45,664 and 48,886 patients where admitted with total hospital days of 3,35,713 and 3,58,411 respectively. The mean DDD of colistin, meropenem, vancomycin and linezolid before intervention was 0.00199, 19.66, 4.14 and 8.02 respectively whereas after intervention was 0.00103, 18.16, 4.54 and 4.12 respectively. There was a statistically significant ($p < 0.05$) decrease in the observed usage of colistin and linezolid.

Conclusions: Educational intervention was helpful in reducing the use of antibiotics, but had shown a statistical difference only in the usage of colistin and linezolid. In depth evaluation needs to be performed in order to evaluate the rationality of high volume use of reserve antibiotics.

1085 | Development of the AbbVie automated commercial exposure system

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Background: Marketing authorization holders are required to produce estimates of exposure to commercially distributed products for regulatory submissions and internal use. At AbbVie, producing exposure estimates was a time-consuming, manual task utilizing three internal commercial databases with differing data orientation.

Objectives: Development of an Automated Commercial Exposure System (ACES).

Methods: ***Data acquisition and reorientation*:** Three large AbbVie datasets (exUS: 01 Jan 1985–31 Dec 2013, US: 01 Jan 1995–31 Dec 2013, and Global Product Sales Cost and Reporting (PSCR), 01 Jan 2014 - present) were acquired. These datasets include commercial distribution information and other relevant AbbVie data. Historical data were reoriented to the PSCR data model, variables renamed and crosswalks developed. All data reorientation was checked for consistency with source data. ***Data filtering:*** Based on list number and description, all observations were identified as an

AbbVie commercially marketed product (ACMP = 1) or not (ACMP = 0). All observations with ACMP = 1 are assigned a molecule name, and each observations array of associated variables evaluated for filtering (was this observation; a finished good, commercial sale, financial adjustment, device, or unique product specific filter). Observations passing the filter test are given a value of 1, not passing, 0. ***Data conversion:*** Observations passing all filter tests are assigned a conversion factor (Conv_Fact) and outcome unit of measure. Conv_Fact is based on list-number, a unique identifier of formulation and packaging. Conv_Fact is a composite calculation including all functions to bridge distribution volume (EQU) to outcome. The calculation for outcome is EQU/Conv_Fact. All outcomes are compared to historical estimates for accuracy ***Additional variables:*** Other variables such as country, region, formulation labels, etc, are recoded to normalize data. ***Data updates:*** PSCR data is updated monthly as described above.

Results: More than 45 products across 33 years are represented in ACES. ACES estimates are generally within 1% from historical estimates based on the algorithms executed. Estimates with >1% deviation are attributed to differing data sources or manual historical calculation errors. Time to produce estimates within ACES, using all available variables is ~15 minutes, while manually, on average ~6 person-hours for summary level calculations.

Conclusions: ACES provides a reliable, comprehensive and efficient patient exposure data system of the entirety of available AbbVie commercial history. This solution may be generalized to other organizations requiring exposure assessment.

1086 | Association between adherence to guideline-recommended preventive medications and in-hospital mortality among non-reperfused ST-elevation myocardial infarction patients admitted to a tertiary care academic center in a developing country

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Background: Although recommended by international guidelines, evidence on the impact of pharmacological interventions in non-reperfused ST-segment elevation myocardial infarction (STEMI) patients is limited.

Objectives: To assess the association between adherence to guideline-recommended preventive medications and in-hospital mortality among non-reperfused STEMI patients.

Methods: We conducted a cohort study using data obtained from the Jakarta Acute Coronary Syndrome (JAC) Registry database from a tertiary care academic hospital in Indonesia. We included 1132 of 2694 patients with STEMI recorded between 1 January 2014 and 31 December 2016 who did not undergo acute reperfusion therapy. Adherence to guideline-recommended preventive medications was defined as the combined administration of aspirin, clopidogrel, anticoagulants, and statins within 24-h of hospital admission. The main outcome measure was in-hospital mortality.

Results: Overall, 778 of 1132 patients (69%) received the combination of preventive medications. Clinical characteristics that were significantly associated with in-hospital mortality included symptom onset of STEMI, Killip class >1, and thrombolysis in myocardial infarction (TIMI) score $\geq$ 4. After adjustments for measured characteristics using logistic regression modeling, exposure to the combination of preventive therapies was associated with a statistically significantly lower risk for in-hospital mortality (adjusted odds ratio: 0.46, 95% confidence interval: 0.30–0.70).

Conclusions: Although unmeasured indication bias may have played a role, adherence to preventive medications was associated with lower in-hospital mortality. These findings reinforce the importance of the use of evidence-based medications in reducing the mortality of patients with STEMI, particularly, when local challenges hamper the provision of acute reperfusion therapy.

1087 | Abstract Withdrawn

1088 | Pre- and post-intervention study to assess the impact of the use of consensus validated criteria explicit criteria on prescribing of potentially inappropriate medication and subsequent adverse drug events-related hospitalization in Pakistani elderly

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Background: Mazhar criteria, an explicit consensus validated criteria of potentially inappropriate medications (PIMs) for Pakistani seniors, was proved to be a sensitive tool for screening PIMs. However, its impact on routine practice and adverse drug events (ADE)-related hospitalization has not been studied.

Objectives: To compare the impact of the use of Mazhar criteria on potentially inappropriate drug prescription (PIP) rate and ADE-related hospitalization pre- and post-intervention.

Methods: We performed a two-phase prospective observational control study. Patients ≥65 years who were admitted with acute illness to

a university teaching hospital from January to April 2017 and from May to August 2017, served as pre-intervention and post-intervention group, respectively. The intervention consisted of the use of PIMs criteria made available to all the departments of the hospital and pharmacist recommendations to the physician on each individual prescription. Adverse drug events were defined by the World Health Organization-Uppsala Monitoring Centre criteria and verified by a local expert consensus panel, which also assessed whether ADEs were causal or contributory to current hospitalization.

Results: A total of 10,453 prescriptions for 943 (n = 424 pre; n = 519 post) patients were analyzed during the study period. Compared with pre-intervention, the proportion of PIP (64% pre vs. 33.5% post; $p < 0.001$), was significantly lower post-intervention. In pre-intervention group, a total of 443 ADEs were detected in 140 patients of 424 patients; 208 of 443 ADEs (57%) were considered causal or contributory to admission of 38 patients. The rate of ADEs were significantly lower by 28% post-intervention (57% pre vs. 29% post; $p < 0.01$).

Conclusions: The use of our consensus validated criteria explicit criteria of PIMs significantly associated with decreased ADEs in older people that cause or contribute to hospitalization.

1089 | Intervention to improve penicillin prescribing in primary care: A controlled interrupted time-series study

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Background: Tackle antibiotic misprescription and overuse is of fully importance to combat drug resistances. One of the important aspects regarding the quality indicators of antibiotic prescribing is the overuse of broad- against narrow-spectrum antibiotics.

Objectives: to assess the impact of an educational intervention on quality indicator of penicillin's prescribing.

Methods: A cluster-randomized trial was designed in the Centre Health Region of Portugal, with a sample size of ~1100 primary care physicians. The multidisciplinary and multifaceted educational intervention targeted physicians' attitudes and knowledge about antibiotic prescribing and resistances, throughout outreach visits and the distribution of educational materials. The impact of the intervention of penicillin's prescribing was assessed through relative ratios of prescription of penicillin's sensitive to β-lactamase (J01 CE) and penicillin combinations including β-lactamase inhibitors (J01CR). Interrupted time-series analysis with control group comparison was made.

Results: The physicians' participation was 64% (197/309) in a total of 25 counties. Simultaneously, significant improvements were obtained in the prescription of penicillin's sensitive to β-lactamase (overall relative increase of +896%) and penicillin combinations including β-lactamase inhibitors (overall relative decrease of −161%).

Conclusions: Simultaneous increase of narrow-spectrum penicillin-prescribing and decrease of broad-spectrum ones is of fully importance to improve the quality indicators of antibiotic prescribing. The results emphasize the potential impact of interventions acting on physicians' attitudes and knowledge regarding antibiotic prescribing and resistances. In order to further promote the appropriate use of antibiotics, it was approved by the FCT (PTDC/SAU-SER/31678/2017) a new project to evaluate the effectiveness of e-Health tools in supporting clinical decision-making and empowerment of patients in the management of upper respiratory tract infections that will be performed in the same region as a reinforced educative intervention. This work was supported by Portuguese Foundation for Science and Technology (FCT/MCTES), grant (PTDC/SAUESA/105530/2008). Project PTDC/SAU-SER/31678/2017, supported by the operational program of competitiveness and internationalization (POCI), in its FEDER/FNR component POCI-01-0145-FEDER-031678, and the FCT, in its state budget component (OE) and Institute for Biomedicine - iBiMED (UID/BIM/04501/2013 and POCI-01-0145-FEDER-007628).

1090 | Patterns of utilization of specific insulin formulations and non-insulin antidiabetic therapies before, during, and after implementation of a health plan insulin switching intervention

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Background: We previously showed that an intervention switching older adults with type 2 diabetes from analog to human insulin (broadly categorized) was associated with no significant differences in hypoglycemic events, a modest, but clinically insignificant increase in mean HbA1c, and large reductions in plan expenditures and patient out-of-pocket costs. It is important to know what impact the intervention had on utilization patterns of specific insulins and other antidiabetic therapies.

Objectives: To describe utilization patterns of specific analog and human insulins formulations and of background antidiabetic therapies before, during and after an insulin switching intervention.

Methods: We obtained enrollment and prescription claims from 14,635 members of a Medicare Advantage Plan who filled at least 1 insulin prescription between 2014 and 2016. We tabulated the total number of insulin prescriptions dispensed across 6 categories (long-acting analog, rapid-acting analog, pre-mixed analog, intermediate-acting human, premixed human and short-acting human). We report overall utilization of each category as a proportion of unique insulin users during each calendar month as well as the proportion of patients using non-insulin glucose lowering medications.

Results: The proportion represented by long-acting analogs decreased from 0.73 (Jan 2014) to 0.23 (Dec 2016). The proportion of rapid-acting analogs decreased from 0.35 to 0.08, while premixed human insulins increased from 0.06 to 0.43. Intermediate acting human insulins increased from 0.04 to 0.26. The proportion of short-acting human insulin increased from 0.04 to 0.12. For non-insulin glucose-lowering medications, proportions represented by metformin decreased from 0.43 to 0.41; SUs decreased from 0.29 to 0.21. DPP-4 s increased from 0.02 to 0.06; TZDs from 0.02 to 0.03. GLP1RAs were stable at 0.02 while SGLT-2 s, meglitinides and alpha-glucosidase inhibitors were all unchanged at <0.01.

Conclusions: A health plan intervention substantially reduced the proportion of insulin filled as long-acting and rapid-acting analogs and increased the use of premixed and intermediate-acting human insulins. Among non-insulin medications, utilization of SUs and metformin slightly decreased, while use of newer agents including GLP1RAs and SGLTs remained largely unchanged. These results suggest that the clinical results from the main insulin switching study were more likely driven by insulin-specific changes rather than by dramatic changes to background therapy.

1091 | The impact of Interprofessional Education (IPE) on the outcomes of pharmacy practice experiences

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Background: Incorporating IPE experiences has shown a significant positive impact on student attitudes towards other health professions and improvement in overall knowledge. However, studies are rare in this field.

Objectives: To examine the impact of exposure to multiple IPE practices on the attitudes of pharmacy students towards their pharmacy program and profession.

Methods: This retrospective cohort study evaluated data from the University of Rhode Island (URI) from 2013–2018. Data was collected using Graduating Student Surveys that were distributed to graduates of the Doctorate of Pharmacy program. The two exposures were defined as the number of required curricular activities and the total number of profession types that students interacted with. Exposure was dichotomized into ≥6 or < 6 to define the high and low intensity of activities. The six outcomes, including: enhanced understanding of a multi-professional team, engagement as a member of an interprofessional healthcare team, collaboration with other healthcare professions, preparedness to enter pharmacy practice, and satisfaction with the study of pharmacy and the URI pharmacy program, were dichotomized into "strongly agree" and "other."A multivariate logistical regression model was used to identify the association between the intensity of the exposure and the six outcomes, while adjusting for demographic variables.

Results: Of the 493 students included, 38% were males, 89% worked in a pharmacy during the academic year, 39% sought continued education post-graduation, 74% of students participated in ≥6 required curricular activities, and 25% of students had ≥6 interactions with students from different professions. The multivariate analysis showed that the high intensity of IPE was significantly associated with enhanced understanding of a multi-professional team (OR 1.8, 95%CI 1.0–3.2) and satisfaction with the URI pharmacy program (OR 3.1, 95%CI 1.7–5.5). Statistically significant associations were also found between a high number of professions that students interacted with and enhanced understanding of a multi-professional team (OR 1.8, 95%CI 1.0–3.4), engagement as a member of an interprofessional healthcare team (OR 2.4, 95%CI 1.3–4.7), and preparedness to enter pharmacy practice (OR 2.1. 95%CI 1.2–3.9).

Conclusions: The results of this study suggest that a higher intensity of curricular activities and exposure to other professions positively enhanced engagement and understanding of interprofessional teams, preparedness to enter pharmacy practice, and overall satisfaction with the pharmacy program.

1092 | Perceptions of Saudis towards generic drugs use

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Background: Generic drugs are a substitute to brand drugs to treat illnesses. The use of generic drugs contributes to reducing costs of patients and health care budgets.

Objectives: The study aims to test the hypothesis on whether Saudis prefer taking brand over generic drugs as well as assessing the difficulties that prevent Saudis from shifting to generic drugs.

Methods: This is a descriptive, cross-sectional study. The study sample included 919 adults who were asked to complete a self-administered questionnaire. The first page in the questionnaire was added

to provide general information about generic and brand drugs. The questionnaire was adopted from the Shrank et al. study and edited to fit the Saudi community. An expert in Arabic language and an expert in the medical field audited the questionnaire.

Results: This study revealed that most of the significant items were Saudi preferred brand over generic (e.g. overall value, Saudis should use brand, insurance should cover, etc.). The main challenging obstacles against shifting to generic was that nearly 40% of the respondents were not able to confront their doctors on the given drug and asking for generic availability. In addition, approximately 35% of respondents felt that doctors should be talking more about generic drugs. Regarding the age and preferences, increase age was correlated to brand drugs preferences, as the older participants, mainly age group of 40–49 agreed with the statement that generic is less effective. Moreover, according to the overall perceptions of Saudis pattern in drug use, there tended to be the belief that Saudis spend too much on prescribed drugs. Although majority of the respondents were indifferent, when asked if Saudis should use more generic. But less than one third of the total respondents agreed with the statement "government/insurance companies should force the patients on using generic as a first option and only use brand if the generic is not effective" and more than one third of the participants agreed on prescribing brand instead of generic. The results are alerting for insurance companies and policymakers to do more education and rebranding of generic drugs to get more acceptance.

Conclusions: To conclude, Saudis preferred taking brand over generic drugs. Quite high percentages indicated that Saudis could not switch to generic drugs. Hence, healthcare providers and institutions should take the responsibility in providing more information about generic and brand. Also, there is a need to communicate more with the patients in order to increase the level of awareness and clarify the differences between the given drugs.

1093 | Impact of the October 2016 policy change on the delivery of MedsCheck annual and MedsCheck diabetes services in Ontario community pharmacies

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Background: MedsCheck (MCA) is a community pharmacy led annual medication review service funded since April 2007 for residents with a valid Ontario healthcard taking three or more medications for chronic conditions. MCA aims to improve patient outcomes by improving medication adherence and identifying potential medication errors; thereby lowering the risk of adverse drug events. In September 2010, MCA was expanded to include follow-up services and include all patients with diabetes (MCD) with added documentation specific to patients with diabetes. In October 2016, documentation requirements changed adding several components to MCA and MCD services.

Objectives: To estimate the impact of the 2016 policy change on the number of MCA and MCD services delivered in community pharmacies.

Methods: We identified all MCA and MCD services claimed from program launch to November 2018 using pharmacy claims data housed at ICES. Interrupted time series analysis (segmented linear regression with autoregressive error models) was used to examine the impact of the October 2016 (intervention date) policy change on the monthly number of services delivered (24 months pre- and post-policy change included in the analyses), accounting for seasonality, non-stationarity, and autocorrelation.

Results: Since program launch, 2,684,142 patients received an MCA and 672,006 received an MCD. The monthly number of services were stable over the two years before the policy change with an average of 78,072 (SD = 6,182) MCA and 26,268 (SD = 2,471) MCD. Immediate decreases in delivery of both services (−50.2% [95%CI:-55.8,-44.6] MCA, −74.5% [95%CI:-80.2,-68.8] MCD) were identified in the first month of the policy change with regional differences identified (range from −55.7% South East to −44.5% North West for MCA; and from −78.1% Central to −65.4% North West for MCD). Gradual increases in the number of services delivered were seen over 24 months after policy change (slope of 1.54% MCA and 1.05% MCD), yet remained lower than before the policy change (monthly mean between April 2017 to November 2018 = 46,534 [SD = 4,414] MCA, 9,606 [SD = 1,149] MCD).

Conclusions: Substantial decreases in delivery of MCA and MCD were seen after the 2016 policy change. Better understanding of how major policy changes can impact the delivery of medication management services by pharmacists is needed.

1094 | Global overview of the relative consumption of access antibiotics within WHO AWaRe categories

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Background: In 2017, World Health Organization (WHO) grouped antibiotics into three AWaRe categories - Access, Watch, and Reserve, based on their treatment profile and the potential for development of resistance. This categorization is designed to ensure that antibiotics are available when needed, the right antibiotics are prescribed for the right infections, and the effectiveness of 'last-resort' antibiotics are preserved when all others fail. The Access category of antibiotics represents the first- and second-line therapy for common infections. WHO GWP 13 target is that Access group antibiotics present at ≥60% of overall antibiotic consumption. Earlier, WHO launched its global initiative to monitor antimicrobial consumption (AMC) through aggregated sales data and was able to collate 2015 country AMC data from 65 countries to establish baseline consumption rates.

Objectives: We aimed to calculate the relative consumption of antibiotics by AWaRe categories to assess Access group rates per country. countries met the cut-off point of 60% for Access category.

Methods: Total antibiotic consumption is presented by the quantity of antibiotics for systemic use (J01, A07AA, P01AB) as DDD per 1000 inhabitants per day. Relative consumption is a percentage of total consumption by AWaRe categories. We counted how many countries met the cut-off point of 60% for Access category.

Results: In 2015, overall consumption of antibiotics in the 65 countries ranged from 4.4 DID to 64.4 DID. The relative consumption of the Access category within AWaRe ranged from 11–89.5% (average 58.3%). In total, 29 countries met the cut-off point of 60% for Access category in 2015.

Conclusions: This study finds the consumption of Access antibiotics made up on average 58.3% of the AWaRE consumption. In total, 29 out of 65 countries met the cut-off point of 60% for Access category. WHO will continue promoting the importance of incorporating the AWaRE categories into national essential medicines lists and treatment guidelines to ensure that first- and second-line therapy is used for common infections, and it is widely available. WHO will repeat the analysis of the AWaRe relative consumption with post-2017 data to check whether more countries meet the GPW13 target.

1095 | Reduction in use of Cyproterone/Ethinylestradiol (Diane-35 and generics) after risk minimisation measures in the Netherlands, UK and Italy

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Background: Cyproterone acetate combined with ethinylestradiol (CPA/EE) is indicated for moderate to severe acne and/or hirsutism in women of reproductive age. In 2013 the European Medicines Agency concluded that the benefits of CPA/EE outweigh the risk of thromboembolism. Among the recommendations for risk minimisation was to emphasize the approved indications of use and to limit use in combination with other hormonal contraceptives (HC).

Objectives: To assess CPA/EE user characteristics and concomitant use of other HC before and after the risk minimisation measures.

Methods: This retrospective drug utilization study included data from the PHARMO Database Network (the Netherlands), the Health Search Database (HSD, Italy) and The Health Improvement Network (THIN, United Kingdom. New CPA/EE users from 2011 until 2017 were followed from their first CPA/EE prescription until 31 December of each respective year. Recordings of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management were assessed during the year preceding CPA/EE initiation and up to 2014. Use of CPA/EE and concomitant use of other HC was assessed during follow-up and up to 2017.

Results: The number of new CPA/EE users per year decreased in all databases between 2011 and 2017; from 2.8 to 0.2 per 1,000 women in PHARMO, from 1.6 to 0.9 per 1,000 women in THIN and from 0.8 to 0.4 per 1,000 women in HSD. A recent record of acne diagnosis or treatment was identified for 47–55% of users in PHARMO, 76–79% in THIN and 18–21% in HSD. A diagnosis of hyperandrogenic conditions other than acne was observed for 3% in PHARMO, 8–9% in THIN and 7–10% in HSD. No evidence of increasing proportions with approved indications over the years was observed. Concomitant use of other HC was observed for 2–3% of users in PHARMO, up to 1% in THIN and 1–2% in HSD. Another 22–28% in PHARMO had overlapping prescriptions, likely indicating a switch from CPA/EE or vice versa. In THIN and HSD, corresponding figures were 4–6% and 2–4%; overall proportions of HC users were lower as well in these data sources.

Conclusions: Apart from a strong overall reduction in CPA/EE use, no major difference was observed between the study periods before and after the referral procedure in any of the databases between proportions with acne or other hyperandrogenic conditions, or with concomitant use of other HC.

1096 | Influence of change in treatment policy and ART regimen in HIV positive patients on treatment out comes; a observation from South Indian state funded hospital

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Background: National AIDS Control Organization (NACO), India has changed the treatment approach for HIV positive patients to test and treat policy (P_2), where patients were prescribed antiretroviral therapy (ART) immediately after being confirmed as HIV + ve, in contrary to previous practices where ART was initiated in patients only if CD4 cell count was less than 350cells/mm^3(P_1). Barriers (including unavailability of medicines, ADRs & treatment failure) to change in ART regimen are common in Indian practices. Its need to ascertain aforementioned changes impact on CD4 cell count which is one of the prominent treatment outcomes measured.

Objectives: To assess variation in CD4 cell count influenced by change in treatment policy and ART regimen.

Methods: An observational study was carried out by recruiting HIV positive patients (n = 847) who were on ART, visiting government

tertiary care hospital (study site) at Warangal, India. Data were collected from patient case notes, patient interviews and laboratory data. The recruited patients were categorized into 2 groups: Catogery 1(C_1): patients in whom there is a change in treatment regimen due to various reasons. (n = 228) Catogery 2(C_2): patients in whom there is no change in treatment regimen. (n = 619) Further, the patients were again sub-categorized into baseline CD4 cell count below 350cells/mm^3(P_1) and above 350cells/mm^3(P_2). Comparison of variation in CD4 cell count was recorded in these patients following treatment for a period of 12 months.

Results: In the C_1P_1 patients, a significant improvement in mean CD4 cell count was observed from 187 to 276 cells/mm^3 ($p < 0.05$). There were no patients in the C_1 with CD4 count above 350 cells/mm^3. In the C_2 patients, the improvement in the CD4 cell count was found to be from 171 to 236 cells/mm^3 (C_2P_1) and from 493 to 533 cells/mm^3 (C_2P_2). The study has clearly indicated a better improvement in CD4 cell count following initiation of ART at a higher baseline CD4 cell count complementing with the decision of NACO for change in policy related to initiation of ART in HIV positive patients as soon as they are detected positive irrespective of their baseline CD4 cell count. Change in the treatment regimen also contributed towards improvement in CD4 cell count.

Conclusions: The study indicated that quick initiation of ART may provide better immunological management in HIV positive patients. A steeper improvement in CD4 cell count was observed in the patients when ART was initiated at a higher baseline CD4 cell count. Moreover, changed ART regimen also affected the CD4 cell count in the patients.

1097 | Impact of drug safety warnings and cost-sharing policies on osteoporosis drug utilization in Spain: A major reduction but with the persistence of over and underuse. Data from the ESOSVAL cohort 2009–2015

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Background: Recent studies in several countries show a significant decrease in the consumption of osteoporosis drugs from a peak in around 2009, including those for secondary prevention after hip fracture (where treatment is widely recommended). Spain has being traditionally one of the countries with the highest utilization rates worldwide, but whether it is following the global trends, for both, low and high risk patients is unknown.

Objectives: The aim of this work is to assess changes in the utilization of osteoporosis drugs in the Valencia Region (Spain) after safety warnings from regulatory agencies and cost-sharing changes, according to patient socio-demographic and risk of fracture characteristics.

Methods: We constructed a monthly series of osteoporosis drug consumption for 2009–2015 from the ESOSVAL cohort (n = 11,035; women: 48%; mean age: 65 years old) and used interrupted time series and segmented linear regression models to assess changes in osteoporosis drug utilization while controlling for previous levels and trends after three natural intervention dates: the issue of the Spanish Agency for Drugs and Medical Products (AEMPS) Osteonecrosis Jaw Warning (Sept 2009), the AEMPS Atypical femur Fracture Warning (Apr 2011) and the modification of the cost-sharing scheme (Jul 2012).

Results: The AEMPS Osteonecrosis Jaw Warning was not associated with a decline in the consumption of osteoporosis drugs, while the warning on Atypical Fracture (a downward trend of 0.11% fewer people treated each month) and the increase in the cost-sharing scheme (immediate change level of −1.07% in the proportion of people treated) were associated with a strong decline in the proportion of patients treated, so that by the end of 2015 osteoporosis drug consumption was around half that of 2009. The relative decline was similar in people with both a high and low risk of fracture.

Conclusions: The AEMPS Atypical Fracture Warning of Apr 2010 was associated with a significant decrease in the number of people treated, reinforced by the increase in the pharmaceutical cost-sharing in 2012. Decreases in treatment affected patients both at a low and higher risk of fracture.

1098 | Impact of European label changes for systematic diclofenac products: Post-referral prescribing trends for initiation of systemic diclofenac products and time series regression

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Background: Non-steroidal anti-inflammatory drugs, such as diclofenac, are widely prescribed agents across Europe for the management of pain, fever and inflammatory conditions. In June 2013, a European Medicines Agency (EMA) referral procedure concluded that diclofenac containing products were associated with an elevated risk of acute cardiovascular events and that contraindications, warnings, and changes to the product information, including direct healthcare professional communication were required to be implemented across the EU.

Objectives: The aim of the study was to evaluate the impact of the EMA risk minimisation measures implemented in 2013 to manage the cardiovascular risks of systemic diclofenac containing medicinal products in Denmark, Netherlands, England and Scotland.

Methods: Drug utilization studies assessing diclofenac-containing medical products covering the regulatory intervention in June 2013. Quarterly time series analysis measuring the prevalence of diclofenac

initiation and discontinuation with statistical significance testing using interrupted time series regression.

Results: The cohorts consisted of 5.6 million in Denmark, 5.3 million in Scotland, 4.2 million in England and 1 million people from the Netherlands. The most common indication for diclofenac in all countries among those assessed was osteoarthritis. In all countries the prevalence of diclofenac prescribing fell during the overall observation period. The 2013 EMA regulatory intervention was associated with a: significant immediate fall in diclofenac initiation in the Netherlands (−0.42%, 95%CI -0.66% to −0.18%), England (−0.09%, 95%CI -0.11% to −0.08%) and Scotland (−0.67%, 95%CI -0.79% to −0.55%) but not Denmark; a significant falling trend in diclofenac initiation in the Netherlands (−0.03%, 95%CI -0.06% to −0.01%) and Scotland (−0.04%, 95%CI -0.05 to −0.02%). There was no significant immediate impact on diclofenac discontinuation or increasing trend in diclofenac discontinuation.

Conclusions: The 2013 EMA referral was associated with reductions in overall diclofenac prescribing the extent of which varied by country and type of exposure.

1099 | Are NHIS clients served inferior and sub-standard medicines? Using standard WHO RUM indicators to determine quality of care under the NHIS in Ghana

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Background: The National Health Insurance Scheme (NHIS) has since its establishment in 2003 become an integral part of Ghana's strategy towards the attainment of Universal Health Coverage (UHC). Increased enrolment and utilization over the years has however been accompanied by client perceptions of quality of care and medicine access that lower confidence in the scheme.

Objectives: To investigate lay perceptions that NHIS clients are being served inferior and sub-standard medicines compared to non NHIS clients.

Methods: The design involved a case study of medicines access under the Ghana NHIS involving a prescription survey in 20 health facilities in four (4) purposively selected regions in all three ecological zones of Ghana. A total of 569 retrospective cases on upper respiratory tract infection for children up to 13 years, malaria cases for any age group and five adult hypertensive cases were obtained for assessment. Main outcome measures were the key WHO rational use of medicines (RUM) indicators.

Results: Descriptive analysis using WHO rational use of medicines (RUM) indicators showed that from a medically rational perspective, the insured are actually receiving slightly more appropriate care. Percent injection use was relatively high in non-insured (29.9%) compared to insured (21.3%). Percentage medicines on Essential Medicines List (EML) was 98% and 96% while % medicines prescribed with generic name was 93% and 95% for insured and non-insured respectively. Quite identical patterns were seen in % prescribed antibiotics for insured (41.5%) and non-insured (41.4%) as well as average number of medicines per prescription for the insured (3.7) and non-insured (3.8).

Conclusions: From a technical biomedical perspective, our data suggested that insured members in the Ghana NHIS are receiving more appropriate care than the non-insured because the scheme has become an important enforcer of rational prescribing through claims auditing, forcing providers to adhere to RUM prescribing rather than lay perceptions. Lay perspective of clients however regard rational medicine use indicators such as less injections, more generic and EML medicines as inferior medicines access. Rational use of medicines values need to be transmitted to clients as well as providers to better harmonize technical and socially driven perspectives of quality of care.

1100 | Impact of European label changes for systematic diclofenac products: Post-referral prescribing trends in switching to alternative products following diclofenac discontinuation

Daniel R. Morales[1]; Tom MacDonald[1]; Steve Morant[1]; Martin Ernst[2]; Jesper Hallas[2]; Lisa Smits[3]; Ron Herings[3]; Lizzie Nicholson[4]; Marion Bennie[5]; Marion Bennie[5]; Li Wei[6]; Rob Flynn[1]

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, are widely prescribed agents across Europe for the management of pain, fever and inflammatory conditions. In June 2013, a European Medicines Agency (EMA) referral procedure concluded that diclofenac containing products were associated with an elevated risk of acute cardiovascular events and that contraindications, warnings, and changes to the product information, including direct healthcare professional communication were required to be implemented across Europe.

Objectives: The aim of the study was to evaluate the impact of the EMA risk minimisation measures implemented in 2013 on unintended switching to alternative products in Denmark, Netherlands, England and Scotland.

Methods: Drug utilization studies measuring trends in the prevalence of initiation of other systemic NSAIDs, topical NSAIDs, paracetamol, opioids and other chronic pain medication in people who discontinued diclofenac-containing medical products covering the regulatory intervention in June 2013. Quarterly time series analysis with statistical significance testing using interrupted time series regression.

Results: Among cohorts consisting of 5.6 million in Denmark, 5.3 million in Scotland, 4.2 million in England and 1 million people in the Netherlands, the regulatory intervention was associated with statistically significant immediate increases in switching to: other systemic

NSAIDs in England (1.51%, 95%CI 0.22% to 2.80%) and Scotland (5.21%, 95%CI 3.70% to 6.72%); topical NSAIDs in Scotland (0.35%, 95%CI 0.12% to 0.58%); paracetamol in Denmark (5.92%, 95%CI 4.07% to 7.77%) and Scotland (0.50%, 95%CI 0.28% to 0.73%); opioids in Scotland (0.12%, 95%CI 0.04% to 0.21%); and other chronic pain medication in England (0.39%, 95%CI 0.05% to 0.72%) and Scotland (1.31%, 95%CI 0.72% to 1.89%). The regulatory intervention was associated with statistically significant rising trends in switching to: topical NSAIDs in Denmark; paracetamol in Denmark and the Netherlands; and opioids in Scotland, whilst other countries were associated with no or falling trends in switching.

Conclusions: The 2013 EMA referral was associated with significant changes in switching to alternative pain medications following diclofenac discontinuation the extent of which varied by country and type of product.

1101 | Policies influencing access to new targeted oncologic drugs in Ecuadorian hospitals: An interrupted time series analysis

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Background: Emerging countries continuously try to influence the growing expenses of new oncologic drugs by applying a wide range of policies.

Objectives: An Interrupted Time Series Analysis was performed to measure the impact of two policy interventions over the accessibility to new targeted oncologic drugs in Ecuador.

Methods: The first intervention decentralized the evaluation process allowing Hospital Drug & Therapeutic Committees (DTCs) directly select new drugs. The second brought back the final decision to a central body but kept the first decision level in hospitals. Dispensing data from the six largest Ecuadorian cancer hospitals (3 public, 3 private) were analyzed over a period of five years (2010–2014). Targeted drugs were defined as monoclonal antibodies, proteinkinase inhibitors, vismodegib and vorinostat. Monthly incidence rate of targeted drug users (out of 1000 cancer patients) was obtained. Level and trend changes after interventions were studied.

Results: In public hospitals, incidence level dropped after the first policy (−18.04, $p < 0.05$). The slope increased by 1.05 until the second policy (not significant). After the second intervention, incidence level dropped by −12.67 and the slope was negative by −0.66 (both not significant). In private hospitals, incidence level dropped after the first policy (−4.46, $p < 0.001$). A statistically significant trend increase (+1.39) was observed until the second intervention. After the second intervention, significant changes in the level and trend were observed: the level dropped by −4.09 ($p < 0.05$), with a negative slope of −1.35 ($p < 0.001$).

Conclusions: Transferring the responsibility to select new drugs to DTCs produced an important increase in prescription intensity of targeted oncologic drugs, mainly in the private sector. It was rapidly corrected by the second intervention. Without the implementation of either the first or second policy, depending on the sector, the consumption of new targeted oncologic drugs would be difficult to control, framing a potential financial risk for the health system. Combination of different levels of decision, meaning a DTC analysis plus a reanalysis by a central body, proved to limit new prescriptions of targeted oncologic drugs. Countries must be aware of the needed capacities to respond to the challenges and pressures to include expensive targeted drugs into benefit packages.

1102 | The part D enhanced medication therapy management model: Monitoring findings as the model enters Year Two

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Background: The Centers for Medicare & Medicaid Services (CMS) Center for Medicare and Medicaid Innovation (CMMI) Part D Enhanced Medication Therapy Management (MTM) model tests whether providing Part D sponsors with additional payment incentives and regulatory flexibilities promotes enhancements in the MTM program, leading to improved therapeutic outcomes, while reducing net Medicare expenditures.

Objectives: Gauge the implementation of the Enhanced MTM model from January 2017–June 2018, including the number of patients selected for and receiving MTM services.

Methods: Six Part D sponsors participate in the Enhanced MTM model, representing approximately 1.7 million Medicare beneficiaries. We independently assessed program implementation and intermediate outcomes for measure domains including Model-Wide Quality Indicators, Beneficiary Targeting, Beneficiary Engagement and Participation, and Unintended Consequences. We analyzed variation across time and sponsors. This analysis reflects our role as the implementation contractor and should be considered independent from CMS' own internal evaluation efforts.

