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Original article

Clinical comparative study regarding interrupted and uninterrupted dabigatran therapy during perioperative periods of cryoballoon ablation for paroxysmal atrial fibrillation

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ABSTRACT

Background: Catheter manipulation in the left-sided heart is known as a risk for cerebral embolisms (CEs). However, anticoagulation therapy is terminated before catheter ablation (CA) of atrial fibrillation (AF) concerning adverse bleeding events. Little is known whether uninterrupted direct oral anticoagulants (DOACs) during perioperative period of CA could render the ablation procedure safer and reduce the incidence of CEs compared to interrupted DOACs. The aim of this study was to investigate the safety and usefulness of uninterrupted dabigatran during the periprocedural period for CA of AF.
Methods: We included 333 patients with paroxysmal AF undergoing cryoballoon CA (CBA). They were prospectively divided into 2 groups based on whether DOACs were interrupted on the day of the CA (Group A, $n = 228$) or dabigatran was not interrupted throughout perioperative period (Group B, $n = 105$) in a non-randomized fashion. When the Group B patients had taken other DOACs rather than dabigatran before assignment, we changed those DOACs to dabigatran. Brain magnetic resonance imaging (MRI) was undertaken on the following day of the CA. Serious bleeding event cases were excluded from the study.
Results: The baseline characteristics including the CHADs2 score did not exhibit any significant differences between the groups. The brain MRI revealed an acute CEs in 82 patients, and was significantly higher in Group A than B (29% vs. 13%, respectively, $p < 0.01$). There were no significant differences regarding the bleeding events (7% vs. 4%, respectively, $p = 0.62$).
Conclusion: Uninterrupted dabigatran therapy during the CBA of paroxysmal AF could significantly reduce the incidence of CEs.

Introduction

Atrial fibrillation (AF) is known as one of the major risk factors of cerebral infarction, and the risk of ischemic stroke events in patients with AF has been reported in the Framingham study to be 5 times higher than that in those without it [1]. Even though it was a silent cerebral embolism, it correlated with the cognitive impairment [2]. In addition, AF-related strokes are more severe than those not related to AF [3]. The morbidity associated with AF provides a rationale to maintain sinus rhythm. Although studies have not been performed to address the question of whether AF controlled by catheter ablation impacts the morbidity and mortality associated with AF, AF ablation has been widely performed aiming for a benefit of AF ablation, which remains a reduction in the symptoms and an improvement in the quality of life.

However, catheter ablation (CA) itself could connote the risk of cerebral embolisms (CEs). Although symptomatic cerebral infarctions related to ablation procedures occur in about 1% of patients undergoing radiofrequency catheter ablation (RFCA) [4], brain magnetic resonance imaging (MRI) after CA reveals silent cerebral lesions in 14–40% of those patients [5–8].

On the other hand, continuation of direct oral anticoagulants (DOACs) during the perioperative period of AF ablation is still

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controversial, as oppose to that for warfarin. The RE-CIRCUIT trial showed that uninterrupted dabigatran during catheter ablation was associated with fewer bleeding complications than uninterrupted warfarin [9]. In addition, there were no events of symptomatic strokes, systemic embolisms, or transient ischemic attacks (TIAs) in patients of uninterrupted dabigatran. Nevertheless, there have been no reports on whether uninterrupted dabigatran could reduce the incidence of CE events after CA compared to conventional interrupted DOACs.

Recently, cryoballoon CA (CBA) has been widely performed for paroxysmal AF because of the efficacy and low complication rate even in elderly patients [10,11].

In the present study, we aimed to investigate the clinical usefulness and safety between uninterrupted and conventional interrupted DOACs in terms of the incidence of CEs diagnosed by brain MRI after cryoballoon CA (CBA).

