
Low-Dose Dabigatran May Be Safely Used as an Alternative to Warfarin for Peri-Procedural Anticoagulation During Atrial Fibrillation Ablation

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Abstract: Peri-procedural anticoagulation for atrial fibrillation (AF) ablation must be optimized to reduce the occurrence of bleeding and thromboembolic complications. In this study, the safety of two anticoagulants were compared between the commonly used warfarin and a potential alternative, orally administered low-dose (110 mg bid) dabigatran. A total of 117 Han Chinese patients undergoing AF ablation were included in the study. In all, 67 patients were administered dabigatran (110 mg) twice daily, while the other 50 received a therapeutically effective dose of warfarin. Thromboembolic and bleeding complications were compared between the two groups. No significant baseline differences were found between the groups. Only one thromboembolic complication (2.0%) occurred in the warfarin group, while no complications occurred in the dabigatran group ($p = 0.43$). Compared to the warfarin group, the dabigatran group showed a similar rate of major bleeding events (2.0% vs. 0; $p = 0.43$), but a significantly lower rate of minor bleeding events (9.0% vs. 22%; $p = 0.048$), total bleeding events (9% vs. 24%; $p = 0.03$), and bleeding and thromboembolic complications taken together (9% vs. 26%; $p = 0.01$). In Conclusion, the incidence of minor bleeding events after AF ablation was lower in those administered low-dose dabigatran (110 mg bid) than in those administered warfarin, while the risks of thromboembolic and major bleeding complications were similar between the two groups. This result indicates that low-dose dabigatran would be safer than warfarin in Chinese patients undergoing AF ablation.

Keywords: Dabigatran, Warfarin, Atrial Fibrillation, Catheter Ablation, Anticoagulation

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and is associated with an increased risk of ischemic stroke and systemic thromboembolism [1]. Catheter ablation is being increasingly used for the treatment of AF, particularly after the failure of antiarrhythmic drug therapy [2]. To reduce the risk of thromboembolic complications during catheter ablation, anticoagulants are administered before, during, and after the procedure. However, aspects of peri-procedural oral anticoagulant use in AF patients undergoing catheter ablation are still under scientific debate.

Warfarin is an effective, low-cost, anticoagulant drug, with a long history of use. However, warfarin administration

involves a high risk of bleeding events and a considerable amount of inconvenience owing to the necessity of continual intensive sampling to monitor the coagulation status [3]. Recently, dabigatran has been used in patients undergoing AF ablation, and may offer a more efficient, safer, and more convenient alternative to warfarin [4]. Studies show that dabigatran is equivalent to warfarin in terms of efficacy as a peri-procedural anticoagulant [5-8]. In the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, dabigatran at a dose of 110 mg twice daily (D-110-bid) was shown to be similar to warfarin in terms of stroke and thromboembolism prevention, and was more efficacious than warfarin when administered at a dose of 150 mg twice daily (D-150-bid) [9].

Of these two doses, the higher dose (D-150-bid) has been

used in most studies on peri-procedural anticoagulation for AF ablation. The lower dose, D-110-bid, is recommended for patients older than 80 years, those treated with verapamil, and those with chronic kidney disease or elevated bleeding risk score [9]. It is unknown whether D-110-bid could be used as an effective alternative to warfarin in anticoagulation therapy during AF ablation in Chinese patients. Therefore, the present study aimed to determine the efficacy and safety of D-110-bid in comparison to warfarin in Chinese patients with paroxysmal AF undergoing catheter ablation.

