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# A single centre experience of the efficacy and safety of dabigatran etexilate used for stroke prevention in atrial fibrillation

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**Abstract** The use of novel anticoagulants such as dabigatran are increasing. Despite increased risks of intracerebral haemorrhage with warfarin among Asians, there is little published data on dabigatran to assess 'real world' efficacy and safety of dabigatran therapy in Asia. This was a retrospective observational study of patients prescribed dabigatran between 2010 and 2013. Data was available for 510 patients: median age 68 years (range 20–91), median CHA2DS2-VASc score was 2 and median HAS-BLED score was 2. The average follow-up duration of 315 days (range: 1–1,096). The overall discontinuation rate was 16 % after a median 252 days of treatment with dabigatran. There were 17 (3.3 %) patients with minor bleeding, 2 (0.4 %) had major bleeding episodes. 20 patients (3.9 %) developed dyspepsia which was the most common side effect. The rate of occurrences of adverse effects and bleeding were lower than those seen in the RE-LY trial. None of the patients had an ischaemic stroke, 1 (0.2 %) patient had a haemorrhagic stroke. Out of 510 patients, 158 patients (31 %) were switched to dabigatran from warfarin. This showed that patients frequently preferred the dabigatran due to convenience when given a choice to switch from warfarin. We report one of the largest registry of Asian patients. Reassuringly, we found that our cohort had a low rate of rate of ischaemic stroke, low rates of side effects and bleeding with the drug.

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## Introduction

Dabigatran etixilate (Trade name Pradaxa®, Boehringer Ingelheim) [1] is an oral anticoagulant which works as a direct thrombin inhibitor, licenced for stroke prevention in non-valvular atrial fibrillation (AF). In 2009, the results of the RE-LY study showed that dabigatran 150 mg dose was more effective at preventing thromboembolism with the same risk of major haemorrhage when compared to the 110 mg dose [2]. The recently published RELY-ABLE study demonstrated that there was a higher rate of major bleeding with dabigatran 150 mg twice daily compared to 110 mg, and similar rates of stroke and death [3]. Dabigatran is one of the several novel anticoagulants (including rivaroxaban [4] and apixaban [5]), which have the potential to significantly change the practice of anticoagulation for patients with high risk of stroke in AF. The latest European Society Guidelines for the management of AF [6, 7] recommends that novel oral anticoagulants such as dabigatran should be considered over than a Vitamin K antagonist for stroke prevention where possible.

It has been suggested from studies that Asians have an increased risk of intracerebral haemorrhage with warfarin over Caucasian patients [8]. Among Far Eastern populations with suboptimal prophylaxis due to warfarin, novel anticoagulants have also been suggested to have the potential for improving stroke prevention in AF [9]. There is currently little published 'real world' data on dabigatran's use among the Asian population.

Dabigatran was licensed for use in our centre since 2010 and our cardiologists have rapidly adopted its use for stroke

prevention in AF, commonly with preference over warfarin. However, despite published data, there remain concerns about its potential risk of bleeding events, use among patients with renal dysfunction and adverse effect profile. So far, there have been documented case reports of haemorrhage [10] and gastrointestinal bleeding [11] associated with dabigatran in clinical practice. Although helpful, they provide limited information regarding relative incidences of adverse effects. There is also little information regarding patient's experience, discontinuation rate and its prescribing trend in clinical practice, including reasons for switching from warfarin. We felt that it would be important to study these aspects. Hence, we carried this single centre study of a large cohort of patients.

## Methods

The National Health Institute in Malaysia is a 400 bed hospital specializing in cardiology and treating a large population referred nationally. The study design was a retrospective cohort registry. Inclusion criteria were patients who were prescribed dabigatran, who were identified via hospital pharmacy records in September 2012. The patients' medical records which were paper based files including both inpatient and outpatient notes, were all available and extracted for data analysis. Data which was collected through manual review of the files and data was recorded into an Access database between the period of October 2012 to March 2013. Baseline patient characteristics were collected including age and sex of patient, CHA2DS2-VASC score and echocardiographic data. Data on blood tests were recorded for liver function as reflected by alanine transaminase (ALT) level before and after dosing with dabigatran, as well as renal function (eGFR) before and after dosing. The dose of dabigatran prescribed and indication for use was documented. For patients switched to dabigatran from warfarin, the reason was recorded. We also collected data on the incidence of any ischaemic cerebrovascular (CVA) or haemorrhagic CVA, major bleeding (transfusion $>$ 2 units of blood) and minor bleeding ($<$2 units of blood transfusion) as defined in the RE-LY trial. All documented adverse effects eg. dyspepsia were recorded. Data on follow up length in days of drug prescription were recorded in order to calculate discontinuation rates. Patients who were lost to follow up were excluded from analysis of rates of discontinuation.