Results: Enhanced MTM enrollment and targeting criteria, engagement strategies, and intervention strategies varied across sponsors. Thus, relative performance across monitoring measure domains was not interpreted as success or failure. Nearly 2/3 of beneficiaries were targeted overall (ranging by sponsor in Q2 2018: 20.56–78.76%). Almost 1/3 of targeted beneficiaries had at least one encounter record indicating participation in Q2 2018 (ranging by sponsor 13.91–98.38%). Performance on Model-Wide Quality Indicators in Q1 - Q2 2018 was similar to 2017. Approximately 1/4 of hospital-to-home discharges were followed by an MTM service. Roughly 7% of targeted

beneficiaries had a medication therapy issue recorded. Review of supporting documentation submitted by sponsors for data validation purposes has indicated that there may be differences in how sponsors record similar activities in their encounter data.

Conclusions: When Part D was developed, CMS estimated one-fourth of enrollees could benefit from MTM, but participation has historically been low. The implementation of the Enhanced MTM model appears to be achieving its goal of increasing enrollment −assessed cumulatively, nearly two-thirds of targeted beneficiaries participated in 2017 and nearly half participated through Q2 in 2018. Model activities may be encouraging medication adherence and other interventions relevant to pharmacoepidemiology studies involving the Medicare population.

1103 | China pharmacovigilance under reformed drug regulations

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Background: The National Medical Products Administration (NMPA) is the Chinese agency for regulating drugs and medical devices (formerly the China Food and Drug Administration, CFDA). NMPA joined the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 2017, and became one of the management committee members in 2018.

Objectives: We aim to perform an overview of the current use, challenges and prospects of applying pharmacoepidemiological methods in the Pharmacovigilance in China after reforming the drug regulatory system, and promote the collaboration with Asian Pharmacoepidemiology Network (AsPEN) and international institutions.

Methods: The reform of China's drug regulatory system and its impact on guiding pharmacovigilance were reviewed.

Results: Since *Opinions on the Reform of Review and Approval Process for Drugs and Medical Devices* issued in August 2015, NMPA has developed series supporting guidelines to encourage new drug development, including reforming clinical trial management, accelerating review and approval process, prioritized review procedures, and expansion of the Marketing Authorization Holder (MAH) Program. Since NMPA has applied five ICH secondary guidelines including M4, E2A, E2D, M1, E2B(R3) and MAHs are required to report adverse reactions directly, the transmission of individual safety reports has become efficient. Moreover, based on the hospital-based electrical health records (EHR), China National Center for ADR Monitoring (NCADRM) has started to establish the active monitoring and evaluation system.

Conclusions: In the past three years, the development and reforming of pharmacovigilance system by NMPA provided solid basis for the drug life-cycle surveillance in China. The following approaches for international communication and cooperation, including, the improvement of the industrial post-marketing research ability, the integration of pharmacoepidemiological methods using multiple databases, the development of drug withdrawal technical system, the development of coding system and the methodology for clinical evaluation of the traditional and herbal medicines, are helpful to further improve pharmacovigilance system in China and eventually achieve global regulatory integration.

1104 | Trends in polypharmacy and dispensed drugs among adults in the Netherlands as compared to the United States

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Background: Polypharmacy is becoming increasingly common in the elderly, but there is limited information about the trends in other age groups.

Objectives: We investigated the trends in polypharmacy and underlying drug groups among adults in the Netherlands from 1999 to 2014 stratified by age, and compared these with findings from the United States (US).

Methods: This was a repeated cross-sectional study using the Dutch IADB.nl prescription database. All patients aged 20 years and older in the period 1999 to 2014 were included. Polypharmacy prevalence was the primary outcome, which was defined as the dispensing of five or more chronic drugs at the pharmacological subgroup level during the last quarter of each year. Secondary outcomes included the prevalence ratios (i.e. relative changes over time), and the prevalence of the top 20 dispensed drug groups at therapeutic level. Chi-square tests were applied to calculate the p-value for trends. Changes in prevalences were compared between the Netherlands and the US.

Results: The overall prevalence of polypharmacy increased from 3.1% to 8.0% (p-value for trend <0.001) over 15 years, and increased in all age groups. The highest prevalences were observed in patients aged 65 years and older, but the relative increase over time was higher in the younger age groups (prevalence ratio 2.5 versus 2.1 in the elderly). At drug group level, large increases were observed for angiotensin-II inhibitors (from 2.25% to 5.41%), statins (from 1.52% to 4.74%) and proton-pump inhibitors (2.55% to 6.01%). The relative increase in polypharmacy was larger in the Netherlands than in the US (prevalence ratio 2.4 versus 1.8). The Netherlands showed larger relative increases for angiotensin-II inhibitors, statins, proton-pump inhibitors,

biguanides, and smaller relative increases for antidepressants, benzodiazepines and insulins.

Conclusions: Polypharmacy more than doubled from 1999 to 2014, and this increase was not limited to the elderly. The relative increase was larger in the Netherlands compared to the US, which was partly due to larger increases in several guideline-recommended preventive drugs.

1105 | Polypharmacy risk among five-year cancer survivors

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Background: Cancer survivors are increasing in the United States. Survivors often face cancer sequelae and side effects from treatment, which can arise during treatment or even months or years later. Survivors may therefore experience greater medication burden than the general population, increasing concerns for polypharmacy and risk of drug interactions and non-adherence.

Objectives: To characterize prevalence of polypharmacy by cancer history in a nationally-representative sample of U.S. adults.

Methods: Using National Health and Nutrition Examination Survey (NHANES) data from 2003–2014, we identified 32,330 individuals 20 years or older, 1,672 of whom had been diagnosed with cancer (excluding non-melanoma skin) at least five years before the survey. The association between cancer history and polypharmacy (5+ medications) was examined using Poisson regression models to calculate multivariable risk ratio (RRs) and 95% confidence intervals (CIs), adjusted for education, ethnicity, marital status, and age at survey.

Results: Among five-year cancer survivors, 35% had a diagnosis within 5–9 years of the survey year, 26% within 10–14 years, 13% within 15–19 years, and 26% had a diagnosis 20 or more years before the survey year. Breast cancer was the most common type of cancer (23%), followed by cervical cancer (18%), prostate cancer (12%), and colon cancer (7%). Prevalence of polypharmacy was higher in cancer survivors (33.6%; 95% CI: 30.7–36.6%) than in those with no cancer history (13.0%, 95% CI: 12.4–13.7%) (RR: 1.32, 95% CI: 1.20, 1.45). Polypharmacy prevalence differed by age group (4.83% in 20–39 year olds; 40.37% in 40–64 year olds; 54.8% in 65 years and older), and within each age group, risk of polypharmacy was higher in cancer survivors than in those with no cancer history, with the most pronounced difference in cancer survivors 20–39 years old (RR: 2.93, 95% CI: 1.69–5.09), followed by 40–64 year olds (RR: 1.52, 95% CI 1.27–1.83) and those 65 years and older (RR: 1.17, 95% CI: 1.07–1.29).

Conclusions: Cancer survivors are more likely to experience polypharmacy burden than those with no cancer history. Findings from this study can increase awareness about the unique challenges cancer survivors face and encourage medication reconciliation services.

1106 | Variation in Belgian polypharmacy: Trends 2013–2016

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Background: Increased drug consumption has implications for both individual health as well as for public health. No comprehensive study of drug consumption has been conducted for the entire Belgian population.

Objectives: This study assesses the prevalence of polypharmacy in the Belgian population by age, sex and district for four consecutive years between 2013 and 2016.

Methods: The data concerned the entire Belgian population and were obtained from the Belgian national institute of health insurance. Polypharmacy was defined as the dispensation of at least 5 prescribed and reimbursed drugs over a 3-month period. Excessive polypharmacy is at the same for at least 10 drugs dispensed. For comparison between districts, prevalence for both polypharmacy and excessive polypharmacy were standardized by age and sex, for each year. For yearly comparisons, prevalence was standardized taking the population structure of 2013 as a reference.

Results: The crude national prevalence of polypharmacy in 2013 was 11.0% (95% confidence interval (CI): 10.9–11.0): 12.7% (95%CI: 12,6-12,7) for women and 9.2% (95%CI: 9.1–9.2) for men. The prevalence of excessive polypharmacy was 1.33% (95%CI: 1.32–1.34): 1.57% (95%CI: 1.55–1.59) for women and 1.08% (95%CI: 1.06–1.10) for men. In 2016, the crude prevalence of polypharmacy was 11.1% (95%CI: 11.1–11.2): 12.8% (95%CI: 12.7–12.8) for women and 9.45% (95%CI: 9.40–9.50) for men. The prevalence of excessive polymedication was 1.36% (95%CI: 1.35–1.38): 1.63% (95%CI: 1.61–1.65) for women and 1.09% (95%CI: 1.07–1.11) for men. In terms of relative variation in the prevalence of polypharmacy, Nivelles recorded the largest decline between 2013 and 2016 with −3.84%, going from 10.8% (95%CI: 10.7–10.9) to 10.4% (95%CI: 10.3–10.4). Arlon had the largest increase with +4.44% from 10.6% (95%CI: 10.3–10.9) to 11.1% (95%CI: 10.8–11.4). For excessive polypharmacy, the greatest relative variation between 2013 and 2016 was also found in Arlon with +9.89% going from 1.19% (95%CI: 1.09–1.30) to 1.31% (95%%CI: 1.20–1.42). The largest decline was recorded in Turnhout with −7.84% going from 1.37% (95%CI: 1.33–1.40) to 1.26% (95%CI: 1.23–1.29). In general, the lowest prevalence of polypharmacy was observed in Flanders and the highest in Wallonia. In 4 years, 28 of 43 districts registered a decline in prevalence, the majority of which are in Flanders.

Conclusions: Overall polypharmacy is on the decline across study years, although some districts in Belgium experienced a rise in prevalence. Wallonia and Flanders differ in polypharmacy prevalence;

however, more studies are needed to understand the variables associated with this difference.

1107 | Comparing prescribing practices of primary care providers using formulary selectivity index, as one measure of conservative prescribing

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Background: Rational prescribing, as advocated by the WHO, limits the use of drugs within a therapeutic class. The use of only a few drugs and learning how to use them judiciously is an essential principle of conservative prescribing. Formulary Selectivity Index (FSI) is a measure of the dispersion and skewness of drug choices that can be used to determine the extent of compliance with this practice.

Objectives: To determine the extent to which primary care providers (PCPs) restrict the number of agents they prescribe within a drug class comparing two academic medical centers descriptively.

Methods: We retrieved new prescription data from the electronic health records of a pilot sample of 23 PCPs at Brigham and Women's Hospital (BWH, Boston, MA) and 83 at the University of Illinois Hospital and Health Sciences System (UIC, Chicago, IL). Using the FSI, we assessed prescribing patterns from 1/1/2016 to12/31/2017 for 12 classes of drugs (statins, antihypertensives, opioids, antidiabetics, antidepressants, gastrointestinal agents, antibiotics, anticoagulants, hormones, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and antivirals). We calculated the FSI as the Gini-coefficient, which is a number between 0 and 1, where 0 is equal prescribing of each analog (no selectivity) and 1 is the prescribing of only one analog (perfect selectivity). The Gini-coefficient is the area between the actual Lorenz curve for a drug class and the diagonal line for a drug with complete equality.

Results: PCPs at BWH were more selective than those at UIC in prescribing statins (FSI: BWH 0.61 vs. UIC 0.58), GI drugs (0.54 vs. 0.30) and anticoagulants (0.26 vs. 0.25). PCPs at UIC were more selective than those at BWH in prescribing opioids (FSI: UIC 0.62 vs. BWH 0.44), antidepressants (0.39 vs. 0.30), antibiotics (0.35 vs. 0.27), antivirals (0.44 vs. 0.40), antihypertensives (0.22 vs. 0.15), and corticosteroids (0.73 vs. 0.62), NSAIDs (0.53 vs. 0.47), antidiabetics (0.52 vs. 0.47), and hormones (0.46 vs. 0.34). Of the opioid prescriptions, oxycodone and hydrocodone accounted for 29.7% and 3.5% in BWH, and 2.1% and 32.2% in UIC, respectively. In addition, rosuvastatin accounted for 11.3% and 3.6% of statin prescriptions in BWH and UIC, respectively.

Conclusions: The findings show differences in prescribing among PCPs at both sites, with more selective use within classes of opioids, GI drugs, and corticosteroids than other commonly prescribed drugs. There is a need to expand the analyses to larger sample of PCP to make statistical inference.

1108 | Trends in inappropriate outpatient antibiotic use in the United States

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Background: In the United States (U.S.), the National Action Plan for Combating Antibiotic-Resistant Bacteria has set a goal for reducing inappropriate outpatient antibiotic use to 15% by 2020.

Objectives: To investigate recent trends in the appropriateness of oral outpatient antibiotic prescriptions from 2010 to 2017 among a privately insured U.S. population.

Methods: A cross-sectional analysis using Truven Health MarketScan database (January 2010–December 2017) was conducted for patients who received at least one oral antibiotic prescription for each calendar year. We included patients who had pharmacy benefit coverage and were continuously insured for all 12 months each year. For each antibiotic prescription fill, all diagnosis codes in medical claims during a 7-day lookback period were used to classify the appropriateness of antibiotic prescribing based on a previously published scheme. The outcomes included mean antibiotic prescriptions per patient and proportion of fills in one of three mutually exclusive categories: 'appropriate', 'potentially appropriate', or 'inappropriate' during the study periods. In addition, three most commonly used antibiotics were assessed among the inappropriate fills for the year 2017.

Results: Approximately 11 and 7 million unique patients filled at least one oral antibiotic prescription in 2010 and 2017, respectively. The mean age of the patients ranged from 33.1 (±19.3) to 34.2 (±19.3) years with 40% to 41% males, and 43.1% to 50.7% from the south. The mean number of new antibiotic prescriptions remained at 2 new fills per patient between 2010 and 2017. During the study periods, the proportion of appropriate (from 9.4% in 2010 to 12.5% in 2017) and potentially appropriate prescriptions increased (from 37.6% in 2010 to 41.3% in 2017), respectively. The proportion of inappropriate prescriptions decreased from 24.3% in 2010 to 20.8% in 2017. However, 37% of individuals who filled antibiotics had at least one inappropriate antibiotic prescription in 2017. Of these inappropriate fills, azithromycin (25.3%), amoxicillin (12.6%), and cephalexin (7.1%) were the three most commonly prescribed antibiotics.

Conclusions: The rate of oral antibiotic utilization and proportion of inappropriate prescriptions decreased from 2010 to 2017 in the U.S. However, one in three privately insured individuals still filled at least one inappropriate antibiotic prescription in 2017.

1109 | A new tool to evaluate and promote rational use of pharmacotherapy available to all Danish general practitioners

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Background: Since 2003, the Danish Medicines Agency has provided general practitioners (GP) with a tool to assist the GP in monitoring own prescription pattern. The agreement between the GP organization and the Danish health authorities has since 2016 included accreditation of the GP. Knowledge of own prescription pattern is a part of the accreditation. The focus has been to promote prescription of cost-effective drugs and reducing adverse drug reactions.

Objectives: By giving the GP an applicable overview of their prescription pattern, the new tool makes it possible to identify and define quality indicators and track development in prescription pattern over time. Thereby, the tool can assists the GP with quality improvement and decision. The purpose of the tool was to give the GP a possibility to enhance rational use of pharmacotherapy.

Methods: In Denmark, we have the opportunity to combine registries for a whole population. In the new tool developed by the Danish Health Data Authority in collaboration with the Danish GP's organization, we have combined data from the Danish heath care databases (The National Health Insurance Service Registry) with information on drug use (Register of Medicinal Product Statistics). We have combined the registries using the social security number and the GP number. Drug groupings are developed according to disease specific treatment (e.g. analgesics), treatment recommendation lists (e.g. narrow- vs. broad-spectrum antibiotics) and health care indicators (e.g. abusable drugs). GP will have access to the tool as an online database with a digital signature obligatory to all Danish companies. Data are presented with the visualization software, Qlik®.

Results: Themes for the prescription of the following drug groupings have been developed: psychotropic and analgesics, and antibiotics. The GPs can compare themselves with clusters of GPs as well as national levels. We are expecting to go live May 2019.

Conclusions: The new tool will make recommendation lists easier to apply for the GPs. The GP will have easy access to prescription pattern and thereby have an increased interest in reducing medicinal costs, reducing use of certain drugs and promoting rational use of pharmacotherapy.

1110 | Which part of unplanned hospital readmissions within 30 days of discharge is medication related and potentially preventable?

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Background: Hospital readmissions pose a major burden on patients and healthcare systems but little is known about medication related hospital readmissions.

Objectives: Primary aim: to identify the percentage and preventability of unplanned readmissions ≤30 days of discharge due to medication related problems. Secondary aims: to assess which types of medication were responsible for potentially preventable readmissions and potential causes of these readmissions.

Methods: A cross-sectional observational study was performed in the OLVG hospital, Amsterdam, the Netherlands, at the departments of internal medicine, pulmonology, cardiology, gastroenterology, surgery, neurology and psychiatry. Inclusion criteria were: patients (≥18 years) with a 30-day unplanned hospital readmission after discharge from one of the participating departments (i.e. index admission). Exclusion criteria were: self-discharge, transfer to another hospital, (re)admitted due to intentional overdose or drugs of abuse, multiple readmissions (≥2), index and readmission are unrelated (e.g. index admission with pneumonia followed by a readmission due to a car accident). Residents of all participating departments and a pharmacist reviewed files of readmitted patients. During multidisciplinary meetings potentially preventable cases were discussed and consensus was reached. Percentage of readmissions that were medication related, and potential preventability were assessed. For potentially preventable readmissions types of medication responsible for the readmission and potential causes were assessed. Potential causes were categorized into three categories: problems due to transitions in care, prescribing and adherence.

Results: 426 readmissions were included. Nineteen percent was medication related and of these, 38% was potentially preventable. Most common types of medication responsible for potentially preventable readmissions were: diuretics (20%), drugs used in diabetes (17%) and cardiac therapy/beta blocking agents (13%). Potential causes of these readmissions were problems due to prescribing (43%), transitions in care (23%), and adherence (33%).

Conclusions: Thirty-eight percent of medication related readmissions is potentially preventable. Problems with prescribing, transitions in care and adherence might be good starting points for implementing interventions to reduce medication related readmissions.

1111 | Appropriateness of otic quinolone use among privately insured patients in the United States

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Background: Otic quinolones have been linked to the development of permanent tympanic membrane perforations, raising concern about their use for conditions in which they have no proven benefit.
Objectives: To assess the extent of otic quinolone use for questionable indications.
Methods: This cross-sectional analysis included children and adults with outpatient pharmacy claims for new prescriptions of otic or ophthalmic (OP) quinolones in Truven MarketScan 2017. Quinolones included ofloxacin and ciprofloxacin, alone or in combination with dexamethasone, hydrocortisone, or fluocinolone. Indication was classified as appropriate, questionable or undetermined by a senior otologist. We considered each dispensing ≥30 days apart as a unique episode and ascertained diagnoses from outpatient encounters within +/− 3 days of dispensing. We excluded OP claims with eye-related diagnoses within +/− 30 days or within +/− 30 days from otic quinolone claims.
Results: We found 214,897 quinolone claims in 200,270 patients. Questionable ear indications were found in 4.5%, appropriate ear indications in 72.5%, and undetermined in 23.0% in the 3-day window. OP quinolones were used in 16% of appropriate and questionable otic episodes. Adults were twice as likely to have otic treatment with questionable indications (6.2% vs 3.0%). Sensitivity analyses with broader time windows to ascertain diagnoses decreased the proportion of episodes with no ear indication but had similar distributions of appropriate vs questionable otic use. Otalgia and cerumen impaction constituted 85% of claims with questionable indications.
Conclusions: Considering demonstrated risk for permanent tympanic membrane perforations, opportunities exist to decrease otic quinolone use, especially in adults.

1112 | Self-medication practices in rural communities, Alexandria, Egypt: Prevalence, perception and attitude

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Background: Self-medication is the use of a medicinal product to manage undiagnosed illness, it is one of the most serious public health problems nowadays specially in developing countries. It involves obtaining medications without having a prescription, using old prescriptions to obtain drugs, sharing medicines with one's social circle.
Objectives: To assess the prevalence of self- medication practices among rural population of Alexandria, Egypt and the reasons contributing to this practice.
Methods: A cross-sectional study was conducted to determine the prevalence and extent of self-medication knowledge, attitudes, and practices in pharmacy purchasers from January 2018 to September 2018. Data analysis was done using the Statistical Package for Social Sciences (SPSS). Results obtained were expressed in counts and proportions. Chi-square ($\chi 2$) and Monte Carlo tests were used to compare between groups. Qualitative data were described as numbers and percentages. A p value of less than 0.05 was considered to be statistically significant. Predictors of self-medications was determined by Logistic regression analysis. The total percentage of some questions is not always 100% as some of the questions had multiple options to choose from.
Results: The prevalence of self-medication among the study participants was 77.4% with highest prevalence among the middle age group (15–45 years). A larger number of females were self-medicating (78.3%) than males (65.5%). Level of education did not affect the prevalence of self-medication ($p = 0.087$) but medical education was independently associated with increase the likelihood of self-medication ($p < 0.001$). Analgesics and antipyretics are the most commonly used groups of drugs in self-medication and considering their illness minor for consultation is the main reason behind this practice in 85% of the study population. Almost 42% of the participants see self-medication as a self-care practice that should be encouraged.
Conclusions: The very high prevalence of self-medication in this study is a cause of concern. General population should be enlightened about the consequences of self-medication, and the risks associated with it. Strict rules should be introduced to forbid the supply of drugs without prescription. The role of socioeconomics and standard of living and its effect on self-medication practice need to be explored in future studies.

1113 | Disparities in all-cause mortality with potentially inappropriate medication use: Analysis of the REasons for Geographic And Racial Differences in Stroke Study

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Background: Prior work has identified disparities in the quality and outcomes of healthcare across socioeconomic subgroups. Mortality with inappropriate medication use may be subject to similar disparities.
Objectives: To assess the association between inappropriate medication use and all-cause mortality and the effect of disparity parameters (gender, age, race, income, education, and rural or urban areas) on this relationship.
Methods: The analyses included 26,399 black and white US adults aged ≥45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, of which 13,475 participants were of age ≥ 65 years (recruited 2003–2007). The appropriateness of

medication use was measured at baseline by the presence of drug–drug interactions (DDIs) and the use of potentially inappropriate medications (PIMs) in older adults. Cox proportional hazards time-to-event analysis followed the participants until their death (all-cause) on or before March 31, 2016, iteratively adjusting for disparity parameters and other covariates. Sensitivity analysis by stratifying censored follow-up time intervals intended to seek the predictive capability of baseline PIM use to assess mortality. The full models included interaction terms between PIM/DDI use and other covariates.

Results: Approximately 87% of the participants aged ≥65 years used at least one drug listed in the Beers criteria, and 3.8% of all participants used two or more drugs with DDIs. The fully adjusted model, censored at all years, found that among whites, PIM use increased the risk of all-cause mortality (hazard ratio [HR] = 1.27, 95% CI 1.10–1.47). DDIs were found to increase the risk of mortality only among females in the fully adjusted model censored at 2 years (HR = 1.77, 95% CI 1.11–2.80). Higher medication use was a significant predictor of mortality across all the fully adjusted models ($P < 0.01$).

Conclusions: In the fully adjusted models, PIM use was associated with a higher risk of mortal events. No significant disparities were observed across the relationship between PIM use and mortality.

1114 | Antidepressants use and persistence in Tuscany: A large regional drug-utilization study

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Background: Among all the Italian regions, Tuscany consistently showed the highest prevalence of AD utilization. Possible inappropriateness of use is therefore a concern. A treatment shorter than 6 months is not effective for depression (DEP), the principal indication for AD.

Objectives: To analyze the utilization of antidepressants in Tuscany both in terms of baseline characteristics and in terms of pattern of utilization.

Methods: We used the healthcare administrative databases of Tuscany. We selected new users of ADs during 2014 with no previous use reported since 2011 and with at least 3 years of follow-up into the database. Demographic characteristics were collected at the index date (ID), and comorbidities were evaluated in the previous period up to 2 months after ID. During the follow-up, presence and persistence (i.e., no gap ≥60 days between dispensations) of ADs were assessed in time windows of 6 months.

Results: In Tuscany, 89,509 individuals claimed at least 1 dispensation of AD in 2014. The majority were females (65%), aged ≥45 years old (76%), with cancer (17%) and diabetes (9%). The index AD was most commonly a SSRI (69%). During the first 6 months, 39,504 individuals (36%) had only 1 dispensation. However, in latter subpopulation new dispensations were registered during the second semester (13%) and the second year of follow-up (25%). Moreover, 22,688 individuals (25% of new users) had at least a treatment gap during the first 6 months. Finally, 27,313 patients (31%) were persistent in the first 6 months. Notably, 14,126 (51%) of them were persistent also in the first year and 7,064 (26%) during the second year. The occurrence of AD dispensations during the third year paralleled the persistence in the previous years: from 16% among those who had only one dispensation in the first 6 months, up to 92% of those who were persistent during the entire period.

Conclusions: Only a minority of new AD users were persistent to the treatment in the first semester. This could indicate a suboptimal use of the drug in patients with DEP, or an over-prescription for other indications (e.g., neuropathic pain). Future studies will address possible inappropriateness of ADs use in Tuscany by comparing detailed patterns of utilization with other Italian regions.

1115 | Prevalence of polypharmacy in Japan

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Background: Polypharmacy in elderly population has been associated with adverse health outcomes including mortality, falls, adverse drug reactions, as well as increased healthcare costs. Japanese government is developing guidelines and policy interventions in the aim of reducing polypharmacy in the elderly.

Objectives: To assess the prevalence of polypharmacy in Japan across different age groups.

Methods: We utilized IQVIA National Prescription Audit database which is a dispensing claims database obtained form approximately 7500 out-of-hospital pharmacies throughout Japan, capturing approximately 15% of all prescriptions. We included all patients with at lease one record of drug prescription in the database between January and March 2018. For each patient, we sampled 1 prescription that was dispensed at a most recent date on record. We counted the number of medications prescribed simultaneously in that prescription, and summarized the number across the patients, by age groups of 0–14, 15–64, 65–74 and 75 and above. We also assessed the therapeutic areas of the medications that were most frequently prescribed for prescriptions with 5 or more simultaneous medications.

Results: We identified 19,428,735 patients in the database; 16.1% aged 0–14, 50.6% aged 15–64, 15.0% aged 65–74 and 18.2% aged 75 and above. In total, the median number of simultaneous drug prescription was 3, with 25 and 75 percentiles as 2 and 4, respectively. The percentage of patients with simultaneous prescription of 5 or more drugs increased with age (20.7% for 0–14 y.o., 22.9% for 15–64 y.o., 24.6% for 65–74 y.o, and 33.2% for 75 y.o. and above). The age difference was more enhanced for prescriptions with 10 or more

drugs: (0.6% for 0–14 y.o., 2.3% for 15–64 y.o., 4.1% for 65–74 y.o, and 8.7% for 75 y.o. and above). While the most frequently prescribed drug areas for prescriptions with 5 or more drugs were alimentary tract and metabolism, cardiovascular system, and masculo-skeletal system drugs for those 65 and above, they were respiratory system, systemic anti-infectives, and cardiovascular system drugs for 0–14 y. o. and 15–64 y.o.

Conclusions: Polypharmacy increased with age in the studied Japanese population, especially evident for prescriptions for 10 or more simultaneous medications. Prescriptions of 5 or more medications were fairly common in younger patients below 65 y.o. Evaluation of therapeutic area and its duration are important factors for assessing potential adverse effects of polypharmacy.

1116 | Medication errors associated with the use of antibiotics in critical care units

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Background: Iatrogenesis is an inevitable reality under the current complex healthcare framework. Medication errors (ME) jeopardizes patient safety. It is important to understand how often and why these errors are occurring and contributing factors. It is essential to reduce their occurrence in the limited resources scenario. Further, safer use of antibiotics will not only reduce the burden of antibiotic resistance, but also limits the patient from unnecessary exposures to the adverse effects.

Objectives: To determine the incidence, and nature of medication errors associated with the use of antibiotics in the critical care units.

Methods: A descriptive cross-sectional study was conducted in inpatients of either gender, aged more 18 years who were admitted to critical care unit for more than 24 hours. All the required data were collected and documented. All the diagnoses and antibiotics were coded according to the International Classification of Disease 10 (ICD 10) and Anatomical Therapeutic Classification (ATC) codes respectively. Each prescription was subjected for review to identify the Medication errors associated with use of antibiotics.

Results: Of the 1162 antibiotic doses prescribed for 500 patients, 36 (7.2%) patients were presented with medication errors. A total of 47 medication errors were detected. The average number of medication error was 1.31 errors/patient. Administration errors accounted for 21 (44%) MEs. Distractions [23 (48%)] and interruptions [16 (34%)] were the major contributing factors for these errors. A total of 14 individual antibiotics, under 4 different classes were implicated in the errors and Ceftriaxone (28%) was widely implicated. Most [27 (57%)] of the errors belonged to the category C as per the NCC MERP index.

Conclusions: The use of antibiotics was found to be high in the Intensive Care Unit. Of the total reported medication errors, Ceftriaxone was most commonly implicated. Clinical pharmacist plays an important role in the detection and management of MEs.

1117 | Distribution and storage of medications in households from Mexico City

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Background: Household storage of medications represent a latent risk for irrational use that may lead to the presence of adverse drug reactions and incorrect dosage to patients. The potential negative effects increase when expired medications are stored.

Objectives: (1) To describe the distribution of medications in households from Mexico City and (2) to determine the prevalence of expired medications in household storage.

Methods: A community based descriptive, cross-sectional, retrospective and observational study was conducted during 2018 in Mexico City. A sample of 229 households were randomly selected and a standardized questionnaire was applied by face-to-face interview to an adult family member. Name of medications and expire date were recorded. Medications were classified according to their ATC class and expiration date was dichotomized as expired or not expired at the moment of data retrieval. Qualitative variables were described using absolute and relative frequencies or median and range accordingly. Categorical variables were compared using Chi-square tests using as statistical significance of $p = 0.05$.

Results: A total of 2,384 medications of 34 pharmacological groups were stored in Mexican households, the median of medications per household was 10 with a wide range of 04–42 medications within the whole sample. There was statistical difference ($p < 0.001$) among the most prevalent therapeutic classes including NSAIDs/analgesics 643(27%), cardiovascular 548(23%), respiratory 452(19%), antibiotics 286(12%) and metabolics 190(8%). The most frequent drug was paracetamol 211(8.8%), this drug was either alone or in combination. Regarding the characteristics of the stored medications in Mexican households, the most prevalent were: oral administration route 2014(84.4%), tablets 1247(52.3%) and generic medications 1786(74.9%). The prevalence of expired medications was 34.8%.

Conclusions: Pain relievers and antihypertensives were the most frequent medications in household storage in Mexico City. Mexican households storage include in average one third of expired medications.

1118 | Insights of the health care work force on establishing a medication error reporting system in a tertiary care teaching hospital: A survey questionnaire

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Background: Iatrogenesis is an inevitable reality under the current complex healthcare framework. Medication errors (ME) jeopardizes patient safety. It is essential to reduce their occurrence and thereby over all associated health care costs in the limited resources scenario.

Objectives: To determine the perceptions of Health care professionals towards establishing a medication error reporting programme.

Methods: A questionnaire was designed, validated and circulated among the health care professionals of a tertiary care teaching hospital by clinical pharmacists to understand their perception on Medication Error Reporting System.

Results: A total of 622 HCPs were approached with this questionnaire. Of which 535 HCPs, i.e., 376 (70.2%) Nursing staff, 32 (5.9%) Interns, 78 (14.5%) Post-graduation students in various disciplines of Hospital, 49 (9.1%) Doctors had responded to the survey with an overall response rate of 86%. General awareness of existence of Medication Error/ Error Reporting Centre was observed in 51.5% of doctors and 61.9% of nurses among whom 18.2% of doctors and 44.4% of nurses only were aware of existence of Medication Error/Error Reporting Centre in India. During their practice, 72.3% of doctors and 5.5% of nurses have reported at least one medication error and 81.7% of doctors and 83.5% of nurses welcomed Medication Error Reporting and Monitoring system at their practice site. Further, the importance of clinical Pharmacist for independent assessment of medication error was appreciated by 22.8% of doctors and 64% of nurses. Medication Error Reporting and Monitoring Centres' role for Health Care Professionals in medication safety was accepted by 18.5% of doctors and 57.3% of nurses. Preference towards electronic reporting of medication error was shown by 26.5% of doctors and 16.2% of nurses. The willingness to report the medication errors to the Medication Error Reporting and Monitoring system if made available at their practice site is observed in 62.2% of doctors and 81.6% of nurses.

Conclusions: The senior workforce entourages the concept of mandatory reporting with the identity of personnel involved in the error while the newer staff wishes to opt the anonymous reporting of medication errors. This has led to the initiation of several dialogs between clinical pharmacists and other health care professionals to understand further about their perceptions of reporting medication errors and thereof to enhance the acceptance of medication error reporting system.

1119 | Polypharmacy and associated factors in primary healthcare users of the unified health system in Minas Gerais state, Brazil

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Background: Despite representing a growing challenge in primary healthcare and health services, few studies have analyzed polypharmacy among the general population, in public health services.

Objectives: This study aimed to characterize polypharmacy and its associated factors in medicine users of primary healthcare of the Unified Health System (SUS) in the state of Minas Gerais, Brazil, 2014–2015.

Methods: A cross-sectional study with a representative sample of users aged 18 years and older. These medicine users were stratified according to the number of medicines used, the difference between the groups being evaluated by the Pearson chi-square test. Logistic regression model ($p < 0.05$) was used to investigate factors associated with polypharmacy (use of five or more medicines). The Hosmer-Lemeshow test was used to evaluate the fit quality of the model.

Results: The prevalence of polypharmacy among medicines users was 13.7% in the general population and 33.3% in the elderly population (≥ 65 years). There was a positive association between polypharmacy and the 45–64 years group (OR = 2.02, 95% CI: 1.03–3.94) and ≥ 65 years group (OR = 4.17, 95% CI: 1.92–9, 17), in addition to the following chronic diseases: stroke (OR = 4.20, 95% CI: 1.53–11.55); diabetes mellitus (OR = 4.03; 95% CI: 2.43–6.68); heart diseases (OR = 3.18; 95% CI: 1.92–5.29); depression (OR = 2.85; 95% CI: 1.80–4.53); hypertension (OR = 2.13; 95% CI: 1.17–3.86); dyslipidemia (OR = 1.73, 95% CI: 1.07–2.80). Marital status (married/common-law marriage) was inversely associated with polypharmacy (OR = 0.34, 95% CI: 0.19–0.62).

