Differences in activated clotting time among uninterrupted anticoagulants during the periprocedural period of atrial fibrillation ablation

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BACKGROUND Close monitoring of intraoperative activated clotting time (ACT) is crucial to prevent complications during the periprocedural period of atrial fibrillation (AF) ablation. However, little is known about the ACT in patients receiving new oral anticoagulant agents (NOACs).

OBJECTIVE The purpose of this study was to evaluate change in the ACT among anticoagulant agents used during the periprocedural period of AF ablation.

METHODS We examined 869 consecutive patients who underwent AF ablation between April 2012 and August 2014 and received NOACs (n = 499), including dabigatran, rivaroxaban, and apixaban, or warfarin (n = 370) for uninterrupted periprocedural anticoagulation. Changes in intraprocedural ACT were investigated among the anticoagulant agents. Furthermore, the incidence of periprocedural events was estimated.

RESULTS The average time in minutes required for achieving a target ACT > 300 seconds was significantly longer in the dabigatran group (DG) and apixaban group (AG) than in the warfarin group (WG) and rivaroxaban group (RG) (60 and 70 minutes vs 8 and 9 minutes, respectively; $P < .001$). In addition, the proportion of patients who achieved the target ACT after initial heparin bolus was significantly lower in the DG and AG than in the WG and RG (36% and 26% vs 84% and 78%, respectively; $P < .001$). Furthermore, the incidence of periprocedural complications was equivalent among the groups.

CONCLUSION The average time required to reach the target ACT was longer in the DG and AG than in the WG and RG.

KEYWORDS Activated clotting time; Atrial fibrillation; Catheter ablation; New oral anticoagulant

ABBREVIATIONS **ACT** = activated clotting time; **AT** = antithrombin; **INR** = international normalized ratio; **LA** = left atrium/left atrial; **PV** = pulmonary vein; **TIA** = transient ischemic attack

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Introduction

Catheter ablation (CA) is a useful treatment as rhythm control therapy in patients with atrial fibrillation (AF). AF ablation is now performed worldwide in several institutions.[1] Recently, new oral anticoagulant agents (NOACs) such as dabigatran, rivaroxaban, and apixaban have been used during the periprocedural period of AF ablation with the enhancement of use for nonvalvular AF through each phase 3 trial.[2–4] In addition, meta-analyses have reported the feasibility and safety of dabigatran and rivaroxaban for the periprocedural period compared with warfarin.[5–7] Meanwhile, the prevention of thromboembolic events during the periprocedural period of AF ablation is extremely crucial. Uninterrupted use of warfarin has been recommended to minimize complications.[8] However, there is still controversy regarding the most suitable method between interrupted and uninterrupted NOAC strategies during AF ablation.

Monitoring of intraoperative activated clotting time (ACT) during CA of AF is also essential for lowering the incidence of periprocedural complications. Gaita et al[9] showed that a low ACT (<250 seconds) was an independent predictor of periprocedural thromboembolic events. Moreover, some studies have demonstrated that the ACT and the response to unfractionated heparin in patients receiving warfarin were different from those in patients receiving dabigatran.[10,11] Understanding these results is important for making decisions regarding heparin requirements, including the first bolus dose, to reach the target ACT early.

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We examined the change in the intraoperative ACT value in response to heparin among patients using anticoagulant agents such as warfarin, dabigatran, rivaroxaban, or apixaban. Subsequently, we estimated the differences in the incidence of periprocedural complications among these anticoagulant agents.

