Clinical Investigations

Dabigatran Compared With Warfarin for Stroke Prevention With Atrial Fibrillation: Experience in Hong Kong

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ABSTRACT

Background: Dabigatran is an oral direct thrombin inhibitor recently approved for stroke prevention in atrial fibrillation (AF) as an alternative to warfarin. The primary advantages of dabigatran are freedom from monitoring and less interaction with other drugs and food. It is ideal for patients who are unwilling to adhere to regular coagulation monitoring or whose therapeutic effect using warfarin is not optimal despite adequate monitoring and management. However, the impact of dabigatran on health-related quality of life (HRQoL) and drug compliance has been less evaluated. This study aimed to evaluate the clinical and humanistic outcomes of dabigatran use in Hong Kong.

Hypothesis: Dabigatran 110 mg twice daily was non-inferior in stroke prophylaxis in AF patients compared to adjusted-dose warfarin; while dabigatran 150 mg twice daily was superior to adjusted-dose warfarin in the real world data in Hong Kong.

Methods: We retrospectively analyzed 244 patients with newly diagnosed AF and prescribed dabigatran (n = 122) or warfarin (n = 122) for stroke prophylaxis from the Prince of Wales Hospital between January 2010 to November 2011. Clinical outcomes including death, stroke, bleeding, and HRQoL using the EuroQol EQ-5D-5L were compared between patients on dabigatran and warfarin.

Results: The median duration of follow-up was 310 days. Stroke occurred in 2 patients (1.64%) in the dabigatran group and 4 in the warfarin group (3.28%) (adjusted hazard ratio [HR]: 0.53, $P = 0.47$). Bleeding of any degree occurred in 28 patients on dabigatran and 38 patients on warfarin (adjusted HR: 0.76, $P = 0.28$), with age over 70 years and renal impairment being significant positive predictors of bleeding ($P = 0.01$ and 0.02, respectively). Dyspepsia was the most common adverse event of dabigatran over warfarin (19.7% vs 8.2%, $P = 0.01$). Rate of discontinuation of dabigatran was 25.4%, with dyspepsia being the most common cause for discontinuation (6 patients, 4.92%). There was no significant difference in drug compliance or HRQoL at 1 year between the 2 groups (utility score 0.77 [dabigatran] vs 0.74 [warfarin], $P = 0.28$).

Conclusions: In Hong Kong, the clinical efficacy and safety of dabigatran were comparable to that of warfarin, and drug compliance and HRQoL of using dabigatran and warfarin were similar after 1 year of use.

Introduction

Atrial fibrillation (AF) is a chronic cardiac arrhythmia that is associated with increase in risk of ischemic stroke by 4-5 times.[1] It is particularly dangerous for elderly patients who are 80 years or older, with a 30% risk of stroke in this patient group compared to 15% risk of stroke in patients of all ages.[2] Traditionally, AF patients are managed with vitamin K antagonists such as warfarin to prevent stroke in patients with moderate to high risk of stroke.[3,4] Warfarin, as well as other vitamin K antagonists, are effective in reducing stroke by over 60%.[5–7] Yet, warfarin is known to have multiple drug-drug and drug-food interactions. It is a narrow therapeutic range medication that requires frequent blood monitoring and increased risk of bleeding.[8] In addition, poor medication adherence to warfarin also leads to undesirable clinical outcomes in AF patients. Kimmel et al demonstrated that over 90% of warfarin patients had at least 1 missed or extra pill-bottle opening during a 3.5-month period, causing up to

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a 40% rate of nonadherence with warfarin therapy.[9] Such nonadherence places many patients at risk for stroke and bleeding complications.

Dabigatran is an oral direct thrombin inhibitor recently approved for stroke prevention in AF as an alternative to warfarin.[8] In the landmark Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran (110 mg twice daily) was noninferior, and 150 mg twice daily was superior to warfarin for prevention of stroke and systemic embolism.[10] However, the higher dose of dabigatran resulted in higher bleeding rates than the lower dose ($P = 0.05$). The primary advantages of dabigatran are freedom from monitoring and less interaction with other drugs and food. It is ideal for patients who are unwilling to adhere to regular coagulation monitoring or whose therapeutic effect using warfarin is not optimal despite adequate monitoring and management. Dyspepsia was a common side effect of dabigatran, contributing to a 21% discontinuation rate within 2 years. The current study aimed to compare the use of dabigatran with warfarin in terms of clinical efficacy, safety, and quality of life in patients with AF in Hong Kong.

