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ORIGINAL ARTICLE

# Differences in prothrombotic response between the uninterrupted and interrupted apixaban therapies in patients undergoing cryoballoon ablation for paroxysmal atrial fibrillation: a randomized controlled study

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**Abstract**
Periprocedural bleeding and thromboembolic events are worrisome complications of catheter ablation for atrial fibrillation (AF). Periprocedural anticoagulation management could decrease the risk of these complications. However, evaluation of the complications from pulmonary vein isolation using cryoballoon related to different anticoagulation strategies is limited. Therefore, we aimed to compare prothrombotic responses as assessed on the basis of D-dimer levels between the uninterrupted and interrupted apixaban therapies during cryoballoon ablation. Ninety-seven consecutive patients with paroxysmal AF scheduled to undergo cryoballoon ablation were randomly assigned in a 1:2 ratio to uninterrupted apixaban therapy (Group 1, $n=32$) or interrupted apixaban therapy (Group 2, $n=65$). D-Dimer levels were measured immediately before the ablation, at the end of the ablation, and 24 and 48 h after the procedure. No statistical difference was observed in the baseline characteristics between the two groups. The rates of hemorrhagic complications were similar in both groups (major bleeding: 3.1 vs. 1.5%; $p=0.61$, and minor bleeding: 3.1 vs. 4.6%; $p=0.73$, respectively). No thromboembolic events occurred in either group. However, D-dimer levels 48 h after the ablation increased more markedly following the procedure in Group 2 than in Group 1 (from $0.58\pm0.16$ to $1.01\pm0.42$ μg/mL vs. $0.58\pm0.20$ to $0.82\pm0.25$ μg/mL; $p=0.01$). In conclusion, uninterrupted apixaban therapy during the periprocedural period of cryoballoon ablation for AF did not increase the risk of bleeding in this study and might reduce the periprocedural risk of subclinical hypercoagulable state.

**Keywords** Cryoballoon ablation · Atrial fibrillation · Apixaban · Uninterrupted · D-Dimer

## Introduction

Pulmonary vein isolation (PVI) is a widely accepted and effective strategy for the treatment of paroxysmal atrial fibrillation (AF) [1, 2]. Radiofrequency catheter ablation has been a standard application for AF; however, PVI using a cryoballoon (CB) has recently become an increasingly popular technique [3–5]. During the catheter ablation of AF, anticoagulation therapy is essential for the prevention of stroke and systemic thromboembolisms [6]. These days, uninterrupted use of warfarin has been generally recommended to minimize the thromboembolic complications without increasing bleeding events during the ablation procedure [7]. More recently, some reports showed the feasibility of uninterrupted direct oral anticoagulant (DOAC) therapy for the periprocedural period of catheter ablation [8–15]. However, the majority of the populations in previous reports consisted of patients undergoing radiofrequency catheter ablation. To date, there are few reports evaluating uninterrupted or interrupted DOAC usage during the CB ablation procedure.

Apixaban is a direct Factor Xa (FXa) inhibitor that does not require anticoagulation monitoring [16, 17]. After the

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introduction to clinical practice, apixaban has been used in numerous patients who were scheduled for catheter ablation for AF. Although a previous study from our institution demonstrated the efficacy and safety of uninterrupted apixaban for periprocedural usage during a radiofrequency ablation procedure [13], it is unclear whether the same result can be obtained in patients undergoing CB ablation.

To evaluate a prothrombotic response, several potential biomarkers were reported to be useful for stratification, prediction and diagnosis of thromboembolic events [18]. D-Dimer is one of those markers that may add valuable and time-sensitive diagnostic information for the early evaluation of ischemic stroke [19, 20]. Moreover, D-dimer level is easy and inexpensive to measure noninvasively in clinical practice.

Thus, the present study investigated the efficacy and safety of uninterrupted apixaban compared to the interrupted apixaban strategy during the periprocedural period of CB ablation for AF, by evaluating change in D-dimer levels as a marker of thrombogenesis and coagulation state.