Methods

Study population

We retrospectively recruited consecutive 869 patients who received warfarin, dabigatran, rivaroxaban, or apixaban and underwent radiofrequency CA for AF at the Nagoya University Hospital in Japan between April 2012 and August 2014. This study was approved by our Institutional Committee on Human Research. In addition, all patients provided written informed consent for study participation. Exclusion criteria were as follows: creatinine clearance <30 mL/min, left ventricular ejection fraction $\leq 40\%$, and left atrial (LA) size >55 mm. The choice of anticoagulant agents depended on the clinician's preference. The warfarin dose was adjusted to maintain a target international normalized ratio (INR) of 1.6–2.6 for older patients (≥ 70 years) and 2.0–3.0 for younger patients (<70 years).[12] The dabigatran dose was determined according to patients' renal function or age. A low dose of dabigatran (110 mg twice daily) was administered to patients who had the following conditions: moderate renal dysfunction (creatinine clearance 30–50 mL/min), advanced age (≥ 70 years), a history of upper gastrointestinal ulcer, or coadministration of glycoprotein inhibitors (amiodarone or verapamil). A low dose of rivaroxaban (10 mg once daily) was administered to patients with mild renal dysfunction (creatinine clearance 30–50 mL/min). Meanwhile, the apixaban dose was determined according to age, body weight, or renal function. A low apixaban dose (2.5 mg twice daily) was administered to patients with any 2 of the following characteristics: advanced age (≥ 80 years), renal dysfunction (serum creatinine concentration ≥ 1.5 mg/dL), and lower body weight (≥ 60 kg). Dabigatran and apixaban were given twice daily, at 7 AM and 7 PM, whereas rivaroxaban was administered once daily at 7 AM. All NOACs were started at least 4 weeks before the ablation procedure and were used without interruption during the periprocedural period. On the procedural day, patients in the dabigatran groups (DG) and apixaban group (AG) received morning and evening doses as usual, whereas only a morning dose was given in the rivaroxaban group (RG). After discharge from the hospital, the patients were followed up at an outpatient clinic for at least 3 months.

Radiofrequency CA procedure

Blood samples were obtained from each patient approximately 3 hours after the patient received the anticoagulant drug in the morning, given that the peak plasma concentration of NOACs was reached on the procedural day. The morning and evening sessions were begun at 9 AM and 1 to 3 PM, respectively. Transthoracic and transesophageal echocardiography were performed in all patients to confirm the absence of atrial thrombus and to evaluate cardiac function, such as left ventricular end-diastolic diameter, LA diameter, and left ventricular ejection fraction, just before the CA procedure. Vascular access was achieved through the right femoral vein, right femoral artery, and left subclavian vein. Subsequently, two 8F sheaths, one 8.5F steerable sheath, and one 6F sheath were inserted into the right femoral vein, with one 8F sheath in the left subclavian vein and one 4F sheath in the right femoral artery for coronary angiography and blood pressure measurement. Intravenous heparin was administered at a bolus dose of 80–100 U/kg immediately after the insertion of all sheaths. ACT was monitored every 30 minutes after the heparin bolus administration, and additional heparin was administered to maintain an ACT of 300 to 350 seconds by bolus injection. The additional dose of heparin was determined as 3000, 2000, or 1000 U for ACTs of <260, 260–279, or 280–299 seconds, respectively. After a transseptal puncture was performed under intracardiac echocardiography, 3 sheaths were placed in the LA. A circular mapping catheter (Lasso, Biosense Webster Inc, Diamond Bar, California) was placed in the ostium of each pulmonary vein (PV) to record electrical activity, and pulmonary venography was performed for each PV. Encircling PV isolation was performed with a 3.5-mm-tip open-irrigated ablation catheter (Biosense Webster Inc) under the CARTO3 mapping system (Biosense Webster Inc) using the double-Lasso technique.[13] The radiofrequency energy output was titrated to 25–35 W at a flow rate of 17–30 mL/min, with a maximum temperature of 42°C. After successful isolation of all the PVs, isoproterenol (5–20 μg/min) was administered, and burst atrial pacing was performed to confirm that neither AF nor another atrial arrhythmia was induced. If AF was induced and sustained, additional procedures, including ablation targeting of the complex fractionated atrial electrograms, linear ablation of the LA, and isolation of the superior vena cava, were performed.[14–16] If AF continued despite all of the above-mentioned procedures, internal cardioversion was performed. Cavotricuspid isthmus ablation was performed as required.[17] Immediately after completion of CA procedure, protamine (30–40 mg) was administered to reverse the effect of heparin, followed by removal of all sheaths from the patient.