2. Methods

2.1. Study Population

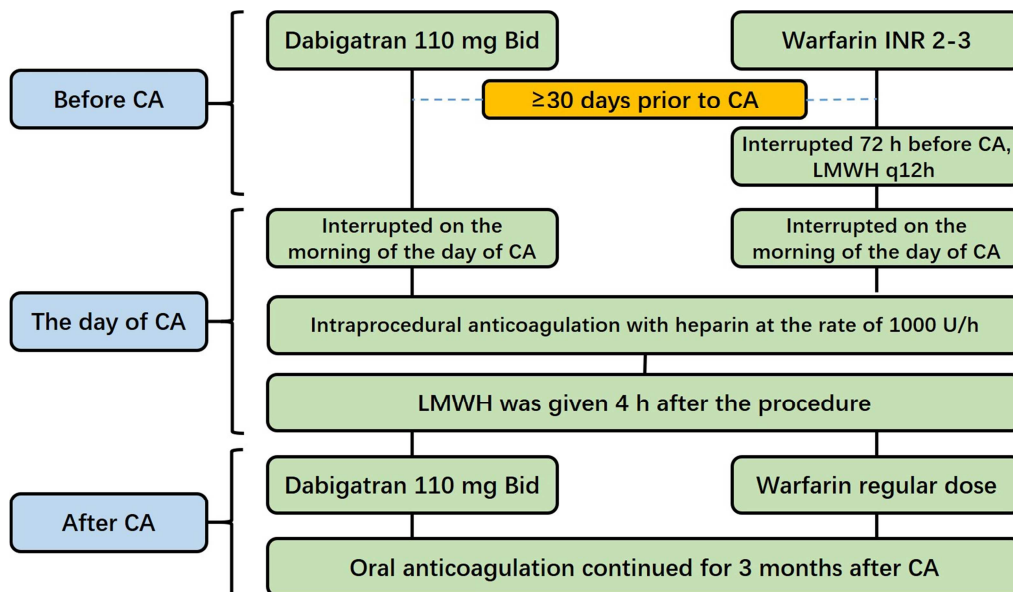
A total of 117 patients with paroxysmal AF who were scheduled to undergo pulmonary vein antral isolation (PVI) in our department were retrospectively analysed between May 2013 and May 2016. Patients were divided into a dabigatran group (n = 67) and a warfarin group (n = 50) based on the drug used for peri-procedural anticoagulant treatment. The patients were offered both drugs, and the actions and side effects of each drug were explained in detail. The patients then selected the drug most suitable to them according to their financial and personal circumstances. The exclusion criteria were as follows: age > 75 years; left atrial diameter > 50 mm; left atrial thrombus; advanced structural heart disease including haemodynamically significant valvular disease; left ventricular ejection fraction < 45%; creatinine clearance < 30 mL/min; known bleeding diathesis, or intolerance to heparin or oral anticoagulants; severe respiratory insufficiency; and severe comorbidities.

Written informed consent was obtained from all patients prior to the procedure, and the study was approved and supervised by the ethics committee at the Affiliated Hospital of Nantong University.

2.2. Peri-Procedural Anticoagulant Administration

All patients had been on effective oral anticoagulation for ≥ 30 days before the procedure. All anti-arrhythmic medications were stopped before the procedure, including amiodarone, which was stopped 1 month before the procedure. Patients in the dabigatran group received D-110-bid and were admitted to the hospital a day before the procedure. Dabigatran was discontinued on the morning of the procedure (Figure 1). The patients in the warfarin group received warfarin at a stable therapeutic level based on the international normalized ratio (INR; 2.0–3.0) prior to the procedure. Warfarin administration was interrupted 72 h before the ablation procedure; subcutaneous low-molecular-weight heparin (LMWH; enoxaparin, 0.5 mg/kg) was then administered twice daily. To exclude the presence of atrial thrombus, transoesophageal echocardiography was performed in all patients within 24 h prior to the ablation. Computed tomography (64-slice dual source scan) was performed to assess the pulmonary veins and left atrial anatomy.

For PVI, an initial bolus of unfractionated heparin (80 U/kg) was administered prior to trans-septal puncture. During the procedure, heparin was continuously administered at the rate of 1000 U/h to all patients via intravenous infusion. Following ablation, catheters were withdrawn, and heparin was stopped. LMWH was administered for 4 h after the procedure in both groups. Patients in the dabigatran group resumed dabigatran treatment the morning after the procedure to ensure continuous therapy and were discharged the day after ablation. Patients on warfarin received their first post-procedure warfarin dose on the morning following PVI, and the beginning of the post-procedure regimen overlapped with LMWH administration. After a therapeutic INR was attained, LMWH was stopped, and the patients' warfarin dose was adjusted as required in the outpatient clinic.