Conclusions: A significant number of adults and elderly, using medicines, primary care users of SUS, in Brazil, were exposed to polypharmacy and some associated factors are relevant, such as specific morbidities and age. The multiple drug combination should be judicious and evidence-based, as it increases the risk of harm that may outweigh the therapeutic benefit.

1120 | Reasons for self-medication with antibiotics among people with secondary education or higher in Hyderabad, India: A cross-sectional study

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Background: The use of prescription and non-prescription medications to treat self-diagnosed illnesses without consulting a medical practitioner refers to self-medication. Antibiotics are commonly purchased without prescription in many developing countries and some developed countries. Self-medication with antibiotics is associated with an increased risk of adverse drug reactions and antibiotics resistance.

Objectives: The study aim was to investigate self-medication with antibiotics among people with secondary education or higher in Hyderabad city, India.

Methods: Design: A cross sectional community based online survey was conducted in the capital of Telangana state Hyderabad, from March 2018 to June 2018. **Setting:** The survey was prepared in a Google form and the link was distributed to the public through social media (WhatsApp© and Facebook©). **Study instrument:** A structured self-administered questionnaire was developed based on extensive review of similar studies worldwide. Validity of the study instrument was determined by experts in the field and a pilot study was conducted on randomly selected persons to ensure the easiness and readability of the questionnaire. Based on the results of the pilot study, the final version of the survey was modified. **Main outcome measure:** The main study outcome was the underline reasons for self-medication with antibiotics. **Statistical Analysis:** Descriptive statistics were utilized to analyze the study result. The data were presented as number and percentages. The data were analyzed using the Statistical Package of Social Science (SPSS) version 24.

Results: The majority of the respondents were male 62.3%. More than half 53.75% were in the age group of 18–24 years. Most common reason for self-medication with antibiotics was disease considered not serious for physician consultation (66.3%). The most commonly used antibiotics were azithromycin (67.9%) and amoxicillin (64.8%). Fever (76.8%), Common flue and cough (70.8%) and dental pain (42.3%) were the most common conditions for which self-medication were thought. The most common sources of information about self-medication were previous physicians' prescription (72.6%) and pharmacist advice (72%).

Conclusions: Self-medication with antibiotics is a common practice among educated people. Regulatory bodies and healthcare professionals need to strengthen and advocate the roles and regulations that mandate the restriction of antibiotics sales without prescriptions.

1121 | Non-prescription paracetamol: Patients' knowledge and habits

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Background: Over the counter (OTC) medicines can be bought without a prescription and they are safe and effective, when patients follow the directions written in the patient's information leaflet or health care professionals' directions (HCPs). Paracetamol is one of the most popular OTC medicines, which is considered to be relatively safe due to its wide use. However, paracetamol is often used in overdose in the developed world - either by accident or on purpose for intentional self-poisoning - which can potentially lead even to acute liver failure. Under this perspective, further investigation is needed with regards to the proper use of paracetamol by patients, potential mistakes and proposals on how to avoid them.

Objectives: The aim of the present study was to investigate the knowledge and habits of patients in the Republic of Cyprus, concerning the use of paracetamol, a well-known and frequently used OTC medicine worldwide.

Methods: Questionnaires were distributed anonymously inside community pharmacies to those people who had just been supplied with an OTC medicine. The statistical analysis was conducted using the SPSS statistic program. There were no exclusion criteria, except for people's unwillingness to answer the questionnaire. Matching and selection was under Chi-Square Tests evaluation. The main questions were whether patients asked for the pharmacist's advice before buying the medication or not and if this medicine had any side-effects.

Results: The original compound was shown to be more well-known compared to the generics. A notable percentage of patients, ranging between 13.0% and 29.8%, answered incorrectly that some Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) contained paracetamol, which increases risk for Public Health. Another notable percentage of patients (6.7%) answered that the maximum allowed daily dose of paracetamol was higher than the correct one, whereas a significant percentage of patients (27.6%) answered that paracetamol is not toxic. Finally, an outstanding percentage of patients (40.2%) consumes alcohol in parallel or slightly after paracetamol consumption, while the same group of patients also uses paracetamol after alcohol consumption (OR 0.379, 95% CI (0.044–0.225), $p = 0.000$).

Conclusions: Paracetamol is frequently consumed by patients, both in its generic and original forms. Nevertheless, a notable percentage of patients is shown to confuse paracetamol medicines with NSAIDs. Paracetamol usage is related to demographic characteristics such as age, level of education and gender. It seems that patients need to be educated and counseled more by HCPs on the safe and effective use of paracetamol.

1122 | Drug overload in HIV management; an Indian countryside clinical picture

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Background: Polypharmacy & unreported usage of medication are frequent in Indian HIV patients. This is due to ease in access to medication in general and socio economic stigmas specific to self reporting of Anti Retroviral Therapy (ART). With a scenario of unaccountable open usage of medication without prescription and unavailability of proper patient records, so this is high time to quantify pill burden on HIV patients.

Objectives: To quantify the number of concomitant medications in patients receiving ART and to assess the associated factors.

Methods: An observational study carried out by recruiting HIV positive patients who are on ART, visiting government tertiary care

hospital (study site) at Warangal, India. Data were collected from patient case notes, patient interviews and laboratory data. Drug usage was considered unreported, when such usage is not on any patient health records & declared by the patient himself following face to face interviews.

Results: Out of 320 patients (*n* = 320) included in the study, 134 were males (41.87%), 183 females (57.18%) and 3 transgender (0.93%). Unreported drug usage was found to be 2395 times in 320 patients from august 2017 - October 2018. The mean of unreported concomitant medication usage was found to be 7.5. 86.56% patients were prophylactically treated with atleast 1 antibiotic with a mean of 1.38. Diabetes (DM) and hypertension (HT) were present in 10.93% and 14.06% subjects, respectively. Tuberculosis (TB) was found in 71 subjects in which 26 subjects were infected with TB in past 15 months and among 26 subjects, 12 subjects approached hospital with TB as presenting illness and were subsequently diagnosed ass HIV + ve and hence started ART & Anti TB therapy simultaneously. The ART pill burden was single pill a day in 229 subjects & 2 pills in 91 patients. Aforementioned co-morbid conditions with ART usage revealed significantly daily pill burden of 4 pills a day in 45 subjects (DM or HT), 3 pills in 18 subjects (TB), 5 pills in 17 subjects (DM & HT) and 6 pills in 3 subjects (DM, HTN & TB), not including drug use for prophylaxis and unreported usage.

Conclusions: It is observed that the high pill burden in study subjects is due to polypharmacy & unreported drug usage. Inspite of considering patients who are having only one opportunistic infection and two co-morbid conditions, it was observed that there was huge rise in pill burden in HIV patients, we can apprehend more pill burden if patients with multi opportunistic infections and co-morbid conditions are considered. The substantial under-reporting of drug use highlights the need accurately record patient data.

1123 | Prevalence of long-term oral corticosteroid use in asthma evaluated from different angles

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Background: Systemic corticosteroids are a mainstay of treatment for asthma exacerbations and are often prescribed orally as part of daily maintenance therapy for patients with severe asthma. Exposure to oral corticosteroids (OCS) is known to be associated with adverse effects that can occur early in a treatment course or at a relatively low dosage. The frequency of long-term (LT) OCS use is not well studied in asthma, given that it has no universal definition.

Objectives: To examine the prevalence of LT OCS use in patients with asthma using different LT OCS use definitions.

Methods: We used data from the Truven MarketScan® Commercial Claims and Encounters, Medicare Supplemental, and Medicaid Multistate Claims databases from January 2012–December 2017. Patients who were at least 12 years old, met the 2-year Healthcare Effectiveness Data and Information Set criteria for persistent asthma, and had 30 months of continuous clinical and pharmacy data coverage (6 months before as baseline and 24 months after the persistent asthma index date) were included. Patients with non-asthma conditions typically treated with OCS were excluded. Patients with LT OCS use were primarily defined as those with filled OCS prescriptions with cumulative doses ≥450 mg in a maximum period of 90 days, corresponding to an average daily dosage of ≥5 mg. Three other definitions were used in sensitivity analyses: (A) continuous OCS use for ≥90 days with no gaps between refills, (B) ≥183 days of OCS use within a 365-day period, and (C) ≥4 OCS prescriptions within a 365-day period. Annual prevalence is presented for 2013–2017 to allow for full follow-up years.

Results: We identified 435,675 patients for this analysis. A quarter of them had severe asthma (Global Initiative for Asthma Steps 4 or 5), and 14.3% had ≥1 exacerbation during the 6-month baseline period. Using the primary definition, 19.3% were LT OCS users at some point during follow up, and 10% were during the first post-baseline year. Annual prevalence of LT OCS from 2013–2017 ranged from 5.3–7.6%, 0.8–1.6%, 1.0–1.4%, and 4.3–4.9% for primary and sensitivity definitions A, B, and C, respectively.

Conclusions: The prevalence of LT OCS use varies depending on how LT OCS use is defined. Prevalence was relatively high when we used the primary definition that accounts for total OCS exposure. LT OCS use was less frequent when we used definitions that considered only prescription duration or number of prescriptions but not dosage. The variety of LT OCS use definitions allows for a comprehensive and objective assessment of actual OCS use in the population.

1124 | A longitudinal observational study describing the prescribing of, and persistence with, multiple-inhaler triple therapy for chronic obstructive pulmonary disease in the United States

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Background: Point-of-care dispensing data from retail pharmacies provides a comprehensive source of prescribing data, including persistence with medication use. Multiple-inhaler triple therapy (MITT), comprised of a long-acting β_2-agonist (LABA), a long-acting muscarinic antagonist (LAMA), and an inhaled corticosteroid (ICS) in two or three separate devices, is currently recommended for patients with chronic obstructive pulmonary disease (COPD) who are symptomatic and at risk of exacerbations. Previous studies have evaluated treatment patterns for patients with COPD, but there is a

knowledge gap about treatment patterns after MITT initiation, including patient persistence with this therapy.

Objectives: This study describes MITT use for COPD, and persistence with these therapeutic regimens, in the United States (U.S.) using a prescription dispensing database. We also describe the most commonly dispensed MITT regimen, as well as the median time to treatment discontinuation among each MITT regimen.

Methods: We conducted a retrospective, longitudinal, observational study of dispensing of MITT via two or three separate devices (overlapping ≥1 day) from retail pharmacy dispensing databases in the U.S. We collected dispensing data between November 1, 2013 and October 31, 2016. Eligible patients were aged 40 years or older, were new users of MITT, and had 12 months of follow-up data.

Results: Among the 50,099 patients who initiated MITT and were followed for 24 months (43.4% male, mean age 66.3 years), approximately 25.9% had an exacerbation in the 90 days prior to MITT initiation. Most patients initiated a regimen comprised of two separate devices (99.5%) and on an ICS/LABA+LAMA regimen (84.7%). The median duration of ICS/LABA+LAMA use among patients who initiated MITT in our study was 150 days (interquartile range: 120–275 days), and 7.7% of these patients were persisting with MITT at 24 months. Among the patients that discontinued the ICS/LABA+LAMA MITT regimen, 38.8% discontinued the ICS/LABA component, 34.4% the LAMA component, and 19.1% stopped MITT altogether.

Conclusions: These results provide additional data on real-world use of MITT in the U.S., and the persistence with MITT among patients using this treatment. We observed that most patients persist with MITT for approximately 4–5 months, which is consistent with findings from other studies. Research through direct observation of COPD patients, with a known diagnosis, receiving MITT is needed to further investigate persistence with MITT in the real-world setting.

1125 | Discontinuation of therapy among COPD patients who experience an improvement in exacerbation status

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Background: A subset of patients with chronic obstructive pulmonary disease (COPD) experience a decrease in exacerbation frequency, leading to a diminished need for treatment with inhaled corticosteroids (ICS).

Objectives: We investigated prescribing and discontinuation patterns of long-acting bronchodilators and ICS in COPD patients according to exacerbation frequency.

Methods: Using the nationwide Danish health registries, we conducted a drug utilization study among patients who had at least two exacerbations or one hospitalization due to an exacerbation during 2011–2012. This study population was stratified according to consistency of exacerbation occurrence after 12-, 24-, 36-, and 48-months of follow-up and the groups were described according to use of ICS, long-acting β_2-agonists (LABA), long-acting anticholinergics (LAMA), and combinations thereof.

Results: We identified 29,010 COPD exacerbators during 2011–2012. Upon inclusion, 70% received ICS-containing regimens, in combination with LABA (23%) or both LABA and LAMA (41%). The proportion of prevalent users of ICS-containing regimens decreased to 56% during follow up among exacerbation-free individuals, while it increased to 86% in individuals who experienced at least one exacerbation annually. Persistence to ICS-containing regimens was 58% after 4 years in individuals without exacerbations compared to 74% among those with annual exacerbations. Similar patterns were observed for triple therapy which was the most extensively used drug combination regardless of consistency of exacerbation occurrence.

Conclusions: The extensive use of ICS and the relatively high persistence to ICS-containing regimens in individuals who had a decrease in exacerbation occurrence highlight a need for the development and implementation of de-escalation strategies in clinical practice.

1126 | Utilization pattern of chronic lung disease treatment prior to the start of respiratory syncytial virus season

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Background: Guidelines recommend palivizumab immunoprophylaxis for preterm children with CLD in their first year of life but in the second year of life only if they continue to receive treatment for CLD within 6 months before the RSV season. Although the use of chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen serve as a proxy for CLD severity to determine the use of palivizumab, treatment utilization patterns of these therapies are not well understood.

Objectives: This study aimed to describe utilization patterns of CLD treatment 200 days before the start of the RSV season.

Methods: This was a retrospective cohort study using Florida and Texas Medicaid claims data linked to birth certificates for children aged 0–24 months and their mothers between 1999–2010. We included preterm children with CLD (gestational age < 32 weeks; having a CLD diagnosis [ICD-9-CM 770.7 or 769]; and oxygen supply or a diagnosis of respiratory distress syndrome within 90 days of birth) who were continuously enrolled during the 200 days before the start of the RSV season. CLD treatment was ascertained from medical and pharmacy claims related to diuretics, steroids, oxygen supplementation; and ventilation requirement on birth certificates. To capture time-varying utilization patterns, we calculated prevalences for each of ten discrete 20-day segments before the RSV season. We also reported the prevalence of respiratory infections to provide background seasonal virulence, which can trigger the intermittent use of steroids in addition to CLD severity.

Results: Among 19,026 preterm children with CLD, 64.8% did not receive treatment for CLD whereas 29.7%, 8.6%, and 3.2% received steroids, oxygen, and diuretics, respectively, within 200 days before the RSV season. Prevalences of oxygen and diuretics use decreased as Infant age increased. The use of corticosteroid therapy was strongly associated with seasonal virulence trends. Higher thresholds for cumulative days' supply of steroids showed the least seasonal trends in utilization patterns, indicating chronic treatment likely due to CLD severity rather than acute infections.

Conclusions: Our findings on utilization prevalences of CLD treatment could help to optimize eligibility thresholds for immunoprophylaxis.

1127 | Assessment of inhalation techniques employed by asthma and COPD patients in Warangal region, India

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Background: Inhalation mode of drug delivery is the mainstay treatment for asthma and COPD, however, incorrect technique prevents patients from receiving maximal therapeutic benefits.

Objectives: The aim was to evaluate the inhalation technique of COPD and bronchial asthma patients using metered dose inhaler and rotahaler to investigate the determinants of incorrect inhalation technique.

Methods: It was a prospective observational study in Warangal region. A consecutive nonrandom sampling method was used to enroll study subjects. Basic sociodemographic information of the study subjects was collected. The inhalation technique was visually observed and scored on checklist, which was carried out in chest hospital in Warangal city. Questionnaires were used for assessment of rotahaler inhalation technique and MDI inhalation technique.

Results: Among the 350 patients observed, 300(86%) subjects are using rotahalers and 50(14%) subjects are using MDI's. In case of rotahaler Common steps missed by 210 (70%) ofrespondents was not breathing out fully prior to inhalation which was followed by 82 (27.3%) ofthe respondents are failed to hold their breathe for 10 seconds after inhalation and 30(10%) ofrespondents are failed to seal the lips around the mouth piece. In case of MDI's commen stepsmissed by 31(62%) of respondents are to shake the inhaler prior to its use followed by half of therespondents 25(50%) are missed to exhale the breath before inhaling medication and 14(28%) of the respondents are failed to hold their breath for 10 seconds after inhalation. No significantcorrelation was found between accuracy of the age, sex, education status, or area of residence ofthe patients.

Conclusions: Most patients used their rotahalers and MDI's incorrectly with most common errors being failure to hold the breath after inhalation, missed to exhale breath prior to inhalation and inability to take deep inspiration after inhalation. Source of information and re-demonstration of technique was found to be significantly associated with proper use. Regular assessment and reinforcement of correct inhalation technique by health professionals and caregivers are essential to improve compliance. Further studies are recommended to assess the role of health professionals' and clinical pharmacists in the proper use of inhalers. Pharmacists are currently less involved in patient education about inhalers use; thus their active involvement in instruction session may aid in correct usage of inhaler by patients.

1128 | Utilization of Olodaterol and Indacaterol in Europe

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Background: Olodaterol and indacaterol are authorized only for the treatment of adults with chronic obstructive pulmonary disease (COPD). Use of these drugs in patients with asthma, irrespective of COPD, has been associated with increased morbidity and mortality, and is considered off-label.

Objectives: To quantify the potential off-label use of olodaterol and indacaterol and characterize use in clinical practice.

Methods: This descriptive drug utilization study used routinely collected health data in the PHARMO Database Network in the Netherlands (PHARMO overall and PHARMO-GP for the subset of patients with general practitioner [GP] data), the population registers in Denmark, and the IMS Real-World Evidence Longitudinal Patient Database (RWE LPD) (GP panel and pulmonologist panel) in France. All new users (treatment naïve) of olodaterol or indacaterol between 2014 and 2017 were included in the study. On-label use was defined as use among adults with a recorded diagnosis of COPD. Off-label use was use among adults with a recorded diagnosis of asthma without a recorded diagnosis of COPD or as use among patients ≤18 years. Potential off-label use was defined as no recorded diagnosis of either COPD or asthma.

Results: The study included 4,158 new users of olodaterol (1,386 in PHARMO, 1,712 in Danish National Registers, and 1,060 in the RWE LDP panels) and 9,966 new users of indacaterol (1,841 in PHARMO, 6,406 in Danish population registers, and 1,719 in the RWE LDP panels). For both drugs, median patient age at treatment start ranged from 63 to 71 years, and approximately 50% were female across the data sources. Initiators of both drugs were similar regarding comorbidity burden and comedications. Prevalence of off-label use ranged from 3.5% for both drugs (PHARMO overall) to 11.9% for olodaterol and 12.4% for indacaterol (RWE LPD GP panel). Prevalence of on-label use ranged from 47.8% (PHARMO overall) to 77.7% (RWE

LPD pulmonologist panel) for olodaterol and from 28.7% (Danish population registers) to 70.1% (RWE LPD pulmonologist panel) for indacaterol. The remaining new users of olodaterol and indacaterol were classified as potential off-label users, with prevalence ranging from 17.3% (RWE LPD pulmonologist panel) to 48.6% (PHARMO overall) for olodaterol, and from 20.5% (RWE LPD pulmonologist panel) to 66.6% (Danish population registers) for indacaterol.

Conclusions: The prevalence of off-label use of both drugs was lower than reported in other studies evaluating off-label use of medications across Europe, and there was no pediatric use. Lack of direct evidence on indication (potential off-label) for a high proportion of patients is a limitation for some data sources.

1129 | A day in the life: Prescription medicine use in Australia

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Background: Australia spends more than $11 billion, annually, on publicly-subsidized prescription medicines via the Pharmaceutocal Benefits Scheme (PBS), but there are few data on how individual Australians are using these medicines on a daily basis.

Objectives: To describe Australians' prescription medicine use on typical day.

Methods: We used dispensing records for a nationally-representative, 10% sample of PBS-eligible Australians to identify people exposed to any prescription medicine on 25 September 2017 (World Pharmacists' Day). We estimated exposure by calculating days between dispensings for each PBS medicine using records from 2013–2017. We considered the time by which 75% of people received a subsequent dispensing as the estimated period of exposure (EPE). For each person, we added each medicine's EPE to the date of the last dispensing prior to the 25th and if that EPE ended on or after the 25th we considered that person exposed to and using that medicine on that day. We grouped medicines by ATC code and examined use by sex and age groups. We defined persons experiencing polypharmacy as those with 5 or more unique medicine exposures on the day. We used the Australian Bureau of Statistics mid-year population estimate for 2017 to extrapolate our findings to the Australian population.

Results: 885,288 people used at least one prescription medicine on September 25, 2017; their median age was 56 years (IQR: 36–69) and 58% were female. In total, 2,327,530 prescripton medicines were in use on the day. Cardiovascular, nervous system, and alimentary tract and metabolism medicines accounted for the majority of use, with 16%, 12%, and 10% of the population using each, respectively. Persons ≥70 years of age accounted for 39% of all use on the day, and 80% of Australians ≥70 were using at least one prescription medicine. 16% of medicine users were using 5 or more medicines (polypharmacy) and 2% were using 10 or more medicines (hyperpolypharmacy). Polypharmacy accounted for 42% of all medicine use on the day and 58% of people experiencing polypharmacy were ≥ 70 years of age. Broadly, the nature of medicine use was similar between sexes, however females were using more genitourinary and sex hormone medicines.

Conclusions: Over one third of the Australian population uses a prescription medicine on a typical day and use increases with age. Nearly half of all medicine use is in the setting of polypharmacy, and this is particularly an issue for older Australians. These population-based estimates highlight potential quality use of medicines issues, particularly in older people, and provide useful baseline data facilitating comparisons of disease epidemiology and medicine use over time.

1130 | Use of ovarian suppression with endocrine therapy among premenopausal women with breast cancer in the United States, 2001–2016

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Background: Clinical trials indicate that adding ovarian suppression (OS) therapy to endocrine therapy (ET) in premenopausal women with non-metastatic breast cancer improves disease-free and overall survival. However, injectable OS may add cost, potential side effect burden, and additional clinic visits to adjuvant therapy. It is not known to what extent OS is being used in contemporary community oncology settings.

Objectives: We describe uptake of OS within a commercially-insured population of US women aged 18–50 diagnosed with incident breast cancer (2001–2016) and using ET. We also describe predictors of OS use in this population.

Methods: We identified women with incident breast cancer based on diagnosis codes from 2001–2016 in the IBM® MarketScan® database. Eligible patients were continuously enrolled for 12+ months prior to cancer diagnosis and filled at least 1 prescription for oral ET (i.e., tamoxifen, toremifene, anastrozole, letrozole, and/or exemestane) in the year after diagnosis. We classified use of OS as any prescription for a gonadotropin-releasing hormone (GnRH) agonist in outpatient pharmacy claims or procedure code for OS implant or injection 1) in the week prior to ET initiation or 2) following ET initiation and for up to 18 months after diagnosis. We estimated the proportion of women that were OS users in each diagnosis year using linear binomial regression, and examined associations between OS use, age at diagnosis, and geographic region.

Results: A total of 26,114 women meeting all inclusion criteria were identified from the MarketScan® database, of whom 1,452 (5.6%)

were OS users. The most common type of OS was leuprolide or leuprorelin (55.2%), followed by goserelin (46.7%), and triptorelin (1.1%); these were most often identified by procedure code. Annual risk of OS use varied from 3.2% in 2001 to 9.3% in 2016, peaking at 11.4% in 2015. OS use varied by region ($\chi 2$ p = 0.0003), with the highest risk of OS use observed in the Northeast (6.5%) and the lowest in the South (5.0%). Younger patients were significantly more likely to use OS than older patients, with each additional year of age at diagnosis associated with a 0.57 percentage point decrease in risk of OS use (95% confidence interval [CI]: −0.63, −0.51). After controlling for age group (≤40, 41–44, 45–46, 47–48, 49–50) and region, each additional calendar year was associated with 0.25 percentage point greater risk of OS use (95% CI: 0.19, 0.31).

Conclusions: OS use with ET appears to be increasing in US breast oncology practice among women under 50.

1131 | Type and characteristics of drug information inquiries in Ethiopia University Hospital: 2 year prospective observational study

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Background: The drug related information demand, extent of inquiry and functionality of existing drug information centers are seldom studied in Ethiopia.

Objectives: This study aimed to identify the types and potential areas of drug information inquiry at Gondar University specialized Hospital (GUSH), Northwest Ethiopia.

Methods: A prospective observational study was employed from January, 2016 to December, 2017 at Drug Information Center (DIC) of GUSH. The study query was collected through 2 batches of graduating class of undergraduate pharmacy students. Descriptive statistics used to describe, characterize and classify drug related queries with various perspectives. Binary logistic regression test was employed to identify predictor variables to the type of drug related queries.

Results: A total of 781 drug related queries collected in the 2 years period and 697 included in the final analysis. Near to half (45.3%) of queries comes from the pharmacists followed by general practitioners (11.3%) and nurses (10.2%). Slightly greater than half of the queries (51.9%) are focused on therapeutic clinical information. 39.6% of drug related queries comes with infectious disease case scenarios followed by cardiovascular cases in 21.3% of queries. More than half of (53.9%) and nearly one in five (19.4%) of the queries take 5 to 30 minutes and 30 minutes to 1 hour of literature searching, respectively. Pharmacists and patients ask patient specific questions in their drug related queries higher than others, with Crude odds ratio of 95% CI, 2.474(1.373, 4.458) and 4.121(1.403–12.105), respectively.

Conclusions: In conclusion, pharmacists are the primary drug information users and frequent drug related information inquirers. Most of the queries targeted therapeutic indications, adverse drug events, infectious and cardiovascular disease related requests. Drug information services are imperative for growing pharmacist's role in patient care and addressing patient specific drug related needs.

1132 | Over-the-counter drugs: A Pharmacoepidemiological study in Greece during the financial crisis

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Background: O.T.C. medicines' purveyance in Greece needs no prescription from physicians. However, we still have no knowledge of how people are informed about their use and whether this might be a public health issue.

Objectives: The goal of this study is to determine the knowledge level, habits, sources of information and selection criteria of Greek population regarding O.T.C. medicines, as well as their opinion about the disposal of these drugs in non-pharmacy settings.

Methods: During 5 months, 920 adults, who have been approached in community pharmacies and gathering points, have been interviewed anonymously. Individuals participated (782, 85.0% response rate) answering a predesigned, cross-sectional questionnaire consisting of 12 multiple-choice questions. The data collection followed and statistical analysis was performed with the IBM SPSS Statistics v.15.0 program using descriptive statistics, chi-square and odds ratios (ORs).

Results: The greatest proportion of respondents (79.8%) exhibited mediocre to good knowledge about which drugs are categorized as O.T.C. and which are not. Healthcare professionals (such as pharmacists and physicians) seem to be the main sources of information about O.T.C. medications for the 84% of the respondents. When asked about the selection criteria for the purchase of O.T.C. medication, physicians seem to play the most critical role (66.1% of the patients), with pharmacists (60%) and friends and family (22.4%) following. Product price also seems to be a critical factor for 30.9% of people over 70+ years, in contrast with 13.8% of people aged 18–29 (p = 0.030). Furthermore, it was found that most of the participants (79%) choose self-medication in case of common cold treatment. Additionally, 61.2% of respondents stated that they are reluctant to buy O.T.C. from a non-pharmacy setting. Older people seem to be more negative about purchasing them elsewhere than pharmacies than younger people: more specifically 72.8% of respondents over 70 years old in contrast to 55.9% of respondents aged 18–29 (p = 0.024). Those high rates of reluctance could be supported by the fact that 69.6% of the

respondents believe that retail of O.T.C. medicines in super-markets will increase their abuse and misuse.

Conclusions: Health professionals such as physicians and pharmacists seem to play a crucial role in people's information about O.T.C. use. On the other hand, self-medication seems to be overspread in Greek society due to financial crisis. Finally, Greek society presents reluctance in accepting O.T.C. disposal elsewhere than community pharmacies.

1133 | Glucocorticosteroids for the treatment of anaphylaxis: A systematic review

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Background: Glucocorticosteroids are widely used in the emergency treatment of anaphylaxis. However, its practical effects in treating anaphylaxis is suspectable.

Objectives: To evaluate the curative effects of glucocorticosteroids for anaphylaxis.

Methods: Highly sensitive search strategies have been developed to retrieve PuMed, Embase, the Cochrane Library, Web of Science, ClinicalTrial.gov and three Chinese databases. These databases were last searched on 7th December 2018. Ramdomised control trials and observational studies reporting comparison of glucocorticosteroids group versus non- glucocorticosteroids group were included. Literature screening and data extraction were performed independently by two reviewers. Studies were pooled using random effects models and presented as risk ratio, or odds ratio, with 95% confidence interval.

Results: 15 studies were included-3 cohort studies and 12 case control studies. For the outcome as length of hospital stay, one cohort study showed non-glucocorticosteroids group had longer length while another cohort study demonstrated an opposite result. Regarding the outcome as allergy-related revisit to the emergency department, two cohort studies showed there was no significant difference between two groups. For subsequent use of epinephrine, one cohort study supported that glucocorticosteroids group was superior. As to the episode of biphasic anaphylaxis, meta-analysis of 12 case control studies showed that the use of corticosteroids was similar between biphasic group and non-biphasic group (odds ratio 0.89, 95% confidence interval 0.47 to 1.68, I^2 = 61%).

Conclusions: Current evidence could not prove the effect of glucocorticosteroids in treating anaphylaxis yet, thought its pharmacological effects suggest it is potentially useful. It is better to regard glucocorticosteroids as second-line therapy or third-line therapy, and not to delay the use of epinephrine, the first-line agent, because of glucocorticosteroids.

1134 | Pharmacoepidemiology capacity building in the Latin American and African regions

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Background: An electronic screening survey of pharmacoepidemiology (PE) capacity building was developed for the Latin America (LatAm) and African regions. The objective of the screening survey was to identify a target population, to inform a second in-depth questionnaire to identify current status, needs, gaps and priorities in pharmacoepidemiology in these regions.

Objectives: To describe the results of the pharmacoepidemiology capacity building electronic screening survey for the LatAm and African Regions.

Methods: Following the Potter systemic capacity building model, a screening survey was developed in collaboration with PE international experts including those from the LatAm and African regions. The screening questionnaire was translated from English to Spanish, French and Portuguese by native speakers who were also PE researchers, and validated by a second set of translators. An online survey builder was used to develop the electronic survey.

Results: There were 110 participants, 91 (83%) from the LatAm and 19 (17%) from the African regions. From LatAm, 24% were from Brazil followed by Colombia (23%), Mexico (11%), Argentina (10%), Chile (9%), Ecuador (7%) and others (16%). From Africa, 26% were from Nigeria followed by South Africa (21%), Ghana (21%), Cameroon

(11%) and others (21%). More than half of all respondents (58%) were pharmacists, followed by medical doctors (23%). In terms of primary work, 35% were from academic institutions, 29% from government, 11% from industry, 10% from hospitals and the rest from other sectors. Eighteen percent were currently working in PE, 34% in pharmacovigilance (PV), 33% in both and the rest in neither. Of the total, 53% had formal training in PE, 66% were involved in teaching and 63% in research. Of those involved in teaching (N = 72), 51% have worked in both, PE and PV and only 14% in PE only. Of those involved in research (N = 68), 47% were in public health, 34% in clinical, 13% in applied research, 3% in basic science and 3% in qualitative research. Regarding main specific activity, 34% were working on policies, 30% in pharmacovigilance, 13% in development, 9% in benefit/risk, 3% in risk management plans and 11% in other areas.

Conclusions: There was a high response rate of the screening survey particularly from the LatAm region. The overall eligibility rate set a positive stage for the in-depth questionnaire. The high proportion of respondents involved in teaching and research will contribute to leverage the topics by region according to specific needs.

1135 | Association between self-assessed NYHA functional class and quality of life in a cohort of Portuguese heart failure patients: The PRIMe study

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Background: Symptoms and quality of life measures are widely used to classify heart failure disease state. It is of major interest to assess the extent in which the self-assessed New York Heart Association (NYHA) classification associates with other quality of life scales.

Objectives: To assess the association between self-assessed NYHA class and quality of life, measured by EQ-5D-3 L and Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Methods: The PRiMe study is a cross-sectional and multicentre study to characterize clinical, sociodemographic and therapeutic characteristics of sacubitril/valsartan (sac/val) users. Adult patients (≥18 years) or caregivers with a prescription (initial or refill) of sac/val are being recruited through Portuguese community pharmacies. Patient-reported outcomes (MLHFQ, EQ-5D-3 L and self-assessed NYHA) are being collected through a paper-based self-administered questionnaire. Higher values of NYHA and MLHFQ and lower values of EQ-5D address worse health status conditions. The association between self-assessed NYHA and quality of life was measured using Spearman Correlation Coefficient. This study was approved by the competent Ethics Committee and is compliant with the General Data Protection Regulation.

Results: As of Jan 2019, a total of 193 eligible patients (51 new users) were recruited in 125 community pharmacies, 26% through their caregiver. Mean age was 70.7 years (SD = 12.7; range: 35–94) and 60.6% were male. Among the 141 patients that self-assessed their NYHA class, 15% were NYHA class I, 43% NYHA II, 25% NYHA III and 17% NYHA IV. Self-assessed NYHA was positively correlated with MLHFQ total score (r = 0.456; p < 0.0001) and was more correlated with MLHFQ physical-score (r = 0.496; p < 0.0001) than with MLHFQ emotional score (r = 0.375; p < 0.0001). Regarding the association with EQ-5D-3 L, self-assessed NYHA was negatively correlated with the index (r = −0.527; p < 0.0001) as well as with the VAS score (r = −0.470; p < 0.0001).

Conclusions: The relationship between self-assessed NYHA class and quality of life measures is of importance to understand the clinical usefulness of patient reported outcomes.

1136 | Assessment of health related quality of life of HIV positive patients in Warangal region (India)

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Background: Access to affordable highly active anti-retro viral therapy (ART) has dramatically improved the life expectancy of HIV positive patients, resulting in increased number of people living with HIV. Many of these patients live with a substantial burden of psycho-social trauma and HIV related morbidity. Hence, the health related quality of life of these people is critically important and need a careful assessment by the healthy communication of a clinical pharmacist.

Objectives: The study objective was to assess the health related quality of life (HRQOL) in patients suffering from HIV by using WHOQOL-BREF scale which includes four major domains (Physical, Psychological, Environmental, Social), to find the influential factors affecting HRQOL in HIV patients. The patients were provided with counseling in-order to reduce the stigma (As in India stigma is the major barrier for miscommunication in HIV patients) they were followed up to assess the impact of the intervention.

