ORIGINAL ARTICLE

A comparison of dabigatran and warfarin for stroke prevention in elderly Asian population with nonvalvular atrial fibrillation: An audit of current practice in Malaysia

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ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common cardiac arrhythmia with significant morbidity and mortality in relation to thromboembolic stroke. Our study aimed to evaluate the safety and efficacy of dabigatran in stroke prevention in elderly patient with nonvalvular AF with regard to the risk of ischemic stroke and intracranial haemorrhage (ICH) in real-world setting.

Methods: A retrospective cohort study of 200 patients on dabigatran and warfarin from January 2009 till September 2016 was carried out. Data were collected for 100 patients on dabigatran and 100 patients on warfarin.

Results: The mean follow-up period was 340.7±322.3 days for dabigatran group and 410.5±321.2 days for warfarin group. The mean time in therapeutic range (TTR) was 52±18.7%. The mean CHA2DS2 -VASc score for dabigatran group was 4.4±1.1 while 5.0±1.5 for warfarin group. None in dabigatran group experienced ischemic stroke compared to one patient in warfarin group (p=0.316). There was one patient in dabigatran group suffered from ICH compared to none in warfarin group (p=0.316). Four patients in warfarin group experienced minor bleeding, while none from dabigatran group (p=0.043).

Conclusion: Overall bleeding events were significantly lower in dabigatran group compared to warfarin group. In the presence of suboptimal TTR rates and inconveniences with warfarin therapy, non-vitamin-K antagonist oral anticoagulants (NOAC) are the preferred agents for stroke prevention in elderly Asian patients for nonvalvular AF.

KEY WORDS:
Atrial fibrillation, dabigatran, warfarin, stroke prevention, bleeding events

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, conferring significant morbidity and mortality predominantly resulting from fivefold increased risk of thromboembolic stroke.[1] Vitamin-K antagonist (VKA), namely warfarin, has been proven to reduce the risk of ischemic stroke by two-thirds in patients with nonvalvular AF.[2-4] The emergence of several non-vitamin-K antagonist oral anticoagulants (NOAC) has offered potential advantages over VKA, such as predictable and stable pharmacokinetic profile, avoiding antagonistic effect of dietary vitamin K, and fewer drug-drug interactions.[5] Dabigatran etexilate, licensed since 2009, is a NOAC that directly and irreversibly inhibits thrombin activity. Dabigatran has been shown to be as effective as warfarin therapy in stroke prevention with lower risk of intracranial haemorrhage (ICH).[6] However, controversies arose with elderly patients who were prescribed with dabigatran, with concerns over higher risk of ICH.[7,8] To complicate matters more, Asian ethnicity also confers higher risk of haemorrhagic stroke as well as ischemic stroke.[9] The aim of our study was to study the safety and efficacy of dabigatran in stroke prevention in elderly Asian patient with nonvalvular AF with regards to the risk of ischemic stroke and ICH in real-world setting.

MATERIALS AND METHODS

This is a single-centre retrospective cohort study at Malaysia's National Heart Institute. The research ethics committee of the National Heart Institute approved the study protocol and informed consent was waived for a retrospective study (IJNREC/208/2017). Two hundred patients aged 75 and above with nonvalvular AF, who were prescribed with dabigatran or warfarin for stroke prevention from January 2009 till September 2016, were selected for analysis. These patients were identified via hospital pharmacy electronic records. The sample size of 100 patients on dabigatran was selected based on the available number of patients at the start of the study and was matched with 100 patients who were prescribed with warfarin therapy during the corresponding period. Hospital case notes were perused and data collected retrospectively. Baseline characteristics including age, gender, CHA2DS2 -VASc score,[10] HAS-BLED score,[11] and echocardiographic report were determined and recorded. The duration of follow up counted from time of anticoagulant initiation (length in days of drug prescription), date of anticoagulant (either warfarin or dabigatran)

Table I: Baseline characteristics, classification of nonvalvular AF, comorbidities, echocardiographic findings, HAS-BLED score, CHA2DS2 -VASc score, and length of days follow up from date of anticoagulant initiation