## Materials and methods

### Study population

This study was designed as a randomized, open-label trial, and was conducted by the Cardiovascular Center of Nagoya Daini Red Cross Hospital. The study protocol was approved by the Institutional Committee on Human Research. All patients provided written informed consent for study participation. This study complied with the Declaration of Helsinki.

We enrolled 97 consecutive patients with drug refractory paroxysmal AF who scheduled to undergo a CB ablation procedure for the first time from July 2014 to February 2017. The indications for catheter ablation of AF were in compliance with the latest guideline [21]. The patient inclusion criteria for enrollment were as follows: (1) anticoagulation with apixaban at a dose of 5 mg twice daily; and (2) aged 20–85 years, regardless of the gender. The exclusion criteria of this study were as follows: (1) having received a low dose of apixaban or other oral anticoagulants, and an inappropriately reduced dose of apixaban, which may lead to an underestimation of the complication risk [22]; (2) aged < 20 or > 85 years; (3) the presence of intra-cavitary thrombus; (4) uncontrolled heart failure; (5) having a prosthetic heart valve or hemodynamically significant valvular disease; (6) advanced liver disease; (7) an estimated glomerular filtration rate of < 15 mL/min/1.73 $m^2$; and (8) any contraindication of the procedure.

### Randomization and study protocol

Patients were randomly assigned (1:2 ratio) to an anticoagulation strategy of either uninterrupted apixaban (Group 1) or interrupted apixaban (Group 2). The randomization was completed using a block-randomization method.

### Anticoagulation management

All patients were treated with apixaban as an anticoagulation therapy for at least 4 weeks before the ablation procedure. Transthoracic and transesophageal echocardiographies were performed for all patients to confirm the absence of atrial thrombus and cardiac function, such as left atrial diameter, left ventricular ejection fraction, and left ventricular diameter before the ablation procedure.

In Group 1, apixaban was used uninterruptedly during the periprocedural period.

In Group 2, apixaban was interrupted on the morning of the procedure. A bridging therapy with heparin was not used throughout the periprocedural period.

During the procedure, intravenous heparin was administered as a 100 unit/kg bolus dose immediately after inserting all the sheaths. The activation clotting time (ACT) was monitored every 20 min after the heparin boluses, and additional heparin was administered to maintain an ACT of 300–350 s. Protamine was used to reverse the heparin effect at the end of the procedure, and then, all the sheaths were removed from the patient.

Apixaban was administered in the evening of the procedure as usual in both Groups 1 and 2.

### Cryoballoon ablation procedure

Details of the CB ablation procedure have been described in previous studies [3–5, 23]. In brief, the 28-mm second-generation CB was advanced into the left atrium via an outer size of 15-French steerable sheath (FlexCath Advance™, Medtronic, MN, USA). The CB was inflated proximal to the pulmonary vein (PV) ostium followed by pushing to obtain an optimal balloon-to-PV ostium contact. To verify complete PV occlusion, a contrast medium was injected through the central lumen of the CB. The inner lumen mapping catheter (Achieve™, Medtronic) was used to obtain the PV potential recordings for real-time monitoring during the CB ablation. Three-minute CB applications were applied to each PV. The CB freezing was terminated when the temperature decreased below − 60 °C to avoid any deeper tissue injury. When the initial freezing failed to isolate the PV, a second freezing cycle was applied to the same PV. A touch-up ablation (Freezor Max,

Medtronic) was performed in case of failure to achieve PVI by CB ablation.