Methods: We conducted a prospective interventional study in a government ART center in Warangal region from April 2018 to September 2018. The study included 668 outpatients who were assessed with WHOQOL-BREF questionnaire. The questionnaire included physical, psychological, social and environmental domains. The QOL scores were assessed pre- and post-counseling. One-way ANOVA (Tukeys multiple analysis) and unpaired t-tests were used to examine changes in HRQOL scores for individual domains following counseling.

Results: The study revealed that in pre-counseling session with patients the mean score (0–100) of domains was highest for the environmental domain (32.0), followed by psychological domain (22.7) then physical (17.4) and lowest for social (16.8). There was a

significant improvement (based on p values of pre and post counseling scores) ($p < 0.001$) in psychological domain (22.7 to 51.3), environmental domain (32.0 to 47.4), physical domain (17.4 to 51.3) and social domain (16.8 to 60.1) after the counseling intervention was done that is the psychological status of the patient was improved with a concerned communication.

Conclusions: The study revealed that after counseling HIV+ patients showed a significant increase in their HRQOL. The study strongly suggests that there is a need for establishing the counseling centers in hospitals for the patients suffering with HIV. Finally the role clinical pharmacist (who actually involved in the counseling of HIV patients) was revealed which lead to the improvement in patient's psychological behavior (which was assessed based on the psychological domain scores taken from WHOQOL-BREF scale).

1137 | Validated instruments of Quality of Life (QoL) in Acute Myeloid Leukemia (AML) patients

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Background: Acute myeloid leukemia is an aggressive and devastating disease for patients, which often requires intensive chemotherapies that negatively impact patients' quality of life (QOL). Multiple QoL instruments have been developed and validated but only few are specific for AML patients.

Objectives: To identify from the published literature validated instruments of QoL specific for AML patients and generic instruments used in AML patients.

Methods: A systematic and cumulative literature review was performed using Pubmed and OVID (Biosis, Embase and MEDLINE) databases through January 1, 2019. The search terms included: QoL, health-related QoL, patient-reported outcomes *and* validity, reliability, validated, tools, instruments, test–retest, *and* leukemia myeloid acute, leukemia, myeloid, acute, acute myeloid leukemia. References of relevant articles were reviewed. Two investigators independently reviewed the abstracts. Only papers with information of validity and/or reliability in AML patients were included. Any discrepancy was resolved by consensus.

Results: Eighty abstracts were reviewed and 10 full papers were selected. Validated instruments included: the Functional Assessment of Cancer Therapy with leukemia (FACT-Leu), the Life Ingredient Profile (LIP), the general European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) and versions EORTC-Leu, and EORTC 8 Dimension EORTC-8D); the 5-level EuroQoL five-dimensional questionnaire (EQ-5D-5 L), the Hematological Malignancy Patient-Reported Outcome (HM-PRO) used for various hematological malignancies, and the health-related QoL questionnaire for patients with hematologic diseases (QOL-E), QLQ-C30. The FACT-Leu scale showed adequate internal consistency (α = 0.75–0.96) and reliability (ICC =0.765–0.89). The LIP and EORTC have shown good validity and reliability. The HM-PRO showed adequate agreement (0.84–0.98) in various categories of QoL and also disease-related symptoms. The QLQ-C30 has an internal consistency of 0.64–0.94. The EORTC-8D, and EQ-5D-5 L included not only QoL domains (physical functioning, role functioning, social functioning, emotional function and cognitive functioning) but also burden of disease. The EORTC QLQ-C30 and QLQ-E have been used in elderly AML patients.

Conclusions: Although there are QoL validated instruments (generic and specific) for AML reported in the literature, more research is required to determine the most responsive and clinically useful instrument in AML especially in patients who relapse, are refractory or respond to treatment.

1138 | Patient participation in PCORnet Patient-Powered Research Networks through payer-initiated member outreach

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Background: Patient-Powered Research Networks (PPRNs) seek to empower patient-centered research by engaging patients and other stakeholders directly to collect patient-reported data and integrate it with electronic health information, such as administrative claims. The ability of payer-initiated member outreach to engage patients in PPRN research is novel and has not been evaluated.

Objectives: To quantify health plan members' registration rates in any of four PPRNs, comparing two common payer-initiated methods for inviting member participation: mail and email.

Methods: This prospective randomized study linked enrollees from a nationally-representative private insurance network of 14 health plans to 4 disease-specific PPRNs patient registries. Members meeting diagnostic criteria who were not registered in any of the four PPRNs were identified and randomly assigned to either mail or email group. The intervention involved two outreach attempts with first contact on 04/23/2018 and one follow-up communication on 05/23/2018. The outcome of new registration with the PPRN was defined through privacy preserving record linkage with the PPRNs. Rates of new

registrants by outreach approach at the time of 8/31/2018 were reported as well as comparison of registrants and non-registrants using bivariate analysis.

Results: A total of 14,571 patients were assigned to the mail group and 14,574 to the email group. Invitations were successfully delivered to 13,834 (94.9%) mail group and 10,205 (70.0%) email group members. A small but significantly larger proportion of the mail group members (n = 78; 0.54%, 95% Confidence Interval [CI] {0.42% - 0.67%}) registered in PPRNs relative to the email group (n = 24; 0.16%, 95% CI {0.11% - 0.25%}), $p < 0.001$. Members who registered had more comorbidities (83.4% vs. 69.9%, p = 0.01), were more likely to be female (87.3% vs. 78.4%, p = 0.03), and had marginally greater medical utilization, especially emergency room visits, relative to non-registrants (52.0% vs. 42.5%, p = 0.05).

Conclusions: A health plan outreach to invite members to participate in PPRNs was modestly effective, offering another means to engage patients in the research opportunities afforded by membership to a PCORnet PPRN. Regular mail outperformed less costly email. Additional studies using mixed modes or more direct ways of engaging patients are needed to guide future outreach decisions.

1139 | Concordance of pharmacist vs patient responses regarding counseling in community pharmacy - a quantitative assessment

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Background: Patient counseling is one of the medication adherence pylons. This activity can be successfully performed in community pharmacy, given that effective communication between both parts involved, pharmacist and patient, takes place.

Objectives: to assess the degree of concordance between the responses of patient and pharmacist to the same questions regarding the counseling provided in the same session.

Methods: Based on the good pharmaceutical practice rules from Romania we developed 2 questionnaires (tailored in terms of language for pharmacists or patients), where we inquired about the counseling provided during the pharmacy visit that just ended. The two questionnaires contained a common block of 14 questions regarding the counseling provided on the medications' way of use (4 questions), the safety concerns (5 questions), the storage, validity term, disposal, lifestyle change, and disease monitoring (1 question each). We paired the questionnaires based on a code and we calculated the Kappa Cohen coefficient[1] (KCc) to quantitatively evaluate the degree of concordance between pharmacist *versus* patient responses to the 14 questions. We interpreted the values of the KCc as *per* Altman (very good concordance, KCc = 0.8–1.00; good, KCc = 0.61–0.8; moderate KCc = 0.41–0.60 acceptable KCc = 0.21–0.40; and week, KCc $\leq$ 0.20)[2].

Results: For the 14 questions, we analyzed data from 2047–2378 questionnaires collected from 520 community pharmacies in 10 of Romania's counties. The highest level of concordance was"very good", and was achieved on the items regarding the counseling on the medicines' route of administration (adjusted KCc = 0.88), time of administration (KCc = 0.80) and doses (KCc = 0.82). The highest disagreement (week concordance) was found on the question regarding the counseling on the medicines' adverse effects (KCc = 0.006), where 44.9% of patients responded that they received counseling as compared to 93.1% of the pharmacists who responded that they offered counseling. The rest of the questions had a moderate concordance, except the one on counseling the patients to return the expired medicines to the pharmacy (KCc = 0.31).

Conclusions: We found a moderate level of concordance between the pharmacist and patient responses to the majority of the questions. The highest discrepancy was found for counseling on the medicines' possible adverse effects. Further studies are needed to investigate the factors that could generate this disagreement.

1140 | What is the availability of follow up pain score in real world databases and who are these patients?

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Background: Pain relief is a strong predictor of patient satisfaction after total knee arthroplasty. Longitudinal pain performance assessments may provide health providers and researchers with a more distinct impression of pain change among the TKA population. However, little is known about its availability and who the patients are that report follow up pain score in real world setting.

Objectives: To evaluate the availability of longitudinal self-reported face-rating pain score (scale 0–10) after TKA surgery in real world data and investigate factors associated with available follow up pain score report.

Methods: Through data partnership with Mercy Technology Services, patients who underwent TKA surgery were extracted from 2011–2018 Mercy electronic health records, which is one of the most comprehensive real-world databases including preoperative and intraoperative information. In this study, we defined patients with follow up pain score as those who had at least one available follow-up pain score 2-week to one-year after index surgery. A descriptive analysis was performed to compare patients who had both baseline and follow up pain score and those who only had baseline score. Preoperative and intraoperative variables associated with follow up pain score availability ($p < 0.2$) in crude analysis were included in the multivariable logistic regression development. Manual backward selection was used to obtain the final model.

Results: Overall, 23,389 (94%) out of 24,830 TKA patients had one-year baseline pain score and were included in this analysis. Of which, 7,750 (33%) patients were with reported follow-up measurement 2-week to one-year after index surgery. Higher baseline pain level (aOR: 1.04, 95% CI: 1.02, 1.05), higher ASA score (aOR: 1.18, 95% CI: 1.11, 1.26), higher number of opiate prescription before surgery (10-increment: aOR: 1.13, 95% CI: 1.02, 1.25), higher number of anticoagulation prescription before surgery (10-increment: aOR: 1.64, 95% CI: 1.25, 2.16), longer TKA operation room time (10-minute increment: aOR: 1.01, 95% CI: 1.002, 1.02), and longer length of stay (aOR: 1.16, 95% CI: 1.13, 1.19) were statistically significantly associated with increased odds of follow up pain score report.

Conclusions: Although baseline self-reported pain report was good (94%), longitudinal follow up pain score report in real world database was poor (33%). Those with reported follow up pain score suffered more pain before surgery and were with inferior general health status compared to their counterparts without reported follow up pain. Future studies using other real-world data sources are warranted.

1141 | Health related quality of life and its determinants in asthmatic patients at a tertiary teaching and Refferal Hospital in Kenya

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Background: Majority of patients seek help from health care providers because they perceive their health and well-being to be impaired. Clinical indices such as spirometry though being objective in measuring asthma control do correlate weakly with asthma symptoms and disease targeted health related quality of life (HRQoL). Since the impact asthma has on a patient's quality of life cannot be directly inferred from clinical indices, it must therefore be directly measured.

Objectives: To assess the Health Related Quality of Life (HRQoL) and its predictors in asthma patients who attend Kenyatta National Hospital (KNH) chest clinic for their routine management.

Methods: Following ethical approval, a cross-sectional study was conducted among 140 consecutively sampled teenage and adult asthmatic patients on treatment for ≥3 months. Data was collected using the Asthma Quality of Life Questionnaire with Standardized activities (AQLQ(S)) and Determinants of asthma control and HRQoL Questionnaire tools in a patient guided interview. Descriptive, bi-variable analysis and logistic regression was done using STATA version 13.

Results: Asthma was found to be controled in 112 (80%) of the participants of whom slightly over half (53%) reported high HRQoL scores. All the 28 (20%) participants in whom asthma was uncontrolled had low HRQoL scores ($p < 0.001$). The independent predictors of asthma control and HRQoL included occupational risk exposure ($p = 0.008$), GERD (0.006), type 2 diabetes mellitus (0.006) and cigarette smoking (0.029). Of the four HRQoL domains studied, the symptoms ($p = 0.004$) and activity limitation ($p = 0.007$) domains of were significantly impacted by poorly controlled asthma.

Conclusions: Asthma-HRQoL outcome among patients was largely dependent upon the degree to which asthma was controlled.

1142 | Generalizability of patient-reported survey data linked with electronic health records

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Background: Electronic health records (EHR) are increasingly being used in population health research and can be linked with other data sources to draw valuable patient insights. Although some studies have evaluated EHR data quality and comparability, currently there is a lack of research on the generalizability of EHR data that has been linked to other data sources.

Objectives: This study aims to assess whether a database comprised of patient-reported survey data linked with clinical data from EHR is representative of the adult US population actively seeking health care. The study uses linked data to estimate and compare the prevalence of patient characteristics with estimates from nationally-representative surveys.

Methods: Patient-Centered-Research (PaCeR) US data (2016; $N = 39{,}610$) consisting of nationally-representative self-reported data were linked with a large US ambulatory EHR database (2012–2018; $N = 50$ million+) using a HIPAA-compliant methodology. Data from two cross-sectional, nationally-representative surveys were compared with the linked data: National Hospital Ambulatory Medical Care Survey (NAMCS) (2016; $N = 13{,}165$) and National Health Interview Survey (NHIS) (2016; $N = 33{,}028$). NAMCS and NHIS estimates were weighted to the general US population, with NHIS analysis limited to respondents reporting a healthcare visit in the past year. Descriptive statistics were used to compare PaCeR-EHR respondent characteristics (e.g., age, gender, BMI) and health behaviors (e.g., smoking, alcohol use) with estimates from NAMCS and NHIS.

Results: Across all three data sources, similar distributions were observed for demographic characteristics including race (PaCeR-EHR: 80.1% White, NAMCS: 68.5% White, NHIS: 79.6% White) and geographic region (PaCeR-EHR: 20.8% Northeast, NAMCS: 20.8% Northeast, NHIS: 19.5% Northeast). The percentage of males was slightly lower in PaCeR-EHR (PaCeR-EHR: 34.3%, NAMCS: 42.0%, NHIS: 45.6%), and patients aged 65+ appeared to be underrepresented in both PaCeR-EHR (25.4%) and NHIS (23.9%) compared with NAMCS (33.8%). Additionally, the prevalence of current smoking (PaCeR-EHR: 13.2%, NHIS: 14.1%), alcohol use (PaCeR-EHR: 65.5%, NHIS: 66.4%), and obesity (BMI $\geq$ 30 kg/m^2; PaCeR-EHR: 33.5%, NHIS: 33.4%) were similar in PaCeR-EHR and NHIS; NAMCS was not compared as data were not available.

Conclusions: Overall, prevalence estimates derived from linked PaCeR-EHR data demonstrated agreement with two nationally-representative surveys. These results suggest that linked data may be generalizable to the US adult population, particularly to those actively seeking health care.

1143 | Attitudes and perceptions towards hypoglycaemia in patients with diabetes mellitus: A multinational cross-sectional study

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Background: patients' knowledge and attitude towards their disease plays an important role in the success of diabetes management and prevention of disease development and complications.

Objectives: to explore hypoglycaemia problem-solving ability of patients who have diabetes mellitus and factors which determine their attitudes and perceptions towards their previous events.

Methods: a cross-sectional study was conducted in three Arab countries (Jordan, Saudi Arabia, and Kuwait) in patients with diabetes mellitus, who were prescribed antidiabetic therapy and had experienced hypoglycaemic events in the past six months, for the duration between October 2017 and May 2018. The Hypoglycaemia Problem-Solving questionnaire was used in this study. This questionnaire contains two subscales; problem orientation (6-questions) and problem-solving skills (18-questions), using 5-point Likert scale (range 0–4). Multiple linear regression analysis was used to identify predictors of hypoglycaemia problem-solving abilities.

Results: a total of 895 patients have participated in this study from the three countries (300 from Jordan, 302 from Saudi Arabia, and 293 from Kuwait). The mean patient age was 53.5 (SD = 13.7) years, of which 52.4% (n = 469) were males. Around 10.4% (n = 93) of the patients had a previous history of severe hypoglycaemia that lead to admission during the past 6 months. Patients had moderate overall problem-solving ability with a median score of 63.00 (IQR = 13.00). Patients had better problem-solving skills score, 68.1% compared to problem-orientation skills score, 58.3%. The highest sub-scale scores were for detection control, setting problem-solving goals, and evaluating strategies, 75.0%. The lowest sub-scale score was for problem-solving perception and immediate management, 50.0%. Older age, being educated, married, having T2DM, prescribed insulin therapy, and not admitted to hospital for hypoglycaemia were important predictors of patients problem-solving ability (p < 0.05).

Conclusions: Healthcare professionals advised to educate patients more on how to self-manage their hypoglycaemic events; specifically, they should focus on the overall problem-solving perception of hypoglycaemia, and its immediate management.

1144 | Anti-diabetic drug utilization knowledge and glycemic index control in patients with uncontrolled diabetes mellitus

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Background: Diabetes has become the seventh leading burden of diseases in South Asia. Roughly 1 in 13 achieves treatment targets to keep control of the glycaemic index, one of the reasons may be lack of diabetic drug utilization knowledge. However, there is not much research done on the impact of drug utilization knowledge to achieve glycaemic control in Bangladesh.

Objectives: We aimed to investigate the proper anti-diabetic drug use and glycemic control among uncontrolled diabetic patients.

Methods: A prospective intervention study carried out from September 2017 to August 2018 in BIRDEM General Hospital, Bangladesh. A structured diabetic education regarding the disease, medication adjustment (e.g. Metformin) and glucose monitoring including exercise management was provided to each patient separately and patients were followed in 3 months. Data were analyzed using a logistic regression through SPSS.

Results: Metformin was used for 47% patients and 59% of patients took Metformin plus Insulin. For the intervention group, the average HbA1c significantly (p < 0.001) changed from baseline (11.59 ± 2.48) to end of the follow-up (7.55 ± 0.58). Similarly, Systolic Blood Pressure and Diastolic Blood Pressure changed from (138.31 ± 15.73) to (126.90 ± 11.15) and from (83.33 ± 6.50) to (80.24 ± 4.12), respectively (p < 0.001). Higher educated patients were more likely to have improved on glycemic control than lower educated patients [OR = 1.5, CI = 0.24–9.30].

Conclusions: Proper knowledge on anti-diabetic drug utilization can help in glycemic control to include prevention of diabetes, improved quality of life and delaying of complications.

1145 | Educational intervention to improve knowledge and skills of drug addiction prevention among health professionals and opinion leaders in Lagos

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Background: Drug Addiction is a problem that is causing serious concern to both individuals and government all over the world. It contributes significantly to morbidity and mortality in our population and to

the cost of health care. However, with effective intervention programme, the problem can be tackled.

Objectives: To evaluate the impact of an educational intervention to improve knowledge, attitude and skills of addiction prevention among health professionals and representative stakeholders in Lagos East Senatorial District.

Methods: A pre-post educational intervention study designed to evaluate knowledge and skills of participants immediately and one month after the workshop using a 36-item structured questionnaire. The participants were a representative group of stakeholders in the health sector with a great potential to influence drug addiction in their respective communities. Descriptive analysis was performed on the data and the overall statistical test among the groups was done using Analysis of variance (ANOVA). The primary outcome was the change in overall score from pre-test to post-test and one month post test.

Results: The mean (SD) pre-test score for the entire cohort was 30.59 (SD 5.85), and the post-test score was 32.81 (5.27). Scores were significantly improved from pre-test to post-test; mean difference (95% CI) = 2.227 (0.1932, 4,260). 26 participants (37%) completed the online follow-up survey. There was no significant difference between mean pre-test scores and mean one month post test scores (30.59 SD5.85 Versus 29.54 SD2.44).

Conclusions: This study shows that although participants had a good addiction related baseline knowledge and skills, this was significantly increased through an educational intervention workshop on Addiction Prevention. This increased knowledge and skills was however not sustained after one month of the workshop. Majority of respondents coped well with the stress that accompany addiction prevention campaign.

1146 | Risk of major bleeding associated with the use of direct oral anticoagulants compared to vitamin K antagonists in patients with atrial fibrillation: A European multi-country population-based cohort study

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Background: Non-Valvular Atrial fibrillation (NVAF) is one of the most common cardiac rhythm disorders. The introduction of direct oral anticoagulants (DOACs) has broadened the treatment arsenal for NVAF compared to the traditional vitamin K antagonists (VKAs), but observational studies on the benefit–risk balance of DOACs vs VKAs are needed.

Objectives: To characterize the risk of major bleeding in DOAC users in a real-world setting using longitudinal data collected in four electronic health care databases from different EU countries.

Methods: A cohort study was conducted among new users (≥18 years) of DOACs or VKAs with NVAF using electronic health care data from the United Kingdom (UK; CPRD), Spain (BIFAP), Germany (AOK) and Denmark (Danish National Registers). The incidence of major bleeding events (both overall and by site) and any stroke was compared between periods of current use of DOACs and VKAs. Cox regression analysis was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) and adjust for confounders. Several sensitivity analyses were performed (changing permissible gap length between prescriptions, using hospital admissions only, excluding certain bleeding sites).

Results: In total 251,719 patients were included in the four study cohorts (mean age ~75 years, % females between 41.3 and 54.3%), with overall HRs of major bleeding risk for DOACs vs VKAs ranging between 0.84 (95% CI: 0.79–0.90) in Denmark and 1.13 (95% CI 1.02–1.25) in the UK. When stratifying according to bleeding site, the risk of gastrointestinal (GI) bleeding (the majority of events) was statistically significant increased by 48–67% in dabigatran (DBG) users and 30–50% for rivaroxaban (RIV) users compared to VKA users in all data sources except Denmark. The risk of any stroke was increased for RIV (HR 1.78, 95% CI 1.29–2.44) and apixaban (APX, HR 2.20, 95% CI: 1.45–3.30) vs VKAs in the UK. Sensitivity analyses did not yield substantially different results.

Conclusions: Compared to VKAs, APX was not associated with an increased risk of GI bleeding in all data sources and seemed to be have with the lowest risk of any major bleeding events vs VKAs when compared to DBG and RIV. An increased risk of stroke was seen in the UK. Differences in risk estimates obtained in randomized controlled trials and other observational studies with this study could be partially due to design (e.g. patient selection, dealing with drug discontinuation) and definition choices (e.g. outcome coding) and ask for more transparency in methods used.

1147 | Adverse drug event reporting among patients who discontinued Empagliflozin or Apixaban in the veterans health administration

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Background: Passive and active surveillance of adverse drug events (ADEs) are used to help inform safe and appropriate medication use. However, providers are often expected to use multiple passive surveillance systems when a patient experiences an ADE, and despite advancements, it is unclear how often ADEs get into these spontaneous reporting databases.

Objectives: To examine reporting rates at increasingly "higher" levels of spontaneous reporting systems (i.e., point of care, then national VA healthcare system, and then the FDA) of apixaban and empagliflozin ADEs that led to discontinuation of the medication.

Methods: This was a retrospective cohort study of outpatients who discontinued apixaban or empagliflozin within three years of FDA approval. To increase the probability of finding patients who experienced an ADE, we used an active surveillance strategy and identified a subset of patients with ICD-9/10 codes associated with a possible ADE (e.g., GI bleed-apixaban, ketoacidosis-empagliflozin). Stratified random samples of charts were reviewed to determine if patients discontinued the medication due to an ADE. Then, we ascertained if ADEs noted in the charts were entered into the VA electronic health record/point of care reporting system (Adverse Reaction Tracking System [ARTS]), VA national web-based system (VA Adverse Drug Event Reporting System [VA ADERS]), and FDA MedWatch, three spontaneous reporting databases.

Results: From the cohort of 2,973 patients who discontinued apixaban, 321 (10.8%) were randomly sampled for chart review (61 patients with ICD codes for GI bleed and/or intracranial hemorrhage). During chart review, 88 ADEs were identified; 40/61 (65.6%) from the subset with ICD codes. Of the 88 total ADEs, 23.3%, 10.2%, and 6.8% were reported in ARTS, VA ADERS, and FDA MedWatch, respectively. Of the 1,555 patients who discontinued empagliflozin, 179 (11.5%) were randomly sampled for chart review (40 patients with ICD codes for ketoacidosis and/or amputation). During chart review, 78 ADEs were identified; 19/40 (47.5%) from the subset with ICD codes. Of the 78 total ADEs, 28.2%, 19.2%, and 7.7% were reported in ARTS, VA ADERS, and FDA MedWatch, respectively.

Conclusions: We found substantial underreporting of apixaban and empagliflozin ADEs that became worse at each "higher" level of spontaneous reporting. Improvements are needed at all levels, but one possibility is the use of ICD codes to identify potential ADEs; then, ensure actual ADEs are included in the electronic health record reporting system so the information is available for patient care decision making.

1148 | Complementary use of US FDA adverse event reporting system and sentinel distributed database to characterize Non-Vitamin K Oral Anticoagulants associated Cutaneous Small Vessel Vasculitis

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Background: Cutaneous Small Vessel Vasculitis (CSVV) has been reported with Non-Vitamin K Oral Anticoagulants (NOACs).

Objectives: To describe the temporal association between NOACs and CSVV and inform subsequent inferential analysis using the FDA Adverse Event Reporting System (FAERS) database and the Sentinel Distributed Database (SDD).

Methods: We queried FAERS for all reports of CSVV associated with NOACs from US approval date of each NOAC to March 16, 2018. We used SDD from January 1, 2010 to June 30, 2018 to identify the incident CSVV cases among adults aged ≥30 who received a NOAC in the prior 90 days with no evidence of select autoimmune diseases in the 183 days prior to their CSVV diagnosis. We used NDCs and ICD-9-CM/ICD-10-CM codes to define inclusion and exclusion criteria. We also identified the recorded history of skin biopsy and corticosteroid treatment within 14 and 90 days of CSVV diagnosis, respectively.

Results: We identified 47 probable cases of CSVV with rivaroxaban (*n*=25), apixaban (*n*=14), dabigatran (*n*=7), and edoxaban (n=1) in FAERS. The mean age for all cases was 74 years (range 28–90 years). Atrial fibrillation (Afib) was the most common indication for all NOACs (*n* = 29). The median time-to-onset was 10 days. When specified, the predominant type of CSVV reported was leukocytoclastic vasculitis (*n* = 24), followed by Henoch-Schonlein purpura (*n* = 4). Hospitalization occurred in most of the cases (*n* = 34). Switching of the offending agent after the development of CSVV was reported [(*n*=23) another NOAC (*n*=8), VKAs (n=7), LMWH (n=8)]. Corticosteroids was the most frequently reported treatment (*n* = 26). Two rivaroxaban (n = 2) cases and one dabigatran case (n = 1) reported a positive rechallenge. In SDD, we identified 3,659 CSVV cases with prior NOAC exposure, with 85% of events occurring within 10 days. The mean age of patients with CSVV in SDD was similar to those in FAERS. Afib diagnosis was present in 2,876 patients (78.6%). Skin biopsy up to 14 days before or after the CSVV diagnosis occurred in 704 patients (19.2%). Corticosteroid treatment within 90 days after CSVV diagnosis occurred in 1,123 patients (30.7%). Similar to the FAERS cases, the most common CSVV diagnosis in SDD was vascular disorders of the skin (1,040 patients; 28.4%), followed by Henoch-Schonlein purpura (752 patients; 20.6%).

Conclusions: In both FAERS and SDD, the majority of CSVV cases occurred within 10 days after exposure to NOACS, suggesting a possible cutaneous reaction. Future efforts will characterize the risk of CSVV among the various NOAC users.

1149 | Fluoroquinolone use and serious arrhythmias: A Nationwide case-crossover study

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Background: Fluoroquinolones have been associated with life-threatening ventricular arrhythmias and even sudden cardiac death.

Objectives: We aimed to assess the temporal relationship of fluoroquinolone use and serious arrhythmias via a case-crossover analysis of a large cohort of serious arrhythmias patients.

Methods: In a national administrative database, we compare the distributions of fluoroquinolone exposure for the same patient across a 30-day period before the serious arrhythmia event and 5 randomly selected 30-day periods before the serious arrhythmia event. Odds ratios (ORs) and 95% Confidence Intervals (CIs) were estimated using conditional logistic regression analysis.

Results: From a total of 2 million participants, 7657 patients with serious arrhythmias were identified. Use of fluoroquinolones within the 30-day period before the event was significantly associated with increased risk for serious arrhythmia (OR: 3.03, 95% CI: 2.48, 3.71). The risk association was attenuated, but remains significant after adjustment for time-varying confounders (OR: 1.48, 95% CI: 1.18, 1.86). A consistent increase in risk of serious arrhythmia was observed for all time windows investigated (7 days, 14 days, 30 days, 60 days and 90 days).

Conclusions: Exposure to fluoroquinolones was substantially associated with serious arrhythmic events, independent of the temporal proximity of fluoroquinolone prescription.

1150 | A self controlled case series of fluoroquinolone exposure and the risk of aortic aneurysm or dissection

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Background: Four recent epidemiologic studies suggest increased risk of Aortic Aneurysm or Dissection (AAD) after exposure to Fluoroquinolones (FQ). Each acknowledged potential biases including those from unobserved patient characteristics. This study evaluated the risk of AAD following exposure to systemic FQs and other common antibiotics as well as untreated febrile illness using a study design that minimizes such biases by controlling for within-patient, unobserved characteristics.

Objectives: Evaluate the risk of AAD following 1) exposure to FQs, 2) exposure to other common antibiotics, and 3) untreated febrile illness.

Methods: We used a SCCS analysis in 3 US claims databases to assess the association of 3 collagen-related outcomes with exposure to FQs, amoxicillin, azithromycin, trimethoprim with and without sulfamethoxazole, and febrile illness not treated with antibiotics. Here we reported the association with AAD. Risk windows were defined as drug exposure period plus 30 days or observed febrile illness duration plus 30 days. Patients of all ages with outcomes and exposures between 2012 and 2017 were included. P values were calibrated using 38 negative control exposures (i.e., exposures known *not* to affect AAD) to adjust for residual bias and pre-exposure windows were used to evaluate timing of outcomes relative to exposures.

Results: Across all databases, negative control exposures produced effect estimates for AAD that were on average greater than the hypothetical null (i.e., incidence rate ratio [IRR] = 1) and indicative of residual bias, supporting the use of calibrated p values. In all databases, a peak in AAD events was observed during the 60 days before first exposure to FQ and trimethoprim with sulfamethoxazole, with IRRs increasing from the 60- to 30-day pre-exposure window to the 29- to 1-day pre-exposure window. The IRR for AAD in the 29 days preceding FQ exposure ranged from 2.38 (95%CI: 2.22–2.55) to 3.45 (95%CI: 3.09–3.85) across databases. The IRR following FQ exposure decreased to values ranging from 1.20 (95%CI: 1.12–1.30, calibrated p 0.82) to 1.85 (95%CI: 1.64–2.08, calibrated p 0.24).

Conclusions: This study does not confirm results from prior studies suggesting an association between FQs and AAD. Using calibrated p values, the IRRs for AAD following FQ exposure were not significant. In addition, a peak in AAD events was observed in the 60 days before the first FQ exposure, casting doubt on the temporality of the effect of FQ on AAD.

1151 | Acetylcholinesterase inhibitors, cardiosuppresive drugs, and adverse cardiac events in patients with dementia

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Background: Acetylcholinesterase inhibitors (AChEI), widely used to treat dementia, have a theoretical chronotropic effect. Thus, patients using both AChEI and cardio-suppressive drugs (CS) can have excessive risks for bradycardia and atrioventricular (A-V) block resulting in syncope and/or pacemaker implantation.

Objectives: To assess the effect of a single and/or combined use of AChEI and CS on syncope and permanent pacemaker implantation in patients with dementia.

Methods: We conducted a cohort study of older adults with dementia (age $\geq$ 65) residing in skilled nursing facility (SNF) enrolled in Medicare Part D (7/2007–12/2013) in the US Medicare and the Minimum Data Set (MDS). We identified four groups within a cohort of dementia patients identified by validated definition; users of 1) concomitant AChEI and CS (dual), 2) AChEI only, 3) CS only (CS), and 4) none of either. The primary and secondary outcomes were syncope identified as emergency department or inpatient diagnosis and new pacemaker implantation. We calculated adjusted hazard ratios (HRs) in multivariable Cox proportional hazard regression models. We estimated relative excess risk due to interaction (RERI) for additive interaction in the primary outcome.

Results: We identified 159,038 subjects (mean age 83 years old, 71.% female). Dual users (*n* = 15,311, 10%) had similar characteristics as CS (*n* = 38,395, 24%) and none users (*n* = 80,548, 51%), had more heart failure, cerebrovascular disease, pulmonary disease, and renal disease compared to AChEI users (*n* = 24,784, 16%). The incidence rates for dual, AChEI, CS and none users were 92, 75, 71 and 29 per 1,000 person-years (PY) for syncope and 4, 4, 3 and 2 per 10,000 PYs, respectively. Adjusted HRs (95% CI,) for syncope comparing single were 2.1 (2.0–2.3) for dual use, 1.8 (1.6–1.9) for AChEI use, and 1.6 (1.5–1.8) for CS use compared to none users. Adjusted HRs for new pacemaker implantation for dual, AChEI, CS use were 2.2 (0.7–6.7), 2.1 (0.7–6.0), and 1.6 (0.6–4.19). The RERI for syncope was −0.1 (95%CI,-0.6–0.4).

Conclusions: A single user of CS or AChEI was associated with a 1.6 or 1.8 fold increase in the risk of syncope among older SNF residents even after adjusting for potential confounders including functional status. The risk was significantly higher in dual users (2.1 fold), but no evidence of additive interaction was found. While the risk patterns were similar for pacemaker outcome, the effect estimates were not statistically significant due to small numbers. Clinicians should be aware of the observed syncope risks from a single or dual use of CS and/or AChEI in older patients with dementia.

1152 | Concomitant use of dronedarone and dabigatran is not associated with increased risk of major bleeding

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Background: Pharmacokinetic and pharmacodynamic studies have shown that concomitant use of dronedarone can increase the exposure to dabigatran 150 mg bid by two-fold compared to using dabigatran alone.

Objectives: To evaluate the risk of major bleeding in patients who concomitantly used dronedarone and dabigatran in comparison to those who used dabigatran alone.

Methods: Patients aged 18 years or older with a diagnosis of atrial fibrillation or flutter who concomitantly used dabigatran and dronedarone or used dabigatran alone between July 20, 2009 and September 30, 2011 were identified in the Clinformatics database. A patient's index date was defined as the date of the first concomitant exposure to dabigatran and dronedarone or the date of the first dispensing of dabigatran in the dabigatran alone users after July 20, 2009. Patients were excluded from analysis if there was less than six months of enrolment in the database prior to the index date or there was a diagnosis of major bleeding, defined using ICD diagnosis and procedure codes, within the last six months prior to the index date. The first major bleeding event while on treatment of interest was identified from the index date to the end of study (September 30, 2011). Adjusted hazard ratio was calculated using Cox proportional hazards model to evaluate the potential association between concomitant use of dronedarone and dabigatran and the risk of major bleeding, controlling for age, sex, year of index date, and use of anticoagulants, antiplatelet agents, heparin, and other antithrombotic agents.

Results: A total of 638 patients who used dabigatran in combination with dronedarone and 5,201 patients who used dabigatran alone were identified. A total of 7 events of major bleeding were identified in the concomitant users (incidence rate = 4.0 per 100 person-years), and 94 events were identified in the dabigatran alone group (incidence rate = 4.4 per 100 person-years). The adjusted hazard ratio of major bleeding was 0.82 (95% confidence interval: 0.32, 2.13) for concomitant use of dronedarone and dabigatran compared to dabigatran alone.

