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Assessing adherence and persistence to non-vitamin K antagonist oral anticoagulants (NOACs) among patients with atrial fibrillation in tertiary-care referral centers in Malaysia

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Abstract

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Original Article

Assessing Adherence and Persistence to Non-vitamin K Antagonist Oral Anticoagulants (NOACs) among Patients with Atrial Fibrillation in Tertiary-care Referral Centers in Malaysia

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ABSTRACT

Introduction: Non-vitamin K antagonist oral anticoagulants (NOACs), such as dabigatran and rivaroxaban, are now available for stroke prevention in patients with atrial fibrillation (AF) and are often clinically preferred over vitamin K antagonists (VKAs), such as warfarin. Data describing adherence and persistence to NOACs in real-life clinical practice in Malaysia are scarce. This study aimed to assess adherence and persistence to NOACs in patients with AF in two tertiary-care referral centers: Hospital Kuala Lumpur (HKL) and Hospital Serdang (HSDG). **Materials and Methods:** This was a retrospective cohort study that included all patients with AF who were treated with NOACs (dabigatran or rivaroxaban) in HKL and HSDG. Data were obtained from medical records and pharmacy databases. Adherence was assessed using proportion of days covered (PDC) over a 1-year duration. High adherence was defined as PDC ≥80%. A gap of >60 days between two consecutive refills was used to define non-persistence. **Result:** There were 281 patients who met the inclusion criteria, with 54.1% (n = 152) male. There were 75.1% (n = 211) patients on dabigatran and others on rivaroxaban. Only 66.9% (n = 188) of patients achieved high adherence with PDC ≥80% and 69.8% (n = 196) were persistence with >60-day gap over 12 months. Adherence and persistence were both influenced by treatment center, whereas polypharmacy only influenced adherence. **Conclusion:** Overall adherence and persistence to NOACs were suboptimal and varied between treatment centers, potentially due to institution-specific administrative and clinical practice differences. Clinical care and outcomes can potentially be optimized by identifying factors affecting adherence and persistence and by implementing interventions to improving them.

Keywords: *Atrial fibrillation, Malaysia, medication adherence, NOACs, non-vitamin K antagonist oral anticoagulants, OACs, oral anticoagulants*

Introduction

Oral anticoagulants (OACs) are used to reduce the risk of stroke and mortality among patients with atrial fibrillation (AF) at moderate-to-high risk of thrombosis events (CHA_2DS_2-VASc score ≥2).[1] Non-vitamin K antagonist oral anticoagulants (NOACs), such as dabigatran and rivaroxaban, have

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been recently developed and approved as alternatives to vitamin K antagonist (VKAs) such as warfarin for venous thromboembolism (VTE) and for prevention of thrombosis in patients with AF.[2]

AF is a chronic disease that often requires long-term pharmacotherapy. Medication non-adherence, according to various measures, can be as high as 30%–50% among patients with chronic diseases and is more prevalent in patients with asymptomatic diseases such as AF and VTE.[3,4] Adherence can be additionally challenging for patients with AF as the majority are elderly with multiple comorbidities and requiring various medications.[5]

NOAC is relatively new within clinical practice in Malaysia with limited practice-based data on its use. This study aimed to assess the patterns of adherence and persistence to NOACs within clinical practice in Malaysia.

Materials and Methods

Setting

This is an observational retrospective cohort study conducted in two tertiary-care referral centers in Malaysia: Hospital Kuala Lumpur (HKL) and Hospital Serdang (HSDG). These two study sites were selected as they have among the highest number of NOAC prescriptions compared to other Ministry of Health centers in Malaysia. Data were obtained from electronic pharmacy dispensing records, treatment-center databases, and relevant records. Patient-level data reflected dispensing from the period between June 2012 and June 2019. Ethics approval from Medical Research Ethical Committee (MREC) was obtained with National Medical Research Register (NMRR) number (NMRR-17-3020-38667).