Postprocedural management and follow-up

Puncture site hematomas, gastrointestinal bleeding, vascular injuries, and pericardial effusion with or without tamponade were considered as bleeding complications. Any bleeding that required blood transfusion, surgical intervention, and pericardial effusion with drainage were classified as major bleeding complications. Small groin or subclavian hematoma and pericardial effusion that did not require any intervention were classified as minor bleeding. Symptomatic ischemic strokes and transient ischemic attacks (TIAs) were classified as thromboembolic complications after intracranial

Table 1 Patient characteristics

	WG (n = 370)	DG (n = 239)	RG (n = 102)	AG (n = 158)	*P* value
Age (y)	61 ± 11	59 ± 12	61 ± 9	61 ± 13	.30
Sex (female)	96 (26)	45 (21)	32 (31)	49 (31)	.15
Body weight (kg)	65 ± 13	68 ± 13	63 ± 12	64 ± 13	.10
Body mass index (kg/m^2)	24 ± 3	24 ± 3	24 ± 3	24 ± 4	.43
Nonparoxysmal AF	100 (27)	69 (29)	21 (21)	35 (22)	.40
Coronary artery disease	19 (5)	14 (6)	6 (6)	8 (5)	.97
Hypertension	133 (36)	86 (36)	36 (44)	44 (28)	.19
Diabetes mellitus	44 (12)	22 (9)	9 (9)	21 (13)	.49
History of heart failure	41 (11)	17 (7)	10 (10)	19 (12)	.41
Prior stroke/TIA	19 (5)	10 (4)	6 (6)	9 (6)	.69
$CHADS_2$ score	0.8 ± 1.0	0.8 ± 0.9	0.8 ± 0.8	0.8 ± 1.0	.50
0	194 (52)	122 (51)	46 (45)	84 (53)	.71
1	117 (31)	74 (31)	32 (31)	46 (29)	.49
≥2	59 (16)	43 (18)	24 (24)	28 (18)	.58
CHA_2DS_2-VASc score	1.5 ± 1.5	1.4 ± 1.4	1.8 ± 1.5	1.5 ± 1.6	.16
HAS-BLED score	0.9 ± 0.9	0.8 ± 0.9	1.1 ± 1.0	0.9 ± 1.0	.21
LA size (mm)	40 ± 7	39 ± 7	39 ± 7	37 ± 6	.19
LVEF (%)	61 ± 9	63 ± 7	62 ± 10	61 ± 9	.47
LAA velocity (cm/s)	65 ± 25	68 ± 23	67 ± 23	66 ± 24	.91
BNP (pg/mL)	44 (22, 85)	32 (16, 73)	41 (20, 83)	32 (16, 73)	.21
Creatinine clearance (mL/min)	89 ± 34	93 ± 26	88 ± 26	93 ± 31	.15
PT (s)	22 ± 5	16 ± 3	20 ± 5	16 ± 4	<.001
aPTT (s)	44 ± 9	54 ± 15	44 ± 7	40 ± 5	<.001
D-dimer (μg/mL)	0.7 ± 0.8	0.7 ± 0.2	0.7 ± 0.4	0.7 ± 0.6	.20
Medication					
Antiplatelet drugs	26 (7)	22 (9)	7 (7)	16 (10)	.76
PPI/H_2RA	93 (25)	67 (28)	22 (22)	30 (19)	.39
NSAID	4 (1)	3 (1)	1 (1)	0 (0)	.70
AAD	107 (29)	53 (22)	27 (26)	36 (23)	.45
Procedural values					
Procedure time (min)	142 ± 52	145 ± 50	133 ± 59	135 ± 48	.34
Morning session	174 (47)	98 (46)	48 (47)	79 (50)	.87
Cardioversion	107 (29)	76 (32)	22 (22)	52 (33)	.22
Additional procedure	122 (33)	93 (39)	35 (34)	58 (37)	.45
Total delivered energy (kJ)	60 ± 36	63 ± 32	69 ± 25	63 ± 28	.22

Values are mean ± SD, n (%), or median (range).

AAD = antiarrhythmic drug; AF = atrial fibrillation; AG = apixaban group; aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; DG = dabigatran group; H_2RA = histamine H_2-receptor antagonist; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PT = prothrombin time; RG = rivaroxaban group; TIA = transient ischemic attack; WG = warfarin group.

hemorrhage was ruled out by computed tomography. Patients who developed complications received prompt and appropriate intervention. Periprocedural complications were defined as adverse events that occurred within 30 days before or after the ablation procedure.