Methods

Subjects were recruited from the Prince of Wales Hospital, a university-affiliated tertiary public hospital in Hong Kong with 1500 beds. Patients were eligible for the study if they were diagnosed with AF and prescribed dabigatran or warfarin for stroke prophylaxis, as indicated in the electronic patient record during the period January 1, 2010 to November 30, 2011. Exclusion criteria included pregnancy, malignancy, and an incomplete patient record. To match the dabigatran group patients, an equal number of warfarin patients were recruited, matching the age, sex, and treatment duration of the dabigatran group. All patients were followed up until March 31, 2012 to allow sufficient anticoagulant treatment and follow-up.

The efficacy end points resembled those in RELY trial[10] and included death, stroke, transient ischemic attack, systemic embolism, pulmonary embolism, myocardial infarction, and unstable angina, whereas safety end points included bleeding of any degree and adverse events as noted in the electronic patient record by the physician in charge of the case. The electronic patient record was available and shared among all public hospitals in Hong Kong. Major bleeding was defined according to the guidelines of International Society on Thrombosis and Haemostasis, namely: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ; and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.[11] Any bleeding that did not match such criteria was considered minor. Baseline characteristics were collected from the electronic record. The present health-related quality-of-life (HRQoL) status of the dabigatran group was compared to that of warfarin group using the EuroQol EQ-5D-5L questionnaire.[12] This quality-of-life questionnaire, together with the drug compliance of patients, were assessed by a telephone interview conducted by the same student pharmacist, who questioned patients on how frequently they took the drug and if they followed the instructions of drug administration. Those who intentionally and constantly missed pills during a day or for some days in a week were counted as noncompliant.

Statistical Analysis

The efficacy end points and bleeding events were compared using a Cox regression hazard model and reported with an adjusted hazard ratio (HR), with 95% confidence interval (CI) and P value given. Adverse events were compared using the χ^2 test. Quality-of-life answers for the EQ-5D-5L descriptive system were converted to a utility score, with the conversion method provided by the Japan time trade-off value set.[13] The scores and visual analogue scale (VAS) of the 2 groups were then compared using a 2-sample t test. The statistical significance was set at $P \leq 0.05$. The study protocol and informed consent forms were approved by the ethics committee of New Territories East Cluster, Hospital Authority Hong Kong. Oral informed consent was provided at the beginning of the telephone survey.

Results

A total of 244 patients were recruited. The mean age of all patients was 70.1 years, and 54.1% were male. The mean $CHADS_2$ score of the patients was 2.4. Median treatment duration was 310 days. The summary of the patient demographic data is shown in Table 1. Patients in Hong Kong are usually followed up every 3 months per year in the public health care system. In the dabigatran group, most patients used the dose 110 mg twice daily (90.2%), whereas 6 (4.9%) patients used the US Food and Drug Administration (FDA)-approved 150-mg twice-daily dose. The remaining 6 patients (4.9%) used a mixture of reduced doses, including 75 mg twice daily, 110 mg daily, and 150 mg daily.

Efficacy end points were summarized in Table 2. Stroke occurred in 2 (1.64%) and 4 patients (3.28%) in dabigatran and warfarin groups, respectively (adjusted HR: 0.53, 95% CI: 0.10–2.96, $P = 0.47$). Among them, the stroke cases in the dabigatran group were all hemorrhagic stroke, whereas in warfarin group, 1 case was hemorrhagic stroke and the remaining were ischemic stroke. There was a lower incidence of all bleeding in the dabigatran group compared to warfarin, but the result was insignificant (HR: 0.76, 95% CI: 0.45–1.25, $P = 0.28$) (Table 2). There was no difference in major bleeding, which occurred in 2 patients (1.64%) and 3 patients (2.46%) taking dabigatran and warfarin, respectively (HR: 0.72, 95% CI: 0.19–4.37, $P = 0.72$)

The adverse events experienced by the 2 groups are summarized in Table 3. Similar to the findings in the RE-LY study, dyspepsia was significantly more common in the dabigatran group compared to the warfarin group (19.7% vs 8.2%, $P = 0.01$). Interestingly, peripheral edema was found to have a significantly higher rate of incidence in the warfarin group compared to the dabigatran group ($P = 0.002$).