Methods

Study patients

Between December 2016 and April 2018, a total of 333 consecutive patients with paroxysmal AF (PAF) undergone CBA. They were prospectively non-randomly divided into 2 groups based on whether they were on conventional interrupted DOACs (**Group A**) or uninterrupted dabigatran (**Group B**) during the perioperative period of the CBA. From December 2016 to October 2017, the patients were classified into Group A, and the other study patients had been allocated to Group B. Patients who could not undergo an MRI on the next day of the CBA for several reasons such as having MRI non-resistant pacemaker implantations, severe valvular disease, or taking warfarin were excluded. We also excluded patients with major bleeding events provoked by the CA, such as cardiac tamponade, an AV-shunt, or a pseudo-aneurysm in the groin, because an MRI examination performed on the day after the ablation procedure might provoke another serious adverse event in patients requiring absolute rest.

All patients had taken DOACs for more than 4 weeks before the CBA. In **Group A**, ordinary DOACs were taken as usual on the first day after hospitalization. On the second day following the CBA, DOACs were discontinued in the morning and given in the evening, depending on start time of the ablation and their consciousness level. An unfractionated heparin bridge was not performed during the CBA. From the morning of the third day, the same DOACs as prescribed before the CBA were resumed. In **Group B**, ordinary DOACs were administered in the morning of the first day. Further, in cases in which DOACs were prescribed twice a day, such as dabigatran and apixaban, the anticoagulants in the evening of the first day were switched to dabigatran. On the second (CBA day) and third day, dabigatran was administered. From the fourth day, the same DOACs as prescribed before the CBA were resumed as shown in Fig. 1. In principle, the dose of dabigatran on day of the CBA was 150 mg twice daily, however, it was adjusted by the physicians discretion considering the age, value of creatinine clearance, and risk of bleeding. The doses of DOACs before and after the CBA were also decided according to the age, body weight, and creatinine clearance level by the attending physicians. All patients were scheduled to be discharged from the hospital on the fourth day.

The study protocol was approved by the ethics committee of the Japan Red Cross Yokohama City Bay Hospital, and written informed consent was obtained from all participants before the study.

Ablation procedure

The CA procedure was performed under the general anesthesia. Unfractionated heparin was administered by one shut at the timing of the insertion of internal jugular and femoral vessel sheaths and then added just after the transseptal puncture. All sheaths were carefully flushed with heparinized saline for every catheter insertion to avoid any ingress of air. In addition, heparinized saline was continuously infused through the Flex Cath (Medtronic, Minneapolis, MN, USA) during catheter manipulation in the left atrium (LA) in order to prevent any thrombus formation in the space between the FlexCath and CB shaft. Before the CB insertion into the FlexCath, the CB was inflated in a heparinized saline bath to totally exclude any air bubbles attached to the balloon surface (extra-corporeal CB inflation). After the transseptal approach, the activated clotting time (ACT) was measured from the blood sample obtained through the venous route every 20 min to maintain an ACT level between 300–350 seconds using unfractionated heparin during catheter manipulation in the LA.