Conclusions: The results of this study suggest that the risk of major bleeding in concomitant dronedarone and dabigatran users was not different from dabigatran alone users.

1153 | Hospitalization for heart failure among patients using aclidinium bromide and other COPD medications: A post-authorisation safety study in the CPRD

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Background: Aclidinium is an inhaled, long-acting anticholinergic (LAMA) approved in Europe in 2012 as a maintenance bronchodilator to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). There have been safety concerns related to a potential increase in heart failure (HF) events with the use of LAMA medications.

Objectives: To estimate the adjusted incidence rate ratio (IRR) for HF in patients with COPD initiators of aclidinium, tiotropium, other LAMA, long-acting beta-agonists/inhaled corticosteroids (LABA/ICS), and LAMA/LABA compared with initiators of LABA.

Methods: This population-based cohort study included patients with COPD aged 40 years or older initiating COPD medications in the Clinical Practice Research Datalink (CPRD) in the United Kingdom from 2012 to 2017. First-ever hospitalizations for HF events were identified in the Hospital Episode Statistics, the Office for National Statistics, and general practitioner (GP) records from the CPRD and validated by a review of patient profiles and questionnaires sent to GPs. Poisson regression models were used to estimate the IRR of HF for current use of COPD medications versus current use of LABA adjusting for age, sex, COPD severity (GOLD 2016 definition), asthma, diuretics, inhaled corticosteroids, and prior outpatient diagnosis of chronic heart failure.

Results: The study included 4,350 new users of aclidinium, 23,405 of tiotropium, 6,977 of other LAMA, 3,122 of LAMA/LABA, 26,093 of LABA/ICS, and 5,678 of LABA (patients could enter more than one

cohort). The mean age ranged from 69 to 70 years, and 48% to 52% were females across study cohorts. Aclidinium users had the highest proportion of severe COPD (category D), and LABA users had the lowest (35% vs. 19%). The number of HF events/person-years during current use was 36/3,783 for aclidinium, 136/24,490 for tiotropium, 40/5,036 for other LAMA, 13/1,571 for LAMA/LABA, 213/29,036 for LABA/ICS, and 30/4,339 for LABA. Incidence rates ranged from 6.9 in LABA to 9.5 per 1,000 person-years in aclidinium. Using LABA as reference, for current use, the adjusted IRRs (95% confidence interval) of HF were 0.90 (0.53, 1.53) for aclidinium, 1.02 (0.69, 1.51) for tiotropium, 0.86 (0.50, 1.47) for other LAMA, 1.09 (0.41, 2.92) for LAMA/LABA, and 1.01 (0.69, 1.48) for LABA/ICS.

Conclusions: Compared with LABA users, the study did not find an increased risk of HF in new users of aclidinium, despite increased COPD severity, nor in users of other COPD medications.

1154 | Major bleeding risk associated with Oral anticoagulant in real clinical practice. A multicentre population-based prospective cohort study over a period years

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Background: Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are widely used in nonvalvular atrial fibrillation (AF), but also in other indications. Real world data assessing safety has mostly made use of administrative data for AF patients. The outcome validity is therefore questionable.

Objectives: Main objective was to compare major bleeding risk per type and dose of DOACs with VKAs, whatever the indication.

Methods: A population-based prospective cohort study, using the French national health data system (SNIIRAM), identified 47,469 adults living within five well-defined geographical areas, who were new users of oral anticoagulants in the period 2013–2015. From all emergency departments within these areas, clinical data for all referred for bleeding was collected and medically validated. Databases were linked for common key variables. The main outcome measure was time to major bleeding: intracranial hemorrhage, major gastrointestinal bleeding and other major bleeding events. Hazard ratios were derived from adjusted Cox proportional hazard models. Used propensity score weighting as a sensitivity analysis with separate analyses according to indications (AF or venous thromboembolism).

Results: Compared to VKAs, full and reduced-dose DOACs were associated with a reduced risk of intracranial hemorrhage (adjusted hazard ratio 0·55, 95% confidence interval 0·37 to 0·82 and 0·36, 0·18 to 0·79, respectively), and a reduced risk of other major bleeding events (0·41, 0·29 to 0·58 and 0·27, 0·14 to 0·51 respectively), irrespective of duration and indication. Neither DOAC dose was significantly different from VKAs in terms of risk of major gastrointestinal bleeding. Among patients with AF, full-dose apixaban was associated with better event-free survival than VKAs or rivaroxaban.

Conclusions: There is a clear benefit in using DOACs with regard to intracranial hemorrhage. The study provides new insight into major gastrointestinal and other bleeding events.

1155 | Heart failure and AKI after hospital admission with AKI among patients taking ACE inhibitors and ARBs

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Background: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are believed to be associated with a higher risk of acute kidney injury (AKI). The drugs are often withheld following AKI. However, the effects of discontinuing these drugs on outcomes like subsequent AKI and heart failure (HF) are uncertain.

Objectives: To compare the rate of admission with HF or AKI among patients who stopped ACEI/ARBs following discharge after AKI to the rate in patients who were re-prescribed the drugs.

Methods: We conducted a cohort study in the United Kingdom using linked primary and secondary care data from the Clinical Practice Research Datalink (CPRD) and the Hospital Episodes Statistics (HES). We included patients with AKI recorded as a primary cause of hospital admission between 2010–2016, and were prescribed an ACEI/ARB within 60 days prior to the AKI admission. The primary outcomes were re-admission to hospital with HF, or (separately) AKI. We compared rates of re-admission for each outcome among patients prescribed or not prescribed ACEI/ARBs post-discharge (excluding the first 60 days post-discharge to capture prescriptions) using multivariable Cox regression. We stratified hazard ratios for HF admission by spironolactone prescription prior to baseline AKI admission.

Results: The study population included 18,816 patients with a mean age of 78 years (SD 11). Crude rates (per 1000 person-years) for re-admission with HF in people with prior spironolactone prescription was 244 (95% CI 222–267), and without a spironolactone prescription was 70.8 (95% CI 67.3–74.5). The crude rate for re-admission with AKI was 105 (95% CI 100–109). Comparing patients who stopped ACEI/ARBs post-discharge with those re-prescribed the drugs, the adjusted hazard ratio (HR) for admission with HF was 0.98 (95% CI 0.88–1.11) among patients not prescribed spironolactone and 1.11

(95% CI 0.90–1.36) for those prescribed spironolactone (p-value for interaction 0.34). For subsequent AKI, the adjusted HR was 0.88 (95% CI 0.81–0.97).

Conclusions: Rates of admission with HF and AKI are high following an initial AKI hospitalization, reflecting a substantial burden on health services. After an initial AKI we did not find an increase in risk of re-admission with HF among patients not re-prescribed ACEI/ARBs after AKI hospitalization including among those previously prescribed spironolactone. There is a potential protective effect of ACEI/ARB cessation on subsequent re-admission with AKI. Ongoing work is exploring the impact of potential limitations including survivor bias and confounding by indication and frailty.

1156 | The cardiovascular safety of anti-obesity drugs

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Background: Over the past several decades, many anti-obesity drugs have been withdrawn from the market due to unanticipated adverse events, often involving cardiotoxicity.

Objectives: This study aimed to evaluate the presence of cardiovascular safety signals with currently marketed anti-obesity drugs.

Methods: We used the US Food and Drug Administration Adverse Event Reporting System (FAERS) database and retrieved data from January 2013 through September 2017. We performed disproportionality analyses to detect cardiovascular safety signals with three anti-obesity drugs recently approved for marketing: lorcaserin, naltrexone-bupropion, and phentermine-topiramate. Three main cardiovascular outcomes were evaluated: cardiovascular events (myocardial infarction, stroke, cardiovascular death, cardiac failure, and arrhythmia), valvular disorders, and pulmonary hypertension.

Results: During the evaluated period, a total of 5,385,720 adverse event reports were submitted to FAERS. Of these, 2,559 involved lorcaserin, 2,503 involved phentermine-topiramate, and 2,609 involved naltrexone-bupropion. None of the anti-obesity drugs were associated with a safety signal for cardiovascular events. However, lorcaserin was associated with a significantly greater proportion of reports of valvular disorders (ROR = 7.32; 95%CI 4.81–11.15) and a small but significant increase in the proportion of reporting of pulmonary hypertension (ROR = 1.91; 95%CI 1.05–3.45).

Conclusions: Our analyses did not detect a safety signal for most cardiovascular events with recently approved anti-obesity drugs. However, a signal was present for valvular disorders and pulmonary hypertension with lorcaserin. Further research is needed to explore and validate this signal.

1157 | Can enzyme-inducing AEDs and DOACs be co-prescribed? Assessing concordance between drug compendia for proposed interactions

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Background: Enzyme-inducing antiepileptic drugs (EI-AEDs) and direct oral anticoagulants (DOACs) are commonly co-prescribed, with an estimated 100,000 concomitant prescriptions from just one large U. S. commercial health insurer. This high prevalence of co-prescriptions is concerning given the mechanistically-probable, yet scarcely researched, pharmacokinetic interactions between these drug classes. A crucial step to understanding current prescribing practices is to assess consistency of classifications for these interactions by major drug compendia.

Objectives: To compare the concordance of proposed interactions between EI-AEDs and DOACs as reported in leading, international drug compendia.

Methods: We assessed consistency of interaction reporting and severity rankings for each DOAC with a group of EI-AEDs among 8 provider and consumer-focused drug compendia: Cerner Multum, Clinical Pharmacology, Drug Facts & Comparisons, Epocrates, Lexicomp, Medscape, Micromedex, and RxList. Discrepant severity ranking systems between compendia were consolidated on a 0–4 scale. Concordance was quantified using quadratically-weighted Scott/Fleiss' Kappa ($w\kappa$).

Results: In ascending order, by DOAC, concordance among drug compendia for presence and severity of interactions with EI-AEDs were: edoxaban ($w\kappa$ 0.08, 95% CI -0.32, 0.47), rivaroxaban ($w\kappa$ 0.34, 95% CI -0.37, 1.00), dabigatran ($w\kappa$ 0.48, 95% CI -0.23, 1.00), and apixaban ($w\kappa$ 0.48, 95% CI -0.27, 1.00). The newest DOAC, betrixaban, was consistently listed as not interacting with EI-AEDs in almost all assessed compendia ($w\kappa$ unreportable due to high concordance), despite overlap in P-glycoprotein induction-based interaction mechanism with other DOACs. Extreme inconsistences in interaction reporting (i.e., some compendia assigning the highest possible severity ranking, while others reported no interactions) were observed for 10 of the 25 individually examined interactions (40%).

Conclusions: We found inconsistent inclusion and severity rankings for EI-AED/DOAC interactions among the current standard drug compendia used to guide prescription. Future studies are needed to: (1) understand underlying reasons for inconsistent evidence reporting within drug compendia; and, (2) generate high-quality evidence regarding EI-AED/DOAC interactions to yield widespread and consistent impacts on drug compendia and clinical practice.

1158 | Celecoxib and cardiovascular safety: Replicating clinical trial evidence from real world data

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Background: The PRECISION cardiovascular outcomes trial compared celecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) and did not show a link between celecoxib use and cardiovascular safety. However, there are uncertainties about this risk in real-world settings.

Objectives: Using real-world data to replicate findings from the PRECISION trial.

Methods: Longitudinal patient data from US Truven Health MarketScan (Truven) and UK Clinical Practice Research Datalink (CPRD) databases were used to compare the incidence of major adverse cardiovascular events (MACE) among adults with rheumatoid arthritis (RA) or osteoarthritis (OA) who initiated celecoxib vs. ibuprofen or naproxen. A composite outcome of MACE comprised of non-fatal myocardial infarction, stroke, or unstable angina was defined by a combination of diagnosis and procedure codes in the corresponding databases. Exposure propensity scores were used to 1:1 match celecoxib initiators with either of other NSAIDs initiators with 36-months follow-up. Patients were followed until the occurrence of MACE, death, end of follow-up, end of data, or disenrollment, whichever occurred first. Risk ratios (RR) and 95%CI were reported to estimate the risk of non-fatal MACE for both cohorts (celecoxib vs. ibuprofen; celecoxib vs. naproxen).

Results: In Truven, a total of 534,368 celecoxib and ibuprofen initiators, and 545,530 celecoxib and naproxen initiators were matched. In CPRD, a corresponding 20,206 and 35,186 were matched. Patients in UK were older than those in US (mean age 67 vs. 60). On average patients in UK had longer duration of RA/OA (3.8 vs. 1.4 years), in part, reflecting the differences between database types. MACE risk in Celecoxib vs. ibuprofen (Truven, RR = 0.96, 95%CI = 0.94–0.98; CPRD, RR = 0.92, 95%CI = 0.75–1.14); celecoxib vs. naproxen (Truven, RR = 0.95, 95%CI = 0.93–0.97; CPRD, RR = 1.04, 95% CI = 0.89–1.22). the main analysis results from both data sources were comparable to those from the PRECISION trial: Celecoxib vs. ibuprofen (RR = 0.87, 95%CI = 0.75–1.01); celecoxib vs. naproxen (RR = 0.97, 95%CI = 0.83–1.12).

Conclusions: Celecoxib initiators are not associated with an increased risk for non-fatal MACE compared to other conventional NSAIDs. Real-world data and analytics replicated the clinical trial evidence with a fraction of the time and cost.

1159 | Oral fluoroquinolones use and risk of aortic aneurysm and dissection: A meta-analysis of epidemiological studies

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Background: Fluoroquinolones are the most commonly prescribed antibiotics globally. In the last few years, several published epidemiological studies raised alarm over its safety profile on its association with aortic aneurysm (AA) or aortic dissection (AD).

Objectives: This meta-analysis is aimed to assess the pooled risk of AA or AD associated with the use of fluoroquinolones.

Methods: Electronic databases (PubMed, Embase, and Cochrane) were searched for published studies assessing the association between fluoroquinolones use and risk of AA or AD. Search was performed by two independent reviewers using a combination of suitable keywords from inception to January 2019. Risk of AA or AD associated with fluoroquinolones use was considered as the primary outcomes. Two reviewers selected the articles, extracted data, and carried out a critical appraisal using the Newcastle-Ottawa Scale. Statistical analysis was performed using Review Manager software v5.3.

Results: Only four studies were eligible for inclusion in the meta-analysis. Two studies were cohort in nature while remaining studies followed case–control and case-crossover design. All of the included studies were of high quality. AA or AD cases were diagnosed based on the international classification of diseases-9 or 10 codes. Due to the absence of significant heterogeneity analysis was performed using the fixed effects model. Fluoroquinolones use was found to be significantly associated with the increased risk of AA or AD with a relative risk (RR) of 2.33 (95% CI: 1.99–2.73), $p < 0.00001$ in an adjusted analysis (adjusted for various confounding factors). In subgroup analysis, the RR for the association with fluoroquinolone use was 2.25 (95% CI: 2.03–2.49), $p < 0.00001$ for AA and 2.79 (95% CI: 2.31–2.79), $p < 0.00001$ for AD.

Conclusions: Fluoroquinolones use was found to be associated with an increased risk of AA or AD. Therefore, physicians should judge critically (benefit–risk assessment) before prescribing fluoroquinolones to patients at risk of AA or AD.

1160 | Use of drugs from the Crediblemeds® list and risk of sudden cardiac death: A population-based cohort study

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Background: Several drugs can lead to torsade de pointes (TdP), a fatal ventricular arrhythmia. Crediblemeds is an authoritative list of drugs with TdP risk.

This list has not been studied systematically for risk of sudden cardiac death (SCD) in a population-based cohort.

Objectives: We investigated in a real-life setting if use of these drugs was associated with SCD. We also tested several genetic variants modifying pharmacokinetics and pharmacodynamics of antiarrhythmic drugs.

Methods: We used data from the Rotterdam study, a population-based cohort of middle-aged and elderly. Drug use was set as a time-varying covariable in a Cox' model with the endpoint SCD. Drug use was defined

as use of any drug from the CredibleMeds list or use of a pharmacological subgroup defined by the 3rd level of the ATC code containing a drug from the CredibleMeds list. Furthermore, we studied the association between use of the antiarrhythmic drugs Amiodarone, Digoxin, Sotalol, Propafenone and Flecainide, and SCD. We selected genetic variants known in the literature to modify the pharmacodynamic or pharmacokinetic characteristics: for Digoxin, three variants of ABCB1 (rs1128503, rs2032582, and rs1045642) and for Amiodarone rs35599367 (CYP3A4), rs3892097 (CYP2D6), rs1799853 (CYP2C9), and rs12143842 (hERG). These genetic variants were set as interaction variables between use of the drug and SCD risk.

Results: The population consisted of 14,603 participants after exclusion of those who died before July 1, 1991, the starting date prescriptions were recorded. 41% were men and the mean age was 66 years. 609 cases of SCD occurred. Use of drugs known to be associated with a high risk of TdP was associated with an increased risk of SCD: HR 1.66 (95% CI 1.28–2.18). Nine of the 45 drug groups were significantly associated with SCD: A03F (propulsives), C01A (cardiac glycosides), C01B (antiarrhtymics class I and III), C07A (beta-blockers), C09A (ACE inhibitors), N01A (general anesthetics), N05A (antipsychotics), N05C (hypnotics), and N06A (antidepressants). We found a significant association with SCD for use of Amiodarone and Digoxin. Of the 11,382 participants with genetic data, there was no significant interaction between the selected genetic variants in combination with use of amiodarone or digoxin, and risk of SCD.

Conclusions: In our population-based cohort, use of drugs from nine drug groups was associated with SCD. For the groups with cardiac drugs this may be confounded by indication, but this is less likely for the non-cardiac groups. Other drugs from the studied drug groups could be studied for risk of TdP and SCD.

1161 | Gender differences in the adverse events induced by cardiovascular drugs: Using National Adverse Event Reporting and health insurance database

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Background: Cardiovascular disease (CVD) is one of the three major causes of death and cardiovascular drugs have been shown to be one of the most frequently reported adverse events (AEs) in both genders. But female patients reported more AEs than male patients in general practice. Given that gender differences are important, to date most studies for gender differences have only focused on disease related pharmacokinetics and pharmacodynamics.

Objectives: Gender differences in the occurrence of drug-induced AEs have not been systematically described, and so far, there have been few studies dealing with that. We aimed to explore the gender differences with regard to AEs associated with cardiovascular drugs between male and female patients.

Methods: This study used data from the National Health Insurance Service-National Sample Cohort Database on the patients and prevalence of CVD in 2015 and Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD) on the number of AEs caused by cardiovascular drugs. Study drugs were included corresponding to C01-C10 of the Anatomical Therapeutic Chemical Classification System. The number of AEs reported to KIDS-KD was divided by the number of patients with CVD as the denominator, using the international classification of disease (ICD-10, I05-I70). We estimated the AEs rate reported per 100,000 people and the ratio of female to male reporting rate. To understand characteristics of reports, the AE report of study drugs were analyzed and to compare by gender each variable chi-square test was performed.

Results: A total of 23,141 drug-AEs pairs (KAERS) were identified from 14,780,300 CVD patients (NHIS). Overall, female patients experienced much higher AEs (162.7 per 100,000 CVD patients in female, 150.2 in male, ratio = 1.1), although they experienced less serious AEs than male patients (9.0 in female, 10.9 in male, ratio = 0.8). There were seven cardiovascular drugs that showed higher female-to-male ratio of AEs rate; digoxins (ratio = 1.4), calcium channel blockers (1.2), diuretics (1.1), statins (1.2), angiotensin II receptor blockers (1.0), antiplatelets (1.1), beta blockers (1.1). In particular, the use of digoxins, calcium channel blockers, and diuretics were associated with more serious AEs in female patients than in male patients.

Conclusions: The reporting rate of AEs was higher in female patients than in male patients with CVD. Gender difference was also observed for specific drug classes. Clinicians should be aware of and monitor gender difference of AEs induced by cardiovascular drugs.

1162 | Risk of Bradyarrhythmia related to Ticagrelor: A systematic review and meta-analysis

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Background: Ticagrelor was related to bradycardia in DISPERSE-II trial. This risk has been integrated into the European risk-management plan and a precaution of use is listed for patients at risk of bradyarrhythmia. Nevertheless this risk was not already systematically assessed nor measured.

Objectives: To estimate the risk of bradyarrhythmia associated with ticagrelor.

Methods: A systematic review of literature and meta-analysis was performed. MEDLINE, Scopus, CENTRAL and ISI databases were searched from 2005 to 2017 to select randomized controlled trials (RCTs) or observational studies on patients with antiplatelet or anticoagulant indication, treated by ticagrelor or comparator(s) and reporting bradyarrhythmia events. ClinicalTrial.gov and ClinicalTrialsRegister.eu were investigated for unpublished studies. In case of missing data, authors and patent owners were contacted. Cochrane risk of bias tool

was used for assessing the quality of each RCT and the GRADE tool was used for the meta-analysis' overall quality. Heterogeneity between studies was assessed by the Cochran Q test and the I^2 index. The pooled relative risks (RR) and their 95% confidence intervals (95% CI) were calculated for each study and pooled using inverse of variance method (fixed-effects or random effects models if Q test $p < 0.10$). Prospero registration number CRD420180938100.

Results: No observational studies were found. Of 53 eligible RCTs 42 studies had not outcome data. Thus, eleven RCT (75% industry funded) were included in the main analysis and comprised a total of 61,900 patients with 1,441 bradyarrhythmia. Significant increased risk of bradyarrhythmia (RR 1.14 [IC95% 1.04 to 1.26]) and severe bradyarrhythmia (RR 1.42 [1.08 to 1.86]) was found, without any evidence of heterogeneity. Concerning severe bradyarrhythmia this increased risk was found to be due to ventricular pauses >2.5 s (RR 1.65 [1.23 to 2.22]). A trend for dose-dependent risk was observed and the risks appeared to be reduced patients at risk of bradyarrhythmia were excluded. The overall quality of the meta-analysis was judged as "moderate".

Conclusions: This meta-analysis suggests the presence of a risk of bradyarrhythmia or severe bradyarrhythmia (ventricular pauses >2.5 s) related to ticagrelor use. Its use in patients without risk factors of bradyarrhythmia seems effective for reducing this risk. The evidence coming from this meta-analysis was moderate because the presence of a huge reporting bias, due to the missing outcome data in 2/3 of eligible studies. Real-world evidences on the risk of bradyarrhythmia related to ticagrelor are also needed to further evaluate this risk.

1163 | Use of Pregabalin and worsening heart failure: A Nationwide cohort study

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Background: Pregabalin is a gamma-aminobutyric acid (GABA) analogue approved for the treatment of neuropathic pain, epilepsy and generalized anxiety disorder and has been increasingly prescribed in recent years. Concerns of increased risk of worsening heart failure with use of pregabalin have been raised.

Objectives: To assess the association between use of pregabalin and risk of worsening heart failure in routine clinical practice.

Methods: We conducted a population based cohort study in Denmark using data from nationwide health and administrative registers, January 1, 2008, to December 31, 2017. The study population consisted of patients 50 years or older with a diagnosis of heart failure who were new users of pregabalin or gabapentin. In a sensitivity analysis, we compared pregabalin with duloxetine. We matched both cohorts in a ratio 1:1 on the propensity score. Using proportional hazards regression, we estimated hazard ratios (HRs) for worsening heart failure, defined as hospitalization with or death from heart failure within 90 days of start of treatment.

Results: 1415 new users of pregabalin were matched to 1415 new users of gabapentin. We observed 35 individuals with worsening heart failure among users of pregabalin (incidence rate [IR], 110.5 per 1000 person-years) vs. 44 individuals among users of gabapentin (IR 135.6 per 1000 person-years) corresponding to a HR of 0.81 (95% confidence interval [CI] 0.52–1.27). The corresponding absolute risk difference was −25 (95% CI -65 to 36) per 1000 person-years. Results of the sensitivity analysis, comparing 847 new users of pregabalin vs. 847 new users of duloxetine, provided similar results (HR 1.05, 95% CI 0.59–1.89).

Conclusions: The present study does not provide evidence to support an association between use of pregabalin and an increased risk of worsening heart failure.

1164 | DPP-4 inhibitors and risk of venous thromboembolism: Analysis of the FDA adverse event reporting system database

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Background: Dipeptidylpeptidase-4 inhibitors (DPP4i) are widely used for treating type 2 diabetes. A recent pharmacovigilance study using French national healthcare insurance system database have showed DPP4i may be associated with venous thromboembolism (VTE).

Objectives: To assess the association between DPP4i and VTE using US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: By running a query on AERSMINE (an open access web data mining tool of FAERS) from 2004 Q1 to 2018 Q1, we obtained the VTE cases related to DPP4i (sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin) and comparator drugs. The VTE events were identified by MedDRA v21.0 and include the following: 1) deep vein thrombosis (DVT); 2) Pulmonary embolism (PE); 3) VTE at gastrointestinal level (GIVTE). We conducted three mutually exclusive comparisons: 1) compared DPP4i to all other glucose lowering drugs (GLDs) excluding insulins; 2) compared DPP4i to two classes of therapeutics alternatives: sulfonylureas and sodium-glucose cotransporter 2 inhibitors (SGLT2i); 3) compared DPP4i to SGLT2i only, as SGLT2i is a new class of GLDs with more similar reporting rates to DPP4i than other GLDs. In each comparison, we calculated proportional rate ratio (PRR) and 95% CI using 2 × 2 tables by SAS 9.4. A signal is defined as PRR more than 2.

Results: A total of 571 DPP4i associated VTE events were identified, 393 cases(68.8%) were DVT, 2 cases(0.35%) were PE,129 cases (22.6%) were GIVTE, including portal vein thrombosis (*n* = 76), splenic vein thrombosis (*n* = 33) and mesenteric vein thrombosis (*n* = 20). Compared to all other antidiabetic drugs excluding insulins, the PRR for overall VTE, DVT, GIVTE was 1.06 (0.97–1.16), 0.91 (0.8–1.01), and 4.87(3.86–6.13), respectively. Compared to sulfonylureas and SGLT2i, the PRR for overall VTE, DVT, and GIVTE was 0.93 (0.83–1.03), 0.74 (0.65–0.84), and 5.10 (3.73–6.99), respectively; The PRR for overall VTE and DVT was 3.54 (2.69–4.64) and 2.87 (2.12–3.87), respectively, when compared to SGLT2i only. Similarly, in the most analyses stratified by individual DPP4i, consistent results were seen with the primary analysis.

Conclusions: Our analysis using FAERS database found signals of VTE at gastrointestinal level for DPP4i. However, this study is limited by reporting bias, lack of denominator data, and FAERS cannot be used to assess the incidence. Thus, further studies are warranted to assess the potential VTE risk associated with DPP4i.

1165 | Major cardiovascular events in adults on antiretroviral therapy in a South African HIV Management Programme

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Background: Studies from high-income settings found increased risk of cardiovascular events (CVEs) in people living with HIV (PLWH). Data on CVE incidence in PLWH in Africa are limited.

Objectives: To describe incidence of and risk factors for major CVEs leading to hospitalization in PLWH on antiretroviral therapy (ART) in the Aid for AIDS (AfA) private sector cohort.

Methods: We included adults (≥18 years) starting ART through AfA from 1 Jan 2011 to 30 Jun 2017. We extracted demographic and laboratory variables and ART regimen at first AfA ART claim. We defined major CVE as hospitalization for stroke, acute coronary syndrome, or coronary revascularization procedure, as coded in claims data. We calculated crude CVE incidence stratified by HIV viral load (VL) suppression at first AfA ART claim. We explored associations with major CVE with Cox regression.

Results: We studied 110,932 patients: median [IQR] follow-up 25 [10 to 48] months, total follow-up 275,191 person-years, median [IQR] age 38 [33 to 45] years, median [IQR] CD4 count 277 [150 to 437] cells/μL, and 67,079 (60%) women. At first AfA ART claim, VL was suppressed in 29,866 (27%), suggesting that these patients were already taking ART. Median [IQR] VL in those unsuppressed at first claim was 4.8 [4.1 to 5.3] $\log_{10}$ copies/mL. 85,145/110,932 (77%) commenced tenofovir, emtricitabine/lamivudine, and efavirenz; 5,123 (4.6%) commenced a protease inhibitor. There were 911 patients with major CVE: 555 (61%) strokes, 317 (35%) acute coronary syndromes, and 39 (4.3%) revascularization procedures. 7,134 patients (6.4%) died. Crude incidence of major CVE was 3.3 events per 1,000 person-years follow-up (PYFU). Incidence in the first 6 months was 3 times higher in the unsuppressed than in the suppressed (5.1 vs 1.7 per 1,000 PYFU, incidence rate ratio 2.9, 95% CI 1.9 to 4.7). Major CVE in the first 6 months was associated with older age, male sex, lower CD4 count and unsuppressed VL: adjusted hazard ratios (95% CI) were 1.8 (1.5 to 2.0) per 10 year age increase; 1.3 (1.0 to 1.8) for male vs female; 4.2 (2.6 to 6.9) for <50 cells/μL, 2.1 (1.3 to 3.3) for 50 to 199 cells/μL, 1.4 (0.9 to 2.3) for 200 to 349 cells/μL, vs ≥350 cells/μL; 1.9 (1.2 to 3.0) for unsuppressed vs unsuppressed. Associations remained significant for the follow-up duration.

Conclusions: Our crude incidence of major CVE is lower than that found in a D:A:D cohort analysis of patients from Europe, USA and Australia (5.3 events per 1,000 PYFU). Strokes were the predominant CVE in our cohort, in contrast to D:A:D. Immune reconstitution may explain the higher incidence of major CVEs soon after ART initiation in the unsuppressed group.

1166 | Antiplatelet agents and risk of stroke

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Background: Publications have reported controversial results about the role of antiplatelet agents (APA) in the prevention of stroke and with little consideration for confounding by indication and the type of stroke to be prevented.

Objectives: To assess the preventive effect of antiplatelet agents on the occurrence of ischemic or hemorrhagic stroke in patients with previous history of cardiac diseases.

Methods: From two systematic national registries, patients with previous history of cardiac diseases defined as ischemic coronary heart disease, peripheral arteriopathy or carotid stenosis were identified. Atrial fibrillation (AF) was confirmed with an EKG. Stroke cases were identified among these registries and documented by CT scan or MRI and matched to patients without stroke on age, gender, index date (date of stroke diagnosis for cases and date of recruitment for non-cases). All treatments received in the previous 12 months before index date were documented (mostly from medical records). APA were considered in two categories, i.e. aspirin used alone and P2Y12 inhibitors (namely clopidogrel, ticagrelor and prasugrel). Associations with the occurrence of stroke vs no APA use, were assessed with multivariable conditional logistic regression models controlled for anticoagulants use, diabetes, history of other cardiovascular diseases, hyperlipidemia, renal impairment, liver disease, hemorrhagic disorder, alcoholism or their indicators in the databases.

Results: Among patients with history of cardiac diseases in the registries, 676 stroke cases were matched to 676 randomly selected patients without stroke at the index date. The adjusted odds ratio (OR) for the association between any stroke and use of aspirin alone was 0.89; 95%CI[0.69–1.16] while it was 0.48; 95%CI[0.34–0.69] for P2Y12 inhibitors. Similar results were found when the analysis was restricted to ischemic stroke: OR = 0.82; 95%CI[0.62–1.10] and 0.40; 95%CI[0.27–0.59] for aspirin alone and P2Y12 inhibitors respectively. In hemorrhagic stroke, the OR for aspirin alone was 1.34; 95%CI[0.62–2.90], and 1.04; 95%CI[0.35–3.03] for P2Y12 inhibitors.
Conclusions: In patients with a previous history of cardiac diseases, P2Y12 inhibitors significantly decreased the risk of ischemic stroke and show no association with hemorrhagic stroke. Results for aspirin need to be confirmed.

1167 | A plausible causal link between antiretroviral therapy and increased blood pressure in patients on highly active antiretroviral therapy- a propensity score-matched analysis

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Background: Two Decades into the highly active antiretroviral therapy (ART) era, there has been improvement in the management of HIV/AIDS. Persons living with HIV (PLHIV) in sub-Saharan Africa are however faced with an epidemiological transition of an increasing burden of non-communicable diseases.
Objectives: This study aimed to determine the prevalence of hypertension and associated factors and also estimate the average treatment effect on the treated (ATT) of ART on hypertension/blood pressure among patients attending HIV clinic at the Korle-Bu Teaching Hospital (KBTH).
Methods: The study design was cross sectional involving 311 randomly selected PLHIV. The WHO STEPwise Approach to Chronic Disease Risk Factor Surveillance instrument was modified and used for data collection. Factors associated with hypertension were determined by logistic regression modeling using purposeful selection of covariates method. Propensity score matching (PSM) analysis was used to determine the ATT of ART on hypertension/blood pressure values using kernel weighting method with a bandwidth of 0.06.
Results: Study participants on ART had a significantly higher prevalence of hypertension (41.3% [95% CI, 35.2–47.3]) compared with their ART-naive counterparts (16.9%, [95% CI, 7.4–26.5]). Regression modeling indicated factors associated with hypertension were, increasing age, family history of cardiovascular disease, inadequate exercising, a BMI $\geq$25.0 kg/m^2, abdominal obesity, hypercholesterolemia and exposure to ART. Post-estimation analysis indicated the generated logistic model was "good" on "discrimination" with an AUROCC of 0.81 (95% CI, 0.75–0.85; $p < 0.001$) and on "calibration", with a Hosmer-Lemeshow goodness-of-fit test χ^2 value of 4.49 ($p = 0.810$). The estimated ATT of ART on systolic blood pressure (12.0 mmHg, [95% CI, 5.7–18.3]; p < 0.001), diastolic blood pressure (6.1 mmHg, [95% CI, 1.3–10.82]; $p = 0.012$) and hypertension (26.2%, [95% CI, 13.3–39.1]; p < 0.001) were significant indicating a high possibility that the epidemiological association between ART and hypertension/increased blood pressure may be causal in nature.
Conclusions: This study showed that hypertension is prevalent among patients on ART attending KBTH HIV clinic and also established a plausible causal relation between ART and hypertension/increased blood pressure.

