ORIGINAL ARTICLE

Safety and Efficacy of Dabigatran Versus Warfarin in Asian Patients With Atrial Fibrillation

Liyana Najwa Inche Mat[1,2], Ooi Qi Wen[3], Nurul Natasha Ashikin Johari[3], Rooban Raao Subramaniam[3], Wan Aliaa Wan Sulaiman[1,2], Hoo Fan Kee[1], Chia Peck Kee[1], Hamidon Basri[1]

[1] Neurology Unit, Department of Medicine, Faculty of Medicine and Health Science, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
[2] Malaysian Research Institute of Ageing(MyAgeing), Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
[3] Department of Medicine, Faculty of Medicine and Health Science, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

ABSTRACT

Introduction: Nonvalvular atrial fibrillation is a common cause of cardioembolic stroke which accounts around 50% of all cardioembolic emboli. Oral anticoagulants remain the main choice of stroke prevention in patients with atrial fibrillation. Our study is aimed to determine the safety (absence or presence of bleeding events) and efficacy (absence or presence of ischemic stroke occurrence) of dabigatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. **Methods:** A retrospective audit study was conducted based on past data obtained from Electronic Hospital Information System (EHIS) records in Serdang Hospital. Our sample was 150 patients with nonvalvular atrial fibrillation who were at risk of getting stroke and being prescribed with oral anticoagulants either warfarin or dabigatran from the year 2013 until 2019. **Results:** Our study showed that there was lesser occurrence of ischemic stroke in patients from dabigatran group (1.3%) as compared to those in warfarin group (2.7%). There were also almost 2 times lesser bleeding events in dabigatran group (6.7%) as compared to those in warfarin group (14.7%). The median of CHA2DS2-VASc Score in warfarin sampled patients (median=3+/-1) was lower than dabigatran sampled patients (median=4+/-1). **Conclusion:** Both warfarin and dabigatran are effective in preventing stroke for patients with nonvalvular atrial fibrillation. However, dabigatran is associated with lesser bleeding events with lower incidence of major bleeds compared to warfarin.

Keywords: Warfarin, Dabigatran, Atrial fibrillation, Stroke

Corresponding Author:
Liyana Najwa Inche Mat, PhD
Email: liyananajwa@upm.edu.my
Tel: +60397692585

INTRODUCTION

Atrial fibrillation is a common cardiac arrhythmia which can increase the risk of cardioembolic stroke by five-fold, leading to significant morbidity and mortality (1). Although not all atrial fibrillation-related strokes are cardioembolic, atrial fibrillation whether chronic (persistent) or paroxysmal accounts for 50% of all cardiogenic emboli.

Nonvalvular atrial fibrillation patients have a significant increased risk of stroke occurrence. Therefore, stroke prevention in nonvalvular atrial fibrillation patients is imperative in order to reduce their morbidity and mortality rate as well as to improve their quality of life. Over the past decade, among the most potent therapies for stroke prevention in patients with nonvalvular atrial fibrillation is the use of anticoagulation therapy but it must be weighed against the risk of hemorrhagic complications (2). A study by Tsai C et in 2013 suggested that Asians has slightly higher rates of stroke incidence and higher rates of intracerebral hemorrhage compared to Caucasian (3).

The emergence of an oral direct thrombin inhibitor, dabigatran as direct oral anticoagulants (DOACs) (licensed since 2009) has offered potential advantages over warfarin, such as predictable, effective and consistent anticoagulation with minimal drug-drug interactions and no drug-food interactions. Unlike warfarin, routine coagulation monitoring or dose adjustment is not required for dabigatran (4). Despite this, the issue of its cost and availability prohibits the wide use of dabigatran in government hospitals in Malaysia (5).

Hence, a real-world study is important to ascertain the safety and efficacy of dabigatran vs warfarin in our local setting. Furthermore, it may help relevant authorities

to increase the quota of the safer and more efficient anticoagulant prescription for stroke prevention in patients with nonvalvular atrial fibrillation.