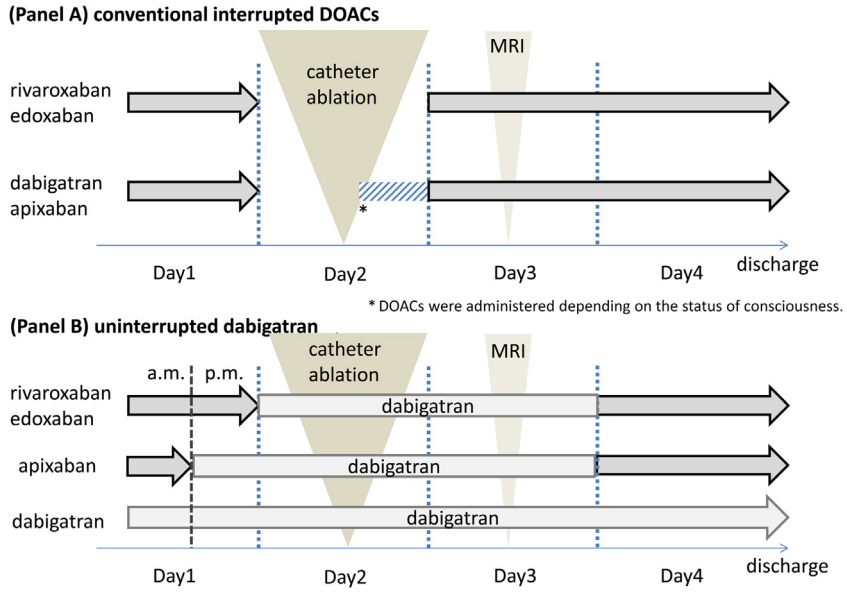

Fig. 1. The DOAC administration schedule during the hospitalization in **Group A** (Panel **A**) and **Group B** (Panel **B**).

All patients underwent pulmonary vein (PV) isolation (PVI) with the CB using exclusively a 28-mm CB (Arctic Front Advance, Medtronic). A circular-mapping catheter (Optima, St. Jude Medical Inc., St Paul, MN, USA or EP star Libero, Japan Lifeline CO., Tokyo, Japan) was inserted into the LA and PVs to confirm the PVI status. In cases of an unsuccessful PVI solely by the CB, touch-up ablation with an irrigated radiofrequency (RF) catheter (Flexability, St. Medical or TactiCath, Endosense SA, Geneva, Switzerland) targeting at conduction gaps between the LA and PVs was undertaken. Internal electrical cardioversion (ECV) with an energy of 10–20 J through a decapolar electrode catheter inserted deep into the coronary sinus was performed in selected patients to terminate AF.

Analysis of the parameters

A brain MRI with a 1.5-T scanner (Achieve, Philips, The Netherlands) was undertaken on the day following the CBA to identify the CEs. We checked the diffusion-weighted imaging (DWI) to assess any newly occurring CE lesions. For each DWI sequence, the apparent diffusion coefficient (ADC) map, which was created by dividing the signal from the trace-DWI by the signal from each corresponding point was obtained to rule out any T2-shine-through artifact. An acute CE lesion was defined as a focal hyper-intense area detected by the DWI sequence with a corresponding hypo-intensity in the ADC map in a typical vascular pattern. Systematic clinical neurological examinations were performed by a certified neurologist at our institution on the day of admission and the following day of the CBA. All MRI images were analyzed independently by a certified radiologist and certified physicians blinded to this study, the clinical status and identification of the patients.

Major bleeding events were defined by the International Society on Thrombus and Hemostasis (ISTH) as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in the hemoglobin level of 1.24 mmol/L or more, or leading to a transfusion of two or more units of whole blood or red cells [12]. We also included bleeding events that required additional medical management, such as repeated procedure for hemostasis at the puncture site, discontinuation of DOACs, necessity of an administration of idarucizumab, and an extension of the hospitalization. These adverse events were assessed after the CBA until discharge from the hospital.

The type of DOAC, catheter ablation parameters, dose of dabigatran, and baseline clinical characteristics, such as the CHADs2 score, were also analyzed using a multivariate analysis.

Statistical analysis

Data are presented as the mean ± standard deviation. The two-tailed Welch *t*-test was used to compare the non- parametrical variables between the groups. A Fisher's exact test was used to evaluate differences in the categorical variables between the groups. A *p*-value <0.05 was considered significant.

A univariate logistic regression analysis was performed to estimate the odds ratios of potential risk factors for CEs. All clinical variables identified in this analysis with a $p < 0.1$ were entered into a multivariate logistic regression model to identify the independent predictors associated with CEs.