1168 | Pharmacogenetic modeling of metformin on stroke, myocardial infarction and cardiovascular mortality

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Background: Detailed pharmacodynamic (PD) modeling is usually not possible in large population-based cohorts. However, it is possible to use genetic variants that modify the PD of drugs to model clinical outcomes.
Objectives: To evaluate candidate genetic variants that influence the PD of Metformin, notably on intermediate endpoints such as glucose and HbA1c. Variants that were significantly associated were subsequently assessed for possible effects on stroke, myocardial infarction (MI) and cardiovascular mortality.
Methods: The setting was the population-based Rotterdam Study. HbA1c measurements were taken as part of routine care in the Stichting Trombosedienst en Artsenlaboratorium Rijnmond-Medisch Diagnostisch Centrum (STAR-MDC). We used linear mixed models to study the change in glucose or HbA1c between two measurements, where the first measurement was without metformin use, and the second measurement was during metformin use. We adjusted for the time between measurements. We tested 23 genetic variants known to influence the pharmacodynamics of metformin. The analysis was first performed stratified on each allele, after that, an interaction with treatment and genetic variants was tested. After the confirmation of previous SNPs, we took the SNPs that were significant, and tested them in three different Cox' models with use of Metformin as time-dependent covariable. In the first model, the outcome was stroke, in the second one it was MI and in the third one it was cardiovascular mortality.
Results: Of the 14,926 participants of the Rotterdam Study, there were 5644 participants with both glucose measurements and genetic data, and 2988 participants with both HbA1c measurements and genetic data. There were 39,094 measurements of glucose and 31,629 measurements of HbA1c. There was a significant interaction

between the variant and change in glucose in starters with metformin for rs3013105, rs6867983, rs11212617, rs11231159, and rs4787778. There was a significant interaction between the variant and change in HbA1c in starters with metformin for rs2457574 and rs11231159. These variants were tested in the Cox regression models for stroke, MI, and coronary heart disease (CHD) mortality. Metformin use was significantly protective for MI and CHD mortality, but there was no significant interaction between use of metformin and any of the SNPs on these three endpoints.

Conclusions: The protective effect of metformin could be explained by confounding by indication. The seven SNPs found to modify the effect of metformin on glucose and HbA1c might be tested in other cohorts for their risk of cardiovascular mortality.

1169 | Association between the risk of venous thrombosis and antidepressants: A meta-analysis

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Background: Venous thromboembolism (VTE) is a major adverse event associated with exposure to select medications. Previous research provides conflicting evidence regarding the use of antidepressants and risk of VTE.

Objectives: The objective of this study was to synthesize published literature that aimed to evaluate the association of antidepressants with VTE.

Methods: Medline, Embase, and Web of Science were searched for relevant studies up to August 2018. All controlled studies that formally evaluated the relationship between antidepressants and VTE were included. Pooled relative risk (RR) and 95% confidence intervals (CIs) were calculated using random effects models. We used univariate meta-regression to explore reasons for between-study heterogeneity including: minimum duration of antidepressant treatment, % of female sex, mean age of subjects, study design, published year, NOS quality score, and sample size.

Results: Ten studies were included in the meta-analysis. Antidepressants were associated with increased VTE risk overall (RR = 1.17, 95% CI, 1.03, 1.32; P = 0.02) which was driven by an increase in VTE risk associated with tricyclic antidepressants (TCAs) (RR = 1.29, 95% CI 1.03, 1.60; P = 0.03). Selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) did not significantly increase the VTE risk. Meta-regression did not reveal systematic associations between study features and reported results.

Conclusions: Pooled literature estimates suggested TCAs but not SSRIs or MAOIs increased the risk of VTE.

1170 | Abstract Withdrawn

1171 | Spironolactone reduces the risk of mortality and hospitalization in veterans with heart failure with preserved ejection fraction

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Background: Results from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial suggested that spironolactone reduced the risk of the composite primary outcome (cardiovascular death, aborted cardiac arrest, or heart failure hospitalization), however results were inconclusive and varied by region. Mechanistically, spironolactone has been shown to decrease the interstitial fibrotic process, which is common in heart failure with preserved ejection fraction (HFpEF).

Objectives: To determine if spironolactone is associated with lower risk of all-cause mortality, all-cause and heart failure hospitalizations in a cohort of veterans with HFpEF.

Methods: We used a validated algorithm to identify HFpEF patients diagnosed between 2002–2012 in the Veterans Affairs healthcare system. Patients were followed from 1 year after HFpEF diagnosis (or 1 year after start of first spironolactone prescription, if it occurred after diagnosis) until death or censoring at their last VA visit or the end of their last spironolactone prescription. Patients were classified as spironolactone users if they had at least 80% compliance for at least a year after initiation and HFpEF diagnosis. Controls were HFpEF patients without spironolactone use. We also did sensitivity analyses extending follow-up by 30-day increments through 180 days past the end of the last spironolactone prescription. All-cause mortality and hospitalizations, for any cause or heart failure, were assessed using Poisson and negative binomial generalized estimating equation models, respectively. Inverse probability weights were calculated for age and multivariable adjustment.

Results: In 53,705 HFpEF patients (96% male; 84% white; mean age 83 ± 12 years), 4,060 used spironolactone. Over follow-up (median of 3.2 years), 1,844 spironolactone users and 26,657 non-users died. Mortality rates were 43% (95% CI: 36–49%) lower and all-cause hospitalization rates were 41% (95% CI: 30–51%) lower for spironolactone users compared to non-users. Sensitivity analyses showed that when censoring 180 days after the end of the last prescription, mortality rates were still 8% (95% CI: 0–16%) lower and all-cause hospitalization rates were still 25% (95% CI: 12–35%) lower for spironolactone users compared to non-users. No significant association was observed between spironolactone use and heart failure hospitalization rates.

Conclusions: Spironolactone use among HFpEF patients is associated with a lower rate of mortality and all-cause hospitalization compared to those who did not take the drug.

1172 | Antidepressants use and the risk of brain hemorrhage

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Background: The use of antidepressants has been steadily increasing. However antidepressants may have an impact on hemostasis and thus may increase the risk of hemorrhages related to antidepressive psychopharmacotherapy. A number of cerebral hemorrhage have been reported, however, study results have not been consistent on their association.

Objectives: To investigate causality between the risk of brain hemorrhage and use of antidepressant drugs by therapeutic class in Korean patients.

Methods: The patients (>18 years old) having first hospitalization or visiting emergency department for brain hemorrhage in the Health Insurance Review and Assessment (HIRA) database from January 2009 to July 2017. The patients diagnosed brain hemorrhage and cerebrovascular diseases in 2009, any head injury before event date, and did not prescribed antidepressants within 8-month before brain hemorrhage were excluded. Antidepressant drugs were classified as TCAs, SSRIs, SNRIs, and Others. Hazard period and control period were matched by 1:4. Characteristics of this study subjects were analyzed by age group, gender, and charlson comorbidity index. Statistical analysis was calculated by odds ratios for brain hemorrhage associated with the use of antidepressants and their 95% confidence intervals using conditional logistic regression with adjusting for confounders including antipsychotics, antithrombotic agents, antidiabetes agents, antihypertensive drugs, lipid modifying agents, and NSAIDs. Sensitivity analyses were conducted using two time window periods.

Results: A total of 2,589 patients with brain hemorrhage, who received antidepressant drugs were included in this study (31.02% male, 68.98% female). The greatest number of these patients were 60 to 79 years old group (54.67%), followed by 40 to 59 years old group (25.34%). Compared with control periods, adjusted ORs were 1.39 (95% CI, 1.20–1.61) in total antidepressant groups, 1.04 (95% CI, 0.68–1.24) in TCA, 1.49 (95% CI, 1.26–1.77) in SSRI, 1.38 (95% CI, 1.03–1.85) in SNRI, and 1.37 (95% CI, 1.15–1.63) in Others group.

Conclusions: Antidepressant use was associated with an increased risk of brain hemorrhage, particularly SSRI, SNRI, and Other antidepressants. For patients with a high risk of brain hemorrhage, close monitoring is needed when prescribing antidepressants.

1173 | The association between direct Oral anticoagulants and gynecological bleeding in women v. standard therapy: A systematic review

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Background: Women receiving anticoagulation are susceptible to the added risk of gynecological bleeding (GB). This may occur in premenopausal women who experience physiological bleeding related to the ovulatory cycle and for whom the risk is greater, or postmenopausal women. Thus, the use of anticoagulation in women requires special consideration in terms of GB risk. It may be that DOACs overall or a particular DOAC are the wrong choice of treatment for women at risk.

Objectives: To examine the association between DOACs and GB in women, by comparing risk in users of DOACs to users of standard anticoagulant (AC) therapy (e.g. vitamin K antagonists (VKAs)).

Methods: 4 databases were searched (July 2018) for clinical trials (CTs) and observational studies (OS) reporting GB in women taking DOACs or a comparator of standard AC therapy for any indication. Abstracts were screened followed by full review of a subset for eligibility. Studies reporting GB with DOACs but with no standard AC comparator were excluded. Due to a high degree of heterogeneity between studies in terms of study design, indications, outcome measures and use of different denominators, a meta-analysis was not performed.

Results: Records identified n = 594; 16 eligible for inclusion (CTs n = 7, OS n = 9). Of the 6 studies specifically designed to evaluate GB in women with DOACs v. standard AC, 3 reported a significantly increased risk of this outcome with DOACs v. standard AC (rivaroxaban (riva) n = 2 (HR 2.13; 95% CI [1.57, 2.89], risk ratio 2.3; p = 0.009), and edoxaban (edox) n = 1 (HR 1.7; 95% CI [1.1, 2.5])). Conversely, no significant difference for 2 studies (riva n = 1, apixaban (apix) n = 1) and a lower risk for 1 (dabigatran (dabi)) was observed (OR 0.59; 95% CI [0.30, 0.90]). The remaining 10 studies were not designed to evaluate GB with DOACs but reported this within study results; 1 reported a higher risk of GB with dabi v. standard AC (HR 2.27; 95% CI [1.32, 3.90]), and for the remaining 9, results were inconclusive due to non-significant/lack of hypothesis test results.

Conclusions: Gynecological bleeding appears to be a common complication of DOACs, however, there is variability between DOACs. More evidence is available for riva, in which the risk of GB appears to be higher than with standard AC. Although limited, evidence suggests a higher risk with edox, lower risk with dabi and no difference with apix v. standard AC. Further research including head-to-head CTs and OS specifically investigating GB is needed to draw firm conclusions on which class of ACs (VKAs v. DOACs) are more favorable for women and the difference in risk between individual DOACs.

1174 | Adverse drug reactions of antihypertensive products

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Background: Arterial hypertension (AH) is one of the leading causes of mortality in world. Patients with AH need life long therapy and in most cases take a few antihypertensive medicines.

Objectives: The aim of this work was to study the patterns and peculiarities of use of following groups of drugs, which are considered as first-line therapy of AH: ACE inhibitors (ACEI) and angiotensin receptors antagonists (ARA), beta-adrenoblockers (BAB), diuretics and calcium channel blockers (CaCB).

Methods: We analyzed records about adverse drug reactions (ADR) in local pharmacovigilance database ARCADe, which contains data of individual case safety reports spontaneously sent by Crimean doctors to local pharmacovigilance office. We restricted our search to 2011–2016 period.

Results: Totally 211 ADR reports were found. More than half of ADR were caused by ACEI (125 cases, 59.2%). Enalapril and Captopril were "leaders" in this pharmacotherapeutic group and provoked 37 and 31 reactions (respectively). 51 (24.2%) patient had ADR caused by CaCB, mainly by third generation drug Amlodipine (36 records, 70.6%). BAB and ARA were suspected reason of ADR in 19 (9%) and 16 (7.6%) cases, respectively. More often ADR were reported for female patients (152 records, 72%) than for male patients (59 reports, 28%), and in age group 51–60 y.o. (73 episodes, 34.6%) and 61–70 y.o. (51 case, 24.1%). There were no reports about ADR caused by diuretic drugs. No lethal ADR were reported. Allergic reactions were registered in 1/3 of cases (70 reports). 13 reactions were life threating due to severe laryngeal oedema. In 64 cases a dyspnoea, rales, bronchoconstriction and dry cough were reported. Rhythm disorders and hypotension were mentioned in 29 reports. Complains on headache, dizziness and vertigo were found in 13 reports. In 86 cases (41%) additinal medicines were prescribed for ADR correction.

Conclusions: Our analysis has shown that allergic reactions is the leading cause of ADR in patients with AH. Nevertheless well-studied safety of first line therapy antihypertensives and long history of their use in medical practice, doctors should pay attention for ADR of them, especially during first days of therapy. ADR of drugs prescribed for AH may negatively affect quality of patient's life and compliance, therefore effectiveness of treatment.

1175 | Comparative effects of sodium-glucose cotransporter 2 inhibitors on serum electrolyte levels in patients with type 2 diabetes: A network meta-analysis of randomized controlled trials

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Background: Previous studies have reported that sodium-glucose cotransporter 2 (SGLT2) inhibitors affect serum electrolytes levels, especially magnesium.

Objectives: This study aimed to integrate direct and indirect trial evidence to evaluate the relative effects of all SGLT2 inhibitors against each other on electrolyte levels in patients with type 2 diabetes (T2D).

Methods: Electronic databases were systematically searched through December 2018 to identify eligible randomized controlled trials (RCTs) that reported the mean changes in serum electrolyte, including magnesium, sodium, potassium, phosphate, and calcium. Random-effects pairwise and network meta-analyses were performed to calculate the weighted mean difference (WMD).

Results: Twenty-five RCTs involving 17,446 patients with five SGLT2 inhibitors were included. Compared with placebo, SGLT2 inhibitors were significantly associated with elevations in serum magnesium by 0.08 mmol/L and serum phosphate by 0.03 mmol/L. Overall, there was no evidence for the changes of serum sodium, potassium, and calcium levels by SGLT2 inhibitors compared to the placebo. Our network meta-analysis showed significant increases in serum magnesium among the patients taking canagliflozin (WMD = 0.08 mmol/L), dapagliflozin (WMD = 0.15 mmol/L), and empagliflozin (WMD = 0.06 mmol/L) compared to their respective controls. Similarly, dapagliflozin (WMD = 0.04 mmol/L), ertugliflozin (WMD = 0.06 mmol/L), and ipragliflozin (0.09 mmol/L) were significantly associated with increases in serum phosphate. Empagliflozin significantly increased serum sodium by 0.28 mmol/L. No statistically detectable differences were evident between any two of SGLT2 inhibitors but between dapagliflozin and empagliflozin in serum magnesium (WMD = 0.09 mmol/L).

Conclusions: SGLT2 inhibitors could significantly increase serum magnesium and phosphate, indicating a potentially similar class-effect. However, more data for long-term efficacy and safety of raising serum magnesium and phosphate in T2D patients with different clinical phenotypes are needed for further investigation.

1176 | Antipsychotic dose and weight gain: Long-term evidence from a retrospective study using electronic health records

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Background: Short-term weight gain, approximately over the first 6 weeks, is a known problem among patients treated with antipsychotics. Nevertheless, further assessment over long term periods and on dose differences is necessary, especially from real-life contexts. Electronic health records obtained from general medical practice are useful sources of this type of information.

Objectives: To describe the short and long-term change in body weight of people with psychotic disorders initiated on high or low doses of the three most commonly prescribed second-generation antipsychotics (olanzapine, quetiapine or risperidone).

Methods: We performed a retrospective cohort study using The Health Improvement Network, a primary care database representative of the UK. In total, 38 865 individuals with a diagnosed psychotic disorder and at least two consecutive antipsychotic prescriptions were observed. The main outcome was change in body weight four years before and four years after initiation of antipsychotic treatment (one cohort per drug), stratified on 'low' or 'high' dose. We modeled weight change over time using continuous linear splines with mixed effect models, from which three slopes of weight change were estimated for: i) pre-treatment (−4 years to baseline), ii) short-term (baseline to 6 weeks), iii) long-term (6 weeks to 4 years).

Results: In total, 22 306 women and 16 559 men were included in the study. Olanzapine treatment was associated with the highest change in weight, with higher doses resulting in more weight gain. Thus, after 4 years, given a high dose of olanzapine (>5 mg), women gained on average 6.1 kg; whereas given a low dose (≤5 mg), they gained 4.4 kg. During the first 6 weeks of olanzapine treatment, they gained on average 3.2 kg on high dose and 1.9 kg on low dose. The trends were similar for men. Individuals prescribed risperidone and quetiapine experienced less weight gain in both the short and long-term and by high and low dose. In general, individuals did not lose the weight gained during the first 6 weeks of treatment. Pre-treatment weight change was negligible or slightly negative across all cohorts. Individuals with lower weight before initiation of olanzapine gained more weight in the short term than individuals with higher weight.

Conclusions: Olanzapine treatment was associated with the highest increase in weight with around 6 kg for individuals on high dose and 4.5 kg for individuals on low dose over 4 years. The weight gain was less dramatic for those treated with quetiapine and risperidone. In general, individuals did not lose the weight gained during the first 6 weeks of treatment.

1177 | Comparative risk of poly-cystic ovary syndrome in young female patients newly initiating anti-psychotic medications

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Background: Antipsychotic medications are commonly used for young females with psychiatric disorders. Recent reports indicated young females receiving antipsychotic medications were at increasing risk of polycystic ovary syndrome (PCOS). However, not all antipsychotics pose identical risk profiles of PCOS.

Objectives: To compare the risk of PCOS in young females newly receiving antipsychotic medications.

Methods: We conducted a retrospective cohort study by using Taiwan National Health Insurance Research Database. We included patients aged 18–30, diagnosed with mental disorders and newly prescribed with antipsychotic medications, including haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, paliperidone and ziprasidone, between years 2004 and 2012. We defined the event of PCOS by two or more diagnosis records of patients. We followed patients until discontinuation, switching, add-on of antipsychotic medications or the occurrence of PCOS. We used multivariate Cox regression hazard models considering patients' age, mental conditions, and concomitant psychotropic drugs to evaluate the risk of PCOS among different antipsychotic medications.

Results: We included a total of 22,586 female patients with a mean age of 24.9 ± 3.4 years. Most of patients were diagnosed with anxiety (54%), major depression disorders (24%), schizophrenia (20%) and bipolar disorder (19%). The most used antipsychotic medications were sulpiride (45%), quetiapine (18%) and risperidone (15%). We found the incidence rates were higher in ziprasidone (105.2 per 1,000 person year), following by haloperidol (51.7 per 1,000 person year) and paliperidone (32.4 per 1,000 person year), compared to risperidone (18.5 per 1,000 person year), quetiapine (17.1 per 1,000 person year) and olanzapine (14.7 per 1,000 person year). The risk of PCOS was higher in patients receiving haloperidol (hazard ratio [HR], 1.86; 95% CI, 1.00–3.44), ziprasidone (HR, 4.65; 95% CI, 1.94–11.16) and paliperidone (HR, 1.12; 95% CI, 0.15–8.25), compared with risperidone.

Conclusions: The findings indicated different antipsychotic medications posed various risk profiles of PCOS. We suggest clinicians should pay attention on PCOS for young female patients receiving antipsychotics especially for those with high risk.

1178 | Impact of Levothyrox formulation change on health and healthcare use in France

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Background: An unprecedented number of pharmacovigilance notifications were reported in France following the introduction in 2017 of a new formulation of Levothyrox (the only levothyroxine product available in France by then), giving rise to a high media coverage. A toxicity of this new formulation was suspected.

Objectives: To measure the impact of Levothyrox new formulation (NF) on health and healthcare use, based on data of the French national healthcare databases.

Methods: The whole population aged 18–85 years treated with Levothyrox in 2016 and/or 2017 was randomly split into two independent groups. Patients of the '2017' group, who initiated Levothyrox NF in April, May or June 2017, were individually matched to patients treated with Levothyrox old formulation (OF) in 2016 ('2016' group). Levothyrox NF first dispensing date was considered as the index date. Matching criteria included sociodemographic characteristics, characteristics of the thyroid treatment, and Levothyrox dispensing date. Patients were followed from the index date up to December, 31 of the same year. Risks of hospitalization or death, sick leaves of ≥7 days among working-aged patients (<65 years), outpatient visits to general practitioners (GP) and specialists, and various medications consumption were compared in 2017 *versus* 2016, using conditional Cox models adjusted for baseline health status indicators. Patients treated with oral antidiabetic drugs (OAD) in 2016–2017 were considered as a control population.

Results: A total of 2,075,106 patients treated with Levothyrox were included (1,037,553 treated with Levothyrox NF in 2017 and 1,037,553 treated with Levothyrox OF in 2016) and followed during 7.5 months in mean. Patients were predominantly women (85.7%), aged 61.6 years in mean. Compared to 2016, in 2017 the risk of all-cause hospitalization was lower (aHR 0.95, 95% confidence interval [0.94–0.96]) and the risk of death was similar (aHR 0.98 [0.94–1.02]). The risk of sick leave was 2% higher in 2017 compared to 2016 (aHR 1.02 [1.01–1.04]); a similar increase was observed in patients with OAD. The mean number of outpatient visits increased by 2%, from 6.08 in 2016 to 6.20 in 2017 ($P < 0.0001$); this increase was limited to visits to GP and endocrinologists and to the period from August to October 2017. Renewals of chronic treatments including psychotropic, anti-hypertensive and lipid-lowering drugs were slightly more frequent in 2017.

Conclusions: Our results do not provide evidence of increased risks of serious health concerns associated with Levothyrox NF. Though, they show a substantial increase in healthcare use following Levothyrox formulation change.

1179 | The association between receptor affinity and metabolic side effects profile of antipsychotics and major adverse cardiac and cerebrovascular events: A case/non-case study in VigiBase

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Background: The association between antipsychotics (APs) use and the occurrence of major adverse cardiac and cerebrovascular events (MACCE) is well established. However, the underlying pharmacological mechanisms by which APs may cause those events are still speculative.

Objectives: Our aim was to elucidate the role of possible pharmacological mechanisms (*i.e.* the degree of receptor affinity and metabolic side effects profile) in the reporting of MACCE in AP users.

Methods: A case/non-case study was undertaken using data (1968–10/2017) from the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, VigiBase, among all reports associated with an AP as suspected drugs. Cases were defined as all ICSRs of MACCE (included cerebrovascular events, myocardial infarction, and cardiovascular death) and non-cases all the other reported suspected Adverse Drug Reactions (ADRs). APs were classified by AP group (typical vs atypical), the degree of receptor affinity for adrenergic, dopaminergic, muscarinic, histaminic, and serotoninergic receptors (low-: >1,000 nM; intermediate-: 10–1,000 nM; and high-affinity: < 10 nM) and metabolic side effects profile (low-, intermediate- and high-risk). The strength of the association was estimated with logistic regression and expressed as crude and adjusted reporting odds ratios (aRORs) with a corresponding 95% confidence intervals (95%CIs).

Results: By October 2017, there were 333,894 ICSRs concerning only APs and MACCE was reported in 1.5% (n = 4,987) ICSRs, the rest being other ADRs. Atypical APs (aROR 2.41; 95%CI 2.15–2.69) were significantly more frequently associated with the reporting of MACCE compared to typical ones. APs with high affinity for alfa$_1$ (aROR 2.77; 95%CI 1.80–4.27), H_1 (aROR 2.24; 95%CI 1.93–2.60), M_1 (aROR 1.79; 95%CI 1.66–1.92), and 5-HT$_{2A}$ (aROR 2.97; 95%CI 1.93–4.58) receptors were associated with a higher frequency of MACCE compared to low affinity. APs associated with higher-risk of metabolic side effects (aROR 1.80; 95%CI 1.65–1.96) were associated with higher reporting of MACCE compared to those with a low-risk.

Conclusions: Data confirm the association between atypical APs and MACCE. Our findings also showed that APs with high-affinity for α_1, H_1, M_1, and 5-HT$_{2A}$ receptors and high-risk of metabolic side effects may be pathways to explain the occurrence of MACCE.

1180 | Identifying type 2 diabetes patients at risk for hypoglycemic events: Dealing with class imbalance

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Background: Between 5–15% of patients with type 2 diabetes (T2D) experience hypoglycemic events in need of a healthcare provider's attention. To give better support and prevent hypoglycemic events, patients at risk need to be identified using routine care data.
Objectives: To test the impact of class imbalance when developing an algorithm for identifying T2D patients at risk for hypoglycemic events.
Methods: A retrospective cohort study was conducted using data from the Groningen Initiative to Analyze Type 2 Diabetes treatment (GIANTT) database. GIANTT contains longitudinal data from general practices in the northern part of the Netherlands. T2D patients using a glucose lowering drug were included. The primary binary outcome was having ≥1 glycemic event or no event in 1 calendar year. To deal with expected class imbalance in this outcome, an undersampling strategy was used to balance the data in which patients without an event were split in random equal groups of the same size as patient with an event. These groups were compared to the patients with an event. Univariate analyses were performed to select predictors from a range of routinely available clinical and medication variables. Multivariate logistic models were compared on accuracy, specificity and sensitivity at a prediction probability cut-off point of 0.5 and on area under the curve (AUC).
Results: The following variables were included in the multivariate models: insulin use, sex, non-chronic infections, glucose variability, diabetes duration, HbA1c, diastolic blood pressure, drug count, non-selective beta-blocker use, anti-depressant use, liver disease and eGFR. The unbalanced model had an AUC of 0.70, an accuracy of 88.2% with a specificity of 99.8% and a sensitivity of 1.0%. The balanced model had an AUC of 0.71, an accuracy of 66.8% with a specificity of 72.7% and a sensitivity of 61.8%.
Conclusions: To develop an algorithm for identifying patients at risk for hypoglycemic events class imbalance should be taken into account. The balanced model showed an improved sensitivity with an acceptable specificity. More advanced feature selection techniques, such as LASSO and elastic net, can be tested to further improve the model.

1181 | Abstract Withdrawn

1182 | Antidepressant-induced hyponatremia: A Pharmacoepidemiological-Pharmacodynamic analysis of suspected adverse drug reactions reported to the US FAERS database

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Background: Hyponatraemia induced by antidepressant drugs is a rare but potentially life-threatening adverse reaction. Whether it is associated with all or only some antidepressant drugs is still unclear.
Objectives: To quantify the strength of association between the use of different a antidepressant drugs and hyponatraemia by using information reported to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). The secondary objective was to investigate the putative relationship between different antidepressant pharmacological targets and the risks of hyponatraemia induced by antidepressant drugs using the 'pharmacoepidemiological-pharmacodynamic' method.
Methods: A case-noncase analysis was used using spontaneous reports from the FAERS database to measure the risk of reporting between suspected antidepressant and hyponatraemia with all other ADRs [expressed as a reporting odds ratio (ROR) while adjusting for gender, age, and concomitant medications associated with hyponatremia]. We assessed to what extent the receptor binding properties of antidepressants could associate to the RORs of hyponatraemia/SIADH of antidepressants, building a linear regression model that included as independent variables the binding affinities (pKi) to the serotonin transporter (SERT), dopamine transporter, norepinephrine transporter, and 5-HT_2C, 5-HT_2A, 5-HT_1A, α_1 and α_2 adrenergic receptors].
Results: 2,233 reports were identified. The adjusted ROR for the association between antidepressant drugs use and hyponatraemia was of 1.91 [95% CI 1.83, 2.00]. The association was strongest for mirtazapine, followed by selective serotonin reuptake inhibitors (SSRIs), and lowest with serotonin modulating antidepressant drugs. A significant linear correlation was found between the adjusted RORs for hyponatraemia/SIADH and pKi for the adrenergic receptors $\alpha_1$and α_2.
Conclusions: Hyponatraemia/SIADH is reported at a disproportionately higher rate with classes of antidepressant drugs (NaSSAs and serotonin modulators) that are in general considered to have a better profile of tolerability in terms of hyponatraemia. The risk of hyponatraemia with mirtazapine appears to be greater than what was reported in the literature. Our PE-PD analysis indicates also that inhibition of SERT may not be involved in the hyponatraemia linked to the use of antidepressant drugs.

1183 | Hyperkalemia risk with spironolactone in patients with heart failure using loop diuretics

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Background: There are a paucity of real-world clinical data on the risk of hyperkalemia when adding spironolactone to loop diuretics in

patients with heart failure, and it is also unclear whether risk differs by kidney function.

Objectives: To measure the absolute and relative risks of hyperkalemia associated with adding spironolactone to loop diuretics among patients with heart failure.

Methods: Patients with heart failure and loop diuretic use were identified in MarketScan commercial claims data (MS) from 2010–15 (*N* = 5448), and the Geisinger Health System (GHS) from 2004–16 (*N* = 7448). Medication use was determined through dispensing data (MS) and prescription orders (GHS). We quantified the incidence of hyperkalemia, defined as inpatient encounters with hyperkalemia diagnosis codes, comparing rates on treatment (from spironolactone initiation among initiators) with those on control (from a randomly selected loop diuretic prescription among those not using spironolactone). We evaluated whether spironolactone use was associated with higher risk of hyperkalemia in patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 compared to ≥60 ml/min/1.73m^2 using negative binomial regression. All models were adjusted for baseline serum potassium, demographics, comorbidities, and medication use and, in sensitivity analyses, we repeated the analysis matching treatment 1:1 to controls using propensity scores.

Results: Among individuals with incident heart failure (MS: treatment *n* = 759 and control *n* = 4689; GHS treatment *n* = 1242 and control *n* = 6206), the treatment groups were younger, and more likely to be male, have liver disease, and take cardiovascular medications (all $p < 0.05$). Baseline mean potassium was lower (−0.06 mEq/L) and eGFR was higher (+2.6 ml/min/1.73m^2) in the treatment group in GHS. Overall, there were 68 hyperkalemia events [4.6 vs 2.5 per 1000 person-months in treatment and controls, respectively] in MS, and 208 (3.4 vs 1.4) in GHS. In adjusted analyses, treatment was associated with an incidence rate ratio of 1.95 [95% confidence interval (CI): 1.05–3.64] and 2.90 (CI: 1.95–4.33) for hyperkalemia events in MS and GHS, respectively. There were no differences in hyperkalemia risk by level of kidney function in either cohort (p for interaction between treatment status and kidney function - MS: 0.89; GHS: 0.64). Results were similar in propensity score matched analyses.

Conclusions: The initiation of spironolactone among loop diuretic users with heart failure was associated with a greater risk of hyperkalemia, but the risk did not differ by baseline level of kidney function.

1184 | Monitoring the safety of Exenatide once-weekly (Bydureon®) in primary Care in England: Results from a PASS

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Background: Clinical trials have reported specific safety concerns such as acute pancreatitis (AP) in patients (pts) taking Bydureon® (exenatide once-weekly) for type 2 diabetes mellitus (T2DM). A Post-Authorisation Safety Study (PASS) was conducted to monitor the real-world safety of Bydureon® in primary (1°) care in England.

Objectives: To estimate the incidence of targeted safety outcomes in pts prescribed Bydureon® in 1° care.

Methods: Pts identified from dispensed Bydureon® prescriptions in England (2012–2016). Questionnaires sent to prescribing general practitioners (GPs) at ≥12-months observation collected event information. Events of interest included AP, pancreatic cancer (PC), thyroid neoplasm (TN), gallstones, biliary colic or cholecystitis (GBC), acute renal failure (ARF), type 1 hypersensitivity (T1H), and cardiac events (CE). 12-month incidence estimates (on Bydureon® or ≤ 10 weeks after stopping) were calculated; results were stratified according to prior exenatide use (i.e. Byetta®).

Results: Questionnaire response rate = 37.2% (7752/20860). Total cohort = 6294 pts prescribed Bydureon® for T2DM (median age 57 years [IQR 50, 65]; 55.2% male). Exenatide naïve *n* = 4556 (72.4%), previous Byetta® users *n* = 1629 (25.9%), previous Byetta® use unknown *n* = 109 (1.7%). Risk of AP in total cohort 0.2% (95% CI [0.1, 0.4]; *n* = 14). 2 pts had a prior history. Risk of AP was similar for exenatide naïve (0.2% (95% CI [0.1, 0.4]; n = 10) and previous Byetta® users (0.2% (95% CI [0.0, 0.5]; *n* = 3). Rate of AP in total cohort was 2.5/1000 person-years (95% CI [1.5, 4.3]) and no statistically significant difference was observed between the 2 user groups. Time-to-event analyses suggested no clear pattern in the hazard function of AP over time. For 12 of the 14 pts, Bydureon® was stopped due to AP. AP complications; necrosis/pseudocyst n = 1, fatal outcome *n* = 1. PC 0.1% (n = 4); a fatal outcome was reported in 3 of these pts. TN 0.0% (*n* = 0). GBC 0.6% (95% CI [0.4, 0.8]; *n* = 38); 15 of which had a prior history of GBC. ARF 0.5% (95% CI [0.3, 0.7]; *n* = 29). T1H 0.7% (95% CI [0.5, 0.9]; *n* = 44). CE 3.6% (95% CI [3.2, 4.1]; *n* = 227). No statistically significant differences in risk between the 2 user groups were observed.

Conclusions: Incidence of AP was low in Bydureon® users and consistent with prior clinical trial/observational data. No unexpected findings were identified. This study has unique strengths, including collection of timely, granular real-world data from GPs, facilitating accurate estimates. The study is part of a broader literature on the safety of Bydureon® and conclusions should be made in context with other post-marketing findings.

1185 | Incidence and risk factors for hypoglycemia in patients with diabetes hospitalized in a quaternary Care Centre in South India

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Background: Hypoglycemia occurs in 8% of hospital admissions and is an important complication of type 2 diabetes that can have a major

impact on health outcomes. The 2017 Standards of Medical Care highlight renal insufficiency and cognitive dysfunction as important risk factors for hypoglycemia but other risk factors remain less documented.

Objectives: To identify potential risk factors in the development of hypoglycemia in hospitalized diabetic patients and to evaluate their influence in patients admitted to critical care and non-critical care units.

Methods: In this prospective, non-randomized study a number of potential risk factors for the development of hypoglycemia in hospitalized patients such as clinical condition of the patient, duration of diabetes, blood sugar level at the time of admission, type of feed and surgical status were predefined based on the literature. The influence of these factors were then evaluated in patients admitted to critical and non-critical care units. Blood glucose measurement was done by point-of-care testing. All Type II diabetic patients admitted to the hospital (>18 years) were included and Type 1 diabetic patients and hyperglycemia without a history of diabetes were excluded. The influence of risk factors in the development of hypoglycemia were analyzed and compared the data of critical and non critical care units using chi square method with $p < 0.05$ to be significant.

Results: The study revealed that 14.3% of the diabetic patients developed hypoglycemia and the incidence of events was found to be 31.25%. There was no significant difference in age (65 ± 9.5 vs 64.5 ± 9.6 $p = 0.764$) and time of hypoglycemic attack (46% vs 54.5% $p = 0.344$) in patients admitted to critical and non critical care units whereas duration of diabetes (44% vs 6% $p = 0.000$), blood sugar at the time of admission (30.5% vs 47% p = 0.000), surgical status (5% vs 30% p = 0.000) significantly differed. There was also significant difference in the incidence of hypoglycemia based on the type of feed in both groups; normal intake (15% vs 50.5% $p = 0.05$), decreased intake (6.8% vs 30% p = 0.05), RT feed (40.7% vs 6% p = 0.05). Terminal illness was considered a major risk factor for hypoglycemia and the relationship between hypoglycemia and mortality(10% vs 1.5% $p = 0.001$) was stronger among patients who had multiple events of moderate hypoglycemia(40–60 mg/dl) during their hospital stay.

Conclusions: Hypoglycemia is a common problem in hospitalized diabetic patients and the influence of these risk factors should be considered in hypoglycemic risk assessment when individualizing diabetes care for older patients.