MATERIALS AND METHODS

Data Source

This is a single-center retrospective audit study at Hospital Serdang which is a tertiary referral center for cardiology surgery in Malaysia. Data from patients aged 18-90 years old diagnosed with nonvalvular atrial fibrillation who have been prescribed with warfarin or dabigatran from 2013 to 2019 were collected for this study. These patients were identified based on the Medication Therapy Adherence Clinic (MTAC) records from Pharmacy Department of Hospital Serdang. Using stratified random sampling, a sample size of 75 patients on dabigatran were matched with 75 patients who were prescribed warfarin therapy. Subsequent data were collected from the electronic medical records of Serdang Hospital known as the electronic Hospital Information System (eHIS). The result was analyzed using IBM SPSS Statistics v25 for Windows. Ethical approval for this study was granted by the National Medical Research Register (NMRR).

Study population

Patients were selected if they aged between 18 to 90 years old and were diagnosed with nonvalvular atrial fibrillation and subsequently prescribed dabigatran or warfarin. Patients were excluded from the study if they had been diagnosed with malignancy or other serious medical conditions with life expectancy less than 6 months, valvular heart disease, heart valve replacement or having a planned surgery. Patients on kidney transplant or dialysis were also excluded.

Outcome measures

The primary outcome which was the ischemic stroke incidence among cohorts was determined using the respective patients' follow-up data. Stroke risk was measured via the CHA2DS2-VASc score for every patient who was diagnosed with nonvalvular atrial fibrillation before the counsel and start of oral anticoagulant. The CHA2DS2-VASc is a validated score by the European Society of Cardiology in which the major risk factors such as age>75 years and previous stroke/TIA are scored 2 points each. Meanwhile other risk factors such as congestive heart failure, hypertension, diabetes mellitus, age of 65-75 years old, vascular disease and female sex are each scored 1 point (6). Anticoagulant is strongly recommended for a person with a CHA2DS2-VASc score of 2 and more. Secondary outcome of minor and major bleeding events was also identified using the respective patients' follow-up data which includes any events of blood transfusion and adverse effects in correlation with bleeding reported by patients since date of oral anticoagulant prescription. Major bleeding consisted of intracranial hemorrhage, gastrointestinal bleeding and bleeding at other key sites. Major bleeding was defined as any bleeding that involves major organs such as central nervous system and gastrointestinal system, clinically overt bleeding with drop in hemoglobin of at least 2g/dL, requiring transfusion of blood of at least 2 units or intravenous vasoactive agents. Meanwhile, minor bleeding is defined as any bleeding that is self-terminating and does not require blood transfusion. Bleeding risk was measured via the HAS-BLED tool for every patient who was diagnosed with nonvalvular atrial fibrillation before the counsel and start of oral anticoagulant. The HAS-BLED tool consists of 9 maximum scores in which risk factors for bleeding are either given 1 or 2 points. The risk factors are hypertension, abnormal renal/ liver function, stroke, bleeding tendency, labile INR, age more than 65 years old and concomitant use of alcohol or drugs such as aspirin and NSAIDs (7). A score of 3 or more indicates more caution is needed when prescribing oral anticoagulation and regular patient review is recommended.

Data analysis

Calculation on statistics was conducted using the standard statistical software package IBM SPSS Statistics V25.0 for Windows. Descriptive analysis of data was presented as mean, frequency and percentage. The participants were divided into two groups, dabigatran and warfarin groups. All the means of the continuous variables were compared using independent sample t-test. Chi square test or Fisher's Exact test was carried out on categorical data. The assumptions for Chi square test of Independence are random sample, two independent samples, two samples are mutually exclusive, not more than 20% of expected count with less than 5 ($E<5$) and all the expected frequencies exceed 1. For condition where there were more than 20% of expected count with less than 5 ($E<5$), Fisher's Exact test was used. The statistical significant was defined as $p < 0.05$. For comparison outcome, a cross table tabulation was used with the number of cases and percentage. Frequency and percentage were mainly used to compare the safety and efficacy of both dabigatran and warfarin. Median was also used to compare the CHA2DS2-VASc and HAS-BLED scores of both dabigatran and warfarin.