| Baseline Characteristic	Dabigatran (N = 100); %	Warfarin (N = 100); %	P-value
Age, years (Mean±SD)	79.8±3.4	80.7±3.3	0.396
Sex (Female)	48 (48%)	49 (49%)	0.887
Classification of AF			
Paroxysmal AF	71 (71%)	85 (85%)	0.017*
Persistent AF	8 (8%)	2 (2%)	0.052
Permanent AF	21(21%)	13 (13%)	0.132
Risk Factors			
Congestive Cardiac Failure	11(11%)	24 (24%)	0.016*
Hypertension	74 (74%)	90 (90%)	0.003*
Diabetes Mellitus	31(31%)	49 (49%)	0.009*
Previous Transient Ischemic Attack	5(5%)	7(7%)	0.552
Vascular Disease	49 (49%)	63 (63%)	0.046*
Previous Stroke	8 (8%)	12 (12%)	0.346
Echocardiogram			
Left Ventricular Ejection Fraction (Mean±SD)	58.2%±10.4%	54.3%±10.8%	0.007*
Mitral Regurgitation (Severe)	2(2%)	7(7%)	0.088
HASBLED Score (Mean±SD)	2.1±0.7	2.2±0.5	0.372
CHA2DS2 -VASc Score (Mean±SD)	4.4±1.1	5.0±1.5	0.004*
Follow-up (Mean±SD)	340.7±322.3 days	410.5±321.2 days	0.074
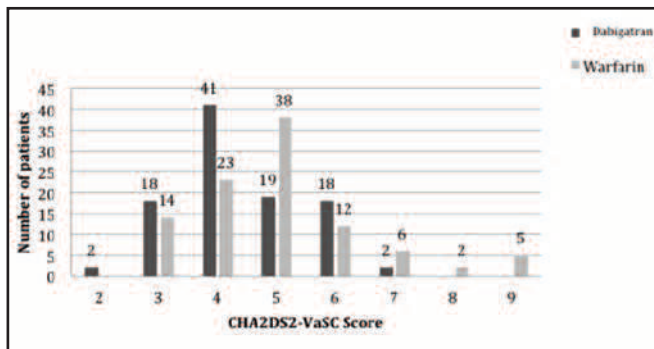
Fig. 1: Distribution of CHA2DS2 -VASc score among elderly Asian patients prescribed dabigatran and warfarin.
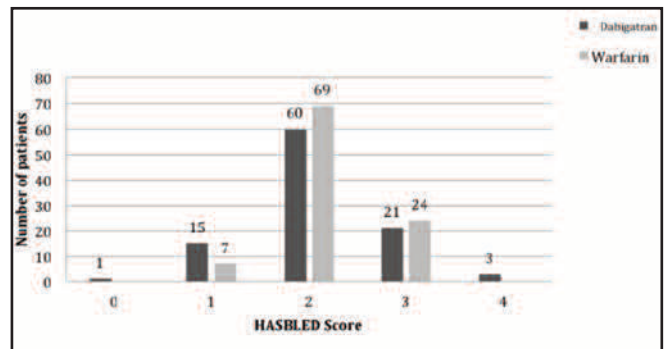

Fig. 2: Distribution of HAS-BLED score among elderly Asian patients prescribed dabigatran and warfarin
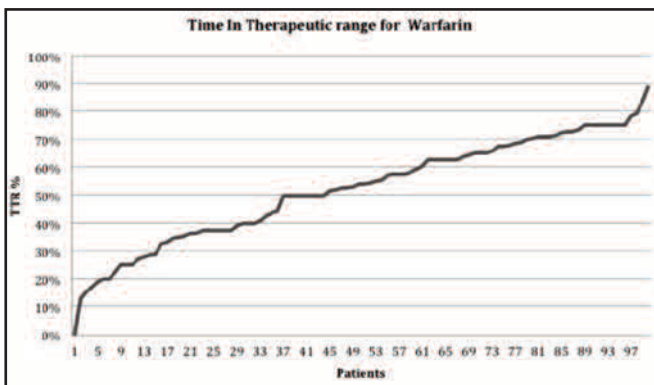

Fig. 3: Cumulative TTR among 100 patients prescribed warfarin.

initiation, date of anticoagulant cessation and reasons for cessation of anticoagulant, if any, were extracted. For patients on warfarin, international normalised ratio (INR) readings on each visit were extracted. Time in therapeutic range (TTR) was calculated based on the number of INR values in therapeutic range between two to three dividing by the total number of INR measurements (percentage of INRs in range) for the patient. For patients prescribed dabigatran, dose of such prescription was determined. Incidence of ischemic and haemorrhagic stroke, major bleeding (transfusion of two or more units of blood), and minor bleeding (any bleeding without transfusion or requiring transfusion less than two units of blood) and adverse events reported by patients were determined.

Data analysis
Continuous and discrete variables were expressed as means with standard deviation and number (percentage), respectively. The baseline characteristics of the cohorts were compared using Chi-square test for categorical data and independent sample T-test for continuous data. The statistical significant was defined as p-value <0.05. For comparison and outcome, cross tabulation table was used with number of cases and percentage. All analysis was carried out using IBM SPSS software version 22.

RESULTS
Baseline characteristics
There were 100 patients in dabigatran group and 100 patients in warfarin group. Eighty patients were prescribed

with dabigatran 110 mg twice daily while 20 patients were prescribed with 150 mg twice daily. Baseline characteristics of patients in each arm were shown in Table I. The mean age was slightly lower for dabigatran group compared to warfarin group. The numbers of female subjects were comparable for both groups. There were more patients with paroxysmal AF and fewer patients with persistent/permanent AF in warfarin group compared to dabigatran group. There were more patients with congestive cardiac failure, hypertension, diabetes mellitus, and vascular disease in warfarin group as compared to dabigatran group, which were statistically significant.