Results

Among 333 patients who had undergone the CBA for PAF, 228 patients in **Group A** and 105 patients in **Group B** were included (Table 1). In **Group B**, 11 patients had taken 110 mg of dabigatran and the rest of them 150 mg of dabigatran twice daily. There were no significant differences in the baseline characteristics, including the medical history, type of DOACs before the CBA, laboratory data, and echocardiographic data, between the two groups. The sum of the CHADs2 score showed no differences at each clinical stage between the two groups. In addition, the CHADs2-VASC score was also similar between the two groups (Table 2). All patients underwent a PVI with the CB. The total CA procedure time and dwelling duration in the LA in **Group A and B** were 144.8 ± 40.0 vs. 151.5 ± 40.2 min ($p = 0.17$) and 80.2 ± 35.3 vs. 76.3 ± 33.9 min ($p = 0.33$), respectively. Additional RFCA in the LA were performed in 55 and 22 patients in **Groups A** and **B** (24% vs. 20%, respectively, $p = 0.57$). An LA roof, bottom, and mitral isthmus block line construction was attempted in 47 vs. 32, 28 vs. 21 and 55 vs. 4 patients in **Groups A** and **B**, respectively (Table 3).

Both Groups had no significant difference regarding the required number of ECV attempts. On the other hand, the average ACT during catheter manipulation in the LA was significantly shorter in the patients in **Group A** than **B** (305.6 ± 65.3 vs. 342.1 ± 43.7 s, respectively, $p < 0.01$). Of note, the ACTs measured immediately after the catheter insertion into the LA ("the first ACT") were significantly shorter in **Group A** than **B** (290.5 ± 51.7 vs. 338.6 ± 63.9 s, $p < 0.01$), however, the average ACT except for the first ACT exhibited no significant differences between the two groups (311.6 ± 187.7 vs. 339.4 ± 50.0 s, respectively, $p = 0.17$) (Table 3).

Table 1
Baseline characteristics between Group A and Group B.

	Interrupted DOAC $n = 228$	Uninterrupted dabigatran $n = 105$	p
Age, years old	64.3 ± 11.6	64.4 ± 10.9	0.94
Male (%)	153 (67)	69 (65)	0.80
Hypertension (%)	105 (46)	54 (51)	0.40
Diabetes mellitus (%)	25 (10)	13 (12)	0.71
Coronary disease (%)	18 (7)	6 (5)	0.76
Cerebral infarction (%)	14 (6)	8 (7)	0.75
DOAC before the procedure			0.10
Dabigatran (%)	43 (18)	28 (26)	
Rivaroxaban (%)	88 (38)	34 (32)	
Apixaban (%)	38 (16)	10 (9)	
Edoxaban (%)	59 (25)	33 (31)	
Antiplatelet medicine (%)	17 (7)	7 (6)	1
Creatinine, mg/dl	0.81 ± 0.21	0.80 ± 0.15	0.65
Ccr	56.9 ± 25.8	57.4 ± 26.5	0.87
LAD, mm	39.0 ± 6.1	39.2 ± 6.0	0.82
LVEF, %	66.4 ± 8.2	66.5 ± 8.4	0.97

DOAC, direct oral anticoagulants; OAC, oral anticoagulant, Ccr, creatinine clearance; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 2
$CHADS_2$ and CHADs2-VASC score in the study patients.

	Interrupted DOAC $n=228$	Uninterrupted dabigatran $n=105$	p
CHADs2			0.72
0 (%)	86 (37)	37 (35)	
1 (%)	88 (38)	44 (41)	
2 (%)	41 (17)	19 (18)	
3 (%)	11 (4)	3 (2)	
4 (%)	2 (0.8)	1 (0.9)	
5 (%)	0	1 (0.9)	
CHADs2VASC			0.08
0 (%)	46 (20)	19 (18)	
1 (%)	44 (19)	21 (20)	
2 (%)	55 (24)	35 (33)	
3 (%)	61 (28)	18 (17)	
4 (%)	13 (5)	9 (8)	
5 (%)	9 (3)	1 (0.9)	
6 (%)	0	1 (0.9)	
7 (%)	0	0	
8 (%)	0	1 (0.9)	

Table 3
Procedure parameters during cryoballoon ablation in the study patients.