RESULTS

Socio-demographic Characteristics

A total of 150 patients were included in this study. The socio-demographic characteristics of the patients are presented in Table I. Baseline measurements includes demographics, comorbidities and clinical risk scores (HAS-BLED and CHA2DS2-VASc). Majority of the respondents were in the age groups of 58-77 years old (n=91, 60.7%), followed by 78-90 years old (n=33, 22%) and 38-57 years old (n=25, 16.7%). The distribution of gender is almost similar while the majority of patient are Chinese (n=66, 44%), followed by Malays (n=63, 42%) and Indian (n=19, 12.7%). Majority of patients had

Table I: Baseline Characteristics of the Study Participants

Socio-demographic characteristics and study profile (N=150)	Frequency y	Percentage (%)
Gender		
Male	76	50.7
Female	74	49.3
Age groups		
18-37	1	0.7
38-57	25	16.7
58-77	91	60.7
78-90	33	22.0
Ethnicity		
Malay	63	42.0
Chinese	66	44.0
Indian	19	12.7
Others	2	1.3
Underlying disease		
Hypertension		
Yes	137	91.3
No	13	8.7
Diabetes Mellitus		
Yes	82	54.7
No	68	45.3
Heart Disease		
Yes	85	56.7
No	65	43.3
Dyslipidemia		
Yes	54	36.0
No	96	64.0
Chronic Kidney Disease		
Yes	23	15.3
No	127	84.7
Previous Stroke History		
Yes	25	16.7
No	125	83.3
Types of oral anticoagulants used		
Warfarin	75	50.0
Dabigatran	75	50.0
Dosage(mg)		
0-2	21	14.0
2.1-4	47	31.3
4.1-6	7	4.7
110	35	23.3
150	40	26.7
Stroke risk		
Low	1	0.7
Moderate	5	3.3
High	144	96.0
Bleeding risk		
Low-intermediate	107	71.3
High	43	28.7

underlying hypertension (n=137, 91.7%). 35 patients were prescribed with dabigatran 110mg twice daily while 40 patients were prescribed with 150mg twice daily. There was no significant association between age groups (p=0.213), gender (p=0.118) and ethnicity (p= 0.521) with stroke occurrence. Similarly, there was no significant association between age groups (p=0.125), gender (p= 1.000) and ethnicity (p= 0.627) with bleeding events.

Apart from the clinical characteristics, we also measure clinical predilection risk scores such as CHA2DS2-VASc and HAS-BLED. Fig 1 shows the distribution of CHA2DS2-VASc score by warfarin and dabigatran sampled patients respectively. The median of CHA2DS2-VASc Score for warfarin sampled patients (median=3+/-1) was lower than dabigatran sampled patients (median=4+/-1). Meanwhile, the HAS-BLED score is used to estimate the risk of major bleeding for patient on oral anticoagulation. A high HAS-BLED score puts the patient at high risk for major bleeding.

Fig 2 shows the distribution of HAS-BLED Score by warfarin and dabigatran sampled patients respectively. The median of HAS-BLED Score in warfarin sampled patients (median=2+/-1) was almost the same as dabigatran sampled patients (median=2+/-2). A large number of patients (96%) had a high stroke risk (CHA2DS2-VASc score of 2 or more) while 28.7% of patient had a high bleeding risk (HAS-BLED score of 3 or more). However, there are no associations between CHA2DS2-VASc score (p=0.796) and HAS-BLED score (p=0.62) with oral anticoagulants prescription.

