CLINICAL STUDY

Feasibility of Uninterrupted Direct Oral Anticoagulants with Temporary Switching to Dabigatran ("Dabigatran Bridge") for Catheter Ablation of Atrial Fibrillation

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Summary

Uninterrupted anticoagulation therapy during atrial fibrillation (AF) ablation minimizes the risk of periprocedural thromboembolic events. Although the use of direct oral anticoagulants (DOACs) has rapidly developed in patients undergoing AF ablation, no antidote is available for factor Xa inhibitors. We sought to investigate the feasibility of an uninterrupted DOAC protocol with temporary switching to dabigatran ("dabigatran bridge") for AF ablation.

The study consisted of consecutive 137 patients in whom DOACs were interrupted on the procedural day with heparin bridging (interrupted group) and 135 in whom DOACs were uninterrupted with temporary switching to dabigatran during the periprocedural hospitalization period ("dabigatran bridge" group). The coagulation markers were measured just before and after the ablation procedure. The adverse events during and up to 8 weeks after the procedure were compared according to the definition of the International Society on Thrombosis and Hemostasis.

The patients were significantly older in the "dabigatran bridge" group; however, the other baseline patient characteristics were similar between the two groups. The incidence of all adverse events was comparable between the two groups (8/137 versus 8/135, P = 0.96); however, one patient from the interrupted group experienced stroke, and another from the "dabigatran bridge" group experienced cardiac tamponade, which was safely managed with an antidote. In the "dabigatran bridge" group, the activated partial thromboplastin time was significantly longer, and coagulation markers (soluble fibrin monomer and thrombin-antithrombin complexes) were significantly lower than in the interrupted group before ablation.

The "dabigatran bridge" seems to be a reasonable anticoagulation protocol to minimize the thromboembolic risk while ensuring safety in patients undergoing AF ablation and taking factor Xa inhibitors.

Key words: Anticoagulation, Switch, Peri-procedural period

Although catheter ablation is an established treatment strategy for atrial fibrillation (AF), there is a substantial risk for thromboembolic events perioperatively. Uninterrupted warfarin at the time of AF ablation is associated with a lower risk of periprocedural bleeding and strokes than stopping warfarin and bridging with heparin. Moreover, it is currently a well-established anticoagulation strategy.1-3) Recently, direct oral anticoagulants (DOACs) offering important advantages beyond their ease of administration, such as less interactions and the nonessentiality of laboratory monitoring, have become available.4,5) With the advent of DOACs, rapidly increasing numbers of patients with AF are on DOACs at the time the decision to proceed with AF ablation is made. Prospective randomized clinical trials have shown that the uninterrupted use of a factor Xa inhibitor is feasible, with no meaningful difference in the thromboembolic events or major bleeding events as compared with uninterrupted warfarin.6,7) However, the major concern of performing AF ablation with uninterrupted factor Xa inhibitors is the risk of bleeding, particularly life-threatening bleeding, such as pericardial tamponade, under the lack of an antidote. For this reason, a minimally interrupted factor Xa inhibitor protocol has been widely used in clinical practice. This raises questions regarding the safety of the procedure given the prior experience with interrupted anticoagulation without bridging.8) To overcome these issues, we sought to investigate the feasibility of an uninterrupted DOAC pro-

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tocol with temporary switching to dabigatran (so-called dabigatran bridge) by comparing that with interrupted DOACs and a heparin bridging protocol at the time of the AF ablation.

Methods

Study population: Among 297 consecutive patients who underwent AF ablation in our hospital, a total of 272 patients in whom DOACs were prescribed at the time of the ablation were included. Among them, 137 patients underwent AF ablation with minimally interrupted DOACs and a heparin bridging protocol between April 2017 and January 2018, and 135 patients underwent AF ablation with uninterrupted DOACs with temporary switching to dabigatran (“dabigatran bridge”) between January 2018 and October 2018. All patients gave their written informed consent. The study complied with the Declaration of Helsinki.

