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Use of dabigatran vs. warfarin with low-molecular-weight heparin bridging in catheter ablation for atrial fibrillation patients with a low CHADS2 score

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Abstract. The purpose of the present study was to compare the efficacy and safety of dabigatran and interrupted warfarin with low-molecular-weight heparin bridging in non-valvular atrial fibrillation (AF) catheter ablation. Previously, there has been concerns that bridging therapy increases bleeding events without the benefit of stroke prevention. It has been suggested that bridging therapy should be considered only for patients at high-risk of thrombosis. Nevertheless, bridging therapy in AF patients with a low CHADS2 score may be safe and effective. The authors performed a prospective, observational study that included consecutive 240 patients undergoing AF ablation in P.R. China. A total of 139 patients received 110 mg dabigatran twice daily and 101 patients took dose-adjusted warfarin that had been bridged with low-molecular-weight heparin. The mean patient age was 55.48 years with 72.1% being men and 74.2% having paroxysmal AF. One thromboembolic complication occurred in the dabigatran group compared to none in the warfarin group. Both the groups presented a similar major bleeding rate, total bleeding rate, and bleeding and thromboembolic complications. In patients undergoing AF ablation, the risk of bleeding or thromboembolic complications was similar for both dabigatran and interrupted warfarin with bridging therapy. Bridging therapy appeared to be safe and effective for the low-risk population.

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Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice and is associated with significantly increased morbidity and mortality (1,2). Catheter-based AF ablation with the primary aim of pulmonary vein (PV) electrical isolation has been established as a treatment option for patients with symptomatic, drug-refractory AF (3,4). AF ablation is a relatively complex procedure, and is associated with the potential risk of periprocedural thromboembolic complications. The endothelial lesion caused by the ablation energy may serve a significant role in activating the clotting cascade. In addition, the cardioversion or the restored contractility post-ablation may dislodge left atrial microthrombi (5,6). However, minimizing thromboembolic complications with periprocedural anticoagulation could potentially increase the risk of bleeding events. As such, maintaining the balance between bleeding and thrombosis is critical to the safety of the ablation procedure.

Warfarin administration has been the mainstay for AF ablation anticoagulation, with a target international normalized ratio (INR) level of 2.0 to 3.0. Bridging anticoagulation refers to the temporary interruption of oral anticoagulation and introduction of a short-acting anticoagulant such as low-molecular-weight heparin (LMWH). Recently, uninterrupted therapeutic warfarin has been demonstrated to be associated with less bleeding events, and it has the benefit of preventing stroke in patients undergoing catheter ablation of AF compared to use of warfarin with bridging LMWH (7). In patients with AF who need to cease warfarin treatment in preparation for an invasive procedure, forgoing bridging therapy was non-inferior to perioperative bridging with LMWH for reducing the risk of stroke and major bleeding (8). The current international guidelines suggest that bridging therapy should be considered for patients at high risk of thrombosis; low-risk patients do not require bridging (9-11). The CHADS2 score can be calculated to assess the risk of stroke. Low-risk patients include those with a CHADS2 score of 0-2, moderate-risk with a CHADS2 score of 3-4, and high-risk with a CHADS2 score of 5 or 6. Previous

studies have demonstrated that Asian patients are more sensitive to the anticoagulant effects of warfarin (12) and warfarin has a long half-life, uninterrupted warfarin without bridging therapy remains controversial and has not been widely accepted in China. Conversely, the direct thrombin inhibitor dabigatran has more predictable pharmacokinetics and the unique property of a rapid onset and short half-life. Therefore, it may not necessitate bridging therapy, and uninterrupted administration appears to be easier to achieve. Although the availability of these new oral anticoagulants (OACs) would obviate the need for bridging, the use of new OACs is limited due to their high medical cost.

Materials and methods

Inclusion and exclusion criteria. A prospective, observational study was performed using patients undergoing AF ablation at an electrophysiology center (at Qilu Hospital, Shandong University, Jinan, Shandong) in China between July 2013 and June 2015. The research protocol was approved by the institutional review board of Qilu Hospital (Jinan, China) and the signed informed consent was provided by each patient. The inclusion criteria were: i) Age 18-75 years, ii) presence of AF as evidenced by a 12-lead electrocardiogram or 24 h Holter monitoring, iii) absence of thrombus in atrium/atrial appendage by transesophageal echocardiography (TEE) and iv) hemodynamic stable non-valvular atrial fibrillation. The exclusion criteria were: i) Hypersensitivity to the active ingredient or any excipients, ii) patients with severe renal impairment (creatinine clearance <30 ml/min), iii) clinically active bleeding, iv) significant risk factors for major bleeding, v) concomitant treatment with any other anticoagulants except switching therapy to or from dabigatran, or when unfractionated heparin is given to maintain an open central venous or arterial catheter, vi) severe hepatic impairment or liver disease, vii) concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone, and viii) a prosthetic heart valve or hemodynamically significant valvular disease. The study included 240 patients with drug-refractory, paroxysmal or persistent AF who underwent AF catheter ablation. Among them, 137 patients received 110 mg dabigatran twice a day (group D) and the remaining 103 received dose-adjusted warfarin (group W). The design flow chart is presented in Fig. 1.