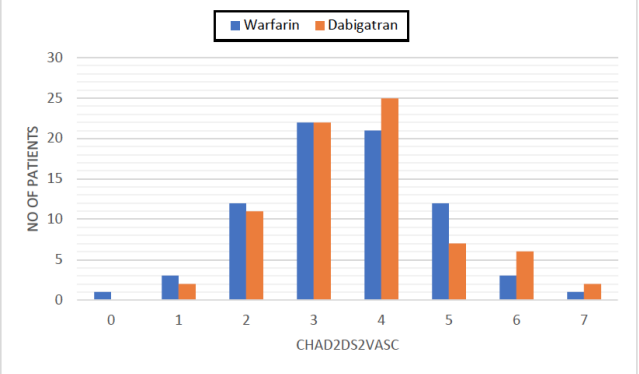

Figure 1: Distribution of CHA2DS2-VASc score by Treatment Group

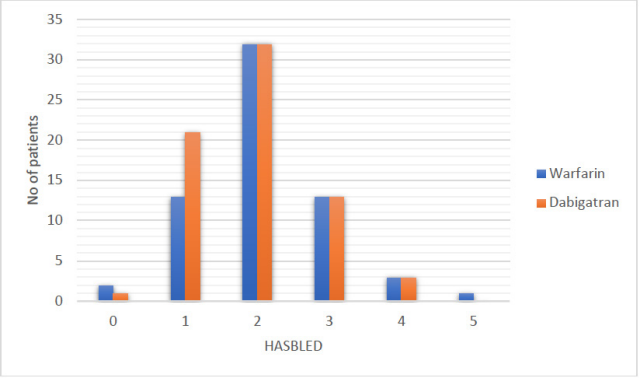

Figure 2: Distribution of HAS BLED score by Treatment Group

Effectiveness Outcomes

Majority of patients (147 out of 150) had no ischemic stroke occurrence during the treatment with oral anticoagulants, either warfarin or dabigatran, while remaining 3 (2.0%) sampled patients developed ischemic stroke during the treatment with oral anticoagulants. 2 of the patients were from warfarin group while 1 was from dabigatran group. Therefore, the stroke occurrence in dabigatran group was lower than the stroke occurrence in warfarin group (1.3 % vs 2.7%). However, there was no significant association between ischemic stroke occurrence and the type of oral anticoagulants prescription in patients with nonvalvular atrial fibrillation (p=1.000>0.05).

Safety Outcomes

There were 16 patients that developed bleeding events during treatment with oral anticoagulants. We found that the bleeding events in dabigatran group was almost two times lower than the bleeding events in warfarin group (6.7% vs 14.7%). A total 5 out of the 16 patients developed major bleeding. There was more major bleeding in warfarin group (3 patients) than dabigatran group (2 patients). The two most common sites for major bleeding were intracranial and gastrointestinal with the occurrence in gastrointestinal (3 patients) higher than that in the intracranial (2 patients).

There was higher rate of minor bleeding in warfarin group (8 patients) compared to that in dabigatran group (3 patients) (72.7% vs 27.3%). The most common site for minor bleeding (90.9%) was urogenital, per rectal and mucosal. The incidence rate for major and minor bleeding are shown in Table II. There were three kinds of oral anticoagulant dosage that caused major bleeding. 2 major bleeding patients (40.0%) were patients treated with 0-2mg of warfarin, 1 major bleeding patient (20.0%) was treated with 2.1-4mg of warfarin, while the remaining 2 patients (40.0%) were treated with 110mg dabigatran.

There were four kinds of oral anticoagulant dosage that caused minor bleeding. 4 out of 11 minor bleeding patients (36.4%) were patients treated with 0-2mg of warfarin, 3 patients (27.3%) were treated with 2.1-4mg of warfarin, 1 patient (9.1%) was treated with 4.1-6mg of warfarin, while the remaining 3 (27.3%) were patients treated with 110mg dabigatran. Interestingly, there were no occurrence of bleeding either major nor mild in the dabigatran 150mg group. Apart from this, there was also no significant association between bleeding events and the type of oral anticoagulants prescription in patients with nonvalvular atrial fibrillation (p=0.113>0.05).