## Postprocedural management and follow-up

We used the International Society of Thrombosis and Hemostasis definition for bleeding complications [24]. Fatal bleeding and/or symptomatic bleeding in critical areas or organs, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular bleeding with compartment syndrome and/or bleeding that causes a decrease in hemoglobin level of 20 g/L or more, or leads to transfusion of two or more units of whole blood or red cells, were classified as major bleeding complications. Small groin hematomas and pericardial effusion that did not require any intervention were classified as minor bleeding episodes. All the patients underwent echocardiography after the procedure to check for pericardial effusion. Symptomatic ischemic strokes and transient ischemic attacks (TIAs), after ruling out intracranial hemorrhage by computed tomography, and systemic emboli were classified as thromboembolic complications. Patients who developed complications promptly received the appropriate intervention. Periprocedural complications were considered from the start of the ablation session to 30 days after the procedure.

## Measurement of the D-dimer

Blood samples for D-dimer measurements were obtained from all patients at the following four timepoints; immediately before the ablation (T1); at the end of the procedure before sheath removal (T2); 24 h after the procedure (T3); and 48 h after the procedure (T4) (Fig. 1). Blood samples were collected from a peripheral vein in the supine position after a resting period. For a quantitative measurement of the D-dimer, a latex-enhanced photometric immunoassay was used (LIAS AUTO D-dimer NEO, Sysmex Corporation, Kobe, Japan).

## Endpoints

The primary endpoint of the present study was the prothrombotic response, as assessed on the basis of D-dimer level, to the different strategies, and the secondary endpoint was bleeding and thromboembolic events.

## Statistical analysis

The sample size estimation was based on the results of the difference in D-dimer levels in our previous studies [25, 26]. To detect a difference of 0.2 μg/mL in D-dimer levels measured at any timepoint, presuming a standard deviation (SD) of 0.2 μg/mL, we calculated that 88 patients were needed, with a randomization ratio of 1:2 (a ratio of Group 1 to Group 2), for the study to have 85% power with a two-tailed alpha value of 0.05. Assuming 10% dropout, 32 patients were required in Group 1 and 65 patients in Group 2. The rationale for the unequal 1:2 randomization was based on our previous report; the D-dimer elevation rate in patients with direct FXa inhibitor discontinuation was higher than those with uninterrupted direct FXa inhibitor therapy [26].