The distributions of CHA2DS2 -VASc scores and HAS-BLED scores were illustrated in Fig 1 and 2 respectively. The mean CHA2DS2 -VASc scores were lower in the dabigatran group compared to warfarin group (4.4±1.1 vs 5.0±1.5, p=0.004). The mean HAS-BLED scores for both groups were similar (p= 0.372).

Efficacy outcome
The mean follow-up period was 340.7±322.3 days (11.3 months) for dabigatran group and 410.5±321.2 days (13.6 months) for warfarin group. No incidence of ischemic stroke was reported for the dabigatran group while 1 event was reported for the warfarin group (p=0.316).

Bleeding
There were four reported minor bleeding events in the warfarin group but none from the dabigatran group (p=0.043). Of those with minor bleeding, one patient had conjunctival bleeding, one presented with haematuria, and two presented with lower gastrointestinal bleeding. Throughout study period, one patient in dabigatran group reported haemorrhagic stroke but none of that developed in the warfarin group (p=0.316).

Adverse effects
The commonest adverse effect of dabigatran was dyspepsia, reported in three patients, while none had such symptoms among those prescribed with warfarin (p=0.081). Other adverse effects experienced by patients from dabigatran group included allergy (one patient) and leg oedema (one patient).

TTR
For patients on warfarin therapy, the TTR ranged from 0% to 88.89%. Mean TTR was 52±18.7% (Fig 3). Out of a total 2329 INR readings taken within the study period, 725 (31.2%) INR readings were less than 2, 1284 (55.1%) INR readings were within two to three, and 320 (13.7%) INR readings were more than three.

Reason for discontinue anticoagulant
None of the patients from the dabigatran group discontinued anticoagulant while 19 (19%) patients from the warfarin group discontinued their anticoagulant for various reasons. The reasons for discontinuation included bleeding, over warfarinisation, non-compliance, post Watchman implantation, concerns raised about possible gastrointestinal bleeding, and switching to dabigatran. Out of 19 patients who discontinued warfarin during the study period,[11] (57.8%)

patients switched to dabigatran use. The reasons for crossovers from warfarin to dabigatran were related to the inconvenience with warfarin and poor INR level achieved.

DISCUSSION
In our previous study, we have shown similar efficacy in ischemic stroke prevention comparing use of dabigatran versus warfarin in a large cohort of Asian patients, without an increase in bleeding events in the dabigatran group.[12] We have also shown the difficulty to achieve good TTR rates among the Asian population in the real-world setting. The current study is a subgroup analysis of elderly Asian patients looking into the challenges of stroke prevention vis-à-vis bleeding risks among this high-risk group in a real-world setting.

Risk of stroke among elderly Asian patients
The aged Asian population has a significantly elevated risk of ischemic stroke as demonstrated by mean CHA2DS2 -VASc score of 4.4 and 5.0 in the dabigatran and warfarin group respectively in our study. Notably, among this group of patients, the cumulative rate of previous ischemic stroke or TIA prior to initiation of anticoagulant was at a staggering rate of 13% and 19% in those who subsequently received dabigatran and warfarin respectively. This is in agreement with the study involving aged Chinese population with atrial fibrillation.13 The estimated annual risk of ischemic stroke was at least 3% in historical cohort of untreated patients with CHA2DS2 -VASc score of 3 or more.[10] Asian ethnicity also seems to confer a 2 times higher risk of ischemic stroke compared to non-Asian population[9], thus highlighting the importance of effective ischemic stroke reduction strategy in such high-risk group.

Efficacy and stroke risk reduction
With a group with such high-risk background, it is encouraging to note that no ischemic stroke events had occurred among those on dabigatran in our elderly cohort with a mean duration of follow up of 340±322 days, which is comparable to one event per 100 patient-year among the elderly patients prescribed warfarin with a mean follow up duration of 410 days±321 days. In the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), elderly patients who received vitamin K antagonist had a 52% reduction of their stroke risk compared to use of aspirin, with annual risk of ischemic stroke reported at 1.8%.[14] This rate of primary outcome of ischemic stroke reduction is also echoed in the RE-LY study as well as the study done in elderly Chinese population.[6,13]