Univariate analysis was performed to investigate predictors for bleeding in dabigatran patients and found that age over 70 years (relative risk [RR] = 2.63, $P = 0.013$) and

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Table 1. Baseline Characteristics of the Study Participants

Characteristics	Dabigatran (n = 122)	Warfarin (n = 122)
Age, y	70.0 ± 11.4	70.1 ± 10.3
Male sex	68 (55.7%)	64 (52.5%)
Smoking		
Yes	9 (7.4%)	9 (7.4%)
No	59 (48.4%)	67 (54.9%)
Ex-smokers	30 (24.6%)	23 (18.9%)
Unknown	24 (19.7%)	23 (18.9%)
$CHADS_2$ score	2.48 ± 1.34	2.32 ± 1.47
0	7 (5.7%)	11 (9.0%)
1	23 (18.9%)	34 (27.9%)
≥2	92 (75.4%)	77 (63.1%)
Medical history		
Hypertension	85 (69.7%)	77 (63.1%)
Diabetes mellitus	35 (28.7%)	42 (34.4%)
Heart failure	31 (25.4%)	38 (31.1%)
Hyperlipidemia	40 (32.8%)	36 (29.5%)
Ischemic heart diseases	30 (24.6%)	25 (20.5)
Prior myocardial infarction	9 (7.4%)	12 (9.8%)
Previous stroke or transient ischemic attack	53 (43.4%)	39 (32.0%)
Dyspepsia	24 (19.7%)	21 (17.2%)
Chronic kidney disease	9 (7.4%)	13 (10.7%)
Medications at baseline		
Aspirin	21 (17.2%)	30 (24.6%)
ACE inhibitors or ARB	63 (51.6%)	51 (41.8%)
β-blocker	65 (53.3%)	65 (53.3%)
Calcium channel blocker (dihydropyridine)	37 (30.3%)	20 (16.4%)
Calcium channel blocker (nondihydropyridine)	11 (9.0%)	14 (11.5%)
Amiodarone or dronedarone	4 (3.3%)	14 (11.5%)
Statins	62 (50.8%)	52 (42.6%)
Proton pump inhibitor	19 (15.6%)	19 (15.6%)
H2-receptor antagonist	54 (44.3%)	52 (42.6%)
Antacid	9 (7.4%)	5 (4.1%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

chronic kidney disease (CKD) (RR = 2.73, $P = 0.015$) to be significant positive predictors of bleeding of any degree in patients taking dabigatran (Table 4).

Among all patients, 31 patients (25.4%) from the dabigatran group and 27 patients (22.1%) from the warfarin group discontinued the medications before the end of the study. The most common reason for discontinuation of dabigatran was dyspepsia (6 patients, 4.92%). Excluding these patients, 53 patients from the dabigatran group and 48 from the warfarin group were successfully interviewed for the drug-compliance assessment and HRQoL. The response rate was 54.3%. Eight patients (15.1%) and 4 patients (8.3%) were noncompliant in the dabigatran and warfarin groups, respectively ($P = 0.121$).

There was no significant difference in the EQ-5D-5L utility score and VAS score between the 2 groups (utility score: 0.77 ± 0.17 [dabigatran] vs 0.74 ± 0.16 [warfarin], $P = 0.279$; EQ VAS: 67.1 ± 19.4 [dabigatran] vs 69.7 ± 17.4 [warfarin], $P = 0.428$) (Table 5).

Discussion

Since the pivotal RE-LY trial, there have been a few real-world individual studies demonstrating the clinical efficacy and safety of dabigatran in European countries and in the United States.[14,15] The current study is the first of its kind in Asia. The main difference of dabigatran usage in Hong Kong, and probably elsewhere in Asian countries as compared to Western countries, is that a lower 110-mg twice-daily dose was more commonly used instead of the FDA-approved 150-mg dose, probably due to a preference of the lower anticoagulation status in Asian countries.[16]

In this study, the efficacy and safety of dabigatran and warfarin were not significantly different, possibly due to the relatively small sample size. Compared to the Japanese subgroup study in RE-LY trial, which involved 107 and 108 patients taking dabigatran (110 mg twice daily) and an adjusted dose of warfarin, respectively, the findings of the 2 studies were similar except for the rate of major bleeding with dabigatran, which was higher in the Japanese study.[17] This can be explained due to the retrospective nature of our study, which can cause imprecise recording of the major bleeding events. Intracranial hemorrhage (ICH) was particularly important for the Asian population, because Asians are associated with higher ICH incidence rates.[18] In this study, 2 cases of ICH were found in each group, and the finding was comparable to the RE-LY trial and its Japanese subgroup analysis, although no significant advantages could be found for dabigatran.