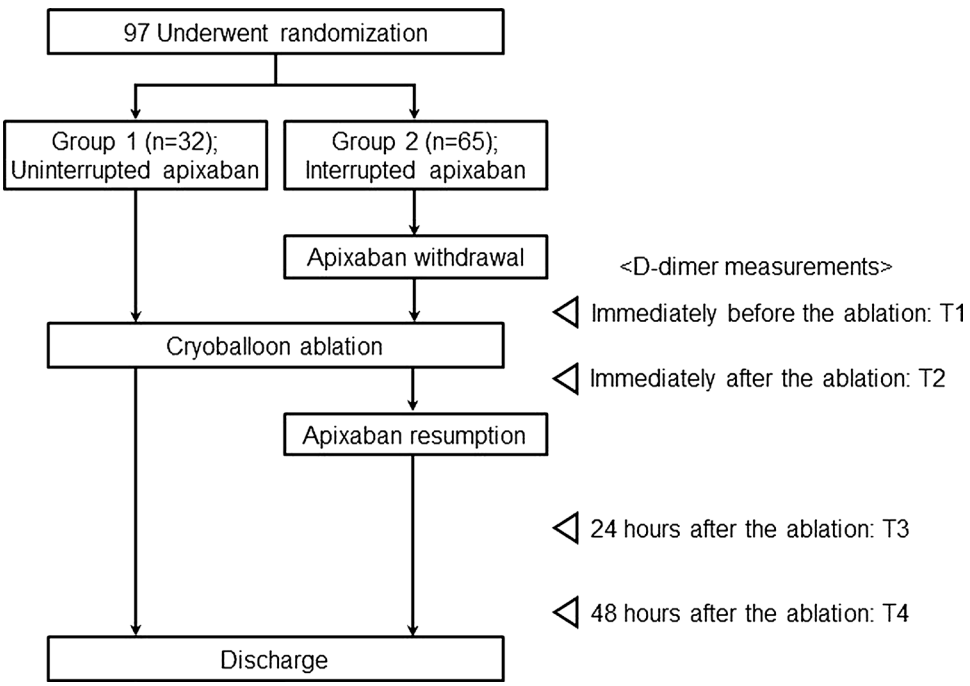


**Fig. 1** Flow chart of the study design

All continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as number (percentage) of patients. Comparisons of the changes in D-dimer levels during the procedure were analyzed by a two-way analysis of variance for repeated measures on one factor followed by the Bonferroni correction for multiple paired comparisons. The statistical analyses were performed using JMP software version 13.0 (SAS Institute, Cary, NC, USA). For all analyses, a $p$ value of $< 0.05$ was considered statistically significant.

## Results

### Patient characteristics

Among the total of 97 patients, 32 and 65 patients were randomly assigned to Groups 1 and 2, respectively (Fig. 1). In the total population, the mean age was 66.7 ± 10.3 years, and 75 patients (77.3%) were male. The clinical characteristics of both patient groups are presented in Table 1. The baseline characteristics and risk factors were well-balanced between the two groups. One patient (3.1%) in Group 1 (urinary tract hemorrhage) and three patients (4.6%) in Group 2 (cerebral hemorrhages in two and uterine hemorrhage in one patient[s]) had a history of bleeding events ($p = 0.73$).

### Procedural values

The ablation procedure was successfully completed in all patients. The procedural findings are summarized in Table 2. The mean procedure times were 121.9 ± 18.2 and 128.5 ± 23.2 min ($p = 0.17$), and mean fluoroscopic times were 24.5 ± 8.2 and 26.3 ± 6.3 min ($p = 0.12$) in Groups 1 and 2, respectively.

### Complications

The complication details that occurred during the periprocedural period are shown in Table 3. In the comparison between Groups 1 and 2, no significant differences were observed in major bleeding (1 patient [3.1%] vs. 1 patient [1.5%], $p = 0.61$) and minor bleeding complications (1 patient [3.1%] vs. 3 patients [4.6%], $p = 0.73$), respectively. No thromboembolic events occurred in either group. As for major complications, pericardial effusion with tamponade occurred in one patient (1.5%) in Group 2. This patient required pericardiocentesis after protamine use to reverse the anticoagulant effect of heparin, and hemodynamic function was restored without the use of blood products. One patient (3.1%) in Group 1 experienced a vascular complication that required surgical intervention. Surgical ligature of the right femoral branch vein for the refractory bleeding at the puncture site was applied the day after the ablation. This patient did not require any blood products during the periprocedural period. Hematomas of the puncture site occurred in one patient (3.1%) in Group 1 and three patients (4.6%) in Group 2 ($p = 0.73$).

### Time-course change in D-dimer levels

D-Dimer levels measured immediately before the ablation were identical in both groups. The level of D-dimer significantly increased after the ablation in both groups. However, the levels increased more markedly in Group 2 than in Group 1 at 24 h (from 0.58 ± 0.16 to 0.98 ± 0.42 μg/mL vs. from 0.58 ± 0.20 to 0.84 ± 0.23 μg/mL; $p = 0.01$) and 48 h after the ablation (from 0.58 ± 0.16 to 1.01 ± 0.42 μg/mL vs. from 0.58 ± 0.20 to 0.82 ± 0.25 μg/mL; $p = 0.01$) (Table 4). In the Group 2 patients, D-dimer levels continued to increase over a period of 48 h after the ablation (T4). On the other hand, in Group 1 patients, the D-dimer levels peaked 24 h after the ablation (T3) (Fig. 2). The change in the level of D-dimer from baseline (immediately before the ablation; T1) to 24 and 48 h after the ablation was significantly smaller in Group 1 than in Group 2 (+47.1 ± 31.6% vs. +68.0 ± 44.6%; $p = 0.03$, and +46.6 ± 34.8% vs. +73.3 ± 72.0%; $p = 0.02$, respectively) (Fig. 3).