	Interrupted DOAC $n=228$	Uninterrupted dabigatran $n=105$	p
Total procedure time, min	144.8 ± 40.0	151.5 ± 40.2	0.17
Stay in LA, min	80.2 ± 35.3	76.3 ± 33.9	0.33
Additional RFCA in LA (%)	55 (24)	22 (20)	0.57
Average ACT, s	305.6 ± 65.3	342.1 ± 43.7	<0.01
First ACT, s	290.5 ± 51.7	338.6 ± 63.9	<0.01
Average ACT except first ACT, s	311.6 ± 187.7	339.4 ± 50.0	0.17
Heparin, 10^3U	9.2 ± 2.7	7.0 ± 2.1	<0.01
Direct defibrillation (%)	77 (33)	37 (35)	0.80

LA, left atrium; RFCA, radiofrequency catheter ablation; ACT, activated clotting time.

In the multivariate logistic regression analysis, only uninterrupted DOACs were a significant independent predictor of CEs (Table 4).

Adverse events

The brain MRI images taken on the following day after AF ablation revealed CEs in 82 patients, 68 patients (29%) in **Group A** and 14 patients (13%) in **Group B** ($p < 0.01$), including a symptomatic cerebral infarction lesion in one patient in each group (0.4% vs. 0.9%, respectively, $p = 0.53$). Patient #1 in **Group A** with a symptomatic cerebral infarction had a left thalamic infarction and aphasia, and hypobulia appeared the day after the ablation procedure. The CHA_2DS_2-VASc score was 1 point (female) and the patient had taken 15 mg of ribaroxaban. After rehabilitation for a few months, her neurological deficit has almost completely resolved. Patient #2 in **Group B** also had a left thalamic infarction (Fig. 2A, B), and motor aphasia was provoked the day after the ablation procedure. His CHA_2DS_2-VASc score was 1 point

Table 4
Univariate and multivariate analysis for investigating predictors for silent CEs.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95%CI	p	Odds ratio	95%CI	p
Age	1.01	0.98–1.03	0.63			
Female	1.28	0.76–2.16	0.34			
Medical history						
Hypertension	0.93	0.56–1.54	0.79			
Cerebral infarction	0.46	0.13–1.61	0.22			
Heart failure	3.21	0.90–11.40	0.07	2.65	0.72–9.70	0.14
Diabetes mellitus	1.29	0.61–2.73	0.50			
CHADs2	1.01	0.77–1.33	0.92			
CHADs2VASC	1.08	0.90–1.29	0.40			
DOAC type before the procedure						
Dabigatran	0.68	0.36–1.28	0.23			
Rivaroxaban	1.17	0.70–1.95	0.54			
Apixaban	1.30	0.64–2.61	0.46			
Edoxaban	0.95	0.54–1.67	0.86			
LAD	1.00	0.96–1.05	0.64			
LVEF	0.98	0.95–1.01	0.44			
Average ACT	1.00	0.99–1.00	0.71			
Additional RFCA in LA	0.90	0.52–1.56	0.72			
Direct defibrillation	1.63	0.97–2.72	0.06	1.67	0.98–2.82	0.05
Uninterrupted dabigatran	0.36	0.19–0.68	<0.01	0.36	0.19–0.69	<0.01

CI, confidence interval, other abbreviation as in Table 1.