Study population

Patients with documented AF diagnosis were included if they fulfilled the following criteria: (1) aged ≥18 years on the index date; (2) were prescribed and dispensed dabigatran or rivaroxaban; (3) have continuous medical and pharmacy records from the index-date until the end of study period (i.e., minimum 1 year in order to describe 12-month adherence); and (4) first dispensing refill reported between 2012 and 2018. The index-date was defined as the first date of dispensing of NOACs. Dabigatran and rivaroxaban were the selected index-agents because these are the most commonly prescribed NOACs in these treatment centers. Patients with defaulted follow-ups were excluded from this study.

Outcomes and study measures

Adherence is defined as "the extent to which a person's behavior (including medication taking) corresponds with agreed recommendations from a health care provider"[6] and was assessed for patients with AF for at least 1 year. Adherence was measured using proportion of days covered (PDC), which is the preferred method of Pharmacy Quality Alliance (PQA).[7] PDC denominator was defined as the number of days from the index-date until the end of study period, where adherence is measured over 12 months and over 24 months, whereas the numerator was defined as the days of medication covered through the study period based on the dispensing refill records. High adherence for an individual patient was defined at as PDC ≥80%.[7] The sensitivity analysis explored high adherence defined as PDC ≥90%.

Persistence is defined as "the interval between the date of the first prescription and the point at which an unacceptable gap between prescription refills occurs."[8] Treatment non-persistence for NOACs was defined as a gap of more than 60 days within a 1-year period.[9] The sensitivity analysis explored treatment non-persistence at a gap of more than 30 days. Statistical analysis was also conducted to identify factors that influenced adherence and persistence in the study population, using Statistical Package for the Social Sciences (SPSS) software program, version 25.0 (IBM Corp. Armonk, NY, USA).

Results

There were 281 patients who met the inclusion criteria out of 481 patients, who were screened in both treatment centers. The majority of patients were above 60 years old, with various comorbidities and scored ≥3 on the Charlson Comorbidity Index, had high risks of stroke (CHA_2DS_2-VASc score ≥2) and bleeding (HAS-BLED score ≥1) and had no prior OACs use. All patients were receiving concomitant medication alongside NOACs. Dabigatran was the most frequently used NOACs in this study population. The baseline characteristics of the study population alongside the findings on adherence and persistence are presented in Table 1.

Adherence for PDC ≥80% and PDC ≥90% were (66.9%, n = 188/281) and (55.2%, n = 155/281), respectively, at 12 months. Adherence at 24 months improved compared to at 12 months for both PDC ≥80% (83.0%, n = 112/135) and PDC ≥90% (68.9%, n = 93/135). Two factors were found to significantly influence adherence, which were the treatment center at 12 months and polypharmacy (≥5 concurrent medications) at 24 months. Persistence for 60- and 30-day gaps were (69.8%, n = 196/281) and (58.4%, n = 164/281), respectively, within a 12-month period. Treatment center was the only factor that influenced persistence. The results of the logistic regression that

Table 1: Baseline characteristics, adherence, and persistence of the study population