Periprocedural anticoagulation. In group D, dabigatran was not discontinued until the morning of the procedure; it was restarted 4 h following hemostasis at the same dosage as was given previously that morning. In group W, all patients received dose-adjusted warfarin with a target INR of 2.0-3.0. Warfarin was discontinued 3 days prior to the procedure and patients were bridged with subcutaneous LMWH until the evening before the ablation procedure. The administration of LMWH was restarted on the evening of the procedure and continued until an INR of 2.0-3.0 was achieved. Warfarin treatment was restarted on the evening of or the day after the procedure. For all patients in the two groups, TEE was performed prior to the procedure to exclude the presence of an intracardiac thrombus.

Ablation procedure. Before the transseptal puncture, intraprocedural anticoagulation was conducted with a weight-based (80-100 U/kg) heparin bolus administered intravenously. Based on the activated clotting time (ACT), infusion of heparin continuously at 1,000 U/h was given and adjusted, which was monitored every 30 min and targeted at 300 to 350 sec. Meanwhile, the transseptal sheaths were continuously infused with heparinized saline. Vascular access was achieved through the right femoral vein and left subclavian vein. A circular mapping catheter was performed to guide pulmonary vein antrum isolation. Electrical activity recorded by placing a circular mapping catheter (Lasso, Biosense Webster, Inc. Diamond Bar, CA, USA) in the ostium of each pulmonary vein (PV), and pulmonary venography was performed for each PV. Following successful isolation of all the PVs, burst atrial pacing was performed to confirm that an atrial arrhythmia was induced. Additional procedures including the complex fractionated atrial electrograms ablation, linear ablation of the LA, and the superior vena cava isolation were performed, if AF/atrial tachyarrhythmia was induced and sustained. Either the elimination or dissociation of the PV potentials was the end-point of the PV isolation, recorded through the circular catheters placed within the PVs. If termination was unsuccessful, cardioversion was performed to restore the sinus rhythm. During the procedure, the blood pressure was noninvasively monitored.

Follow-up. Following the ablation, the patients leave hospital in 3 to 5 days, and were checked at the outpatient clinic 1 week and 1 month after the ablation for any postprocedural complications. Thromboembolic complications defined as ischemic stroke, transient ischemic attack (TIA), or systemic thromboembolism were the primary end-points (efficacy end-points). Major (requiring a transfusion or surgical intervention) and minor bleeding complications were the secondary end-points (safety end-points).

Statistical analysis. Statistical analyses were performed using SPSS software (version, 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the as mean ± standard deviation and compared using a Student's t-test or Mann-Whitney U test. Categorical variables were presented as counts and percentages then analyzed using either a Chi-squared test or Fisher's exact test. Bleeding complications (minor and major), thromboembolic complications and total complications were compared between groups. $P<0.05$ (two-sided) was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 240 patients presenting with AF between July 2013 and June 2015 were enrolled in the present study. Patients were treated according to their preference to undergo the procedure with an anticoagulation strategy of dabigatran (group D, n=139) or warfarin with bridging therapy (group W, n=101). The baseline characteristics of the two groups were similar with no significant differences in age, sex, body mass index, blood pressure, left atrial size, left ventricular ejection fraction, CHADS2

Table I. Patient baseline characteristics.