## Results

### Baseline characteristics

510 patients were included in the study. Population characteristics of the patients who underwent analysis are shown in Table 1.

**Table 1** Population characteristics of all study patients

| | |
|---|---|
| Mean age (range) | 68 (20–91) |
| Female sex | 195 (38 %) |
| Paroxysmal AF | 375 (73.5 %) |
| Persistent AF | 57 (11.2 %) |
| Permanent AF | 73 (14.3 %) |
| Age 65–75 | 160 (31.4 %) |
| Age >75 | 109 (21.3 %) |
| Congestive cardiac failure | 30 (5.8 %) |
| Hypertension | 353 (69 %) |
| Diabetes | 161 (31.5 %) |
| Previous TIA/stroke | 62 (12.1 %) |
| Vascular disease | 84 (16.5 %) |
| Mean LVEF (range) | 56 % (16–79 %) |
| Baseline eGFR >60 (ml/min/1.73 m2) | 284 (70.4 %) |
| Baseline eGFR 30–60 (ml/min/1.73 m2) | 119 (29.6 %) |

| CHA2DS2-VASc score | Number of patients |
|---|---|
| 0 | 45 |
| 1 | 93 |
| 2 | 136 |
| 3 | 108 |
| 4 | 82 |
| 5 | 36 |
| 6 | 10 |

| HAS-BLED score | Number of patients |
|---|---|
| 0 | 70 |
| 1 | 173 |
| 2 | 197 |
| 3 | 60 |
| 4 | 9 |
| 5 | 1 |

Echocardiographic data was available in 476 patients. There were 80 patients with moderate mitral regurgitation and 6 with severe mitral regurgitation. Four patients had documented rheumatic disease. There were 2 patients with bioprosthetic mitral valves and one with a Mitraclip. The mean left ventricular ejection fraction (LVEF) was 56 % range (16–79 %). The median CHA2DS2-VASc score was 2. Our study population also included patients with CHA2DS2-VASc score of 0 due to patients being prescribed dabigatran for procedures such as AF ablation and DC cardioversion of AF. The median HAS-BLED score was 2.

eGFR results at baseline were available in 397 patients. eGFR results for both before and after (within 6 months) starting dabigatran were available on 250 patients. Three patients demonstrated a rise in creatinine >50 % after starting the drug, dabigatran was stopped in all three

**Table 2** Adverse effects not related to bleeding

| | |
|---|---|
| Dyspepsia | 20 (3.9 %) |
| Shortness of breath | 6 (1.2 %) |
| Leg oedema | 5 (1 %) |
| Palpitations | 3 (0.6 %) |
| Dizziness | 3 (0.6 %) |
| Chest pain | 2 (0.4 %) |
| Headache | 2 (0.4 %) |
| Allergy | 2 (0.4 %) |
| Generalised pain | 1 (0.4 %) |
| Sweating | 1 (0.2 %) |
| Vertigo | 1 (0.2 %) |
| Bloatedness | 1 (0.2 %) |

**Table 3** Bleeding events

| | |
|---|---|
| Minor bleeding | |
| Haematuria | 5 (1 %) |
| Gum bleeding | 5 (1 %) |
| Subconjunctival haemorrhage | 2 (0.4 %) |
| Retinal haemorrhage | 1 (0.2 %) |
| Epistaxis | 1 (0.2 %) |
| Major bleeding | |
| Gastrointestinal bleed | 2 (0.4 %) |

patients. ALT results were available in 265 before and after (within 6 months) of starting dabigatran. None of the patients had a demonstrable rise in ALT of >3 times from baseline.

## Adverse effects

47 of (9.2 %) 510 patients reported adverse effects (not due to bleeding) from treatment with dabigatran (Table 2). The majority of adverse effects were minor.

The commonest adverse effect was dyspepsia. Among the 20 patients who reported dyspepsia, 13 patients continued with dabigatran with either a proton pump inhibitor or antacid. Seven patients discontinued dabigatran.

## Bleeding

A total of 16 (3.3 %) patients had adverse effects of bleeding as illustrated in Table 3. There were 14 (2.7 %) patients with minor bleeding and 2 (0.4 %) patients with major bleeding due gastrointestinal bleeding. Of the major bleeding patients, one patient had a haemoglobin (Hb) drop of from 13 to 7.8 g/dl and the second patient had a Hb drop from 12.7 to 6.6 g/dl.