Statistical analysis

All continuous variables were expressed as mean ± SD or as median and interquartile ranges. All categorical variables were reported as number (percentage) of patients. Unpaired Student *t* test, Mann-Whitney *U* test, 1-way analysis of variance, or Kruskal-Wallis test were used to compare continuous variables when appropriate, and categorical variables were compared with a χ^2 or Fisher exact test. $P < .05$ was considered statistically significant. All results were analyzed with SPSS version 18.0 (SPSS Inc, Chicago, Illinois).

Results

Patient characteristics and procedural values

A total of 869 patients underwent LA CA; 499 patients were assigned to the NOACs group and 370 to the warfarin group (WG). Baseline characteristics are summarized in Table 1. Overall, no significant difference was observed in any of the characteristics among the groups. In the WG, there were 166 patients with preoperative INR of 1.6–1.9 (45%), 148 with INR of 2.0–2.5 (40%), and 56 with INR of 2.6–3.0 (15%). In the WG, the highest proportion of patients had a preoperative INR <2.0 (45%).

ACT values and heparin requirements in each anticoagulant group

The changes in mean ACT values were relatively similar between the morning and afternoon/evening sessions in each group, as shown in Figure 1. The proportion of patients reaching target ACT after an initial heparin bolus was

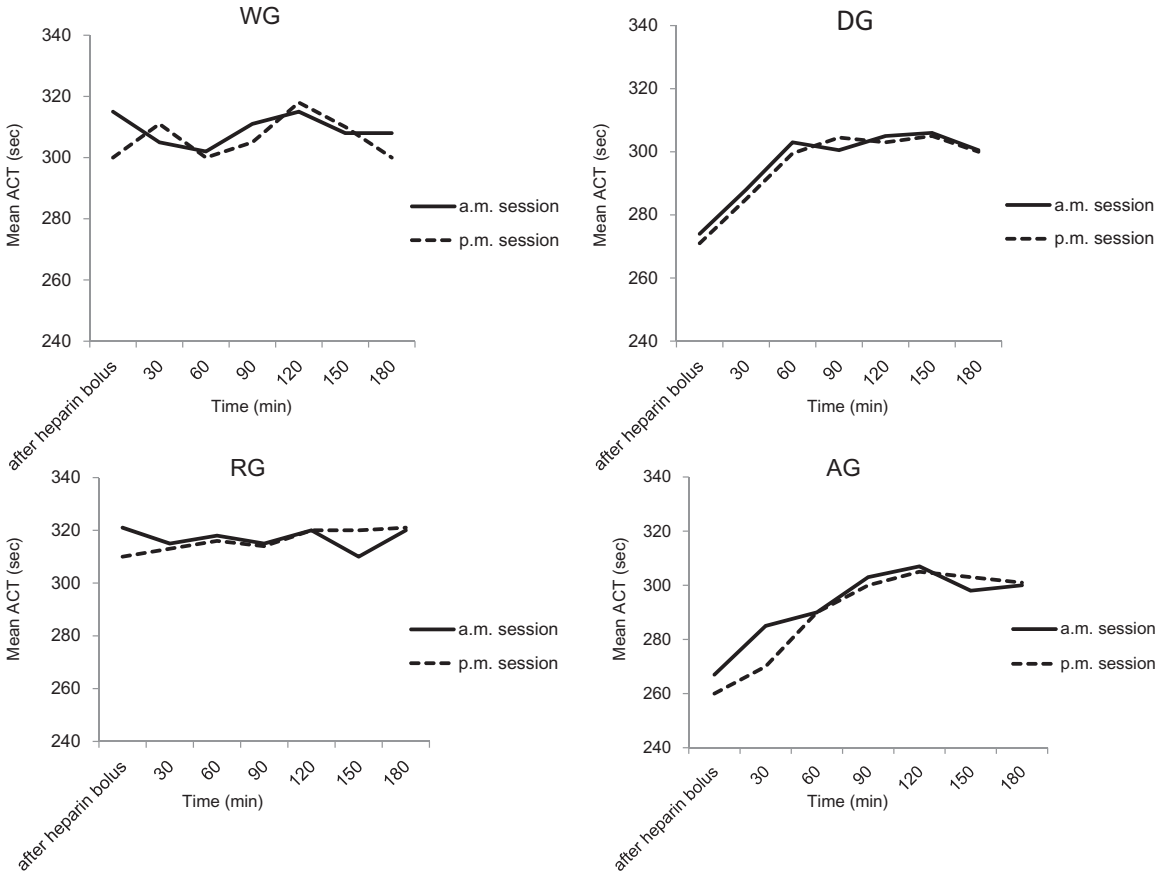

Figure 1 Changes in mean activated clotting time (ACT) in each anticoagulant group. AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; WG = warfarin group.