Anticoagulation protocol: In the minimally interrupted DOAC group, the DOACs were interrupted only on the day of the procedure (for 1 day). A 10,000 U heparin dose was given 24 hours after the procedure, and the DOACs were restarted in the morning of the next day. In the uninterrupted DOAC group, all DOACs were temporarily switched to dabigatran 110 mg twice daily from the day before the procedure to 3 days after the procedure. Dabigatran was interrupted during the periprocedural period without heparin bridging. Then, dabigatran was switched back to the original DOAC prescribed before the procedure.

Mapping and ablation protocol: Cardiac enhanced computed tomography and transesophageal echocardiography were performed pre-procedurally to evaluate the pulmonary vein anatomy and exclude any left atrial (LA) thrombi. The surface electrocardiogram and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system. The procedure was performed under moderate sedation obtained with dexmedetomidine. A bolus of 5,000 U of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300-350 seconds. A single transeptal puncture was performed using a radiofrequency needle (Baylis Medical., Montreal, QC, Canada). Pulmonary vein isolation was performed with either a 28-mm second-generation cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) or contact force sensing irrigated-tip radiofrequency catheter (SmartTouch Surround Flow, Biosense Webster, Diamond Bar, CA, USA) guided by 3D mapping system (CARTO3, Biosense Webster). Bidirectional conduction block was created at the cavo-tricuspid isthmus, and additional substrate modification was performed according to the operators’ preference.

Follow-up and endpoint: After the procedure, in-hospital electrocardiogram (ECG) monitoring was continued for 3-5 days. All patients were prescribed proton-pump inhibitors for 1 month after the procedure. Regular follow-up consisted of outpatient clinic visits at 1, 2, and 3 months after the procedure. Anticoagulation was continued for at least 2 months after the procedure.

The efficacy and safety endpoints were the incidence of the following events during and up to 8 weeks after the ablation procedure: strokes, systemic embolisms, and TIA events; major bleeding events, minor bleeding events according to the definition of the International Society on Thrombosis and Hemostasis (ISTH), and all adverse events, which were defined as any untoward medical occurrence.

Blood sampling and anticoagulation markers: In 158 patients, blood samples were taken for an analysis of the activated partial thromboplastin time (aPTT), D-dimer, soluble fibrin monomer complex (SFMC), and thrombin-antithrombin complex (TAT) levels at the beginning and end of the AF ablation procedure to evaluate the coagulation status.

Statistical analysis: Continuous data are expressed as mean ± standard deviation for normally distributed variables or the median [25th, 75th percentiles] for non-normally distributed variables and were compared using Student’s t-test or Mann-Whitney U-test, respectively. Categorical variables were compared using the chi-squared test. A probability value of P < 0.05 indicated statistical significance.

Results

Study population: Of a total of 297 patients who underwent AF ablation, 22 in whom warfarin was prescribed and 3 whose data were not available were excluded (Figure). Among the remaining 272 patients, AF ablation was performed with a minimally interrupted DOAC protocol and “dabigatran bridge” protocol in 137 and 135 patients, respectively. The patients in the “dabigatran bridge” group were significantly older than those in the interrupted DOAC group; however, the other baseline patient characteristics and procedural parameters were similar between the two groups (Table I). In the “dabigatran bridge” group, all patients could continue taking dabigatran without any complications during the 4-day bridging period. Regarding the procedural details, the cryoballoon was more frequently used, and ablation targeting complex fractionated potentials was less frequently performed in the “dabigatran bridge” group (Table II).

Adverse events on the ISTH definition: As shown in Table III, the incidences of all adverse events were comparable between the two groups (8/137 versus 8/135, P = 0.96); however, one patient experienced stroke in the interrupted DOAC group, and another experienced cardiac tamponade in the “dabigatran bridge” group. There was no significant difference between the incidence of bleeding events and timing of the last administration of dabigatran (Table IV).

The stroke patient was a 75-year-old man with a CHADS2 score of 3 and CHA2DS2-VASc score of 4, who was admitted for the treatment of recurrent persistent AF. Pre-ablation transesophageal echocardiography showed no LA thrombi, no spontaneous echo contrast, and a low LA appendage flow velocity (diastolic emptying velocity: 21 cm/second, filling velocity: 15 cm/second). Anticoagulation with apixaban 5 mg twice daily was interrupted on the day of the procedure with heparin bridging. During
Figure. Inclusion criteria of the present study. AF indicates atrial fibrillation; and DOACs, direct oral anticoagulants.