**Table 4** Comparison of adverse events and outcomes comparing dabigatran doses

| Dabigatran dose | 110 (mg) | 150 (mg) |
|---|---|---|
| Dyspepsia | 11 | 9 |
| Minor bleeding | 9 | 5 |
| Major bleeding | 2 | 0 |
| Haemorrhagic CVA | 1 | 0 |

**Table 5** Reasons for switching from warfarin to dabigatran

| | |
|---|---|
| Patient preference | 150 |
| Doctors recommendation | 22 |
| INR not in therapeutic range | 7 |
| Convenience (blood taking) | 5 |
| Difficulty getting to INR clinic | 3 |
| Bleeding due to warfarin | 3 |
| Allergic to warfarin | 3 |
| Bleeding due to warfarin | 1 |
| Gastritis on warfarin | 1 |
| Fatigue on warfarin | 1 |
| Diet restrictions on warfarin | 1 |

## Cerebrovascular outcome

None of the patients had ischaemic stroke and one (0.2 %) patient had a haemorrhagic stroke. This was an 86 year old patient who was prescribed 110 mg of dabigatran and had a frontoparietal brain haemorrhage (which was felt to be acute on chronic subdural haematoma) in June 2012. This required burr hole and subdural drainage, the patient recovered following surgery and dabigatran was discontinued.

## Comparison of the 110 and 150 mg doses

Dabigatran of 110 mg strength were prescribed for 206 patients (40.4 %) while the remaining 304 patients were prescribed the 150 mg dose (59.6 %). The 110 mg dose was first approved in 2010 and a year later, the 150 mg dose was approved. Many of the early prescriptions were thus at the 110 mg dose but the 150 mg dose has been more frequently prescribed recently. We compared the main adverse effects and CVA outcomes for both doses of dabigatran. There were no significant differences or trends observed (Table 4) in the adverse effect profiles.

## Patient attitudes to dabigatran versus warfarin

355 (69.6 %) patients were started straight to dabigatran whilst 158 (31 %) patients switched from warfarin. Convenience and patient preference were frequent documented

**Table 6** Reasons for discontinuing dabigatran

| | |
|---|---|
| Patient requested switch to warfarin | 17 |
| Procedure completed (e.g. AF ablation) | 14 |
| Switch to antiplatelet | 5 |
| Dyspepsia/gastritis/peptic ulcer | 5 |
| Worsening renal function | 3 |
| Patient request | 4 |
| Switch to rivaroxaban | 2 |
| Unable to tolerate | 2 |
| Per rectal bleeding | 2 |
| Haematuria | 1 |
| Gum bleeding | 1 |
| Subcunjunctival haemorrhage | 1 |
| Haematoma from fall | 1 |
| Minor bleeding | 1 |
| Haemorrhagic stroke | 1 |
| Cost of drug | 1 |
| Allergy | 1 |
| Dizziness and tremors | 1 |

reasons for switching away from warfarin. These reasons are listed in Table 5.

### Follow up

There were 18 patients with no follow up data (e.g. patients started on dabigatran but could not return for follow up at our hospital). The mean follow up period was 291 days (range 1–1,096 days) and median follow up period was 252 days.

### Discontinuation of dabigatran

After excluding patients with no follow up information, 400 of 492 patients were still on pradaxa at the end of the follow up period (92 discontinued dabigatran). There were documented reasons for discontinuing dabigatran in 63 patients. Of note there were 17 (27 %) of patients who reverted back to warfarin. The reasons for discontinuing dabigatran are listed in Table 6. After excluding patients where procedure only required a defined period of anticoagulation and those without follow up data, the discontinuation rate was calculated to be 78/492 (16 %).

## Discussion

This is the largest study so far capturing a single centre's experience of the efficacy and effects of dabigatran. Although there have been other registries reporting data from electronic databases, none have recorded patient's views and preferences, which can only be obtained through review of medical records. Our population confers some differences in baseline characteristics (including an ethnically Asian population) when compared to the RE-LY study. Although ethnically different, rates of hypertension and diabetes were similar among our patients (68 and 31 %) compared to RE-LY (78 %, 23 %). One difference was that the RE-LY trial population had a third proportions of paroxysmal, persistent and permanent AF but our patients had predominantly paroxysmal AF (74 %). Despite this, they would still require anticoagulation for AF as guided by the CHA2DS2-VASc score, as it has been shown from that stroke risk is similar for all 3 subtypes of AF [12]. In comparison to the RE-LY trial where the CHADS2 score was 2, our population had a CHA2DS2-VASc of 2 suggesting a group with lower stroke risk. This may be because of the nature of our hospital being a tertiary cardiology centre and hence the differing background characteristics of patients referred with AF. We also found a subset of patients with CHA2DS2-VASc of 0 among our patients reflecting real world clinical practice of using dabigatran in patients with AF undergoing ablation or cardioversion. Both of these indications for dabigatran are increasingly accepted in clinical practice and studied in trials of the use of dabigatran in AF ablation [13] and cardioversion [14].