CA, catheter ablation; INR, international normalized ratio; LMWH, low-molecular-weight heparin

Figure 1. Flowchart illustrating treatment regimens and timing of drug interruption and resumption as well as employment of bridging heparin therapy.

2.3. Catheter Ablation Procedure

For all patients, the same qualified operators performed AF ablation to ensure similar results. In the right femoral vein or left subclavian vein, two sheaths were inserted, and a decapolar catheter (St. Jude Medical, Minneapolis, MN) was positioned in the coronary sinus via a 7-French short sheath (Cordis Corporation, Fremont, CA). After trans-septal puncture, two 7-French decapolar circumferential catheters (Lasso, St. Jude Medical, Minneapolis, MN) and a 7.5-French irrigation catheter with a 3.5-mm distal electrode (St. Jude Medical, Minneapolis, MN) were inserted into the left atrium. A three-dimensional geometrical map of the left atrium and pulmonary veins was subsequently created using the EnSite Velocity mapping system (St. Jude Medical, Minneapolis, MN) and the double Lasso technique. Radiofrequency energy was delivered for 20 s at each site at a power of 30–35 W and a target temperature of 40–42°C, under irrigation at an infusion rate of 15 mL/min via the ablation catheter. The procedural endpoint of this ablation strategy was the achievement of entry and exit blocks.

2.4. Post-Procedural Follow-Up

All patients were followed up in the cardiology clinic every month for 3 months after discharge, and any procedure-related complications were recorded. Thromboembolic complications were defined as stroke, transient ischemic attack, or systemic embolic events. Major bleeding was defined as intracranial haemorrhage, cardiac tamponade, late cardiac tamponade (occurring 48 h after the procedure), any bleeding resulting in a > 2 g/dL decrease in the haemoglobin level, or an event resulting in a need for surgery or blood transfusion [10]. Minor bleeding complications included pericardial effusion

and bleeding that did not require surgery or transfusion.

2.5. Statistical Analysis

All statistical analyses were performed using SPSS v22.0 software (IBM Corporation, New York, NY). All continuous variables were recorded as mean values \pm standard deviation and were compared using the Student t-test. The chi-square test was used for categorical variables. The Fisher exact test was used when the observed value in any of the 2×2 contingency table cells was < 5. A multivariate logistic model was used for identifying significant predictors of complications. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

The baseline clinical characteristics of the patients are summarized in Table 1. Age, sex, body mass index, comorbidities, biochemical parameters, left atrial size, and left ventricular ejection fraction did not differ between the dabigatran and warfarin groups. The CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores were well-matched between the two groups ($p > 0.05$). The percentages of patients using the antiplatelet agents aspirin or clopidogrel, and other clinical characteristics were similar in both the groups. In addition, there were no differences in the prevalence of transient ischemic attacks or cerebrovascular accidents between the two groups (4.0% vs. 3.0%, $p > 0.05$). As anticipated, the INR was significantly lower ($p < 0.01$) and the activated partial thromboplastin time was significantly higher ($p < 0.01$) in the dabigatran group than in the warfarin group.

Table 1. Baseline clinical characteristics of the study patients.