Old age and chronic kidney disease were established risk factors indicated in the package insert for dabigatran. Patients over 75 years of age were said to have an increased risk of bleeding, and it was suggested that patients 80 years of age should have a reduced dosage[19]; the age threshold for dose reduction should be further investigated. The ongoing Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed RE-LY Trial (RELY-ABLE) safety study, carried out by the manufacturer, would probably better address such issue.[20] The exact dose to be used in these patients is another significant concern. In this study, although a 110-mg twice-daily dose was used as the normal dose, reduced dosing

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Table 2. Efficacy and Safety Outcomes

Event (Efficacy Outcomes)	Dabigatran, n = 122	Warfarin, n = 122	Dabigatran vs Warfarin, Adjusted HR (95% CI)	*P* Value
Stroke	2 (1.64%)	4 (3.28%)	0.53 (0.10–2.96)	0.469
Hemorrhagic	2 (1.64%)	1 (0.82%)	1.50 (0.01–227.74)	0.875
Ischemic	0 (0%)	3 (2.46%)	—	—
TIA	2(1.64%)	2(1.64%)	1.06 (0.15–7.60)	0.958
MI	0	1(0.82%)	—	—
Systemic embolism	0	0	—	—
Pulmonary embolism	0	0	—	—
UA	1 (0.82%)	2 (1.64%)	0.50 (0.04–5.71)	0.579
Death from stroke	1 (0.82%)	2 (1.64%)	0.65 (0.06–7.55)	0.734
Death from any cause	3 (2.46%)	4 (3.28%)	0.99 (0.22-4.48)	0.986
Event (safety outcomes)				
Intracranial bleeding	2 (1.64%)	2 (1.64%)	1.94 (0.01–402.82)	0.808
GI bleeding	8 (6.56%)	15 (12.30%)	0.57 (0.24–1.35)	0.199
Subconjunctival hemorrhage	4 (3.28%)	5 (4.10%)	0.81 (0.22–3.03)	0.754
Gum	2 (1.64%)	3 (2.46%)	0.62 (0.11–4.02)	0.654
Hemoptysis	1 (0.82%)	3 (2.46%)	0.32 (0.03–3.15)	0.330
Hematuria	4 (3.28%)	5 (4.10%)	0.97 (0.26–3.65)	0.968
Nose	1 (0.82%)	4 (3.28%)	0.25 (0.03–2.22)	0.212
Bruising	7 (5.74%)	9 (7.38%)	0.66 (0.23–1.65)	0.428
Hematoma	2 (1.64%)	0	—	—
Others	1 (0.82%)	1 (0.85%)	—	—
Major bleeding	2 (1.64%)	3 (2.46%)	0.72 (0.19–4.37)	0.719
Minor bleeding	26 (21.31%)	37 (30.33%)	0.71 (0.43–1.18)	0.188
All bleeding[a]	28 (22.95%)	38 (31.15%)	0.76 (0.45–1.25)	0.281

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; UA, unstable angina.
[a]For those who encountered both major and minor bleeding, each of them were only counted once in all bleeding events. Thus, the sum of major bleeding and minor bleeding events did not necessarily equal that of all bleeding.

Table 3. Adverse Events

Variable	Dabigatran (n = 122)	Warfarin (n = 122)	*P* Value
Dyspepsia	24 (19.7%)	10 (8.2%)	0.010[a]
Dizziness	20 (16.4%)	11 (9.0%)	0.084
Dyspnea	14 (11.5%)	13 (10.7%)	0.838
Chest pain	14 (11.5%)	7 (5.7%)	0.110
Peripheral edema	10 (8.2%)	27 (22.1%)	0.002[a]
Insomnia	3 (2.5%)	0 (0.0%)	0.123
Constipation	2 (1.6%)	0 (0.0%)	0.249
Poor appetite	2 (1.6%)	0 (0.0%)	0.249

[a]denoted $P \leq 0.05$.

in high-risk patients was diverse, ranging from 75 mg daily to 150 mg daily, all of which were not well studied in the RE-LY trial.[10] The reduced-dose issue should be addressed in future studies.

The most common side effect of dabigatran was dyspepsia. It was found to be higher in our study and the Japanese subgroup analysis of the RE-LY trial compared to the international RE-LY trial.[17] Although such inter-trial difference could not be tested statistically, from the numerical difference it may be postulated that Hong Kong population, or Asian population in general, may be more sensitive to the gastrointestinal side effects of dabigatran. Further studies are required to address this observation.