Patient Characteristics	Study population (total=281), n(%)	Adherent population at PDC≥80% over 12-months (total=188/281)	Persistent population at 60-days gaps over 12-months (total=196/281)
Age(yrs), mean(SD)	67.2(10.0)	67.3(10.0)	67.5(9.9)
Age(yrs)			
<60	54(19.2)	36/54(66.7%)	36/54(66.7%)
≥60	227(80.8)	152/227(67.0%)	160/227(70.5%)
Sex			
Male	152(54.1)	106/152(69.7%)	109/152(71.7%)
Female	129(45.9)	82/129(63.6%)	87/129(67.4%)
Race			
Malay	117(41.6)	74/117(63.2%)	80/117(68.4%)
Chinese	140(49.8)	101/140(72.1%)	103/140(73.6%)
Indian	24(8.5)	13/24(54.2%)	13/24(54.2%)
Treatment-center			
HSDG	200(71.2)	**119/200(59.5%)**	**126/200(63.0%)**
HKL	81(28.8)	**69/81(85.2%)***	**70/81(86.4%)***
Charlson comorbidity index score, mean (SD)	3.6(1.6)	3.6(1.5)	3.5(1.5)
Charlson comorbidity index score			
0	5(1.8)	3/5(60.0%)	3/5(60.0%)
1-2	62(22.1)	42/62(67.7%)	44/62(71.0%)
3-4	143(50.9)	95/143(66.4%)	101/143(70.6%)
5-6	61(21.7)	43/61(70.5%)	43/61(70.5%)
≥7	10(3.6)	5/10(50.0%)	5/10(50.0%)
CHA_2DS_2-VASc score			
Mean(SD)	3.4(1.5)	3.4(1.5)	3.5(1.5)
Low(score=0,1)	20(7.1)	15/20(75.0%)	14/20(70.0%)
High(score=2,3)	141(50.2)	93/141(66.0%)	98/141(69.5%)
Very-high(score≥4)	120(42.7)	80/120(66.7%)	84/120(70.0%)
HAS-BLED score			
Mean(SD)	1.65(0.921)	1.63(0.942)	1.64(0.942)
Low(score=0)	19(6.8)	14/19(73.7%)	14/19(73.7%)
Medium(score=1-2)	213(75.8)	144/213(67.6%)	149/213(70.0%)
High(score≥3)	49(17.4)	30/49(61.2%)	33/49(67.3%)
Index medication			
Dabigatran	211(75.1)	144/211(68.2%)	151/211(71.6%)
Rivaroxaban	70(24.9)	44/70(62.9%)	45/70(64.3%)
No.of concomitant medications, mean(SD)	4.9(2.1)	4.8(2.0)	4.8(2.0)
No.of concomitant medications			
<5	128(45.6)	92/128(71.9%)	**97/128(75.8%)***
≥5	153(54.4)	96/153(62.7%)	**99/153(64.7%)**
Previous use of OACs			
No	195(69.4)	130/195(66.7%)	135/195(69.2%)
Yes	86(30.6)	58/86(67.4%)	61/86(70.9%)

PDC = proportion of days covered, SD = standard deviation, HKL = Hospital Kuala Lumpur, HSDG = Hospital Serdang, OACs = oral anticoagulants

Bold indicate significant difference between variables ($p<0.05$) where (*) indicate the favourable trend.

identified factors associated with high adherence and persistence are presented in Table 2.

Discussion

The main findings in this study are as follows: 12-month adherence was suboptimal with one-third of patients being non-adherent; adherence at 24 months improved compared to at 12 months. Adherence was influenced by treatment center and polypharmacy. Persistence was also suboptimal with one-third of patients being non-persistent; and was only influenced by treatment center.

Previous studies in various countries have described adherence to NOACs by PDC in patients with AF to be between 45.2% and 93.6%.[10,11] The findings of this study are within this range. Variations of adherence to NOACs in patients with AF between studies could potentially be related to multiple factors including differences between health-care settings, period of evaluation, administrative policies, clinical practice, interaction between physician and patients, patients' education level and knowledge, medical conditions, risk of adverse events, and socioeconomic status of the patients.[12,13] Awareness about these predictors and efforts to identify relevant factors within a patient population and subsequently overcoming them are important steps to improve adherence to NOACs within an institution.

Adherence over 12 months in our study population was 66.9% and improved over 24 months to 83.0%. This is in contrast to other studies which found NOACs adherence to decrease over time between 6 and 24 months.[9,11,14] The improved adherence over 24 months in this study could potentially be influenced by attrition of less adherent patients, either by transfer to other institutions or by mortality. However, institutional data was not available to explore this further.

Adherence was significantly influenced by two factors: treatment center at 12 months and polypharmacy at 24 months. Higher adherence rate in HKL over the first 12 months is potentially due to administrative differences between the two institutions. In HKL, there is a centralized NOAC clinic with dedicated specialists providing clinical care within a structured process of care where patients on NOACs receive specialized and personalized clinical management alongside counselling by pharmacists. In HSDG, only physicians from the cardiology department could prescribe NOACs but there was no dedicated process of care specific to patients on NOACs. It is also possible that there were differences in the pharmacy supply stock of NOACs between these two institutions, where a stable supply would lead to higher adherence as measured by PDC, but the retrospective design did not allow further exploration of this.