Baseline characteristics	Warfarin group n = 50	Dabigatran group n = 67	p-value
Age (years)	57 \pm 12	59 \pm 10	0.14
Sex			0.81
Male	28	36	
Female	22	31	
BMI (kg/m ²)	24.63 \pm 3.59	24.63 \pm 2.83	0.47
Hypertension	24 (48.0)	30 (44.8)	0.73
Diabetes	6 (12.0)	7 (10.4)	0.79
Heart failure	11 (22.0)	15 (22.4)	0.96
Coronary artery disease	2 (4.0)	3 (4.5)	1.00
Prior stroke/TIA	2 (4.0)	2 (3.0)	1.00
CHADS ₂ score			
0	26 (52.0)	33 (49.3)	0.77
1	19 (38.0)	25 (37.3)	0.94
≥ 2	5 (10.0)	9 (13.4)	0.57
CHA ₂ DS ₂ -VASc (x \pm s)	1.3 \pm 1.15	1.4 \pm 1.25	0.31
HAS-BLED (x \pm s)	0.87 \pm 0.86	0.85 \pm 0.86	0.66
CR (μ mol/L)	65.16 \pm 14.19	65.53 \pm 15.56	0.47
ALT (U/L)	32.43 \pm 20.56	32.76 \pm 26.18	0.33
AST (U/L)	25.47 \pm 10.98	27.07 \pm 12.5	0.79
TG (mmol/L)	1.47 \pm 0.69	2.14 \pm 4.94	0.24
TC (mmol/L)	4.42 \pm 1.09	4.78 \pm 1.20	0.83
LDL-c (mmol/L)	2.38 \pm 0.66	2.28 \pm 0.72	0.46
INR	2.02 \pm 0.73	1.00 \pm 0.23	0.00001*
D-dimer (μ g/mL)	0.30 \pm 0.47	0.36 \pm 0.35	0.44

Baseline characteristics	Warfarin group n = 50	Dabigatran group n = 67	p-value
Mean left atrial size (mm)	34 ± 3.4	34 ± 3.8	0.65
Mean LVEF (%)	0.68 ± 0.064	0.64 ± 0.048	0.33
Medication use			
Aspirin	3 (6.0)	4 (6.0)	
Clopidogrel	0	0	1.00
ACE inhibitor/ARB	15 (30.0)	27 (40.3)	0.25
Beta-blocker	30 (60.0)	30 (44.8)	0.10
Calcium-channel blocker	11 (22.0)	15 (22.4)	0.96
Diuretic	4 (8.0)	4 (59.7)	0.67
Digoxin	0	0	1.00
Statins	20 (40.0)	23 (34.3)	0.53

BMI, body mass index; LVEF, left ventricular ejection fraction; INR, international normalized ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; ALT, alanine transaminase; AST, aspartate transaminase; CR, creatinine; TIA, transient ischemic attack.

* Indicates significant differences ($p < 0.05$).

3.2. Complications

The complications in both groups throughout the 3-month follow-up period are presented in Table 2. All patients were discharged with no clinical problems. No patient died during the follow-up period. Stroke occurred in 1 (2.0%) patient in the warfarin group, whereas no thromboembolic complications occurred in the dabigatran group ($p = 0.43$). The warfarin-group patient who had a stroke was a 66-year-old woman with paroxysmal AF, a CHADS₂ score of 1 (hypertension), and a CHA₂DS₂-VASc score of 3. PVI ablation was successfully performed on her using the irrigated ablation catheter. She arrived at the outpatient clinic 1 month following her discharge, complaining of left lower-limb weakness and numbness. Neurological consultation revealed mild impairment of left lower-limb muscle strength, and cerebral magnetic resonance imaging revealed cerebral infarction in the right temporal lobe. Fortunately, she was found to have suffered no stroke sequelae or minor disability when her case was followed up 6 months later. Despite this single case, no statistically significant difference was found in the overall rate of thromboembolic complications between the study groups.

One patient in the warfarin group developed a major

bleeding complication (cardiac tamponade) requiring pericardial drainage. Pericardiocentesis was successfully performed in this patient, and haemodynamic function was immediately restored. No patient required surgery. Overall, the incidence of major bleeding complications was lower in the dabigatran group than in the warfarin group, but the difference was not significant.

The following minor bleeding events were observed: pericardial effusion, 5 patients; oozing from puncture sites in the femoral vein or left subclavian vein, 2 patients; gastrointestinal haemorrhage, 1 patient; haematuria, 2 patients; skin petechiae, 3 patients; and bleeding gums, 4 patients. Compared with the warfarin group, the dabigatran group had significantly a lower incidence of minor bleeding events (9.0% vs. 22%; $p = 0.048$), total bleeding events (9% vs. 24%; $p = 0.03$), and total bleeding and thromboembolic complications (9% vs. 26%; $p = 0.01$; Figure 2).