## Discussion

### Major findings

To the best of our knowledge, this is the first randomized study to compare the anticoagulation effect as assessed on the basis of a specific coagulation biomarker, D-dimer level, between the uninterrupted and interrupted apixaban therapies during the periprocedural period of CB ablation for paroxysmal AF. The major findings in the present study were as follows: (1) The periprocedural complication rate of the CB ablation under both uninterrupted and interrupted apixaban administration at the usual dosage was limited; (2) there was no difference in the bleeding and thromboembolic events between the two groups; and (3) the increase rate of the D-dimer levels from the baseline to 24 and 48 h after the ablation was significantly smaller in patients with uninterrupted apixaban therapy than in those with interrupted apixaban therapy.

### Periprocedural complications in uninterrupted and interrupted apixaban therapies in CB ablation

Periprocedural use of DOACs during radiofrequency catheter ablation has been reported by several previous studies to be more feasible and safer than warfarin therapy [8–15,

**Table 1** Baseline characteristics of the study population

| | Group 1 (uninterrupted apixaban) | Group 2 (interrupted apixaban) | *p* value |
|---|---|---|---|
| Age (years) | 67.2 ± 10.8 | 66.4 ± 10.2 | 0.73 |
| Gender, male | 26 (81.3) | 49 (75.4) | 0.51 |
| Body mass index (kg/m$^2$) | 22.9 ± 3.3 | 23.3 ± 2.9 | 0.52 |
| Duration of AF (years) | 2.5 ± 3.6 | 2.6 ± 4.5 | 0.92 |
| Congestive heart failure | 2 (6.3) | 5 (7.7) | 0.80 |
| Hypertension | 18 (56.3) | 28 (56) | 0.36 |
| Diabetes mellitus | 4 (12.5) | 9 (13.9) | 0.85 |
| Stroke or/and TIA | 2 (6.3) | 6 (9.2) | 0.62 |
| Previous bleeding | 1 (3.1) | 3 (4.6) | 0.73 |
| Dyslipidemia | 6 (18.8) | 17 (26.2) | 0.42 |
| Structural heart disease | | | |
| Coronary artery disease | 1 (3.1) | 4 (6.15) | 0.53 |
| Hypertrophic cardiomyopathy | 1 (3.1) | 1 (1.5) | 0.61 |
| Tachycardia-induced cardiomyopathy | 1 (3.1) | 3 (4.6) | 0.73 |
| $CHADS_2$ score | | | 0.88 |
| 0–1 | 23 (71.9) | 49 (75.4) | |
| 2 | 5 (15.6) | 10 (15.4) | |
| 3–6 | 4 (12.5) | 6 (9.2) | |
| $CHA_2DS_2$-VASc score | | | 0.33 |
| 0–1 | 14 (43.8) | 19 (29.2) | |
| 2 | 8 (25.0) | 17 (26.2) | |
| 3–4 | 7 (21.9) | 25 (38.4) | |
| 5–9 | 3 (9.3) | 4 (6.2) | |
| HAS-BLED score | | | 0.80 |
| 0–2 | 30 (93.7) | 60 (92.3) | |
| 3–9 | 2 (6.3) | 5 (7.7) | |
| Echocardiographic data | | | |
| Left atrial diameter (mm) | 37.2 ± 5.9 | 38.1 ± 5.4 | 0.45 |
| Left ventricular ejection fraction (%) | 60.7 ± 11.5 | 61.9 ± 8.2 | 0.60 |
| Left ventricular diameter (mm) | 46.3 ± 4.7 | 46.9 ± 4.8 | 0.58 |
| Laboratory data | | | |
| eGFR (mL/min/1.73 m$^2$) | 62.8 ± 13.2 | 60.3 ± 13.6 | 0.39 |
| BNP (pg/mL) | 102.6 ± 108.3 | 92.8 ± 167.7 | 0.73 |
| Medication | | | |
| Antiarrhythmic drugs | 16 (50.0) | 38 (58.5) | 0.43 |
| Beta-blockers | 16 (50.0) | 31 (47.7) | 0.83 |
| ACE inhibitors/ARBs | 8 (25.0) | 23 (35.4) | 0.30 |
| Antiplatelet drug | 2 (6.3) | 7 (10.8) | 0.47 |
| Proton-pump inhibitors | 10 (31.3) | 20 (30.8) | 0.96 |
| NSAIDs | 0 (0.0) | 1 (1.5) | 0.48 |
| Statins | 6 (18.8) | 19 (29.2) | 0.27 |