significantly lower in the DG and AG than in the WG and RG (36% and 26% vs 84% and 78%, respectively; $P < .001$) (Figure 2). In addition, the time required to achieve target ACT (>300 seconds) was significantly longer in the DG and AG than in the WG and RG, as shown in Figure 3 (60 and 70 minutes vs 8 and 9 minutes; $P < .001$). The unfractionated heparin requirement for the procedure was higher in the AG than in the WG, DG, and RG (71 ± 28 U/kg/h vs 51 ± 21, 59 ± 20, and 57 ± 15 U/kg/h, respectively; $P < .001$), whereas it was equivalent between the morning and afternoon sessions in each anticoagulant group (Figure 4) (Table 2). With regard to the aforementioned results, there was no difference between morning and afternoon sessions in each group (Figures 1, 2, and 3).

Complications

Details of complications experienced during the periprocedural period are shown in Table 3. In a comparison of all groups, no differences were observed in bleeding and/or thromboembolic complications. In addition, there were no differences in the events that occurred in each anticoagulant

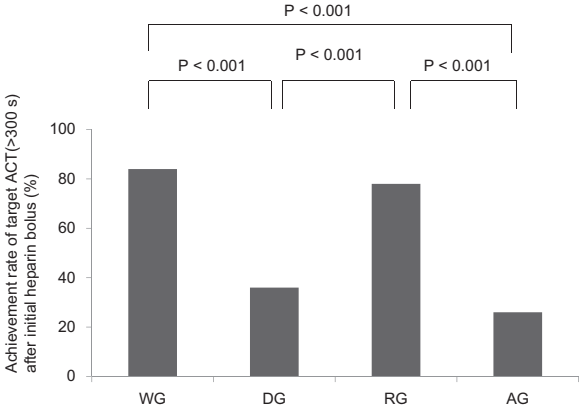

Figure 2 Comparison of proportion of achievement rate of target activated clotting time (ACT) > 300 seconds after initial heparin bolus among anticoagulant groups. AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; WG = warfarin group.

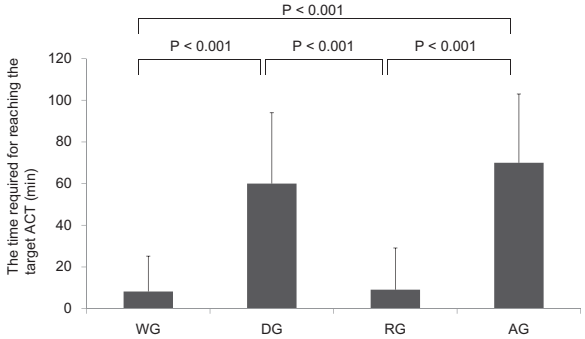

Figure 3 Comparison of time required to reach target activated clotting time (ACT) >300 seconds. AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; WG = warfarin group.

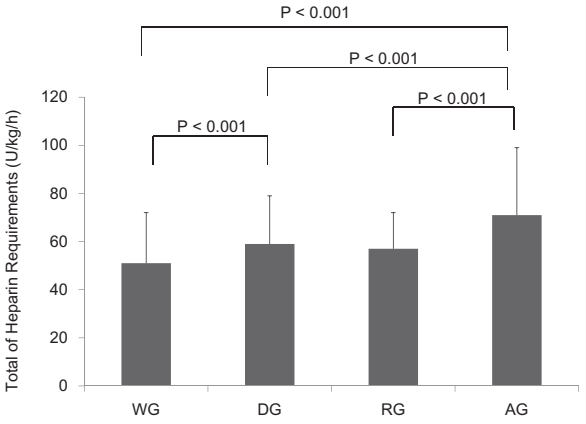

Figure 4 Comparison of requirements for unfractionated heparin (UFH) among anticoagulant groups. Error bars indicate mean and standard deviations. AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; WG = warfarin group.