In addition to the above complications, 5 (7.5%) patients in the dabigatran group complained of dyspepsia after starting dabigatran, but this improved or resolved following oral intake of a proton pump inhibitor without requiring disruption of the dabigatran regimen.

Table 2. Complications in the dabigatran and warfarin groups.

Complication	Warfarin group n = 50	Dabigatran group n = 67	p-value
Thromboembolic complications			
Stroke/TIA	1 (2.0)	0	0.43
DVT	0	0	1.00
Pulmonary embolism	0	0	1.00
Major bleeding complications			
Cardiac tamponade	1 (2.0)	0	0.43
Late pericardial tamponade	0	0	1.00
Cerebral haemorrhage	0	0	1.00
Retroperitoneal bleeding	0	0	1.00
Life-threatening bleeding	0	0	1.00
Minor bleeding complications	11 (22.0)	6 (9.0)	0.048*
Pericardial effusion	3 (6.0)	2 (3.0)	0.65
Puncture haematoma	1 (2.0)	1 (1.5)	1.00
Pseudoaneurysm	0	0	1.00
Gastrointestinal haemorrhage	1 (2.0)	0	0.43
Haematuria	2 (4.0)	0	0.18
Skin petechiae	2 (4.0)	1 (1.5)	0.58
Epistaxis	0	0	1.00
Bleeding gums	2 (4.0)	2 (3.0)	1.00

Complication	Warfarin group n = 50	Dabigatran group n = 67	p-value
Total bleeding complications	12 (24.0)	6 (9.0)	0.03*
Total bleeding/embolic complications	13 (26.0)	6 (9.0)	0.01*
Gastric discomfort	0	5 (7.5)	0.07

TIA, transient ischemic attack; DVT, deep vein thrombosis

*Indicates significant differences (p < 0.05).

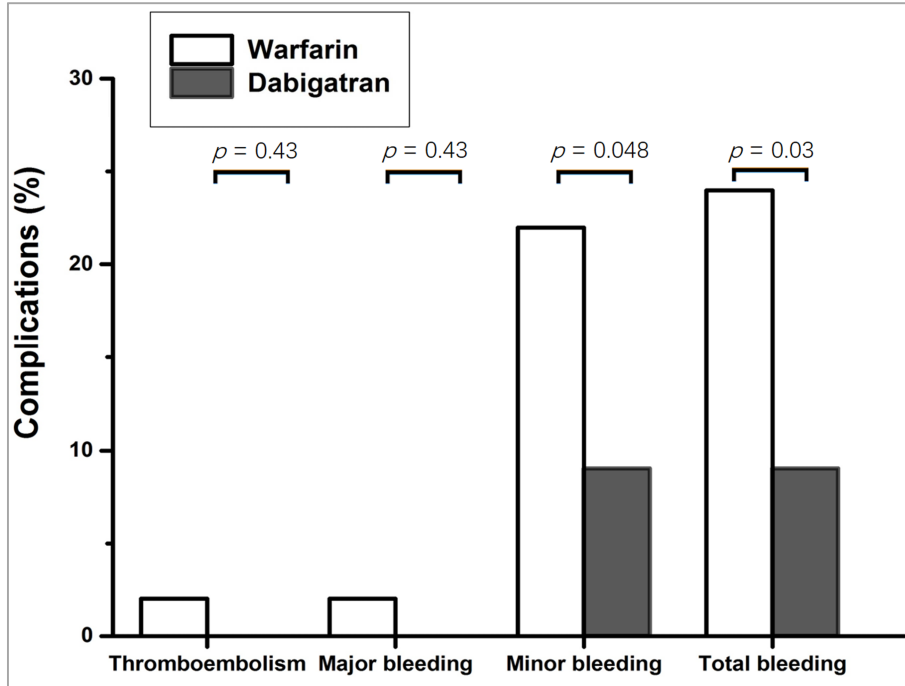


Figure 2. Complications in the dabigatran and warfarin groups.