Bleeding events
With an aim of anticoagulation therapy to reduce morbidity and mortality among patients with atrial fibrillation, the bleeding risks and real-world bleeding events amongst those on anticoagulation is an important consideration to achieve nett benefit from anticoagulation. The equation is made difficult as Asian population portends an increased risk of intracranial haemorrhage compared to the Caucasian population, more so in a cohort of advanced age. The RE-LY trial did show a reduction of ICH among patients who received dabigatran 110 mg BD compared to warfarin, but

controversies arose among the elderly patients who seemed to have heightened risk of ICH with the use of dabigatran.[8,15] Elevated risk of other major bleeding events with dabigatran use, especially gastrointestinal bleeding,[16,17] have also been reported elsewhere and remains a cause of concern among prescribers. In our study, the elderly Asian population do have a high estimated bleeding risk with majority of them having HAS-BLED score of two to three in both dabigatran and warfarin groups. The distribution of HAS-BLED score agreed with figures in other studies of high-risk elderly Asian patients.[13] However, the actual major bleeding event was not reflective of the estimated bleeding risks, with one documented haemorrhagic stroke requiring neurosurgical intervention among those using dabigatran while no other major bleeding episodes were documented in both dabigatran and warfarin groups after a period of around one year follow up. Minor bleeding, on the other hand, is more common among those prescribed warfarin compared to those prescribed dabigatran.

Time in therapeutic range
Prescription dose for both dabigatran and warfarin remain important determinants of outcome in the real-world setting. TTR is an important determinant of effectiveness of warfarin prescription for stroke prevention in atrial fibrillation. However, in the real-world setting, TTR among those prescribed warfarin is often suboptimal.[18,19] As a result, the benefits of warfarinisation are likely to be lower than intended and, conversely, more side effects are likely. Our study does show similar TTR results compared to international cohorts. When compared to the entire cohort in our previous study that included younger patients, the TTR achieved was similar. This is in contrast with the ORBIT-AF registry showing lower TTR rate among those at higher risk of stroke and bleeding.[18] Among those with suboptimal INR reading, majority of them were sub-therapeutic than supra-therapeutic. With the proportion of patients achieving TTR of 60% and above only around 40%, translation to full potential of warfarin in stroke prevention for patients with atrial fibrillation remains elusive in the real-world setting, especially among patients of highest risk. The direct oral anticoagulants with stable pharmacokinetic and pharmacodynamics properties, such as dabigatran, were intended to bypass such difficulty of achieving TTR while maintaining the benefits of stroke prevention. Hence, in the elderly Asian cohort group with highest risk of stroke as well as bleeding, more so in those with low TTR, dabigatran is an appealing option to achieve optimal stroke risk reduction compared to warfarin.

Dropout rate and crossovers
The rate of treatment cessation is also noteworthy, as 19% of all elderly patients on warfarin in our cohort stopped warfarin eventually for various reasons, while all patients who were prescribed dabigatran maintained the prescription during the study period. More than half of those who stopped warfarin were crossovers to dabigatran prescription, reflecting the ease of dabigatran administration absolving the need for INR monitoring. Minor symptoms of dyspepsia reported in three elderly patients on dabigatran did not result in treatment failure. Although such a high rate of drop out among patients prescribed warfarin does not directly imply

non-compliance, or conversely high compliance among the dabigatran group, it serves as a reference to prescribers during initiation of anticoagulation therapy on choice of anticoagulation and the eventual maintenance of therapy.

LIMITATIONS
As with all retrospective study, the accuracy of data depended on quality of documentation and reporting from patients. Some minor side effects may not be reported by patients or documented by clinician as they were deemed not life threatening. Some patients could have presented to other centres when adverse events developed, resulting in lower reported stroke events or bleeding events. Concomitant medications include antiplatelet therapy prescribed to the patients as well as over the counter were not accounted for in this retrospective study, which could have a bearing on TTR as well as increase risk of bleeding events among those prescribed with anticoagulants. It is also difficult to determine the reason for initial choice of anticoagulation as it may be dictated by many social circumstances, initial doubts by the clinician on compliance to INR monitoring or follow-up, or even perceived risk of side effects versus efficacy by each individual clinician. With the retrospective nature of this study, allocation bias in the initiation of different anticoagulants cannot be excluded. Significant differences in CHA2DS2-VASc scores between the two groups exist, with the warfarin group exhibit higher CHA2DS2-VASc scores as reflected in higher prevalence of heart failure, hypertension, diabetes mellitus, and vascular disease. Future studies would ideally be conducted in a prospective cohort of elderly Asian population, or consider propensity score matching in a larger retrospective cohort to adjust for baseline differences.

CONCLUSION
We present the efficacy and safety of dabigatran among elderly Asian population vis-à-vis warfarin in the real world setting and challenges of anticoagulation in this high-risk group. Our study suggests similar efficacy between dabigatran use and warfarin use in terms of ischemic stroke prevention in high risk-elderly Asian patients. By extension, dabigatran should be the preferred option among elderly Asian patients with atrial fibrillation stemming from suboptimal TTR results among those on warfarin as well as high likelihood of conversion to dabigatran over the course of follow-up.

ACKNOWLEDGEMENTS

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