The important message from this study is that dabigatran is safe among our population in clinical practice. The adverse effect profile for dabigatran among our patients are lower than that in the RE-LY trial population. Our population experienced a dyspepsia rate of 3.9 % compared to a rate of over 11 % with dabigatran in the RE-LY trial. Although rates of side effects are lower among our population, there were similarly reported adverse effects of shortness of breath, dizziness and leg oedema when compared to the RE-LY trial. The lower rate of side effects could be in part due to under-reporting of effects and higher vigilance for such effects in a trial setting, but are nevertheless reassuring. We found significantly lower numbers of patients who had major bleeding (0.4 vs 3 % in RE-LY) and minor bleeding (3.3 vs 14 % in RE-LY) in our study. Our patients also had an overall discontinuation rate of 16 % after a median 252 days of treatment with dabigatran. This follow up period is comparable to that in the RE-LY trial population which had a discontinuation rate at 15 % after a follow up period of 1 year. The follow up period and treatment duration of patients in our study was relatively short since dabigatran was only licenced for use in 2010. Among patients who discontinued dabigatran where reasons were documented, 27 % of patients had chosen to switch back to warfarin. It was likely that these patients made the switch due to adverse effects rather than socioeconomic reasons.

It has recently been shown by the RE-LY Asia study that haemorrhagic stroke occurred significantly more frequently with warfarin when compared to both doses of dabigatran [15]. Annual rates of haemorrhagic stroke with warfarin was 0.75 % in Asians and 0.32 % in Non-Asians. They were 0.11 % in Asians and 0.12 % in Non-Asians with the dabigatran 110 mg dose, and 0.17 % in Asians and 0.09 % in Non-Asians with the 150 mg dose. The rate of haemorrhagic stroke in our study for both doses of dabigatran was 0.2 % over 3 years was comparably low (in the RE-LY study it was 0.12 % per year for the 110 mg dose and 0.10 % for the 150 mg dose).

Importantly, our study has captured data reflecting the trends of a novel anticoagulant for the first time in a developing country. Our data (Table 5) already shows that there were many reasons that patients find warfarin to be inconvenient, and that a novel anticoagulant provides a welcome alternative. Many of the reasons for a patient to switch from warfarin to dabigatran would be influenced by a patients' perception of the disadvantages of warfarin as well as the clinician's guidance and reassurance about dabigatran's risks. We found that among our patients, 160 (31 %) on dabigatran were switched from warfarin, demonstrating the significant proportion of patients keen to try an alternative to warfarin. It has already been demonstrated that warfarin's efficacy is affected by low periods of time in therapeutic range (TTR). A subgroup analysis of the RE-LY study showed that the TTR in Malaysia has been as low 56 % [16], and these figures further highlight the potential advantages of novel anticoagulants.

There are some other published registries on dabigatran. One retrospective study based in Hong Kong compared 122 patients on dabigatran with 122 patients with warfarin, and found that efficacy and bleeding rates were similar [17]. There is also a published registry of dabigatran compared to warfarin in Denmark ($n = 13{,}914$) with data captured with the Danish National Prescription Registry and also Danish National Patient Register [18]. In contrast, our study involves obtaining data from individual patient records and is able to capture events related to dabigatran recorded during the patients' consultation with doctors. The Danish study found that there were similar rates of stroke/systemic embolism and major bleeding when comparing dabigatran with warfarin. Another study of patients in the real world was based in New Zealand ($n = 70$) [19] found discontinuation rates of 10 % compared to our study of 16 % although their median follow up period was shorter at 140 days compared to our study's follow up period of 262 days.

### Study limitations

There are limitations due to this study's retrospective nature. The sample size of the study is inadequate for analysis of comparisons between dabigatran 110 and 150 mg doses as well as for mortality. The accuracy of data relied on the completeness of the hospital clinical records of a busy cardiology tertiary centre. Data capture is also dependent on patient reporting adverse effects or reason for any discontinuation to the clinician. Data collection may have been subject to inter-observer variability.

## Conclusions

We report a registry of efficacy and adverse effects of dabigatran therapy among a large cohort of Asian patients. Reassuringly, we found a low rate of ischaemic stroke and low rates of side effects, and bleeding, thus confirming the findings of the RE-LY trial in the 'real world' among this cohort.

**Conflict of interest** The authors declare that they have no conflict of interest.

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