3.3. Predictors of Complications

Warfarin use was much more common on average among patients who exhibited bleeding and/or thromboembolic complications than among patients who did not develop these complications (Table 3). However, a univariate analysis did not reveal any independent predictors of complications.

Table 3. Univariate and multivariate predictors of bleeding and thromboembolic complications.

	Univariate analysis			Multivariate analysis	
	No complications (n = 98)	Complications (n = 19)	P-value	β value	P-value
Age (years)	58 ± 11	59 ± 11	0.79		
Male	58 (59)	10 (52)	0.90		
BMI (kg/m ²)	24.89 ± 3.07	23.31 ± 3.66	0.71		
CR (μmol/L)	65 ± 15	67 ± 13	0.47		
INR	1.52 ± 0.69	1.78 ± 0.83	0.45		
Left atrial size (mm)	34 ± 3	33 ± 3	0.33		
LVEF (%)	0.65 ± 0.09	0.67 ± 0.05	0.19	55.9	0.25
CHADS ₂ score (x ± s)	0.61 ± 0.67	0.72 ± 0.73	0.64		
CHA ₂ DS ₂ -VaSc (x ± s)	1.36 ± 1.2	1.47 ± 1.1	0.48		
0	23 (23)	5 (26)	0.19	28.9	0.78
1	38 (39)	5 (26)	0.50		
≥2	37 (38)	9 (47)	0.66		
HAS-BLED score (x ± s)	0.90 ± 0.88	0.94 ± 0.95	0.43		
Dabigatran	61 (62)	6 (32)	0.94		
Aspirin	8 (8)	1 (5)	0.53		

BMI, body mass index; CR, creatinine; INR, international normalized ratio; EF, ejection fraction.

4. Discussion

In this study, the safety of low-dose dabigatran (D-110-bid)

was compared with that of warfarin when used as peri-procedural anticoagulants during catheter ablation for paroxysmal AF in Chinese patients. Patients were recruited

from our hospital, non-randomly divided into two groups, and administered dabigatran to one group of patients and warfarin to the other. There were no significant differences in major bleeding complications or thromboembolism between the two groups. However, compared to warfarin administration, the use of low-dose dabigatran significantly decreased minor bleeding complications. The low-dose dabigatran regimen might be employed clinically to provide safe and effective peri-procedural anticoagulation in Chinese patients undergoing ablation for paroxysmal AF.

Warfarin has a slow onset and offset of action and requires frequent monitoring owing to its narrow therapeutic window. Studies have suggested that performing AF ablation under continued warfarin administration is safe and not associated with an increased probability of bleeding complications [6, 8, 10, 11]. However, the disadvantage of continued warfarin administration is that in the event of major bleeding complications such as cardiac tamponade or intracranial haemorrhage, it takes some time for vitamin K to fully antagonize the drug. In contrast, anticoagulation with heparin is easily induced and can be conveniently reversed with protamine. For this reason, interruption of warfarin before catheter ablation and use of heparin or LMWH (as a “bridging strategy” for peri-procedural anticoagulation) is the most frequently used method in low-volume centres [12].

A large multicentre study reported that major complications were more frequent in the continuous warfarin group (4.3%) than in the dabigatran (0.8%) or warfarin-and-bridged heparin (2.6%) groups [13]. It should also be noted that it is difficult to reverse the effects of dabigatran with idarucizumab, which has not yet been widely used. Dabigatran is a direct thrombin inhibitor and has a rapid onset of action (0.5–2 h), with a terminal half-life of 12–17 h [10]. The timing of dabigatran discontinuation before the procedure and its resumption after the procedure varies from study to study. In our investigation, dabigatran was discontinued 12 h before ablation. On the basis of our findings, the final dose of dabigatran was suggested before the procedure is begun may be safely withheld, and full anticoagulation can be resumed within a few hours following ablation.