Table I. Patient Clinical Characteristics

|                                | Dabigatran bridge group (n = 135) | Interrupted DOAC group (n = 137) | P value |
|--------------------------------|-----------------------------------|----------------------------------|---------|
| Age, years                     | 67.3 ± 9.8                        | 64.4 ± 10.9                      | 0.02    |
| Male gender, n (%)             | 82 (60.7)                         | 90 (66.4)                        | 0.40    |
| Height (cm)                    | 162.7 ± 9.2                       | 164.4 ± 9.4                      | 0.15    |
| Weight (kg)                    | 62.0 ± 11.3                       | 63.8 ± 10.9                      | 0.22    |
| Body mass index (kg/m²)        | 23.3 ± 3.4                        | 23.6 ± 3.4                       | 0.59    |
| CHADS2 score                   | 1.37                              | 1.12                             | 0.40    |
| CHA2DS2-VASc score             | 2.51                              | 2.05                             | 0.13    |
| HAS-BLED score                 | 0.80                              | 0.59                             | 0.09    |
| Coronary artery disease, n (%) | 12 (8.9)                          | 6 (4.4)                          | 0.30    |
| LV ejection fraction, %        | 60.5 ± 11.2                       | 62.9 ± 10.9                      | 0.07    |
| Left atrial diameter, mm       | 38.0 ± 5.7                        | 37.4 ± 6.6                       | 0.43    |
| LAA emptying velocity, cm/second | 51.0 ± 25.8             | 50.3 ± 24.2                      | 0.82    |
| SEC 1 ≤, n (%)                 | 37 (27.4)                         | 44 (32.1)                        | 0.20    |
| Atrial fibrillation type       |                                   |                                  | 0.74    |
| Paroxysmal, n (%)              | 86 (63.7)                         | 101 (73.7)                       |         |
| Persistent, n (%)              | 49 (36.3)                         | 36 (26.3)                        |         |
| Session                        |                                   |                                  | 0.17    |
| 1st session, n (%)             | 115 (85.2)                        | 108 (78.8)                       |         |
| 2nd or 3rd session, n (%)      | 20 (14.8)                         | 29 (21.2)                        |         |
| Ablation therapy               |                                   |                                  | 0.04    |
| Radiofrequency ablation, n (%) | 58 (43.0)                         | 76 (55.5)                        |         |
| Cryoballoon, n (%)             | 77 (57.0)                         | 61 (44.5)                        |         |
| Total procedure time, minutes  | 194 ± 48                          | 202 ± 57                         | 0.22    |
| eGFR, mL/minute/1.73 m²        | 70.3 ± 21.8                       | 75.6 ± 24.1                      | 0.06    |
| eGFR < 50 mL/minute/1.73 m², n (%) | 25 (18.5)                             | 24 (17.5)                       | 0.83    |
| Antiplatelet therapy, n (%)    | 6 (4.4)                           | 7 (5.1)                          | 0.80    |
| Baseline DOACs                 |                                   |                                  | 0.01    |
| Apixaban, n                    | 62                                | 39                               |         |
| Edoxaban, n                    | 28                                | 36                               |         |
| Dabigatran, n                  | 16                                | 14                               |         |
| Rivaroxaban, n                 | 29                                | 48                               |         |

Values are reported as the mean ± standard deviation or number of patients (%) unless otherwise noted. DOAC indicates direct oral anticoagulant; eGFR, estimated glomerular filtration ratio; LAA, left atrial appendage; LV, left ventricular; n, number; and SEC, spontaneous echo contrast.
isolation, re-cavo-tricuspid isthmus ablation, and superior vena cava isolation, and he was discharged 7 days after the procedure. Aspiration of 350 mL of blood and administration of idarucizumab and protamine stabilized his hemodynamic parameters. The drain was removed 24 hours later, and he was discharged 7 days after the procedure without any sequela. During a follow-up period of 6 months, the patient was free from AF.