Table II: Safety Outcomes According to Treatment Group

Events	Dabigatran 110mg	Dabigatran 150mg	Warfarin
Major Bleeding			
• Intracranial	0	0	1
• Gastrointestinal	2	0	2
Minor Bleeding	3	0	8

Discontinuation of Oral Anticoagulants

Among the 23 patients with nonvalvular atrial fibrillation who discontinued their oral anticoagulant therapy, 22 (95.7%) of them were from warfarin group and only 1 (4.3%) was from dabigatran group. Most of the warfarin users discontinued warfarin due to the side effects of warfarin (n=7), others were due to bleeding, own decisions and others such as the high risk of fall, poor compliance and allergy. Most of the warfarin users who discontinued warfarin (n=12) changed to other DOACs or oral antiplatelets while the others changed to dabigatran. There is only one dabigatran user who discontinued dabigatran and changed to other NOACs/ oral anticoagulants due to bleeding.

DISCUSSION

The prevalence of atrial fibrillation in Asia is on the rise due to the increasing number of elderly populations. Despite oral anticoagulants such as warfarin being the mainstay of therapy for stroke prevention in non-valvular atrial fibrillation patient, a vast number of Asian patients are not being prescribed this treatment due to fear of bleeding complications and limited access to monitoring facilities. Studies have also shown that Asian patients on warfarin have a higher risk of intracerebral hemorrhage and major bleeds compared to Caucasians (8). The emergence of DOACs such dabigatran as an alternative to warfarin has been shown to be highly cost effective in stroke prevention in the real-world setting (9).

Based on our study, the median of CHA2DS2-VASc score of warfarin group was lower than dabigatran group while the median of HAS-BLED score in both warfarin and dabigatran groups were almost the same. Our findings showed that patients with nonvalvular atrial fibrillation were more likely to be prescribed with warfarin if they had a lower CHA2DS2-VASc score (lower stroke risk) while those with higher stroke risk were prescribed with dabigatran. A retrospective study on a large cohort of patient by University of Pittsburgh concluded that DOACs was more effective than warfarin to prevent stroke in patients with nonvalvular atrial fibrillation, but the effect was more pronounced in patients with lower stroke risk (10). Another study by Ajoe John Kattoor also showed that patients with higher CHA2DS2-VASc scores were more likely to be prescribed with warfarin than those with lower scores (P < .001) (11). Many studies also showed that the introduction of CHA2DS2-VASc score taking over CHADS2 score caused an increase in the number of patients recommended for oral anticoagulation therapy as the newer scoring system included more stroke risk factors than the older one (12). A high score on HAS-BLED score should not deter physicians from prescribing oral anticoagulants.

However, these patients require more frequent follow-ups to assess any bleeding complications (13). Counselling sessions should be performed for all patients diagnosed with atrial fibrillation before starting any oral anticoagulants to fully inform the patients about the side effects and importance of oral anticoagulant therapy, allowing them to make an informed decision regarding the treatment they are receiving. Therefore, despite all the scoring systems, patient's decision remained the utmost important. Many patients with better financial situations may even consider self-purchase of the dabigatran to prevent stroke. Our study also found that there are no associations between both CHA2DS2-VASc and HAS-BLED score with oral anticoagulants prescription. This means that both CHA2DS2-VASc and HAS-BLED score were not the direct determinants of the type of oral anticoagulants prescribed to patients. Patients with renal failure or renal impairment tend to be treated with warfarin than dabigatran as the excretion of dabigatran is mainly via kidney, therefore warfarin may be a safer choice for patients with lower creatinine clearance (14).