*ACE* angiotensin-converting enzyme, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TIA* transient ischemic attack

25, 27–29]. However, data on periprocedural DOAC therapy for CB ablation are still limited. Cryoballoon ablation uses a different application technology to damage the myocardium in the atrium compared to radiofrequency ablation, and a possible formation of thrombi due to an injury of endothelial cell in the atrium might be different between the two ablation techniques [30]. Moreover, a thick sheath of CB ablation could lead to concern regarding bleeding complications after the removal of sheaths, especially under uninterrupted DOAC administration. The present study demonstrated

**Table 2** Procedural findings during ablation

| | Group 1 (uninterrupted apixaban) | Group 2 (interrupted apixaban) | *p* value |
|---|---|---|---|
| Procedure time (min) | 121.9 ± 18.2 | 128.5 ± 23.2 | 0.17 |
| Fluoroscopic time (min) | 42.2 ± 12.9 | 43.4 ± 10.9 | 0.65 |
| Touch-up ablation | 10 (31.3) | 25 (38.5) | 0.49 |

that no patients experienced symptomatic thromboembolic events, and the total bleeding complications rate was low (approximately 6%) in periprocedural apixaban usage during the CB ablation. We confirmed the feasibility and safety of DOAC administration in patients undergoing CB ablation for AF, regardless of the regimen used for periprocedural DOAC administration. Certainly, this result can be predicted from the result of a recent multicenter randomized trial, FIRE AND ICE [4]. Moreover, previous large trials also showed a similar rate of clinical complications between interrupted and uninterrupted DOAC use [8, 10, 11]. However, a recent study regarding CB showed lower risks of clinical bleeding and ischemic events, but a higher incidence of silent cerebral ischemic lesion detection using an imaging study in patients who received interrupted DOAC therapy [31]. Furthermore, the CB procedure has a higher possibility of causing micro-air embolism than the radiofrequency procedure [32]. Some reports also showed that the silent ischemic lesion was associated with the development of dementia and worse neuropsychological outcome [33–35]. Therefore, it may be important to evaluate subclinical ischemic brain damage beyond the clinical symptomatic feature and to assess the difference in potential risk of the anticoagulant regimen used during the catheter ablation procedure. Usually, silent ischemic stroke is evaluated using magnetic resonance imaging (MRI) examination in the post-ablation procedure, and many studies reported finding a considerable number of silent ischemic lesions on magnetic resonance images [7, 9, 11, 31]. In the present study, we evaluated subclinical ischemic brain damage by focusing on the D-dimer level, a potential biomarker of thromboembolic events, as an alternative approach [18–20].

## Lower level of the D-dimer in the patients who underwent uninterrupted apixaban therapy

There is no common laboratory marker that can assess the anticoagulant effect of apixaban. D-Dimer is a fibrinogen degradation product that reflects thrombus formation and blood coagulation. D-Dimer level has been recognized to reflect a prothrombogenic state and could be a potential marker of thrombosis [19, 20, 36–38]. Therefore, we chose