Several reports have addressed the efficacy and safety of the higher dabigatran dose (D-150-bid) [5-7, 12-17]. In the RE-CIRCUIT trial, peri-procedural anticoagulation with uninterrupted dabigatran (D-150-bid) was associated with fewer bleeding events than uninterrupted warfarin [17]. Thus far, there have been only two studies comparing low-dose dabigatran (D-110-bid) with warfarin as anticoagulants administered during AF ablation [11, 18] and little research has been conducted on peri-procedural anticoagulation using low-dose dabigatran. Kaseno *et al.* reported that 220 mg/day dabigatran was safe for AF ablation in patients with a relatively low risk of thromboembolism [11]. Another meta-analysis suggested a similar incidence of thromboembolic events and major bleeding events for both dabigatran usage and warfarin administration [5-8, 10, 14]. Maddox *et al.* (2013) suggested a similar safety profile of the two drugs [19], while Efremidis *et al.* (2015) found low-dose

dabigatran to be safe and effective for peri-procedural anticoagulation in patients undergoing left atrial ablation for AF, when compared with uninterrupted acenocoumarol therapy [20].

In a registry of efficacy and adverse effects of dabigatran therapy in a large cohort of Asian patients, low rates of ischemic stroke, side effects, and bleeding were recorded [21]. On the other hand, Lakkireddy *et al.* (2012) reported more major bleeding events with dabigatran administration than with warfarin therapy in their multicentre study [12]. A recent meta-analysis has shown no significant differences in the rate of bleeding events between interrupted dabigatran administration and warfarin therapy [5-8, 22, 23].

Despite these reports, there is still limited information (especially on the optimal dose for Chinese patients) due to heterogeneous racial, genetic, weight, and other factors in the studies conducted so far. The present study was conducted on Chinese AF patients undergoing catheter ablation, and the rates of adverse events and bleeding complications in this study were lower than those seen in the RE-LY trial [21]. Our study is consistent with most previous reports in that no significant differences in the occurrence of thromboembolic events were observed between the warfarin and dabigatran groups.

Patients receiving warfarin anticoagulation therapy are required to have an INR between 2.0 and 3.0. However, it has long been recognized that up to 50% of patients may not have an INR within this therapeutic window [24]. INR levels may often vary due to slight changes in diet and medication. In contrast, it has been shown that dabigatran is highly cost-effective in a clinical practice setting where warfarin has been significantly underused [25].

There were no independent predictors of complications in this study. In the RE-LY study, the CHADS₂ score was associated with bleeding complications and stroke in both the warfarin and dabigatran groups. An association between clopidogrel use and risk of bleeding complications (independent of concomitant warfarin use) has also been reported previously [14]. Our study sample was not large enough to accurately infer a relationship between dabigatran use and potential predictors of complications, and multicentre studies with larger sample sizes and long-term follow-up would help to reveal such correlations.

This was a relatively non-randomized post hoc study, with all data prospectively collected and two well-matched groups, and it therefore included the general limitations of such studies. Additionally, the relatively small size of groups drawn from a single institution may have limited the statistical power of the study. Even though a multivariate analysis was conducted after adjusting for known predictors of bleeding complications, it is possible that other unknown confounding variables affecting the results were unaccounted for in the study. Nevertheless, a scarcity of data on the safety of low-dose dabigatran administration during AF ablation makes our study important to current clinical practice, especially with the increasing use of dabigatran in the field. Multicentre studies with greater numbers of patients are required to confirm our results.

5. Conclusions

The present study demonstrated that the use of low-dose dabigatran (110 mg twice daily) peri-procedurally for AF ablation engenders similar risks of thromboembolic complications and major bleeding events as does interrupted warfarin anticoagulation. However, dabigatran administration was associated with significantly lower rates of minor bleeding events than was warfarin use. These findings may lead to low-dose dabigatran becoming an alternative to warfarin for peri-procedural anticoagulation therapy in AF ablation candidates.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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