1186 | Incretin mimetic drugs (GLP-1 receptor agonists and DPP-4 inhibitors) and associated adverse events and renal outcomes: A Pharmacoepidemiologic analysis using the FAERS database

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Background: Clinical studies demonstrated the efficacy and safety of incretin memetic drugs among patients with diabetes, however, the impact of these drugs on renal function is still not settled.

Objectives: 1) To identify potential signals of adverse events that are frequently reported but not currently stated on drug labels. 2) To explore the potential impact of incretin mimetic drugs on renal outcomes using a real world data.

Methods: Retrospective descriptive analysis of adverse events reported to the US Food and Drug Administration Adverse Events Reporting System (FAERS) database from quarter 1, 2012 to quarter 2, 2018. Our Analysis focused on three drugs of the incretin mimetic class resulted in a postmarket safety communications by the FDA, namely Exenatide, Sitagliptin and Saxagliptin. The most common adverse events (AEs) were compared with the current warnings on each drug label. Renal adverse event reports AE reports were identified using text string search queries of preferred terms related to the renal system.

Results: A total of 72,035 AEs were identified for the study drugs (Exenatide, 41,089, Sitagliptin, 25,091, Saxagliptin, 5,855). The most common AEs that are not posted on label N(%) were: For Exenatide, Hypertension 317(1.26%), Bladder Cancer 234 (0.93%), Anxiety 230(0.92%), Depression 181 (0.72%), Myocardial Infarction 159 (0.63%), and Pneumonia 142 (0.57%); For Sitagliptin, Pneumonia 1127(2.74%), Asthenia 1015 (2.47%), Hypertension 889(2.16%), Anemia 857(2.09%), Bladder Cancer 847(2.06%); For Saxagliptin, Hyperglycemia 424 (7.24%), Diarrhea 279 (4.77%), Nausea 233 (3.98%), fatigue 231(3.95%), weight reduction 233 (3.81%). The most common renal AEs for Exenatide were: Acute Kidney Injury 217 (0.86%), Renal failure 213 (0.85%), Urinary Tract Infections 112 (0.45%); for Sitagliptin were: Renal failure 907 (2.21%), Acute Kidney Injury 768 (1.87%), and Urinary Tract Infection 705 (1.72%); and for Saxagliptin: Urinary Tract Infections 123 (2.1%), Renal Failure 115 (1.96%), Acute Kidney Injury 80 (1.37%).

Conclusions: Renal adverse events seem more commonly reported for Sitagliptin and Saxagliptin compared with Exenatide. Hypertension, myocardial infarction and pneumonia were identified for all drugs and not currently addressed on drug labels and need further assessment.

1187 | Diabetes management protocol: Impact in the incidence of hypoglycemia

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Background: Hypoglycemia occurs in 7.7% of hospital admissions and is associated with increased length of stay and increased mortality. It is suboptimally treated and has severe consequences. There remains a need for the development, implementation and adherence to a diabetes management protocol that reduces the incidence of hypoglycemia.

Objectives: To develop a protocol in the management of hospitalized diabetic patients and to evaluate its impact during post interventional phase.

Methods: In this prospective, interventional, non randomized study, diabetes management protocol was developed according to ADA

guidelines. All Type II diabetic patients admitted in a Quaternary Care Centre in South India in the age group ≥18 years of either sex irrespective of comorbidities and medications were included in the study and those with gestational diabetes or hyperglycemia without a history of diabetes were excluded. Blood glucose measurement was done by point-of-care testing. The impact of protocol in reducing hypoglycemic events were analyzed and compared the data of pre intervention with post intervention using chi square method with $p < 0.05$ to be significant.

Results: Pre intervention data showed 85 hypoglycemic events (15.8%) in 535 diabetic patients and in post intervention phase,57 (14.3%) events were observed in 400 patients. There was statistically significant reduction in the severity of hypoglycemia (23.5% vs 6.4%, $P = 0.035$), incidence in patients with normal diet (73.3% vs 43.2%, $p = 0.00$) and an increase in referral to specialist(30.6% vs 43.2%, $P = 0.000$) and regular monitoring (47.1% vs 94.4%, $P = 0.001$) after implementing the protocol.

Conclusions: Development and implementation of a diabetes management protocol, significantly reduces the incidence and severity of hypoglycemia. Adherence to protocol, regular monitoring, proper feed and early referral to specialists may help to reduce the hypoglycemic episodes.

1188 | Risk and signals of ketoacidosis among sodium-glucose Cotransporter-2 (SGLT2) inhibitors: Analysis of post marketing FDA adverse event reporting system (FAERS) database, 2013–2018

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Background: Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors are considered a novel treatment option for patients with diabetes, due in part to their cardiovascular protective effects and their availability as oral medications. However, the risk of ketoacidosis has substantially increased in par with reports concerning the health effects of this group of medication, as regarded by health institutions and regulatory authorities.

Objectives: To analyze and compare the risks of ketoacidosis among Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors in the FDA Adverse Event Reporting System (FAERS) database over 5 years.

Methods: Reports of ketoacidosis and related terms events (e.g. diabetic ketoacidosis) submitted to FAERS in the period between March 2013 and March 2018 were retrieved and analyzed by the reporting odds ratio (ROR). Using FAERS database, the ROR of case/non-case reports of ketoacidosis and its related terms associated with SGLT2 inhibitors was compared. All data were analyzed by using the Statistical Analysis Software (SAS), version 9.4.

Results: 6,809 reports of ketoacidosis were reported during the study period in FAERS database among the total of 6,583,341 unique reports. Majority of reports of ketoacidosis during the study periods were linked to SGLT2 inhibitors (73%). Around 2,692 reports linked canagliflozin to ketoacidosis and the proportion of ketoacidosis reports with canagliflozin—among all canagliflozin reports—was 11.5%. There were 1,217 reports linked dapagliflozin to ketoacidosis, and the proportion of this was 12.2%, while it was 13.2% for empagliflozin with 1,064 reports connected to ketoacidosis. The annual number of reports increased yearly (2013 to 2018) with a high spike in 2015. The association between ketoacidosis and its related terms was statistically significant with the use of all three medications with different with the degree of association. ROR was 162 [95% CI 152–173]) with dapagliflozin, ROR 173 [95% CI 161–186] with empagliflozin, and ROR 205 [95% CI 195–216] with canagliflozin.

Conclusions: There is a significant risk of ketoacidosis with the use of the SGLT2 inhibitors. However, the risk varies within SGLT2 inhibitors, with an increase among canagliflozin and a decrease with dapagliflozin.

1189 | Pancreatic safety of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: A systematic review and meta-analysis

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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a novel class of oral antidiabetic drugs, have been suggested a potential risk of acute pancreatitis in patients with type 2 diabetes (T2D). However, the pancreatic safety of SGLT2 inhibitors in patients with T2D is not well known.

Objectives: This study aimed to systematically evaluate the association between SGLT2 inhibitors and pancreatic safety in patients with T2D.

Methods: We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov through May 2018 to identify randomized controlled trials that reported adverse events on acute pancreatitis, pancreatitis, or pancreatic cancer among the adults with T2D treated with SGLT2 inhibitors compared with placebo or other active antidiabetic drugs. Peto odds ratio (OR) with 95% confidence interval (CI) was used to pool the data. The GRADE framework was introduced to assess the quality of evidence.

Results: Thirty-one trials involving 39,002 patients with T2D, with a median duration of 52 weeks were included. Meta-analysis of 16 trials

(37 acute pancreatitis events among 27,301 patients) did not find an increased risk of acute pancreatitis with SGLT2 inhibitors compared to controls (Peto OR, 0.80; 95% CI, 0.41 to 1.57; I^2 = 0%; moderate quality evidence). A similar result was found for risk of pancreatitis (Peto OR, 0.79; 95% CI, 0.47 to 1.34; I^2 = 0%; moderate quality evidence). When pooling the data from seventeen trials (14 pancreatic cancers among 17,664 patients), SGLT2 inhibitors were significantly associated with increased risk of pancreatic cancer (Peto OR, 3.74; 95% CI, 1.25 to 11.21; I^2 = 0%; very low quality evidence).

Conclusions: Our comprehensive analysis of randomized trial data suggests that SGLT2 inhibitors are not associated with increased risk of acute pancreatitis but with an increased risk of pancreatic cancer among patients with T2D. Despite suggestive evidence, these findings call for future safety monitoring in trial participants and in real-world settings.

1190 | Acute pancreatitis associated with opioid use: A nested case–control study

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Background: The annual incidence of acute pancreatitis (AP) in the general population ranges from 1.3 to 4.5/10,000 persons and drugs are responsible for 0.1% to 2% of cases. Opioids are among the suspected agents as they may induce spasms of the sphincter of Oddi (SSO), which can reduce biliary secretion, disrupt the enzyme's excretion from the pancreas and thus, lead to AP. In France the regulatory Agency considers opioid-induced pancreatitis as an emerging signal requiring additional data.

Objectives: i)To estimate the incidence of AP in adults (aged ≥18) who have initiated an opioid; ii)To identify the characteristics of opioid treatment and of patients that are associated with an increased risk of AP.

Methods: We conducted a nested case–control study within a random sample of adults who initiated an opioid between January 1, 2014 and December 31, 2016, identified in the administrative claims databases of Quebec (RAMQ). Cases were patients with a claims diagnosis of AP and/or SSO during the 12 months following the first opioid fill. Index date was the date of first diagnosis. For each case, 4 controls were identified through incidence density sampling and matched on age group (5-year intervals), gender and calendar date of cohort entry (± 6 months). Suspected risk factors were treatment characteristics (type of opioid, dose in MME and duration). Covariables included: history of AP, gallstones, alcoholism, hypertriglyceridemia, cholecystectomy, immune-related comorbidities and use of drugs known to increase the risk of pancreatitis. The incidence rate of AP in the cohort was estimated along with 95% confidence interval (95% CI). The association with treatment and individual patient characteristics was assessed through conditional logistic regression analysis. Risk modifiers were assessed using interaction terms in the model.

Results: The cohort included 84,825 new opioid users and the incidence of AP was estimated at 27.0/10,000 person-years (95% CI 2.4 to 3.1). The mean time to event was 141 days (median 108) for PA and 74 days (median 14) for SSO. Overall, 233 cases (229 PA, 4 SSO) were matched with 932 controls. Cases were more likely to have initiated an opioid treatment with morphine than controls (40.3% vs 32.3%), but less likely with codeine (38.2% vs 43.9%). Only 8 cases (4.4%) were long-term opioid users (≥90 days) compared to 21 controls (2.2%).

Conclusions: According to the standard threshold of 0.1%, acute pancreatitis is not a rare event in the population of opioid users. The identification of at-risk patients may be useful to minimize or mitigate the risk and therefore improve the follow-up care of patients initiating opioids.

1191 | Cinacalcet use and risk of gastrointestinal bleeding in secondary hyperparathyroidism patients receiving maintenance hemodialysis

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Background: Gastrointestinal (GI) bleeding is a frequent complication among hemodialysis (HD) patients. It has been hypothesized that cinacalcet use increases GI bleeding risk in HD patients with secondary hyperparathyroidism (SHPT).

Objectives: To assess the potential association between cinacalcet use and risk of GI bleeding in HD patients with SHPT.

Methods: We conducted a case–control study nested within a cohort of adult Medicare patients with SHPT who received chronic HD in a large dialysis provider in the US between 2007 and 2010. We excluded patients with evidence of cinacalcet use or a GI bleeding event in the year before cohort entry. Patients were followed from cohort entry to the earliest of death, parathyroidectomy, GI bleeding event, loss of Medicare coverage, change to peritoneal dialysis, transplant, or 12/31/2010. We defined a case who experienced a fatal or non-fatal GI bleeding event during follow-up. We matched up to four controls to each case based on age, race, sex, time on dialysis, and PTH level using incidence density sampling. The date of case event and matched control date were assigned as the index date. Exposure to cinacalcet preceding the index date was defined as any use (yes/no) and recency of use (within 61 days preceding index [current], more than 61 days preceding index [past], and no use). Multivariable conditional logistic regression was used to estimate the OR and the corresponding 95% CI for the association between cinacalcet use and risk of fatal and non-fatal GI

bleeding adjusting for potential confounders. Subgroup analyses were conducted by age, sex, race, time on dialysis and PTH levels groups.

Results: Among 51,007 patients, we identified 2570 cases, and of those, 2465 (96%) could be matched to 9400 controls. Matched cases and controls were on average 66 years, 48% were female, and 19% had PTH ≥600 pg/mL. Comorbid conditions were generally more prevalent in cases than controls, such as hepatitis (36% vs. 30%), COPD (27% vs. 20%), coronary artery diseases (50% vs. 42%) and upper GI diseases (31% vs. 22%). Cinacalcet use at any time before the index date was similar among cases and controls, 17.2% and 15.8%, respectively. The adjusted ORs and associated 95% CI's for the association between any use, current use and past use and GI bleeding were 1.04 (0.9–1.2), 0.97 (0.8–1.1), 1.22 (0.99–1.5), respectively. Results were consistent across subgroups.

Conclusions: In this study over 50,000 patients receiving HD, we found no evidence of an increased risk of GI bleeding associated with cinacalcet use, a treatment commonly used to manage SHPT.

1192 | Measuring the risk of liver injury in UK primary care patients prescribed a second course of Flucloxacillin: A cohort study using the clinical practice research datalink (CPRD)

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Background: First-time users of flucloxacillin are at an increased risk of serious liver injury. It is currently unknown, however, whether people with previous flucloxacillin exposure remain at-risk during subsequent courses of flucloxacillin therapy. Increasing rates of flucloxacillin prescriptions in the UK, particularly in the elderly, warrant further investigation into the side effects of this drug.

Objectives: To calculate the absolute and relative risks of drug-induced liver injury (DILI) during a second course of flucloxacillin and identify risk factors for second course DILI.

Methods: We used data from the UK Clinical Practice Research Datalink (CPRD) (1 January 2000 to 1 January 2012) to conduct a cohort study comparing the risk of DILI in patients prescribed a second course of flucloxacillin with patients prescribed a first course of oxytetracycline. Outcomes were (i) symptom-defined and (ii) laboratory-confirmed DILI within 1–45 days of second course initiation. Absolute 1–45 day risks were estimated, before applying multivariable logistic regression to calculate the relative risks. Secondary analyses were stratified by age, sex, and number of flucloxacillin prescriptions.

Results: There were 259,395 patients prescribed a second course of flucloxacillin (25 symptom-defined cases, 10 lab-confirmed) and 184,737 patients prescribed a first course of oxytetracycline (10 symptom-defined cases, <5 lab-confirmed). The 1–45 day adjusted risk ratio of symptom-defined DILI for flucloxacillin compared to oxytetracycline was 2.09 (95% CI 0.90–4.85). The absolute risk of symptom-defined DILI during the second course of flucloxacillin was 9.64 per 100,000 patients (95% CI 6.24–14.23), compared to 3.79 per 100,000 patients (95% CI 1.52–7.81) for the first course of oxytetracycline. Patients 80 years-of-age or older had 8 times the risk of symptom-defined DILI compared to those aged 18–49 (RR 7.99, 95% CI 2.44–26.15), and those with repeat flucloxacillin prescriptions within the second course had 2.4 times the risk compared to those with only one (RR 2.39, 95% CI 0.99–5.75).

Conclusions: There was weak evidence suggesting patients remain at an elevated risk of DILI during a second course of flucloxacillin; however, the risk appears to be lower when compared to a previous analysis of the risk in first-time users (14.15 per 100,000 during the first course vs. 9.64 per 100,000 during the second). Second-course DILI risk factors include older age and repeat prescriptions. Further work is ongoing to increase the sample size of this cohort.

1193 | Main drug classes dispensed prior to hospital admission for acute liver injury

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Background: Hepatic injury is a major safety issue. Most drugs and drug classes have been associated with liver toxicity.

Objectives: To quantify exposure to different drug classes prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS.

Methods: All hospital admissions for acute liver injury (K71.1,.2,.6,.9, K72.0) over 2009–2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were all drug classes at the highest ATC level, dispensed from 7 to 60 days before hospital admission. Reference populations were a) the French population over the study period, extrapolated from the 1/97thpermanent representative sample, EGB in a case-population analysis. b) 5 controls/case from EGB, matched on age, gender, and index date, for case–control analysis. Results are provided as a) number of cases per million users (MPt) or ten thousand patient-years (TPY), with 95% confidence intervals [95%CI]; b) Odds Ratios [95% CI], compared to non-exposure.

Results: 4807 ALI were matched to 24035 controls, with 3619 cases and 12793 controls exposed (OR 3.1 [2.9–3.4]). The greatest number of cases was exposed to analgesics (1954) followed by cardiovascular drugs (1858), the smallest was antimycobacterial (AMB, 86 cases). On the other hand, AMB were associated with by far the highest rates per MPt (399.9) and per MPY (909) and OR (72 [31–1646]) Second worst per million patients were antithrombotics (mostly aspirin) (86/MPt, 33/MPY, OR 1.54 [1.42–1.6], then cardiovascular drugs (74/MPt, 11/MPY, OR 1.8[1.66–1.94]. Analgesics including paracetamol were at 36/MPt, 88/MPY, OR 2.04 [1.91–2.18], and NSAIDs at 18.3/MPt, 77/MPY, OR 1.4[1.28–1.52]. Drugs for functional gastrointestinal disorder and antiemetics had OR above 3, maybe reflecting protopathic bias rather than actual risk. Risk per patient increased and risk per

MPY decreased with increasing average duration of treatment up to one year, then became very similar and stable for treatment dispensed for more than one year on average, in this five-year study.

Conclusions: The apparent risk of hospital admission for hepatic injury with previous exposure to drugs was probably increased by the ICD10 codes chosen, which selected for toxic liver injury, with a three times higher exposure to any drugs in cases than in controls. Antimycobacterial had by far the highest risk of hepatotoxicity, and NSAIDs among the lowest. Data was collected for over 200 drugs.

1194 | Antibiotic exposure prior to hospital admission for acute liver injury

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Background: Hepatic injury is a major safety issue. Several antibiotics (AB) have been concerned. Antimycobacterials (AMB) are known hepatotoxic drugs.

Objectives: To quantify exposure to AB or AMB prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS.

Methods: All hospital admissions for acute liver injury (K71.1,.2,.6,.9, K72.0) over 2009–2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were AB (ATC codes J01AA to J01MA) and AMB (J04) dispensed from 7 to 60 days before hospital admission. Reference populations were a) the French population over the study period, extrapolated from the 1/97thpermanent representative sample, EGB in a case-population analysis. b) 5 controls/case from EGB, matched on age, gender, and index date, for case–control analysis. Results are provided as a) number of cases per million users (MPt) or ten thousand patient-years (TPY), with 95% confidence intervals [95%CI]; b) Odds Ratios [95% CI], compared to non-exposure.

Results: 4807 ALI were matched to 24035 controls, with 3619 cases and 12793 controls exposed (OR 3.1 [2.9–3.4]). 1108 cases had been exposed to at least one AB, vs. 2606 controls (OR 2.47 [2.29–2.68]). All AB together had 1.3 [1.2–1.5] cases per TPY, 22.7 [20.2–25.2] per MPt. Individual drugs ranged per TPY from erythromycin 28.8 [21.8–37.5] to Doxycycline 0.4 [0.2–0.6]. Other commonly used drugs were amoxicillin 0.9 [0.8–1.0], co-amoxiclav 1.5 [1.3–1.7], clarithromycin 1.9 [1.5–2.5] /TPY. Per MPt rates were erythromycin 189 [141–242], clindamycin 31 [15–58], cotrimoxazole 26 [20–34], Co-amoxiclav 15 [13–18]. Odds ratios ranged from 93 [29–298] for erythromycin to 1.36 [0.85–2.18] for roxithromycin. Co-amoxiclav's OR was 3.55 [3.05–4.13], amoxicillin 1.76 [1.5–2.1].AMB ranged from 108/TPY for the triple association isoniazid, rifampicin, ethambutol to 17/TPY for isoniazid alone; per patient rates were 1728/MPt for the triple association, to 780 for isoniazid. The OR for all AMB pooled was 73 [31–164]. Many Individual AMB had no exposed controls. Estimated OR went from 174 for triple therapy, ethambutol 125, isoniazid 35.

Conclusions: The risk of hospital admission for hepatic injury with AB was similar for most AB, with some outliers: in addition to AMB, erythromycin was associated with a clearly much higher risk of admission for hepatic injury.

1195 | Antidepressant and anxiolytic-hypnotic exposure prior to hospital admission for acute liver injury

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Background: Acute liver injury (ALI) is a major drug safety issues. Several antidepressant (AD) and anxiolytic-hypnotic (BZ) drugs have been associated with ALI.

Objectives: To quantify exposure to AD/BZ prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database SNDS (66 million persons).

Methods: All hospital admissions for ALI (K71.1,.2,.6,.9, K72.0) over 2010–2014 were identified in SNDS. Cases with diagnoses of liver disease/injury were excluded. Exposures of interest were BZ (ATC codes N05B, N05C) and AD (N06A) dispensed from 7 to 60 days before hospital admission to avoid indication and protopathic biases. Reference populations were a) the whole French population over the study period extrapolated from the 1/97thpermanent representative sample EGB, in a case-population analysis: b) 5 controls/case from the same database matched on age and gender using the same index date for the case–control analysis:. Results are provided as a) number of cases per million users (MPt) or patient-years (MPY) with 95% confidence intervals [95%CI] b) Odds Ratios (OR) [95% CI] compared to non-exposure.

Results: 4807 cases with hospital admission for ALI were identified matched to 24035 controls. 3619 cases and 12796 controls had been exposed to any drug within 7–60 days preadmission (OR 3.1 [2.9–3.4]). 914 cases were exposed to at least one anxiolytic BZ and 495 to at least one hypnotic (vs. 2289 and 1207 controls (OR 2.3 [2.1–2.5] and 2.2 [2.0–2.5])): ranging from 244 cases for zolpidem to 5 for estazolam. Rates of ALI was 43 [37–47]/MPY for all BZ with individual drugs risk from 132 for clotiazepam [62–244] or hydroxyzine [113–153] to 32 [18–51] for loprazolam. Zolpidem was associated with 55 [47–62] cases/MPY. Per MPt rate was 45 [41–51] for all BZ, ranging from clorazepate 68 [49–94] to prazepam 26 [21–33]. Zolpidem was associated with 36 [31–41] cases/MPt, alprazolam 28 [24–32], bromazepam 30 [26–35]. OR ranged from 7.5 [1.2–45] for flunitrazepam to 1.5 [1.2–1.9] for lorazepam, with 2.1 [1.8–2.5] for zolpidem and 1.7 [1.5–2.0] for bromazepam 732 cases were exposed to AD vs. 1809 controls (OR 2.3 [2.1–2.5]) from 137 for escitalopram to 5 for fluvoxamine. Event rates/MPY ranged from 115 [88–146] for

mianserin to 32 [26–40] for escitalopram; per MPt from 118 [38–275] (fluvoxamine) to 31 [26–37] (escitalopram). OR ranged from moclobemide 7.5 [1.2–45] or agomelatine 6.36 [2.9–14] to escitalopram 1.8 [1.5–2.2].

Conclusions: Risks associated with most BZ or AD were within the same order of magnitude within each class, with a few outliers, none unexpected.

1196 | Liver enzymes during and after antimalarial therapy in Nigerian children with uncomplicated *Plasmodium falciparum* infection

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Background: Derangement of liver enzymes could occur during antimalarial treatment according to literature and this has been attributed to drug-induced liver toxicity. However, it remains unclear whether these changes in liver enzyme levels persist following the completion of antimalarial therapy.

Objectives: To determine the effect of artemether-lumefantrine on plasma levels of four liver enzymes, namely; alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and gamma glutamyl transpeptidase [GGT] in children with uncomplicated *Plasmodium falciparum* infection.

Methods: We reviewed the records of all children who participated in a clinical trial of antimalarial drug in Ibadan, Nigeria and a sample of 102 children who met eligible criteria and with microscopically-proven *Plasmodium falciparum* infection treated with artemether-lumefantrine at recommended age-specific doses for 3 days. Study participants were followed up on days 3, 7, 14, 21, and 28 according to the World Health Organization recommendation for treatment of malaria research participants. Inclusion criteria included symptoms attuned with acute uncomplicated malaria, including parasite density of at least 1000/μL and absence of chronic illness or danger signs of severe malaria. The results of ALT (U/L), AST (U/L), ALP (U/L) and GGT (U/L) at baseline (day 0), on day 3, and day 28 post-treatments were extracted and compared using Friedman tests.

Results: The median age of participants was 25 months (range = 3 to 119), and 49% were male. The mean values of ALT and AST did not change significantly over the course of the 28-day follow-up from baseline (25.8–19.1 U/L p = 0.0984 and 50.4–52.2 U/L p = 0.1943 respectively). GGT decreased substantially between baseline 17.0 U/L (11.0–22.5) and day 28 15.0 U/L (10.5–21.5) p = 0.0010 while ALP increased over time (baseline: 305.0 U/L (216.0–403.5); day 28: 345.0 U/L (241.0–492.5) p = 0.0303. Elevated ALT, AST, ALP and GGT were observed in 8.5%, 20.0%, 20.9%, and 14.8% of participants, respectively.

Conclusions: Considerable rise in plasma levels occurred in ALP which could be indicative of liver injury occurring during antimalarial treatment among Nigerian children. Further research is needed to identify the underlying mechanism responsible for this drug-induced liver toxicity.

1197 | Drug-induced liver injury associated with Antituberculosis and/or antiretroviral therapy: A case series from a prospective registry in the Western cape, South Africa

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Background: Drug-induced liver injury (DILI) is one of the most common adverse drug reactions resulting in hospital admission and death in South Africa. Antituberculosis therapy (ATT) and antiretroviral therapy (ART) are frequently implicated. We established a prospective registry of cases of liver injury that were suspected to have been caused by ATT and/or ART.

Objectives: To describe participant characteristics, liver injury presentation, potentially implicated drugs and outcome for DILI cases enrolled during the first 12 months after establishing the registry.

Methods: We enrolled adults (≥18 years) admitted to three Cape Town hospitals with a liver injury suspected to be due to ATT and/or ART, who fulfilled American Thoracic Society criteria for tuberculosis treatment interruption: ALT≥5 times ULN with no symptoms/ALT≥3 times ULN with symptoms/total bilirubin≥1.5 times ULN). We also enrolled patients meeting these criteria who developed a DILI during admission. Participants were followed until DILI resolution and drug rechallenge completion.

Results: We enrolled 48 patients with a median age of 38 years (interquartile range [IQR] 32 to 46), of which 25 (52%) were women. Forty-seven (98%) were HIV positive with a median CD4 count of 88 cells/mm^3 (IQR 31 to 302). DILI presentation was hepatocellular in 19 (40%), mixed in 8 (17%), cholestatic in 17 (35%), and uncategorized in 4 (8%). There was a median of 4 suspect drugs per case (range 1 to 7). ATT was potentially implicated in 38 cases (isoniazid in 38, rifampicin in 34, pyrazinamide in 31), ART in 36 cases (efavirenz in 34, ritonavir-boosted lopinavir in 2) and cotrimoxazole in 16 cases. Other potentially implicated drugs were carbapenems (3 cases), fluconazole (3 cases), amoxicillin-clavulanate (1 case) and paracetamol (1 case). Median hospital admission duration was 17 days (IQR 10 to 28). Rechallenge with ATT and/or ART was attempted in 30 participants, and was successful in 21. In 9/30 rechallenged participants the liver injury recurred, of which 3 died. In total 8/48 patients died (17%).

Conclusions: Patients with liver injury in this case series were receiving multiple concomitant potentially implicated drugs, which complicates causality assessment. Hospital admissions were prolonged, and mortality was high. Drug rechallenge is frequently attempted in liver injury due to ATT and/or ART because of limited

alternative treatment options, which resulted in DILI recurrence in 30% of rechallenged patients in this case series, and should be attempted with caution.

1198 | A multifactorial algorithm to automate screening of drug-induced liver injury cases in clinical and post-marketing settings

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Background: Hepatotoxicity can be linked to many different clinical symptoms and histopathological signs, making the surveillance of the suspected drug-induced liver injury (DILI) cases in the safety database a huge challenge. Additionally, a majority of the cases are rare, idiosyncratic, highly unpredictable, and with unique individual susceptibility. This ultimately makes the pharmacovigilance monitoring tedious and time-consuming.

Objectives: Develop a multifactorial algorithm to help identify high-risk hepatotoxicity cases from the safety database that lead to DILI.

Methods: Multifactorial selection criteria were established using a combination of word fragments, wildcard strings, and mathematical constructs based on Hy's law and pattern of injury (R-Value) for excluding non-eligible cases from monthly line listings. The capabilities and limitations of these criteria were verified by comparing a manual review of all monthly cases with system generated monthly listings over 11 months.

Results: The algorithm was easily programmable and could successfully identify 80–90% of non-eligible cases in both clinical and post-marketing settings. The automated process could easily compare enzyme elevations with baseline values, which reduced screening activity time to under 10 minutes. Approximately 25% of the monthly cases required manual reviews, as the algorithm could not screen them due to a non-standard laboratory test, naming conventions, and incomplete or incorrectly processed laboratory values, suggesting a partial elimination of the manual review process.

Conclusions: This multifactorial algorithm proved to be useful for the early detection of DILI cases before it leads to a Hy's Law case that might get missed by conventional methods. It also has the potential for universal application, due to its product-agnostic data and keyword mining features.

1199 | Analysis of 172 cases with drug-induced liver injury between 2017 and 2018 in a general Hospital in Central China

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Background: Drug-induced liver injury (DILI) is a rare clinical event, it carries significant morbidity and mortality. The causes and features of DILI vary in different regions.

Objectives: The main objective is to provide detailed description and characterization of DILI in a general hospital in Central China.

Methods: This study was conducted in a general hospital in Central China. In this retrospetive study, we collecting data on individuals with suspected DILI admitted from January 1, 2017 to December 31, 2018. Criteria for enrollment included alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN), or alkaline phosphatase level > 2 times ULN, or (ALT>3 times ULN and total bilirubin >2 times ULN). Descriptive statistics were used to describe the features of the patients. Between group difference was tested using the x^2test for categorical variables and Wilcoxon/Kruskal-Wallis test for the continuous variables. A P value <0.05 was considered statistically significant.

Results: Of the 172 cases, 44.8% were males, the mean age was 51 years. 55.2% of DILI cases occurred within 30 days and 76.6% of DILI cases occurred within 90 days after starting drug administration. 19.8% of patients had allergic history. 76.2% of patients received combined medication before admission. Leading causes for liver injury were herbal medicinal products (40.7%), antineoplastic drugs (15.1%) and antimicrobials (11.6%). The pattern of liver injury was hepatocellular in 57.6%, mixed in 27.3% and cholestatic in 15.1%. There were no differences in latency and severity of liver injury among different patterns of liver injury. In 60 patients with pre-existing liver disease, age is younger (46.7 years vs 53.3 years, P = 0.006) and proportion of hepatocellular type is higher than in those without liver disease (73.3% vs 49.1%, P < 0.01). Compared with liver injury caused by antineoplastic agents, liver injury induced by herbal medicinal products has shorter latency (P = 0.04), is more likely to be hepatocellular injury (P = 0.006), appeared to be more severe (P < 0.001), peak values of ALT and total bilirubin are higher (P < 0.001).

Conclusions: Leading causes for 172 DILI cases were herbal medicinal products, antineoplastic drugs and antimicrobials. In patients with pre-existing liver disease, age is younger and proportion of hepatocellular type is higher than in those without liver disease. Compared with antineoplastic agents, liver injury induced by herbal medicinal products has shorter latency, is more likely to be hepatocellular type injury, appeared to be more severe.

1200 | Proton pump inhibitors vs Histamine-2 receptor antagonists and risk of mortality in critically ill patients - a pilot analysis of multi-institutional study

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Background: Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly used for stress ulcer prophylaxis in intensive care units (ICUs). PPIs might possess higher potency in suppressing acid secretion to prevent gastrointestinal bleeding (GIB) than H2RAs; however concerns of adverse events such as *Clostridium difficile* infection and pneumonia limit the use of PPIs. The use of PPIs vs H2RAs to the overall survival and GI outcome for ICU patients remains controversial.

Objectives: To compare the risk of mortality and gastrointestinal bleeding between PPIs versus H2RAs in ICU patients.

Methods: We conducted a retrospective cohort study using medical records from two hospitals in Taiwan. We included ICU patients receiving either a PPI or a H2RA for prophylaxis of stress ulcer in 2018. We included patients' demographics and factors associated with GIB in the analysis, including use of invasive ventilator, shock, trauma, surgery, kidney and liver injury, coagulopathy, head injury, concurrent use of steroids or antithrombotic agents and hospital level. To reduce selection bias, we used propensity score methods to balance patients' characteristics between PPI and H2RA groups. We compared the risk of in-hospital mortality and GIB between two groups by using conditional logistic regression. We compared length of hospital stay between two groups by using generalized linear model.

Results: We included 89 PPI and 87 H2RA users with age of 61 ± 17 (mean ± SD) and 69 ± 17 (mean ± SD) years, respectively. We found PPI users with higher proportion of ventilator use (69% vs 36%), shock status (35% vs 17%), use of steroids (51% vs 13%) and antiplatelets (25% vs 15%) compared with H2RA users. The risk of in-hospital mortality was higher in PPI than in H2RA group (21.8% vs 12.6%; adjusted OR, 2.18; 95% CI, 0.59–8.02). PPI group had slightly lower risk of GIB than H2RA (adjusted OR, 0.83; 95% CI, 0.10–6.65), although no statistical significance. We found PPI and H2RA group had similar length of hospital stay (beta value, 0.97 days; 95% CI 0.65–1.47).

Conclusions: Although PPIs could possibly pose favorable effect in preventing GIB for ICU patients, it caused a higher risk of in-hospital mortality compared to H2RAs. This pilot study provides a fundamental ground for future multi-institutional study to confirm this finding.

1201 | Nsaid and analgesic exposure prior to hospital admission for acute liver injury

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Background: Hepatic injury is one of the major drug safety issues. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with liver injury.

Objectives: To quantify exposure to NSAIDs/analgesics prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS.

Methods: All hospital admissions for ALI (K71.1,.2,.6,.9, K72.0) over 2010–2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were systemic NSAIDs (ATC codes M01A), non-overdose paracetamol (N02AA, N02BE) and tramadol (N02AX02) dispensed from 7 to 60 days before hospital admission, to avoid indication and protopathic biases. Reference populations were a) the whole French population over the study period, extrapolated from the 1/97thpermanent representative sample, EGB in a case-population analysis; b) 5 controls/case from EGB, matched on age and gender, using the same index date for the case–control analysis. Results are provided as a) number of cases per million users (MPt) or patient-years (MPY) with 95% confidence interval [95%CI], b) Odds Ratios (OR) [95% CI], compared to non-exposure.