**Table 3** Complications

| | Group 1 (uninterrupted apixaban) | Group 2 (interrupted apixaban) | *p* value |
|---|---|---|---|
| Total bleeding complications | 2 (6.3) | 4 (6.2) | 0.99 |
| Major bleeding complications | 1 (3.1) | 1 (1.5) | 0.61 |
| Cardiac tamponade | 0 (0) | 1 (1.5) | 0.48 |
| Vascular complications requiring intervention | 1 (3.1) | 0 (0) | 0.15 |
| Gastrointestinal hemorrhage | 0 (0) | 0 (0) | N/A |
| Minor bleeding complications | 1 (3.1) | 3 (4.6) | 0.73 |
| Hematomas of puncture site | 1 (3.1) | 3 (4.6) | 0.73 |
| Pericardial effusion without tamponade | 0 (0) | 0 (0) | N/A |
| Thromboembolic complications | 0 (0) | 0 (0) | N/A |
| Symptomatic ischemic stroke or TIAs | 0 (0) | 0 (0) | N/A |
| Systemic emboli | 0 (0) | 0 (0) | N/A |
| Total complications | 2 (6.3) | 4 (6.2) | 0.99 |

*TIA* transient ischemic attack

**Table 4** Time-course change in D-dimer levels

| | Group 1 (uninterrupted apixaban) (μg/mL) | Group 2 (interrupted apixaban) (μg/mL) | *p* value |
|---|---|---|---|
| T1 (immediately before the ablation) | 0.58 ± 0.20 | 0.58 ± 0.16 | 0.96 |
| T2 (immediately after the ablation) | 0.64 ± 0.17 | 0.69 ± 0.30 | 0.46 |
| T3 (24 h after the ablation) | 0.84 ± 0.23 | 0.98 ± 0.42 | 0.01 |
| T4 (48 h after the ablation) | 0.82 ± 0.25 | 1.01 ± 0.42 | 0.01 |

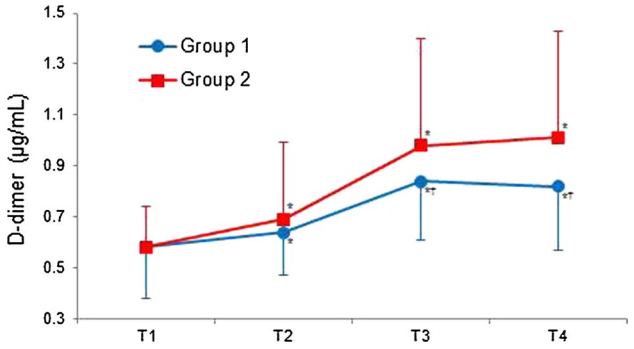


**Fig. 2** Time courses of D-dimer levels in the uninterrupted apixaban (Group 1) and interrupted apixaban groups (Group 2). Data are presented as a mean value. Error bars indicate standard deviation. T1–4 indicate the timepoints at which the D-dimer was measured: T1, immediately before the ablation procedure; T2, immediately after the ablation; T3, 24 h after the ablation; and T4, 48 h after the ablation. *$p < 0.001$; vs. T1, †$p < 0.05$; vs. Group 2

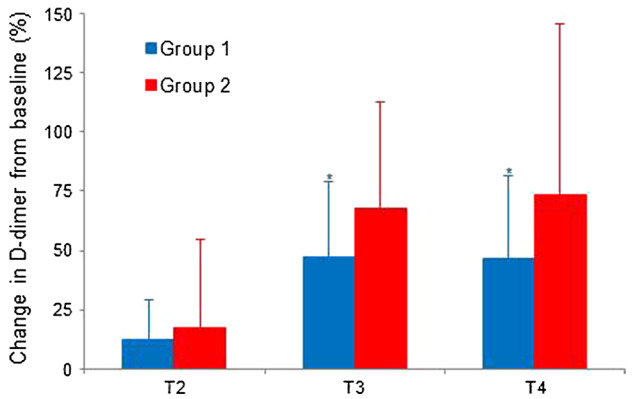


**Fig. 3** Comparison of change in the level of D-dimer at each timepoint from baseline between the uninterrupted apixaban (Group 1) and interrupted apixaban groups (Group 2). Data are presented as a mean value. Error bars indicate standard deviation. T2–4 indicate the timepoints at which the D-dimer was measured: T2, immediately after the ablation; T3, 24 h after the ablation; and T4, 48 h after the ablation. *$p < 0.05$; vs. Group 2