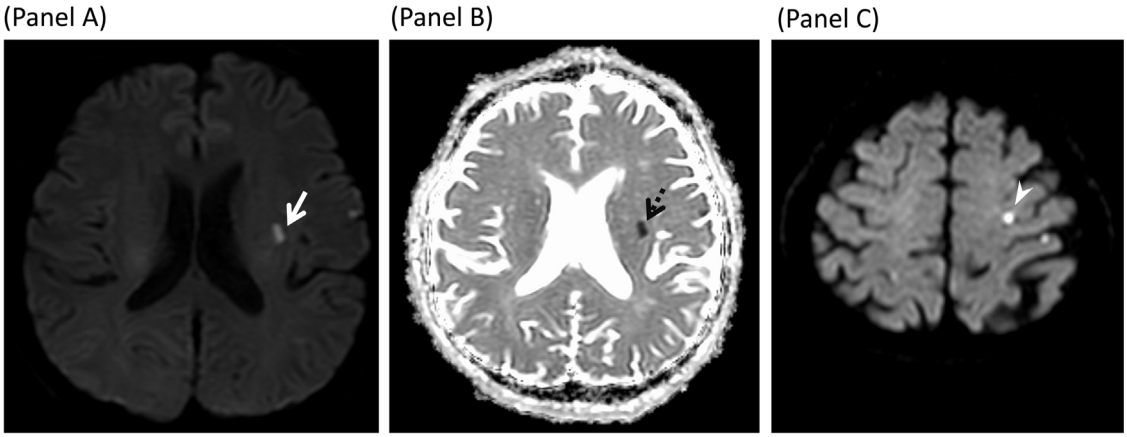

Fig. 2. Exhibits brain MRI images of patient #2 and a patient with asymptomatic CEs. Panel A: DWI showed high intensity in the posterior limb of the internal capsule (solid white arrow). Panel B: The hyper intense area in DWI corresponded with hypo intensity in ADC map (dashed black arrow), which indicated typical vascular pattern. Panel C: A high intensity in the frontal lobe was exhibited in DWI (white arrowhead). DWI, diffusion-weighted imaging; ADC map, apparent diffusion coefficient map.

(as age older than 65) and he had taken 60 mg of edoxaban. His verbal impairment had also completely recovered. Fig. 2C shows an MRI image of a small infarction in the frontal lobe observed in a representative asymptomatic patient.

There was no difference in the adverse bleeding events between **Groups A** and **B** (7% vs. 4%, respectively, $p = 0.62$), including groin hematomas, epicardial effusions, and hemorrhagic gastric ulcers (Table 5).

Discussion

The major findings observed in the present study were; (1) uninterrupted dabigatran was able to significantly reduce the incidence of the CEs caused by the CBA in the patients with PAF compared to the interrupted DOACs, and (2) adverse bleeding events were not increased by uninterrupted dabigatran throughout the perioperative period of the CBA.

Dabigatran use for CA

There were two reasons why we chose dabigatran as an uninterrupted DOAC; first, the RE-CIRCUIT study showed the rate of major bleeding events, especially with pericardial bleeding and groin hematomas, was significantly lower in patients with uninterrupted dabigatran (150 mg twice daily) than in those with uninterrupted warfarin. The mechanism of that was considered to be stable anticoagulation due to the pharmacological effect of only direct thrombin inhibition without affecting the other coagulation factors such as warfarin. Second, dabigatran has a specific antidote called idarucizumab, which could have a rapid effect of neutralizing dabigatran [13]. However, there were no patients who had to be administered idarucizumab in the present study.

Even though the incidence of symptomatic CEs was comparable between Groups A and B, the total embolic event rate was significantly higher in Group A. Therefore, an uninterrupted dabigatran strategy during the perioperative period seemed to be superior to interrupted one in terms of preventing any thromboembolic events.

Mechanism of cerebral infarctions after the CBA

There is not so much evidence supporting the strategies to prevent thromboembolic complications in patients undergoing the CBA of PAF. Some reports have shown that the factors affecting the incidence of silent cerebral embolisms after CA, including RFCA and CBA, are the age, length of an AF history, ablation strategy, such as the type of ablation modality and substrate modification in addition to PVI, number of ECV attempts, and an average ACT of less than 300 s [5–8,14–17]. From these findings, several mechanisms of the CEs could be proposed. First, detachment of a preexisting left atrial thrombus could be provoked by catheter manipulation in the LA. Although all the patients had taken DOACs for a sufficient period of time prior to the CBA, a micro-thrombus could be overlooked by the transesophageal echocardiography (TEE). Second, fresh thrombus may be formed during ablation procedures even under appropriate anticoagulation. Ret et al., [18] reported that a thrombus was observed by intracardiac echocardiography in 10.3% of patients who underwent CA in the LA under an ACT that extended for over 250 s, and those thrombi were attached to the sheath or catheter. Third, an air bubble ingress from an unknown origin could also induce CEs. One patient in the present study had gaseous emboli presumably due to this mechanism.