Results: 4807 ALI were matched to 24035 controls. 3619 cases and 12793 controls had been dispensed any drug within 7–60 days before admission (OR 3.1 [2.9–3.4]. 815 cases had been exposed to an NSAID (from 228 for ibuprofen to 5 for nimesulide, among 18 NSAIDs with at least 5 exposed cases); 1698 cases had been exposed to paracetamol, 162 to tramadol. Rates of Hospital admission were 75/MPY or 18/MPt [16–20] for any NSAID, and ranged from 299/MPY [120–616] for mefenamic acid to 37.9/MPY [11–88] for nimesulide, or from 14/MPt [1.5–19] for celecoxib to 2.7/MPt [0.9–6.3] for nimesulide. Other individual NSAIDs were ibuprofen 8.9/MPt [7.6–10.2], diclofenac 8.7/Mpt [7.6–10.2]. Paracetamol (alone or in combination) association with ALI was 105/MPY [95–117], 32/MPt. [28–35], tramadol used alone 91/MPY [77–106], 19/MPt [16–22].OR from the case–control analysis were 1.4 [1.3–1.5] for any NSAID, from 3.5 [1.3–9.2] for mefenamic acid, to 0.6 [0.25–1.6] for nimesulide, 1.4 [1.2–1.6] for ibuprofen, diclofenac 1.5 [1.3–1.9], celecoxib 2.1 [1.4–3.2], etoricoxib 2.1 [1.1–4.2]; OR for paracetamol was 1.95 [1.8–2.1], tramadol 2.3 [1.9–2.8].

Conclusions: The risk of hospital admission for hepatic injury was lower for NSAIDs than analgesics. There were no striking differences between NSAIDs. Risk of ALI after NSAIDs was generally lower that for all drugs combined.

1202 | Rates and predictors of post-surgical infections for common surgical approaches

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Background: More than 10 million patients undergo surgical procedures each year. The most common types of inpatient surgical procedures include cesarean section (CS), hysterectomy (HT), primary and revision total hip/knee replacement (P_THR, R_THR, P_TKR, R_TKR), spinal surgery (SS) and colorectal surgery (CRS). Post-surgical infection (PSI) are a significant cause of hospital readmissions, morbidity and mortality after surgery.

Objectives: To evaluate the rates of PSI by types, deep, superficial and organ/space for different surgical approaches (CS, HT, P_THR, R_THR, P_TKR, R_TKR, SS and CRS). This study also evaluated the risk factors for any PSI by surgical approaches.

Methods: This was a retrospective study of patients undergoing surgery (CS, HT, P_THR, R_THR, P_TKR, R_TKR, SS AND CRS) between 2014 and 2017 using IBM® MarketScan® Commercial, Multi-State Medicaid and Medicare Supplemental databases. Separate cohorts were created based on the surgical approach. The rates for new diagnoses of PSI, categorized as deep, superficial and organ/space within 6 months of surgery were calculated. Logistic regression models were evaluated to examine patient demographic and clinical comorbidities associated with any PSI.

Results: A total of 362,132 CS, 150,000 HT, 92,029 P_THR, 6,298 R_THR, 153,335 P_TKR, 10,429 R_TKR, 31,416 SS and 83,691 CRS patients were included in the analysis. For CS, PSI included 0.3% deep, 3.5% superficial, 0.9% organ/space and 0.04% both organ/space and deep cases with payer type and obesity as key risk factors associated with PSI. For HT, PSI included 0.5% deep, 4.7% superficial, 1.7% organ/space, and 0.1% organ/space and deep cases with cancer and renal failure as key risk factors associated with PSI. Overall 6.1% P_THR and 14.9% R_THR patients developed any PSI (deep infection: 2.7% in P_THR and 11.0% in R_THR) with obesity, liver disease and fluid/electrolyte disorders as key variables associated with PSI. Overall 5.9% P_TKR and 16.4% R_TKR patients developed any PSI (deep infection: 2.2% in P_TKR and 11.4% in R_TKR) with age, psychoses and cancer as key variables associated with PSI. For SS, PSI included 3.9% deep infection and 4.6% superficial cases with paralysis and blood loss anemia as the key factors associated with PSI. For CRS, PSI included 1.0% deep, 10.4% superficial, 9.0% organ/space and 0.8% both organ/space and deep cases with weight loss and fluid and electrolyte disorder as key factors for PSI.

Conclusions: The rate of any PSI was high for all common surgical procedures and ranged from 4.7% for CS to 21.2% for CRS. The risk factors identified differed by surgical approaches.

1203 | The role of sleeping pills in the development of shingles in veterans

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Background: There is continuing evidence that the chronic use of sleeping pills may be a risk factor for infection. One infection of concern in the aging veteran population is Herpes Zoster (HZ). Veterans are commonly prescribed sedative-hypnotics (sleeping pills) for chronic conditions such as insomnia, generalized anxiety disorders, mood disorders, alcohol withdrawal, seizures, panic attacks.

Objectives: To study the role of chronic use of commonly prescribed sedative-hypnotics in the development of shingles.

Methods: We studied the relationship between commonly prescribed sedative-hypnotics (benzodiazepines and Z-drugs) and incident HZ among veterans who received care at the James A. Haley Veteran's Hospital. A total of 22,000 veterans were randomly selected from each quarter year from 2007–2011 from CPRS/VISTA Patient Record System. All outpatient diagnoses, procedures and pharmacy data between 2006–2015 were then drawn from this cohort. To eliminate confounding by calendar date, patients without HZ were frequency matched on a visit date that was close to a HZ diagnosis date in the patients with HZ. Hypnotic use was examined in the 365 days prior to the HZ diagnosis date or a matching control date. Patients who had an acute hypnotic use (e.g. for a medical procedure) prior to the 90 days of HZ diagnosis date were excluded from that analysis. Logistic regression was used to calculate odds ratios (OR).

Results: Of 3522 patients on sedative-hypnotics, 200 (5.7%) developed HZ; out of the 18422 patients with no prescription for hypnotics, 741 (4.0%) developed HZ (OR = 1.437, 95%CI = 1.224, 1.687). The association remained significant (OR = 1.22, 95%CI =1.024,1.453) after adjusting for age, sex, BMI, Charlson comorbidity index, race, Hispanic ethnicity, marital status, combat status, opioid use.

Conclusions: Chronic use of sleeping pills is associated with later development of HZ. This supports a premise that long-term use of sleeping pills lowers immune status.

1204 | Medication related problems and associated risk factors among HIV/AIDS patients on antiretroviral therapy at a National Referral Hospital in Kenya: A cross-sectional study

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Background: Medication Related Problems (MRPs) are untoward events or circumstances that occur during drug therapy and interfere with desired therapeutic outcomes. HIV/AIDS patients on complex antiretroviral drug regimens are predisposed to medication related problems and associated morbidity and mortality.

Objectives: To evaluate the prevalence and risk factors of MRPs among adult HIV/AIDS patients on antiretroviral therapy at Kenyatta National Hospital (KNH).

Methods: A cross-sectional study was conducted in July and August 2018, at the Comprehensive Care Center at KNH, where patients on antiretroviral drugs are seen. Adults 18 years old and over were recruited, regardless of the antiretroviral regimen they were on. Data was collected prospectively through patient interviews and evaluation of patient records. A pharmacotherapy work up form developed by Cipolle, Morley and Strand was used as an interview guide. MRPs were identified and classified according to the Hepler-Strand classification. Descriptive and bi-variable data analysis was conducted using STATA (v.13).

Results: A total of 248 patients, of whom 62.0% were female were recruited into the study. MRPs were present in 118 (47.6%) patients. MRPs included: sub-therapeutic dosage (31.9%); untreated indication (21.3%); adverse drug reactions (17.9%); failure to receive drugs (15.5%); drug interactions (5.3%); overdose (4.4%); improper drug selection (2.4%); and drug use without indication (1.5%). The risk factors for sub-therapeutic dosage were poor adherence (p = <0.001), on transit patients (p = <0.001), and social/marital problems (p = 0.0001). For untreated indication, risk factors were clinician error (p = <0.001), financial constraints (p = <0.001), and stigma (p = 0.0002). Confusion due to complex regimens (p = 0.001) was the main risk factor for adverse drug reactions.

Conclusions: The prevalence of MRPs among adult HIV/AIDS patients in a single Kenyan referral hospital was high. The most prevalent MRPs were sub-therapeutic dosage, untreated indication and adverse drug reactions. Comprehensive pharmaceutical care is required to reduce the high prevalence of MRPs.

1205 | Medication related problems among HIV/AIDS patients on antiretroviral therapy at a National Referral Hospital in Kenya

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Background: Medication Related Problems (MRPs) are untoward events or circumstances that occur during drug therapy and interfere with desired therapeutic outcomes. HIV/AIDS patients on complex antiretroviral drug regimens are predisposed to medication related problems and associated morbidity and mortality.

Objectives: To evaluate the prevalence and risk factors of MRPs among adult HIV/AIDS patients on antiretroviral therapy at Kenyatta National Hospital (KNH).

Methods: A cross-sectional study was carried out at the Comprehensive Care Center (CCC) at KNH, where patients on antiretroviral drugs are seen. Adult patients over 18 years old were recruited. Data was collected through patient interviews and evaluation of patient records, over a period of two months. A pharmacotherapy work up form developed by Cipolle, Morley and Strand was used as an interview guide. MRPs were identified and classified according to the Hepler-Strand classification. Descriptive and bi-variable data analysis was conducted using STATA version 13 software. The level of significance was set at 0.05.

Results: A total of 248 patients, on different antiretroviral regimens were recruited in the study, of which 62% were female and 38% male. MRPs were present in 118 (47.58%) of the 248 patients. MRPs identified were sub-therapeutic dosage (31.88%), untreated indication (21.26%), adverse drug reactions (17.87%), failure to receive drugs (15.46%), drug interactions (5.31%), overdose (4.35%), improper drug selection (2.42%) and drug use without indication (1.45%). The risk factors for sub-therapeutic dosage were poor adherence (p = <0.001), on transit patients (p = <0.001) and social/marital problems (p = 0.0001). For untreated indication, risk factors were clinician error (p = <0.001), financial constraints (p = <0.001) and stigma (p = 0.0002). Mix up due to complex regimens (p = 0.001) was the main risk factor for adverse drug reactions.

Conclusions: The prevalence of MRPs in adult HIV/AIDS patients was high (47.58%). The most prevalent MRPs were sub-therapeutic dosage, untreated indication and adverse drug reactions. There were no documented interventions by a pharmacist.

1206 | Rare adverse effects analysis of new generation hepatitis C medications using EMR and FAERS data

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Background: New generation drugs for treating Hepatitis C have been introduced to the market in 2014, including Harvoni, Sovaldi, Olysio, Mavyret, Vosevi and Epclusa. The new treatments have been proven to be more effective and better tolerated, compared to the old interferon based treatments. However, the rare adverse effects of these drugs are largely unknown, due to the limited sample size of the clinical trials and lack of post-marketing evidence of these drugs.

Objectives: In this paper, we conduct a comparative study of the drug safety of the old and new generation Hepatitis C medications, aiming to find some important rare adverse effects, especially for the new medication.

Methods: We use the data from the post market spontaneous reporting systems such as the FDA/CDC Adverse Event Reporting System (FAERS), as well as health system data such as electronic medical record (EMR) data. For FAERS data, we search over 6,000,000 reports between 2004 to 2015 and extractthe AEs for both the old and new medications. For EMR data, we define a selection window from the medication started date to 180 days after the medication stopped date for any patient that ever had old or new Hepatitis C medication. The diagnosis code of any encounter during the selection window are extracted and mapped to the MedDRA terms. Rare AEs

that happen only for new medications are identified and their risk rates are calculated.

Results: For the new drug-specific rare AEs, the number of total encounters and risk rates are calculated and ranked, using both FAERS and EMR data sets. For example, using EMR data the identified AEs include toxoplasmosis (1.1%, [0.9%, 1.3%]), meningitis due to other organisms (1%, [0.8%, 1.2%]), malignant neoplasm of rectum (0.9%, [0.7%, 1.1%]) and slow virus infection of central nervous system (0.7%, [0.5%, 0.8%]).

Conclusions: The two data sources, FAERS and EMR, agree on some identified AEs but are not consistent on some others. We interpret the importance of the identified AEs from the clinical perspective. We also discuss the strengths and limitations of the two data sources in post-marketing pharmacovigilance research and the need for novel data integration methods that can effectively combine the strengths of these two data sources.

1207 | Tenofovir-associated renal toxicity in a cohort of HIV-infected patients in Ghana

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Background: Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue recommended in international HIV treatment guidelines. The association of TDF with renal dysfunction has remained an area of interest due the structural similarity between tenofovir and the nephrotoxic acyclic nucleotide analogues adefovir and cidofovir.

Objectives: Purpose of study was to estimate the long term effects of TDF on renal profile in a cohort of HIV patients in Ghana.

Methods: We selected 300 consecutive HIV-positive patients (with baseline creatinine clearance ≥50 mL/min) who initiated TDF-based antiretroviral treatment in 2008 from a database of patients on antiretroviral therapy at the Korle-Bu Teaching Hospital. Socio-demographic, clinical and laboratory details were extracted from patients' medical records. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation at baseline and renal impairment was defined as CrCl values of 30.0–49.9 mL/min (moderate renal impairment) and < 30 mL/min (severe renal impairment) as per institutional guidelines for renal function test. The proportion of patients with moderate or severe renal impairment was calculated. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for factors associated with renal impairment.

Results: Median follow up time was 2.9 years (IQR 2.3–3.4 years). Females were dominant (n = 213, 71.1%) and the mean age of study participants was 39.1 ± 11.1 years. The median CrCl rate at initiation of TDF-containing ART was 76.8 mL/min [IQR 58.3–105.4]. At study endpoint, 63 participants (21.0% [95% CI: 6.5–26.1]) recorded CrCl rate below 50 ml/min indicating incident renal impairment, made up of 18.3% moderate renal impairment and 2.3% severe renal impairment. Factors associated with the incidence of renal impairment were increasing age (RR = 1.04 [95% CI, 1.03–1.06] per year), decrease in creatinine clearance rate at baseline (RR = 1.05 [95% CI, 1.04–1.08] per every 1 mL decrease), WHO HIV stage III (RR = 3.78 [95% CI, 1.42–10.06]) or Stage IV (RR = 3.42 [95% CI, 1.16–10.09]) compared with stage I and participants with BMI of <18.5 kg/m^2 underweight (RR = 3.87; 95% CI, 2.49–6.03) compared with patients with BMI of >18.5–24.9 kg/m^2 (normal weight).

Conclusions: The use of TDF based regimen led to 18.3% developing moderate renal impairment and 2.3%, severe renal impairment. Patients with identified renal impairment risk factors at ART initiation should be targeted and monitored effectively to prevent renal injury.

1208 | The effects of amoxicillin on acute COPD exacerbations in the outpatient setting: A retrospective cohort study based on real-world data

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Background: Previously the effects of antibiotics for COPD exacerbation were only established in ICU patients. Recent updated Cochrane review (Vollenweider et al., 2018) shows a significant effect of antibiotics in treating COPD exacerbations in the outpatient setting. However, effects have not been established using real-world data.

Objectives: To assess both the short-term and long-term effects of amoxicillin on the prognosis of COPD exacerbation in outpatients.

Methods: We conducted a retrospective inception cohort study using the widely researched University of Groningen prescription database IADB.nl. Eligible patients had a first exacerbation treatment with or without amoxicillin to exclude the influence of prior exacerbation history. The main outcome was treatment failure, which was defined as a new prescription of prednisone/prednisolone or antibiotics between 15 to 30 days after the first exacerbation. A secondary outcome was the time to second exacerbation within 12 months.

Results: In all, we identified 4,775 eligible COPD patients. Among these patients, 736 (15%) were treated with combined treatment of amoxicillin plus prednisone/prednisolone, while 4039 (85%) were given only prednisolone/prednisone. We did not observe a significant difference in rates of treatment failure between amoxicillin and comparison group (relative risk (RR) of treatment failure: 0.96 [95%CI: 0.78–1.20]). After adjustments for differences in age, gender, drug use for COPD and other comorbidities, the adjusted RR indicated a small non-statistically significant effect (RR 0.91 [95%CI: 0.73, 1.13]). Median time to 2nd exacerbation was 174 days [95% CI 151–197]) in amoxicillin group compared with 180 days [95% CI 169–191] in the control group (hazard ratio: 1.07 [0.97–1.17], p = 0.17).

Conclusions: The data were compatible with a potential small effect of amoxicillin added to oral corticosteroids in acute COPD exacerbations treated in an outpatient setting. However, unmeasured confounding by indication should in future studies be quantified to confirm or refute this finding.

1209 | Risk of interstitial lung disease among patients treated for atrial fibrillation with selected anti-arrhythmic drugs in two healthcare databases

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Background: Dronedarone is an anti-arrhythmic drug (AAD) indicated to reduce risk of hospitalization for atrial fibrillation (AF) among patients in sinus rhythm with a history of paroxysmal or persistent AF. Interstitial lung disease (ILD) is an identified risk for dronedarone, and ILD is also related to other AADs, notably amiodarone.

Objectives: To investigate if there is an increased ILD risk with dronedarone when compared to amiodarone and other anti-arrhythmics.

Methods: Retrospective cohort studies were conducted using records from two healthcare databases, the US Department of Defense Military Health System (MHS) and HealthCore Integrated Research Database (HIRD), for services from 7/20/2008 to 9/30/2014. Eligibility criteria were an AF diagnosis and new prescription for dronedarone, amiodarone, sotalol or flecainide. Prevalent cases of ILD were excluded. Propensity scores were used to adjust for confounding and potential selection factors associated with dronedarone treatment relative to the three comparator treatment groups.

Incident ILD cases were identified from inpatient ICD-9-CM diagnosis codes 515, 516.3–516.37, 516.8 or 516.9. An expanded definition of ILD, used for sensitivity analysis, added ICD-9-CM codes 495.9 and 518.82. Cases were adjudicated by expert pulmonologists and only confirmed cases were retained.

Separate Cox proportional hazards models were used to compare the hazard of ILD for each comparator to that of dronedarone (reference).

Results: Following adjudication there were 72 ILD cases (52 in the MHS and 20 in the HIRD). Risk of ILD in the MHS was elevated for amiodarone when compared to dronedarone (HR 2.5; 95% CI 1.1–5.3; $p < 0.05$). No significant differences were seen with any of the other AADs in either database.

Conclusions: Dronedarone was not associated with an increased risk of ILD when compared to other AADs, while patients prescribed amiodarone were at an increased risk for ILD compared to dronedarone in the MHS. Despite propensity score matching, the potential for residual confounding, selecting older and sicker patients for treatment with amiodarone, is an important limitation to these findings.

1210 | Risk of developing chronic obstructive pulmonary disease or lung cancer in smokers taking enzyme-inducing antiepileptic drugs

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Background: Enzyme-inducing antiepileptic drugs (AEDs) can increase the activity of pulmonary enzymes involved in the bio-activation and metabolism of toxic chemicals in tobacco smoke. Smokers who take these drugs may therefore have an altered risk of developing chronic obstructive pulmonary disease (COPD) or lung cancer (LC).

Objectives: To determine whether enzyme-inducing AEDs affect the risk of developing COPD or LC in people who smoke.

Methods: We conducted a matched case–control study using UK primary care data from the Clinical Practice Research Datalink. We performed multivariate logistic regression analyses to compare prior exposure to enzyme-inducing AEDs between cases with incident COPD or LC and controls without these lung diseases among smokers having ≥1 prescription for any type of AED (enzyme- or non-enzyme-inducing) before the index date. We stratified analyses by duration of enzyme-inducing AED use and level of tobacco exposure.

Results: We identified 5952 incident COPD and 1373 incident LC cases, and 59 328 and 13 681 matching controls, respectively, between 1995 and 2016. Overall, compared with never use, ever use of enzyme-inducing AEDs was associated with a slightly decreased risk of COPD (adjusted odds ratio [aOR]: 0.84, 95% CI: 0.80–0.89) and LC (aOR: 0.82, 95% CI: 0.73–0.92). However, the risk of COPD and LC was not altered among medium- and long-term users of enzyme-inducing AEDs who were moderate or heavy smokers, which argues against a consistent protective effect of enzyme induction in preventing these smoking-related lung diseases.

Conclusions: We did not find robust evidence for an association between the use of enzyme-inducing AEDs and the development of COPD or LC in people who smoke.

1211 | A comparison of outcome-related diagnostics for propensity scores

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Background: Propensity scores are commonly used to reduce confounding bias in observational data by balancing covariate distributions between exposure groups. However, it is unclear how best to assess their performance. Outcome-related diagnostics which prioritize balance on covariates strongly associated with outcome would be of value, since these covariates contribute most towards confounding bias. One idea is to calculate a weighted average of balance across all covariates. Alternatively, we could use the standardized mean difference in prognostic scores (i.e. predicted outcome under the control condition) between exposure groups. There is little research available comparing the performance of these diagnostics.

Objectives: To compare seven outcome-related diagnostics in terms of their correlation with bias in a simulation study.

Methods: Diagnostics included the standardized difference in prognostic scores and six weighted averages of balance across covariates. Weighted averages were defined by the combinations of three balance metrics (standardized difference, Kolmogorov–Smirnov statistic and overlapping coefficient) and two weighting methods. For covariate X, Weights 1 and 2 were defined as the coefficient for X obtained after regressing the outcome on X and all covariates respectively, multiplied by the standard deviation of X.

Results: Using the Kolmogorov–Smirnov statistic or overlapping coefficient led to negligible correlation with bias in all scenarios. For scenarios with independent covariates and linear outcomes, prognostic scores and weighted standardized differences (using either weights) performed well (all correlations above 0.9). When covariates were correlated, the correlation between bias and weighted standardized differences using Weights 1 decreased to 0.4, but remained high for prognostic scores and weighted standardized differences using Weights 2. For nonlinear outcomes, weighted standardized differences and prognostic scores estimated using a linear model demonstrated poorer performance. For example, in scenarios with moderate nonlinearity in the outcome, using Weights 1, 2 and linear prognostic scores obtained correlations of 0.2, 0.3 and 0.4 respectively. Only prognostic scores estimated using the correctly specified model performed consistently well across all scenarios.

Conclusions: A correctly estimated prognostic score would be a useful diagnostic for assessing how well propensity scores have removed confounding bias. In real data however, the true prognostic scores are unknown and it is unclear what the best estimation strategy would be.

1212 | A systematic review of the use of propensity scores in cardiovascular literature

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Background: Previous assessments have found that propensity score (PS) methods are implemented and reported inadequately in clinical literature. As cardiovascular studies increasingly use these methods, a comprehensive review of their reporting and use in cardiovascular literature is needed.

Objectives: To conduct a systematic review of the use, reporting, and interpretation of PS methods in cardiovascular publications.

Methods: Articles using PS methods, published between 2010–2017 in high-impact medical (5) and cardiovascular (3) journals and focusing on cardiovascular drugs, devices, diseases, and outcomes, were identified. Keywords included *propensity*, *inverse probability weighting (IPW)*, *marginal structural models*, *targeted maximum likelihood estimation*, *and doubly robust*. Elements for data extraction were based on PS literature, with an additional focus on causal interpretations and target population. Data collection form was reviewed by all investigators and pilot tested. Each article was assessed independently by two reviewers.

Results: A total of 296 articles were included. The most commonly used PS method was matching (53% of studies), followed by more than one method (19%), direct adjustment (13%), IPW (12%), and stratification (3%). In almost half (48%) of reviewed articles, interpretations of the effect estimates (average treatment effect (ATE), average treatment effect in the treated (ATT), average treatment effect in the untreated (ATU)) did not correspond to the PS method conducted. Whereas *a priori* identification of confounders or predictors of the outcome is preferred, 17% of publications used statistical testing to identify variables for the PS model. Assessment of balance, a critical step in the appropriate use of PS methods, was not assessed in 16% of articles. Of those who assessed balance, 55% reported standardized differences, the recommended measure for assessing balance, and 45% reported other measures. Among articles that used PS matching, 21% did not describe their matching strategy and 8% did not describe the post-match balance of covariates. Furthermore, 17% of studies matched fewer than half of the available treated (or untreated, based on targeted parameter) subjects.

Conclusions: Detailed reporting of PS methods provides transparency and helps accurately evaluate the results and the population to which the results apply. This systematic review shows that details of PS methods in cardiovascular studies were generally well reported in high-impact cardiovascular journals. In almost half of the studies, however, the interpretation of the effect estimates was inaccurate.

1213 | Comparisons of propensity score-based estimates in the presence of treatment effect modification

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Background: Clinical studies using both PS based methods (matching, stratification, covariate adjustment, weighting) and conventional regression have compared estimates from both approaches. Although each of the methods provides different estimand particularly in the presence of treatment effect modification, differences or similarities in the treatment effect estimates have been misinterpreted as limitations of the methods per se.

Objectives: To describe different PS-based estimates in the presence of treatment effect modification using a clinical example.

Methods: We used the UK Clinical Practice Record Datalink (CPRD) data to evaluate the association between bariatric surgery (BS) on the risk of type-2 diabetes mellitus (T2DM) as an example. We followed patients from index date until T2DM, death, loss-to follow-up or end of study (31-December-2014), whichever came first. We fitted DRS in the patient groups without the exposure (Bariatric Surgery) and predicted baseline risk of T2DM for the entire cohort using logistic regression. We then applied 1:1 PSM with caliper width of 0.20 standard deviation on the logit of the PSto estimate the treatment effect in the Bariatric surgery groups (ATT), non-surgery group (ATU), and the total population (ATE). In addition, we used inverse probability of treatment weighting (IPTW) and conventional Cox model to estimate ATE. We evaluated covariate balance using absolute standardized mean difference (ASMD) in the PSmatched dataset. We estimated hazard ratios and 95% confidence intervals (95%CI) using Cox proportional hazards models.

Results: In total, we had 17030 patients with 1596 developing T2DM during follow-up and after PSM, 5,132 patients with 406 developing T2DM during follow-up to estimate ATT and 5134 patients with 439 developing T2DM during follow-up to estimate ATU. In both PSM, all patients in the bariatric surgery group were retained. Bariatric surgery reduced the risk of T2DM, the PSM estimated ATT was 0.57 [95%CI; 0.47, 0.70] compared to the ATU 0.58 [0.48, 0.71]. Both estimates were similar to the ATE estimated using IPTW, 0.57 [0.47, 0.69], and conventional Cox models, 0.56 [0.47, 0.66].

Conclusions: We observed similar results among PS methods even in the presence of treatment effect modification. This could partly be explained by retention of the patients in the treatment group after PSM. Specifications of treatment effect estimands are important when patients from one treatment groups are excluded due to matching particularly in studies using combinations of methods.

1214 | Propensity score matching with bootstrapping and "divide and recombine" approaches in huge data

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Background: Propensity score matching has been a popular approach in pharmacoepidemiology; however, the computational load associated with propensity score matching in huge data such as "the 100 Million Brazilian Cohort" pose a big challenge. Several alternatives such as bootstrap sampling and "Divide and Recombine" (R&D) using parallelization have been suggested as ways to increase the procedure speed by utilizing multiple processors/cores simultaneously. However, the performance of these approaches has not been evaluated.

Objectives: To evaluate the performance of PSM using bootstrap sampling and "D&R" approaches in huge data.

Methods: We used Monte Carlo simulations to generate datasets of 5 million and 10 million records. Covariates were created using binomial, normal and multinomial distributions. Treatment was generated using binomial logistic regression model conditional on covariate and outcome data was generated using the Poisson model conditional on treatment and covariates. PSM was performed: 1) in each of 500 bootstrap samples from the full data; and 2) with D&R approach, in each of the k-sample data after the full dataset was split into k-samples, all being parallelized. PSM was performed with and without caliper and covariate balance was assessed using absolute standardized mean difference (ASMD). Afterwards, treatment effect estimates were recombined using weighted average and). In addition, inverse probability weighting and PS stratification were used to estimate treatment effect on the entire sample. The performance was evaluated using percentage bias and coverage probability.

Results: PSM based approaches (both bootstrapping and D&R) and IPTW gave similar treatment effect estimate with an average percentage bias close to 2%. However, PSM approaches resulted in improved covariate balance (SMD for all covariates <2.5%) and high coverage probability (100%) compared to IPTW methods (ASMD for some covariates was as big as 15%). On the other hand, PS stratification with five quintiles resulted in a greater bias in the treatment effect estimate, up to 8%.

Conclusions: PSM using bootstrap sampling and D&R approaches are efficient alternatives to IPTW approaches with huge data when full sample PSM cannot be conducted.

1215 | Improving confounder adjustment: Translating high-dimensional propensity score principles to United Kingdom electronic health records

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Background: A recent United Kingdom (UK) electronic health record (EHR) study found that among clopidogrel users, co-use of a proton pump inhibitor (PPI) was associated with an increased

risk of myocar-dial infarction (MI). However, the study authors highlighted evidence suggesting that this finding was driven by unmeasured confounding. In situations like this, use of the high-dimensional propensity score (hd-PS) algorithm has become increasingly popular amid evidence in US claims data suggesting it improves adjustment for confounding. Despite this enthusiasm, it is unclear how best to adapt hd-PS principles outside its original setting, especially given the potential disparity between databases.

Objectives: To adapt the hd-PS algorithm in the setting of UK EHRs.

Methods: A cohort of clopidogrel users was derived from the UK Clinical Practice Research Datalink linked with the Myocardial Ischaemia National Audit Project. All analyses estimated the hazard ratio of MI comparing PPI users with non-users using a Cox model adjusting for confounders via propensity scores. We conducted hd-PS analyses incrementally applying modifications that included varying the coding system and adapting the existing assessment of code recurrence to reflect recording practice in UK EHRs. Results were compared to an analysis incorporating only the original confounders. Sensitivity analyses investigated the impact of varying the number of covariates selected for inclusion in our adapted hd-PS model.

Results: 24471 patients took clopidogrel, of whom 9111 were prescribed a PPI. Of PPI users, 313 (3.4%) had an incident MI versus 421 (2.7%) in non-users. Including the original confounders via propensity scores obtained a HR for the association between PPI use and MI of 1.17 (95% CI: 1.01–1.36). Standard implementation of the hd-PS algorithm obtained a HR of 1.10 (95% CI: 0.88–1.36), while applying our modifications resulted in effect estimates closer to the expected null result (HR 0.99; 95% CI: 0.79–1.24). Sensitivity analyses found that selecting fewer than 500 variables improved the precision of effect estimates (HR 1.00; 95% CI: 0.86–1.18).

Conclusions: Use of hd-PS provided improved adjustment for confounding compared with non-hd approaches, suggesting hd-PS methods can be usefully applied in UK EHR data.

1216 | Evaluation of observational study data with multi-level propensity scores: The planning process

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Background: Pharmacoepidemiology database studies often utilize propensity scores (PS) to adjust for confounding between two exposure groups while reducing dimensionality by including fewer independent variables within outcome models. A multi-database study was originally planned with a binary exposure, but then modified to 4 exposure levels at FDA request.

Objectives: To codify a process for shifting the design from a binary to 4-level exposure, highlight considerations for discussion.

Methods: Three distinct parts of PS model development were discussed in considering the change from binary to 4-level exposure: (1) determine the model to develop the PS, (2) assess balance in the PS model, and (3) decide on whether and how to do trimming. The FDA requested specific documentation of how covariate balance would be assessed and achieved and how the 4-level PS would be incorporated into outcome models.

Results: After deciding that PS was still appropriate for the study, PS model development was discussed. (1) Exposure levels could be treated as ordinal or nominal; nominal and multinomial logistic regression models were chosen. (2) Balance could be assessed using standardized bias assessment (e.g., absolute standardized differences [ASD]) either as summary measures or via pairwise comparisons between all pairs of exposure levels (n = 6 comparisons) or as comparison versus a single referent (n = 3 comparisons). Summary measures could be created via averages, min/max of pairwise comparisons, or as a composite score accounting for distance between all 4 levels simultaneously. Pairwise comparisons versus the referent category of ASD for all variables included in the PS model was chosen. If any ASD was above 0.2, further refinement of the PS model would be used. (3) Overlap could be considered as the range of PS covered by any pair of exposure levels, the coverage between the referent and each of the other 3 levels, or the coverage only for the range of PS occurring in all 4 levels of the exposure. "Fully overlapping" regions would be ideal for interpretation but would narrow the range of PS. A broader PS range of any overlapping may be more robust analytically and was deemed appropriate for the primary analysis, with the caveat that this would be revisited after examination of the data.

Conclusions: This process allowed the study team to discuss and decide upon changes to PS model development to address regulatory research questions.

1217 | Deep learning-based propensity score computation: Cohort study in second line treated advanced non-small cell lung cancer (aNSCLC) patients

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Background: Autoencoders are unsupervised deep learning encoder-decoder architectures which learn a nonlinear lower-dimensional feature representation from unlabelled data. Propensity score (PS) computation utilizing autoencoder-learned patient representations might

be an attractive alternative to manual variable selection in pharmacoepidemiology.

Objectives: To investigate and compare PS balancing and adjustment generated from manual variable selection versus autoencoder-derived PS. To this end, both approaches were applied to replicate the result of a meta-analysis of randomized trials (RCTs) investigating the comparative effectiveness of checkpoint inhibitors (CPIs) versus docetaxel as second line (2 L) treatment in aNSCLC patients.

Methods: Within the Flatiron Health EHR-derived database, aNSCLC patients were identified who initiated either CPI or docetaxel as 2 L treatment. In a first approach, PS were computed using logistic regression with manually selected variables. In a second approach, representation learning among all 2 L treated patients was employed using a 7-layer symmetric autoencoder architecture with all available baseline covariates as input vector. The learned patient embeddings in the 64-dimensional bottleneck layer were used within the eligible aNSCLC study population to compute the PS via logistic regression. In the final outcome model, overall survival (OS) was estimated using Cox proportional hazards regression with trimmed and stabilized PS weights. Balance in PS distributions for both settings was graphically examined by plotting density functions before and after weighting.

Results: The study population comprised 4,781 CPI and 900 docetaxel initiators. Kaplan–Meier analysis suggested a significant survival benefit for CPI initiators with a median OS of 9.1 (95% CI 8.6–9.6) months compared to 6.1 (95% CI 5.5–6.6) months among docetaxel initiators ($p < .0001$). Graphical comparison of PS overlap between CPI and docetaxel initiators indicated well-balanced cohorts for both settings after PS weighting. In the adjusted analysis, both approaches led to similar results with hazard ratios (HR) of 0.72 (95% CI 0.65–0.80) with manual variable selection and 0.75 (95% CI 0.69–0.81) in the autoencoder setting. In comparison, the meta-analysis of RCTs resulted in an estimate of HR 0.69 (95% CI 0.63–0.75).

Conclusions: In line with RCTs, both PS computation approaches similarly suggest a significantly enhanced OS among patients receiving 2 L CPI therapy. Autoencoders might be alternatively used to derive PS in a more automated way.