Table 2 Requirements for UFH in each session

	Morning session	Afternoon session	*P* value
WG	51 ± 22	52 ± 21	.91
DG	58 ± 16	61 ± 25	.35
RG	56 ± 15	58 ± 15	.83
AG	70 ± 20	72 ± 37	.80

Values are mean ± SD (U/kg/h).

AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; UFH = unfractionated heparin; WG = warfarin group.

group between morning and afternoon sessions (Figure 5). Pericardial effusion with tamponade occurred in 4 of 370 patients in the WG (1%), 2 of 239 patients in the DG (1%), and 1 of 158 patients in the AG (0.6%). All patients with pericardial tamponade required pericardiocentesis after protamine was used to reverse the anticoagulant effect, which was performed successfully, and hemodynamic function was restored in all patients without the use of blood products. NOACs were discontinued for only 2 days in the aforementioned patients. In the WG, 3 of 4 patients with cardiac tamponade received prothrombin complex concentrate as blood products after the administration of vitamin K. Warfarin was interrupted for only 4 days in the

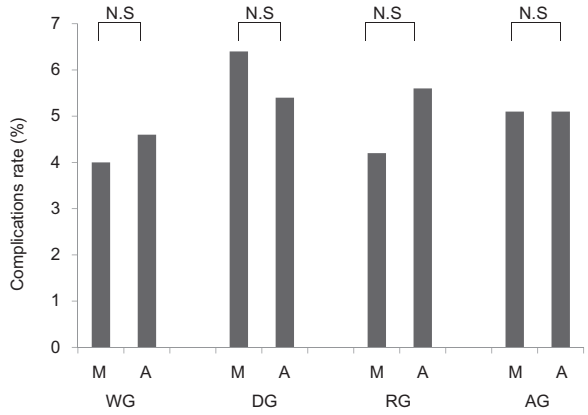

Figure 5 Comparison of incidence of complications between morning (M) and afternoon (A) sessions in each anticoagulant group. AG = apixaban group; DG = dabigatran group; RG = rivaroxaban group; WG = warfarin group.

aforementioned 4 patients. Furthermore, lower gastrointestinal bleeding (1%) occurred in 2 patients with apixaban, which was diagnosed as angiodysplasia in the ascending colon by colonoscopy. This patient required a blood transfusion for recovery, with interruption of apixaban for 10 days. One patient experienced vascular complications that required surgical intervention (0.4%). Ligature of the right femoral branch vein at the puncture site was applied by surgeons after AF ablation. This patient did not require any blood products during the periprocedural period and no interruption of dabigatran. No symptomatic thromboembolic events occurred in the NOACs group, and 1 patient in the WG experienced a TIA on the procedural day.

Discussion

Main findings

The present observational study demonstrated a variety of ACT values and responses to heparin among different groups of uninterrupted anticoagulant agents used during the periprocedural period of AF ablation. The rate of patients reaching the target ACT after an initial heparin dose was low in the DG and AG. Furthermore, the average time required to reach the target ACT was significantly longer than that in the WG and RG regardless of session starting time. The

Table 3 Complications

	WG (n = 370)	DG (n = 239)	RG (n = 102)	AG (n = 158)	*P* value
Death	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Total bleeding complications	15(4)	14 (6)	5 (5)	8 (6)	.78
Major bleeding complications	4 (1)	3 (1)	0 (0)	2 (1)	.71
Cardiac tamponade	4 (1)	2 (1)	0 (0)	1 (0.6)	.81
Vascular complication	0 (0)	1 (0.4)	0 (0)	0 (0)	.48
Gastrointestinal hemorrhage	0 (0)	0 (0)	0 (0)	1 (1)	.12
Minor bleeding complications	11 (3)	11 (5)	5 (5)	6 (4)	.80
Hematomas of puncture site	7 (2)	10 (4)	5 (5)	6 (4)	.40
Pericardial effusion without tamponade	4 (1)	1 (0.4)	0 (0)	0 (0)	.44
Thromboembolic complications					
Symptomatic ischemic stroke or TIA	1 (0.3)	0 (0)	0 (0)	0 (0)	.75
Total complications	16 (4)	14 (6)	5 (5)	8 (6)	.89

Values are n (%).