D-dimer level as the primary endpoint of the incidence of thrombus formation and a hypercoagulable state. We found that the patients allocated to the uninterrupted apixaban therapy group had a lower level of the D-dimer measured 24 and 48 h after the ablation. This finding suggests a higher ability of uninterrupted apixaban therapy to prevent the formation of thrombi as compared to interrupted apixaban therapy. Conversely, this may suggest that the patients with interrupted apixaban therapy were at a higher risk of hypercoagulability than those with uninterrupted apixaban therapy. Rebound phenomenon caused by sudden discontinuation of anticoagulants that leads to the occurrence of unexpected thromboembolic events during the periprocedural period has been reported [39]. Specifically, this phenomenon has been known to occur when warfarin and heparin are abruptly withdrawn [39, 40]. A similar phenomenon has been reported from sub-analyses of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [16, 17, 41]. Indeed, the incidence of silent cerebral ischemic lesions was detected in more than 20% of the patients with interrupted DOACs undergoing CB ablation in a previous report [31]. Although the significance of the slightly elevated D-dimer levels in the interrupted apixaban group is unknown and we did not directly confirm the correlation between the high D-dimer levels and the silent ischemic lesions on MRI in our study, brief withdrawal of apixaban prior to ablation might be a potential risk of thromboembolism as indicated by the high D-dimer levels during the periprocedural period. The uninterrupted strategy of apixaban may contribute to a reduced risk of hypercoagulability after the ablation, which might decrease formation of thrombi linking to the incidence of silent ischemic strokes.

By contrast, one major concern about uninterrupted DOAC use during the ablation procedure is that effective antidotes of apixaban are still currently under development [42]. When anticoagulants are used uninterruptedly during the periprocedural period, the possibility of severe bleeding complications must be considered. However, in patients in this study who had major bleeding complications, apixaban administration was interrupted for only few days after the bleeding events, and as a result, all patients recovered hemodynamically without the need of specific antidotes or blood transfusions.

## Study limitations

First, the D-dimer levels may reflect myocardial damage from the CB ablation and the local condition of the vascular access sites [43]. Thus, there is no strict consensus that D-dimer has a sufficient ability to stratify the risk of thromboembolic events. Moreover, we assessed the prothrombotic response after ablation using only D-dimer level and did not evaluate other coagulate system markers. Second, this study evaluated only symptomatic ischemic stroke events during the ablation, and asymptomatic ischemic strokes detected by MRI were not evaluated. Third, the number of patients recruited at a single center in this study was relatively small. We estimated the sample size of the present study just to determine the difference in D-dimer level, not the differences in clinical bleeding and thromboembolic complication rates. Therefore, the study was underpowered to evaluate the differences in the clinical events of complications between the two groups. Fourth, the effect of catheter ablation for AF on D-dimer levels may differ among different DOACs [44]. We confirmed only the difference in D-dimer levels in the apixaban group and did not assess the same result in other

different DOACs, or the differences in the effects of various DOACs on D-dimer level. A prospective, randomized multicenter study that compares various uninterrupted and interrupted DOACs in worldwide populations, including the determination of the occurrence of silent ischemic stroke, is required.

## Conclusions

Although the rates of clinical thromboembolic events and bleeding complications between the uninterrupted and interrupted apixaban therapies were similar during the periprocedural period of CB ablation for AF, the uninterrupted apixaban therapy may decrease the risk of hypercoagulability during the periprocedural period of ablation as compared to the interrupted apixaban therapy.

### Compliance with ethical standards

**Conflict of interest** None declared.

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