At 24 months, only polypharmacy was found to significantly influence adherence, with patients without polypharmacy being more likely to be adherent. Polypharmacy has been found to be adversely associated with medication adherence in various studies potentially due to a high likelihood for missing doses and increased complexity of pharmacotherapy regimens,[15,16] with a majority of studies describing polypharmacy as negatively influencing medication adherence.[15]

Current evidence has described adherence to be linked to health outcomes, with poor adherence to NOACs found to be an important predictor for increased risk of all-cause mortality and stroke, with hazard ratios (HRs) of 1.13 and 1.54, respectively.[5,17] The suboptimal adherence in this study indicates that health outcomes could potentially be improved in this study population by implementing suitable interventions and improved clinical care to enhance adherence, particularly as the simplicity of NOAC regimens can also counterintuitively lead to poor adherence due to reduced routine follow-up and its indication for stroke prevention in generally asymptomatic patients with AF.[18] This is especially so as nearly all of the patients in this study had CHA_2DS_2-VASc score of 2 and above, which has been found have nearly three times [HR 2.73] higher risk of stroke compared to patients with CHA_2DS_2-VASc scores 0–1.[18]

Persistence in the study population, at 69.8%, was close to the upper level found in other studies in patients with AF with similar study design and definitions, which ranged between 31.6%[9] and 82.8%.[19] Persistence over 12 months for both 30- and 60-day gaps was only significantly influenced by treatment center with persistence observed to be better in HKL compared to HSDG. This observation may be due to the same factors discussed above that may have influenced adherence.

Table 2: Factors associated with high adherence and persistence for the study population

	Odds ratio (95%CI)	*P* Value
12-month adherence (PDC ≥ 80%)		
HKL vs. HSDG	3.91(1.99,7.68)	<0.0001
24-month adherence (PDC ≥ 80%)		
Concurrent medications <5 vs. ≥5	0.32(0.12,0.89)	0.029
Persistence (60-day gap)		
HKL vs. HSDG	0.26(0.13,0.53)	<0.0001
Persistence (30-day gap)		
HKL vs. HSDG	2.42(1.38,4.26)	0.002

PDC = proportion of days covered, HKL = Hospital Kuala Lumpur, HSDG = Hospital Serdang, CI = confidence interval

Despite being conducted in two tertiary-care referral centers with a catchment population of more than 1 million people within the Klang Valley, this study identified a relatively small number of patients with AF on NOACs. This reflected the currently limited use of NOACs within Ministry of Health (MoH) tertiary-care referral centers, with various administrative prescribing restrictions applied which allow only selected specialties and consultants to prescribe NOACs to a limited number of patients. This restriction on NOACs prescribing is likely due to the comparatively high acquisition cost of NOACs, which has been estimated to be around MYR2945 per patient annually for dabigatran and MYR2894 per patient annually for rivaroxaban compared to only MYR651 per patient for warfarin.[20]

Care must be taken when generalizing the findings of this study. These findings were based on the availability and accuracy of the electronic pharmacy dispensing records, treatment-center databases, and relevant records in the study institutions. As measuring adherence by PDC reflects the amount of medication dispensed over a period of time, a stable pharmacy supply would contribute to higher PDC adherence rate. It is also possible that some patients could have obtained NOACs from community pharmacies and primary care clinics, which could potentially have influenced adherence. The retrospective design did not allow further exploration of these factors between the two study institutions. Without national health-care databases available across all health-care institutions and community pharmacies nationwide, conducting a more comprehensive assessment of persistence and adherence from secondary resources remained challenging. The resource intensive and time-consuming nature of the data collection process in this study pointed to a need to develop large and well-validated national databases to monitor routine clinical care, which could inform improvement of health-care service delivery and optimization of health outcomes in Malaysia.

Conclusion

Adherence and persistence of patients with AF on NOACs in this study population were suboptimal but were within the ranges documented in the literature. Variations of adherence and persistence between the two study institutions indicated that incorporating adherence enhancing measures within routine clinical care with dedicated specialized services, such as having dedicated NOACs clinics with follow-up clinical care and pharmacists' counselling, can have a positive impact on adherence and persistence.

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Conflicts of interest

There are no conflicts of interest.

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