**Coagulation markers:** The coagulation markers were compared between the 46 patients in the minimally interrupted DOAC group and 112 in the “dabigatran bridge” group. Before the procedure, a significantly higher aPTT level and lower SFMC and TAT values were observed in the “dabigatran bridge” group than in the minimally interrupted DOAC group. After the procedure, the SFMC value still remained significantly lower in the “dabigatran bridge” group than in the minimally interrupted DOAC group (Table V).

### Discussion

The present study showed no significant difference in the incidence of all adverse events between the minimally interrupted DOACs with heparin bridging protocol and uninterrupted DOACs protocol (“dabigatran bridge”) de-

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**Table II. Ablation Device and Strategy**

|                    | Dabigatran bridge group | Interrupted DOAC group | P value |
|--------------------|-------------------------|------------------------|---------|
| Number of patients, n | 135                     | 137                    | 0.04    |
| Ablation device     |                         |                        |         |
| Radiofrequency ablation, n (%) | 58 (43.0)               | 76 (55.5)              |         |
| Cryoballoon ablation, n (%)   | 77 (57.0)               | 61 (44.5)              |         |
| Ablation strategy    |                         |                        |         |
| Cavo-tricuspid isthmus line, n (%) | 113 (83.7)           | 111 (81.0)             | 0.56    |
| Superior vena cava isolation, n (%) | 17 (12.6)            | 26 (19.0)              | 0.15    |
| Mitral isthmus line, n (%)      | 41 (30.4)             | 33 (24.1)              | 0.24    |
| Roof line, n (%)            | 48 (35.6)              | 40 (29.2)              | 0.26    |
| Bottom line, n (%)          | 8 (5.9)                | 6 (4.4)                | 0.56    |
| Continuous fractionated atrial electrogram, n (%) | 0 (0.0)               | 7 (5.1)                | 0.008   |
| Low voltage area, n (%)      | 7 (5.2)                | 14 (10.2)              | 0.12    |
| Non-pulmonary vein foci, n (%) | 7 (5.2)                | 13 (9.5)               | 0.17    |

DOAC indicates direct oral anticoagulant.

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**Table III. All Adverse Events**

|                    | Dabigatran bridge group | Interrupted DOAC group | P value |
|--------------------|-------------------------|------------------------|---------|
| All adverse events, n | 8                       | 8                      | 0.96    |
| Stroke or TIA, n   | 0                       | 1                      |         |
| Major bleeding events, n | 1                      | 0                      |         |
| Minor bleeding events, n | 7                      | 7                      |         |

Values are reported as the number of patients (%) unless otherwise noted. DOAC indicates direct oral anticoagulant; and TIA, transient ischemic attack.

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**Table IV. Bleeding Events and the Timing of the Final Administration of Dabigatran in the “Dabigatran Bridge Group”**

|                    | Total | Bleeding events | P value |
|--------------------|-------|-----------------|---------|
| Number of patients, n | 135   | 8               |         |
| Timing of the final administration of dabigatran |       |                 |         |
| < 4 hours, n (%)     | 45    | 1 (2.2)         | 0.25    |
| 4-8 hours, n (%)     | 63    | 6 (9.5)         |         |
| < 8 hours, n (%)     | 27    | 1 (3.7)         |         |
spite an older population in the latter group. Notably, stroke was observed only in the minimally interrupted DOAC group, and major bleeding events occurred but were safely managed with an antidote in the “dabigatran bridge” group. In addition, the data on the coagulation markers suggested there was a hypercoagulability in the minimally interrupted DOAC group rather than the “dabigatran bridge” group.