In the present study, the type of AF, strategies of the PVI, age, catheter dwelling time in the LA, rate of optional ablation in the LA, and number ECV attempts were almost all comparable between **Groups A** and **B**. Moreover, the average ACTs were over 300 s in both Groups. Even in such a situation, uninterrupted dabigatran throughout the perioperative ablation procedure could significantly reduce the incidence of the CE events. Considering these findings, we may be able to speculate that fresh thrombus

Table 5
Incidence of adverse events in the study patients.

	Interrupted DOAC $n = 228$	Uninterrupted dabigatran $n = 105$	p
Cerebral embolisms (%)	68 (29)	14 (13)	<0.01
Symptomatic embolism (%)	1 (0.4)	1 (0.9)	0.53
Bleeding event (%)	16 (7)	5 (4)	0.62
Groin hematoma (%)	9 (3)	4 (3)	
Epicardial effusion (%)	6 (2)	1 (0.9)	
Hemorrhagic gastric ulcer (%)	1 (0.4)	0	

formation during the CBA procedure could provoke CEs, and uninterrupted dabigatran might exert significant inhibitory effects on such thrombus formation.

The prevention of cerebral embolisms due to the CBA

DOACs during the CA were conventionally discontinued concerning hemorrhagic events. However, the present study showed uninterrupted dabigatran did not significantly increase the adverse bleeding events compared to interrupted DOAC. Therefore, uninterrupted dabigatran could render the ablation procedure safer concomitant with a significant reduction of the incidence in the CEs than the interrupted one.

On the other hand, uninterrupted dabigatran could sufficiently prolong the ACT even with a smaller dose of heparin than interrupted dabigatran. In particular, the ACT measured immediately after the catheter insertion into the LA was significantly prolonged in the uninterrupted dabigatran patients. The stable maintenance of an extended ACT throughout the CBA procedure was thought to be one of the reasons for the significant reduction in the incidence of CEs. Of note, the ACT was also maintained over 300 s even in patients with interrupted DOAC, and the incidence of the CEs was significantly higher in this group than in those uninterrupted DOACs. Therefore, the cutoff value of the ACT in the interrupted DOAC patients might have to be longer for the sake of preventing embolic events.

Moreover, even with uninterrupted dabigatran, 13% of the patients had silent CEs. This might have been associated with an air bubble ingress presumably from a long guiding sheath due to negative pressure inside the sheath or an air bubble trapped in the folded CB. Tokuda et al., [19] reported the clinical usefulness of an extracorporeal balloon inflation in a heparinized saline water bath, which was related to a reduction in asymptomatic CEs. In the present study, we implemented those procedures such as a balloon massage and extracorporeal CB inflation in the heparinized saline bath to remove the air bubbles. These methods might not have been adequate to completely prevent air ingress, and further investigation is needed on how to minimize air embolisms.

Study limitations

The present study had several limitations. First, the study was a non-randomized single center study. Second, the different pharmacological effects among the DOACs might have had an influence on the results, and the timing of the discontinuation of the DOACs could not be integrated because of a different start time of the CA procedure. Third, the number of patients with adverse bleeding events was very small. The major reason was that in the patients with major bleeding events from the CA, such as a cardiac tamponade, AV-shunt, or pseudo-aneurysm in the groin, it was mostly difficult to perform MRI tests due to extensive nursing care or surgery and were excluded from this study. Therefore, it might not be possible to widely apply the results of this study to other patients due to the lack of including all study patients and might not be appropriate for addressing the safety issue by the results of the present study. However, the present study was able to investigate the safety of uninterrupted dabigatran in patients, excluding those with iatrogenic adverse events.

Conclusions

Uninterrupted dabigatran during the CBA of PAF could significantly reduce the risk of CEs compared to an interrupted DOAC. Both sufficiently extending and stabilizing the maintenance of the ACT by uninterrupted dabigatran throughout the CA procedure in the LA might have contributed to the present results.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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