Both warfarin and dabigatran were effective in preventing stroke in nonvalvular atrial fibrillation. However, when both warfarin and dabigatran were compared, we found that the stroke occurrence in dabigatran group (1.3%) was lower than the stroke occurrence in warfarin group (2.7%). This showed that dabigatran can better prevent patients with nonvalvular atrial fibrillation from stroke than warfarin (15). Although our study did not specifically analyze and discuss about the dosage of dabigatran usage, our study is still able to agree with the findings of the Randomized Evaluation of Long Term Therapy (RE-LY) With Dabigatran Etexilate study in which dabigatran administered at a dose of 110 mg twice daily was associated with lower rate of major bleeding but have similar efficacy compared with warfarin (16). Meanwhile, a higher dose of dabigatran at 150mg showed similar rates of major bleeding with higher efficacy of stroke prevention (17). In addition, the Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients (ARISTOPHANES) study involving a total of 285292 patients also concluded that direct oral anticoagulants such as dabigatran had lower rates of stroke in comparison to warfarin (18). Apart from being an effective primary stroke prevention therapy, DOACs also prove to be effective to prevent systemic embolism with lower risk of intracerebral bleeding, vascular and all-cause mortality compared to warfarin (19).

Majority of patients with non-valvular atrial fibrillation prescribed with either warfarin or dabigatran had no bleeding events during the treatment. Despite the cumbersome nature of warfarin prescription such as frequent INR monitoring and dietary restrictions, bleeding events were low in our population of patients. This could be contributed by good match between patient and the type of anticoagulation used, high adherence and optimal clinic monitoring.

Dabigatran is also associated with less critical and more manageable major bleeding complications compared to warfarin therapy. In the dabigatran group, the worst major bleeds were mostly gastrointestinal compared to intracerebral which is more challenging to treat (20). Dabigatran related major bleeds were also shown to have shorter intensive care requirement with lower mortality rate than warfarin (21). A retrospective study done in two tertiary hospitals in Malaysia showed that although the rate of bleeding with dabigatran is low, a patient with a high stroke risk and high bleeding risk is more at risk of getting a bleeding event (22).

In terms of dosing, we found that major bleeding events was higher in patients treated with 0-2mg of warfarin and 110mg of dabigatran. This is in contrast with many studies which showed that higher doses of oral anticoagulants are associated with higher risk of bleeding (23). However, there are still many factors that can contribute to bleeding such as the age of the patients, hypertension, clotting disorder, abnormal renal or liver function. Our study agrees with the findings by Jordan K. Schaefer et al that concluded hemorrhagic stroke rate and intracranial bleeding events were lower in all doses of direct oral anticoagulants, except 150mg dabigatran in comparison to warfarin (24).

From our study, majority of oral anticoagulant discontinuation come from warfarin users. This showed that patients with nonvalvular atrial fibrillation on anticoagulant therapy had lesser or almost no issues with dabigatran. A nationwide audit done on 56 MOH healthcare facilities in Malaysia showed that most common reasons of switching from warfarin to DOACs were labile INR, history of bleeding/overwarfarinisation and difficulty in monitoring (25). According to the guideline from National Institute for Health and Care Excellence (NICE) in 2014, it is appropriate to change from warfarin to dabigatran if INR readings were unstable within the last six months or there were less than 65% time within the therapeutic change (26). However, it is substantial to examine patient's adherence to warfarin treatment before oral anticoagulant is changed. Patients that are noncompliant to a once-daily dosing of warfarin are less likely to adhere to dabigatran.

Since our study was a retrospective study, the accuracy of the analysis and conclusion drawn from our research is highly dependent on the accuracy of the data. Certain minor side effects might not be documented if the clinician deemed them as not life-threatening. Another limitation we came across in our study was the sample size for our study. There was a huge margin between patients who are prescribed with warfarin and dabigatran. Thus, there was a limitation to the study sample to accommodate the finite number of dabigatran patients. The small sample size of dabigatran users in our

case was due to the limited quota, lack of affordability and availability in dabigatran prescription as dabigatran is a new drug in Malaysia and its usage has yet to gain favorable popularity. Future prospective randomized trials are recommended.

CONCLUSION

We reported the safety and efficacy of dabigatran compared to warfarin therapy in nonvalvular atrial fibrillation patients in a single study cohort. Our study suggests similar efficacy between both agents. However, dabigatran patients encountered fewer bleeding events which makes it the favored treatment in Asians with nonvalvular atrial fibrillation. Furthermore, patients on warfarin were more likely to discontinue treatment compared to dabigatran due to its side effects and inconvenience.

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