Clinical outcomes: In clinical practice, the use of DOACs in patients undergoing AF ablation has rapidly developed. Randomized clinical trials have revealed that uninterrupted factor Xa inhibitors are similarly effective and safe compared with uninterrupted warfarin therapy to prevent strokes. On the contrary, dabigatran has idarucizumab, a dabigatran-specific reversal agent that can achieve an immediate and complete reversal of the anticoagulant effect, but a specific antidote is not available for factor Xa inhibitors. Unfortunately, a relatively high rate (> 20% at 1 year) of discontinuation of dabigatran was reported in the RE-LY trial and prospective cohort studies due to dyspepsia or abdominal pain. As a result, in clinical practice, the majority of patients undergoing AF ablation take factor Xa inhibitors, and one or two doses of the factor Xa inhibitors are held prior to catheter ablation considering the risk of major bleeding events in most of the studies. Given these issues, we temporally switched the factor Xa inhibitors to dabigatran during the periprocedural period to ensure safety. We selected a 110-mg twice-daily dosing because the RE-LY trial proved that dabigatran given at a dose of 110 mg was associated with higher rates of strokes and systemic embolisms that were similar to those associated with warfarin, as well as lower rates of major hemorrhages.

This “dabigatran bridge” protocol has several potential advantages compared with the other anticoagulation protocols. First, AF ablation can be performed under an uninterrupted dabigatran therapy. The RE-CIRCUIT trial showed that uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin, and dabigatran is the only DOAC superior to warfarin with respect to procedural safety. The mechanisms may be related to the specific mechanism of action (direct thrombin inhibition rather than a Xa inhibitor). Second, dabigatran is the only DOAC that can be reversed with an antidote when unexpected major bleeding events occur, providing reassurance about the safety. Proper handling of factor Xa inhibitor-related major bleeding is quite challenging due to the absence of available specific antidotes. The efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients who present with serious bleeding or who required urgent surgery or intervention were well proven in RE-VERSE AD trial. Third, the protocol does not require heparin bridging or a switch to warfarin, which seems to be troublesome, to avoid interrupted anticoagulation therapy. A “dabigatran bridge” is much simpler than a heparin bridging protocol in patients taking factor Xa inhibitors at the time of AF ablation. Moreover, the patients can continue on the original DOACs after the bridging period. Fourth, the protocol can be applied to all patients taking any DOAC. In clinical practice, as abovementioned, the majority of the patients undergoing AF ablation take factor Xa inhibitors. Fifth, the medication adherence can be easily checked because the patient is in the hospital during the bridging period, and thus, the risk of discontinuation of dabigatran can be minimized. Although the study population was too small to obtain a sufficient statistical power, our study results that reveal that strokes occurred in the interrupted DOAC group and that cardiac tamponade was safely managed in the “dabigatran bridge” group suggested the advantage of the “dabigatran bridge” protocol.

Coagulation markers: Dabigatran has been shown to prolong the aPTT, and a higher aPTT level at the beginning of the procedure in “dabigatran bridge” group appears to reflect the impact of the uninterrupted dabigatran therapy. TATs, SFMCs, and D-dimers generally indicate thrombogenesis, coagulability, and fibrinolysis. TATs are formed by an interaction between antithrombin III and
thrombin after thrombin is cleaved from prothrombin, and SFMCs are a biomarker of fibrin formation. The formation of the D-dimer follows chronologically after thrombin is generated and reflects lysis of fibrin. Elevated TAT and SFMC levels indicate hypercoagulability and have been seen in many clinical settings, such as deep vein thrombosis. Higher TAT and SFMC values in the minimally interrupted DOAC group at the beginning of the procedure might indicate, even if the period of interruption is very short, that the interruption increases the risk of thromboembolic events. Interestingly, even after a sufficient anticoagulation therapy with heparin during the AF ablation procedure, the SFMC level still remained significantly higher in the minimally interrupted DOAC group. These data suggested that an uninterrupted DOAC therapy is more recommended than a minimally interrupted DOAC therapy from the viewpoint of the thromboembolic risk.

**Study limitations:** This study was a single-center observational study, and the study population was relatively small. The study period was different in the two groups; however, all the procedures were performed similarly by experienced operators.

**Conclusions**

An uninterrupted DOAC therapy with temporary switching to dabigatran might be feasible and reasonable to minimize the thromboembolic risk while ensuring safety during the periprocedural period of AF ablation.

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**Disclosure**

**Conflicts of interest:** None.

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