	Dabigatran group (n=139)	Warfarin group (n=101)	P-value
Age (years)	55.12±11.10	55.96±10.40	0.554
Male (%)	101 (73)	72 (71)	0.815
Body mass index (kg/m^2)	27.25±3.78	26.32±3.49	0.055
Blood pressure (mmHg)			
Systolic	132.87±18.33	130.70±17.55	0.358
Diastolic	82.14±13.37	80.47±15.21	0.368
Persistent atrial fibrillation (%)	33 (24)	29 (29)	0.385
Duration of atrial fibrillation (months)	37.08±51.69	45.34±41.74	0.037
Hypertension (%)	64 (46)	43 (43)	0.594
Diabetes (%)	18 (13)	16 (16)	0.526
Coronary artery disease (%)	9 (7)	13 (13)	0.090
Heart failure (%)	2 (1)	1 (1)	P>0.99
Transient ischemic attacks or stroke (%)	6 (4)	8 (8)	0.240
Smoking (%)	60 (43)	30 (30)	0.033
Alcohol drinking (%)	37 (27)	24 (24)	0.616
Alanine aminotransferase (U/l)	22.05±11.87	22.36±11.12	0.840
Serum creatinine (μmol/l)	71.63±14.06	69.74±11.59	0.272
Fasting blood glucose (mmol/l)	5.03±1.00	5.26±1.74	0.202
Platelet count (x10^9/l)	218.24±45.20	208.76±47.59	0.118
INR	1.04±0.13	1.07±0.23	0.900
APTT-S	31.22±8.80	32.21±4.23	0.649
CHADS2 score[a]	0.68±0.80	0.77±0.89	0.598
CHADS2 ≥2 (n, %)	17 (12)	19 (19)	0.159
CHA2DS2VASc score[b]	1.14±1.17	1.32±1.21	0.241
CHA2DS2VASc ≥2 (n, %)	42 (30)	35 (35)	0.467
HAS-BLED score[c]	1.04±0.96	1.11±1.10	0.900
HAS-BLED ≥ 3 (n, %)	8 (6)	15 (15)	0.018
Left atrial size (mm)	39.75±5.83	39.51±5.63	0.746
Left ventricular ejection fraction (%)	61.49±5.03	60.56±6.28	0.207
AF ablation procedure			
Cryoablation	28 (20)	15 (15)	0.291
Intraprocedural cardioversion	22 (16)	18 (18)	0.682
Anticoagulation-experienced (n, %)	19 (14)	13 (13)	0.858
Warfarin (n, %)	3 (2)	9 (9)	0.038
Dabigatran (n, %)	16 (12)	4 (4)	0.242

[a]CHADS2 score [congestive heart failure; hypertension; age ≥75 years; type 2 diabetes; and previous stroke, transient ischemic attack, or thromboembolism (doubled)]. [b]CHA2DS2-VASc score [congestive heart failure; hypertension; age ≥75 years (doubled); type 2 diabetes; and previous stroke, transient ischemic attack, or thromboembolism (doubled); vascular disease; age 65-75 years; and sex category (female)]. [c]HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly). AF, trial fibrillation.

score, CHA2DS2VASc score, alcohol consumption, proportion of patients with persistent AF or the number of patients with a history of previous stroke/TIA (Table I). In group D, 8 patients (6%) had a HAS-BLED ≥3 compared with 15 (15%) in group W (P<0.05). Those receiving dabigatran were more likely to be smokers and had a shorter duration of atrial fibrillation, when compared with the warfarin patients. During the procedure, 28 patients (20%) in group D and 15 patients (15%) in group W (P>0.05) received cryoablation. Intraprocedural cardioversions were conducted in 22 patients receiving dabigatran (16%), compared with 18 patients receiving warfarin (18%, P>0.05).

Study outcomes. Complications associated with the procedures are presented in Table II. A periprocedural stroke event occurred in one patient in the dabigatran group and

Table II. Comparison of complications between patients on dabigatran and warfarin.

	Dabigatran (n=139)	Warfarin (n=101)	Total (n=240)	P-value
Major bleeding complications (n, %)	0	0	0	
Cardiac tamponade	0	0	0	
Intracranial bleeding	0	0	0	
Extracranial	0	0	0	
Minor bleeding complications (n, %)	23 (17)	11 (11)	34 (14)	0.215
Groin hematoma	11 (8)	5 (5)	16 (7)	0.364
Hemothorax	1 (1)	1 (1)	2 (1)	>0.050
Hemoptysis	1 (1)	0	1 (1)	>0.050
Urogenital bleeding	7 (5)	3 (3)	10 (4)	0.643
Gastrointestinal bleeding	3 (2)	2 (2)	5 (2)	>0.050
Total bleeding complications (n, %)	23 (17)	11 (11)	34 (14)	0.215
Embolic complications (stroke/TIA) (n, %)	1 (1)	0	1 (1)	>0.050
Composite of bleeding and embolic complications	24 (17)	11 (11)	35 (15)	0.167
Other complications (n, %)	5 (4)[a]	0	5 (2)	0.076

[a]Five types of gastrointestinal discomfort, including gaseous distention and sour regurgitation. TIA, transient ischemic attack.