It was anticipated before the study that dabigatran would confer a higher compliance to patients, due to its convenient dosing and much fewer food restrictions. The finding in

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Table 4. Univariate Analysis of Bleeding of Any Degree in Patients Taking Dabigatran

Baseline Characteristics	Frequency	*P* Value
Sex		
Male	17/68 (25.0%)	0.550
Female	11/54 (20.4%)	
Age		
≥70[a]	22/71 (31.0%)	0.013[b]
<70	6/51 (11.8%)	
Hypertension		
Yes	21/85 (24.7%)	0.489
No	7/37 (18.9%)	
DM		
Yes	4/35 (11.4%)	0.056
No	24/87 (27.6%)	
Prior TIA or stroke		
Yes	13/53 (24.5%)	0.719
No	15/69 (21.7%)	
Prior GI Bleeding		
Yes	4/10 (40.0%)	0.184
No	24/112 (21.4%)	
CKD		
Yes	5/9 (55.6%)	0.015[b]
No	23/113 (20.4%)	
Baseline medications		
Aspirin		
Yes	5/21 (23.8%)	0.919
No	23/101 (22.8%)	
NSAID		
Yes	1/2 (50.0%)	0.363
No	27/120 (22.5%)	

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack. [a]Age threshold of 70 years old was calculated to have the most statistically significant difference in the rate of bleeding among all age thresholds. [b]denoted $P \leq 0.05$.

Table 5. Quality-of-Life Measures

Variable	Dabigatran (n = 53)	Warfarin (n = 48)	*P* Value
Utility score	0.77 ± 0.17	0.74 ± 0.16	0.279
Mobility	1.65 ± 0.86	1.94 ± 0.93	0.117
Self-care	1.27 ± 0.74	1.23 ± 0.75	0.789
Usual act	1.60 ± 0.98	1.54 ± 0.97	0.780
Pain	1.69 ± 0.78	1.92 ± 1.07	0.231
Anxiety/depression	1.46 ± 0.70	1.40 ± 0.61	0.619
EQ VAS	67.1 ± 19.4	69.7 ± 17.4	0.428

Abbreviations: EQ VAS, EuroQoL visual analogue scale.

this study was thus surprising, because the compliance rate of the dabigatran group was numerically lower than that of warfarin group, with a trend toward significance ($P = 0.121$). Although the sample size in our study might have been too small to suggest a significant difference, the high compliance of the warfarin group in our study could be due to comprehensive warfarin education in the established warfarin clinics in Hong Kong public hospitals, where the importance of compliance to warfarin is emphasized and reinforced.[21] Another reason could be due to the high cost of dabigatran, which is currently not subsidized in Hong Kong public hospitals.

No study on the quality of life of patients taking dabigatran compared to warfarin has been published. Although it was expected that dabigatran possessed the advantages of avoiding frequent blood taking and dietary restriction, the results of the current study were surprising. During the telephone survey, some warfarin patients expressed their adaptation to the treatment, and a few were even willing to have more frequent monitoring and restriction so that their health states could be more closely monitored. On the other hand, some dabigatran patients explained their concerns for the high cost and gastrointestinal upset issues. The quality of life of the 2 groups was thus not significantly different. Notably, there was significant in-group difference in age and treatment duration between patients who responded to the survey and those who did not in the dabigatran group (73.62 years vs 67.37 years, $P = 0.001$; 358.79 days vs 263.36 days, $P = 0.003$). Such age and treatment duration difference possibly influenced the HRQoL result in dabigatran group, although the direction and magnitude of impact could not be known.

There are several limitations in the study. One limitation was the retrospective nature of the study, and another limitation was that the study was not powered to show a difference in efficacy and safety, although the findings were similar to those in the Japanese subgroup analysis of the RE-LY trial. For the humanistic outcome, as this study was the first to measure quality of life of patients taking dabigatran, there were no baseline utility scores and VAS of the patients. They were thus assumed as having the same baseline utility score. Questions enquiring into patients' drug compliance were also not robust enough in this study, as compared to the validated Morisky questionnaire.[22]

Conclusion

The current study did not show clinical superiority of dabigatran over warfarin. Dabigatran was as effective and safe as warfarin in the management of AF patients. Dabigatran did not show improved quality of life or drug compliance in AF patients as compared to warfarin

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therapy. Given the nature of the current being retrospective, unblended, and observational with a small sample size, continuous postmarketing studies are necessary to evaluate the real-world benefit of dabigatran in the management of AF patients.

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