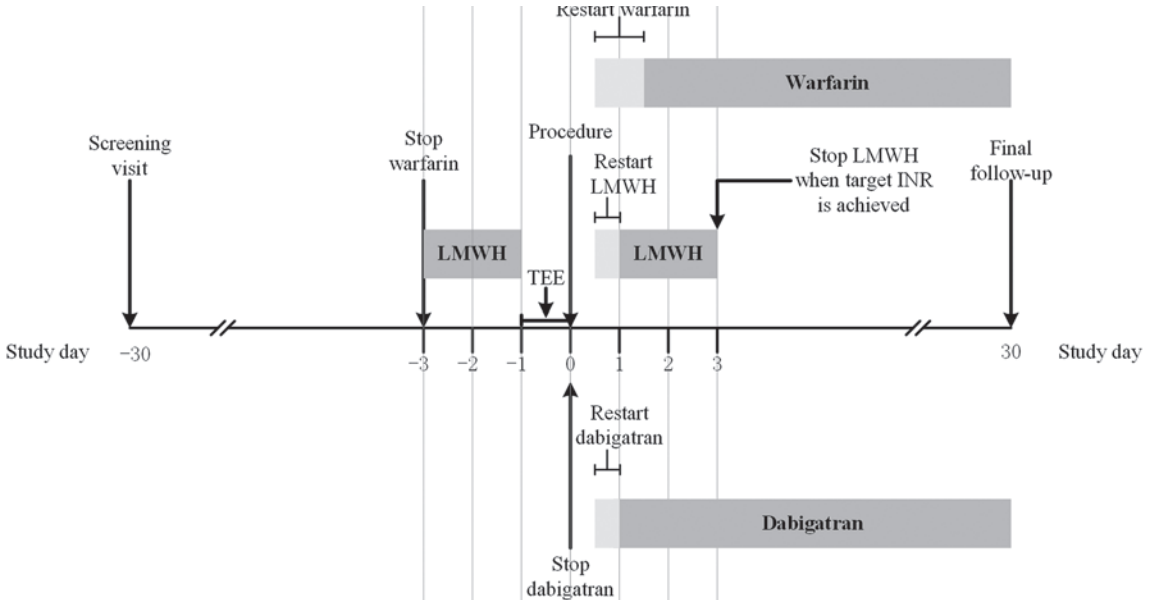

Figure 1. Study design flow chart. Screening visits occurred between 30 days and 3 days prior to the ablation procedure. For all patients, the absence of intra-cardiac thrombus was proved by TEE prior to the procedure. In group W, warfarin treatment was discontinued and the administration of the LMWH was initiated 3 days prior to the procedure. LMWH was restarted on the evening of the procedure and continued until an INR of 2.0-3.0 was achieved. Warfarin treatment was restarted on the evening of or the day after the procedure. In group D, dabigatran was not discontinued until the morning of the procedure and was restarted 4 h following hemostasis. The final patient follow-up occurred 30 days following the ablation procedure. TEE, transesophageal echocardiography; LMWH, low-molecular-weight heparin.

no patients in the warfarin group. No major bleeding complications were observed in any patients within the study population. The incidence of minor bleeding complications was 23 in group D (17%) and 11 in group W (11%, P>0.05). In addition, 11 patients receiving dabigatran treatment developed a groin hematoma compared with five patients receiving warfarin. All of these patients underwent an ultrasound scan that excluded the presence of a pseudo-aneurysm or an arteriovenous (AV) fistula. As a result, one patient in each of the groups was indicated to have an AV fistula. A hemothorax was observed in one patient in the dabigatran group and one patient from the warfarin group. Hemoptysis occurred in one patient who received dabigatran treatment, and the patient developed a large groin hematoma two days following the procedure and a high fever of 38.6˚C. Dabigatran was discontinued imminently. Two days later, massive hemoptysis occurred and pulmonary computed tomography (CT) presented bilateral pulmonary frosted glass. At three days later, no hemoptysis occurred and a lung CT presented markedly reduced frosted glass. Overall, there were no significant

differences in complication rates between the two groups (P>0.05; Table II).

Discussion

Stroke is the most serious complication in patients with AF. Therefore, in AF patients with a CHADS2 score ≥2, conventional OAC is recommended to reduce the risk of stroke (13,14). During the period of anticoagulation therapy, the risk of both stroke and bleeding complications are highest when OAC is initiated. During the initiation of OAC, there is a theoretical transient hypercoagulable state, because the vitamin K-dependent anticoagulant proteins C and S are decreased, while the vitamin K-dependent procoagulant factors II and X remain elevated due to their longer half-lives (15). Bridging anticoagulation therapy is designed to minimize the risk of thromboembolism in high-risk patients when anticoagulation therapy is suspended and to minimize the risk of bleeding following procedures, and it is usually used in patients receiving warfarin treatment when warfarin has been discontinued and the INR falls below the therapeutic range (16). During the interruption of warfarin treatment, typically LMWH bridging anticoagulation therapy can be given to minimize the interval that patients do not in a state of anticoagulation, with the purpose of decreasing the risk of perioperative stroke (8,16). In patients who require temporary interruption of warfarin therapy for invasive procedures, a standardized periprocedural bridging anticoagulant therapy with subcutaneous LMWH is feasible and associated with a low risk of thromboembolic and major bleeding complications (17,18). Some studies have assessed perioperative bridging with LMWH, however, the practice guidelines have provided weak and inconsistent recommendations regarding whether bridging anticoagulation is necessary during perioperative warfarin interruption (19-21). Previous research has indicated that use of bridging anticoagulation is associated with an increased risk of bleeding and adverse events after interruption (22,23) and in patients who interrupted dabigatran or warfarin in the RE-LY trial, bridging anticoagulation appeared to increase the risk for major bleeding irrespective of dabigatran or warfarin interruption (24). The use of interrupted warfarin bridging with LMWH has been widely used, although studies have suggested that continuous warfarin treatment protects against the risk of periprocedural stroke with no increased bleeding risk (8,22-24).

Given the growing concern regarding hemorrhagic complications associated with bridging therapies, some experts suggest that bridging should only be considered in those at highest risk for thrombosis (11). A recent study indicated that performing AF catheter ablation with uninterrupted warfarin in patients at high risk for stroke and with nonparoxysmal AF reduced the periprocedural stroke and bleeding complications compared to bridging therapy (7). The results of the present study suggested that interrupted warfarin bridged with LMWH is safe and effective among the low-risk population compared to anticoagulation with dabigatran. In the current study, there was no difference in thromboembolic events in the two anticoagulant groups. The incidence and outcomes of bleeding complications were also similar between the two groups. Of note, some of the complications were likely the result of technical or mechanical complications, as opposed to the choice of anticoagulant.

In the present study, the mean CHADS2 score was 0.68±0.80 vs. 0.77±0.89 in dabigatran and warfarin groups, respectively (P>0.05). There were 17 patients with CHADS2 ≥ 2 (12%) in the dabigatran group and 19 patients in the warfarin group (19%, P>0.05). This also applied to the CHA2DS2VASc score and HAS-BLED score. As such, the entire population tended to have a low risk of both thromboembolic and bleeding events. Anticoagulation-experienced is defined as the total lifetime use of the anticoagulant for more than two months. There was no difference between the two groups in ratio of the anticoagulation-experienced (P>0.05) and only >20% of the patients were treated with OAC at baseline. Asian patients are more sensitive to the anticoagulant effects of warfarin and have higher rates of bleeding when they are in the therapeutic range (12). Therefore, frequent therapeutic monitoring and concern about bleeding events remains an important barrier to the appropriate use of anticoagulant therapy in the Chinese population (25,26). The cost of routine dabigatran or rivaroxaban anticoagulation is too high to be affordable for ordinary patients. Therefore, it is convenient and likely safe to leave low-risk patients on aspirin or no OAC pre-ablation. In addition, the interrupted anticoagulation strategy with LMWH bridging was safe and effective for the AF patients who had a low risk score.

Despite a recent trend towards uninterrupted OAC for AF ablation (7,27,28), interrupted OAC provides several advantages. Some patients on uninterrupted warfarin will not have a stable INR pre-ablation and may arrive with a subtherapeutic or supratherapeutic INR (29). With the NOACs, there is no test to verify patient compliance pre-ablation, and the lack of proven reversal agents may add additional risk if they are not interrupted. In addition, bleeding complications are easier to handle with interrupted OAC. The use of uninterrupted warfarin was followed by an era of using interrupted warfarin. Thus, published retrospective comparisons have been conducted by examining these two different time periods of AF ablation. It was demonstrated that some of the apparent advantages of uninterrupted warfarin may instead be due to improvements in ablation safety over time. Arshad *et al* (30) recently compared peri-ablation anticoagulation at four experienced AF ablation centers and indicated that major complications (stroke/TIA, pericardial tamponade, major bleeding and surgical intervention) occur more frequently in the uninterrupted warfarin group (4.3%) vs. both the dabigatran group (0.8%) and the bridged warfarin group (2.6%) (P<0.01).

In conclusion, the administration of dabigatran during AF ablation procedures did not cause any significantly different effects on the safety and efficiency as compared to those of the conventional anticoagulation with warfarin bridged with LMWH for patients with a low CHADS2 score. Low-risk patients may remain on aspirin or no OAC pre-ablation and do not need to receive warfarin or dabigatran before ablation.

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