AG = apixaban group; DG = dabigatran group; N/A = not available; RG = rivaroxaban group; TIA = transient ischemic attack; WG = warfarin group.

incidence of complications was equivalent among the anticoagulant agents.

Differences in intraprocedural ACT values among anticoagulant agents

Recent studies have shown that patients with interrupted dabigatran use throughout a CA procedure require a higher dose of heparin and more time to reach the target ACT than those with uninterrupted warfarin.[10,11] In the present study, it was more difficult to achieve the target ACT in the DG and AG than in the WG and RG, which might be explained by the differences in preoperative activated partial thromboplastin time (aPTT) in each anticoagulant group. ACT is considered to evaluate the function of the entire intrinsic pathway of the coagulation cascade, which is currently estimated by aPTT. Preoperative aPTT was similar between the WG and RG, which might have led to similar changes in ACT after administration of heparin (Table 1) (Figures 1, 2, and 3). However, the proportion who reached target ACT after a heparin bolus was lower in the DG than in the RG or WG despite the higher aPTT in the DG than in any other group (Table 1) (Figure 2). Patients receiving dabigatran are reported to exhibit poorer response to heparin than those receiving warfarin, because continuous administration of dabigatran causes downregulation of antithrombin, to which heparin is bound.[11] In addition, dabigatran would compete by binding to thrombin when heparin/antithrombin complex binds to thrombin.[11] Therefore, the poor responsiveness to heparin in the DG might be explained by the above-mentioned speculation by Konduru et al,[11] regardless of high aPTT levels before the procedure. Meanwhile, the prolonged low ACT in the AG might have arisen from a low preoperative aPTT value and the interaction between heparin and apixaban, as with dabigatran. However, further detailed investigation is needed to clarify these mechanisms.

Investigation of the incidence of periprocedural complications according to session start time

NOACs have the unique properties of a rapid onset and short half-lives compared with warfarin. These characteristics cause a diurnal variation of drug concentration. This fact seems more remarkable in rivaroxaban administered once daily than in dabigatran or apixaban administered twice daily. Therefore, an evaluation of the difference in the incidence of complications in consideration of the session start time is crucial, especially in patients receiving uninterrupted NOACs during the CA procedure. However, the current study demonstrated that no differences in hemorrhagic or thromboembolic events were observed between the morning and afternoon sessions in each group.

Uninterrupted periprocedural anticoagulant therapy

A continuous warfarin strategy has been considered superior to an interrupted warfarin strategy that includes bridging low-molecular-weight heparin for the periprocedural thromboembolic events of AF ablation.[8,18–20] Meanwhile, use of NOACs during CA has been reported to be feasible and safe compared with warfarin by several published studies, including meta-analyses.[6,7,21] However, most of these studies describe the interrupted therapy of NOACs. Thus, data on uninterrupted NOAC therapy to date are still inadequate for application of this strategy to actual clinical practice, although the RE-CIRCUIT trial (Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy) of uninterrupted dabigatran therapy and the VENTURE-AF trial for uninterrupted rivaroxaban therapy are ongoing.[22,23] In the present study, the findings that no patients experienced symptomatic thromboembolic events and that there was a low rate of bleeding complications in the NOAC groups, whereas 1 patient in the WG developed TIA, might mean that continuous optimal anticoagulation condition during the periprocedural period of AF ablation was maintained by the uninterrupted strategy. Moreover, this strategy of NOAC use might contribute to the decrease in the incidence of silent ischemic stroke detected only by postoperative magnetic resonance imaging.[9]

Study limitations

First, this is a single-center, nonrandomized observational study. Second, patients at a high risk for thromboembolic and bleeding events were not evaluated sufficiently, because only patients with a low $CHADS_2$ score, CHA_2DS_2-VASc score, and HAS-BLED score were analyzed in this study. Third, investigation of silent ischemic stroke detected by magnetic resonance imaging might lead to the detection of differences in the incidence of thromboembolic complications among anticoagulant agents. Furthermore, these results are data for Japanese patients only; therefore, their application to worldwide populations must be careful given the differences in physique, the target INR range, and dose setting of NOACs compared with European and American patients. A prospective, randomized multicenter study that compares NOACs and warfarin in worldwide populations and includes the determination of the occurrence of asymptomatic ischemic stroke is required.

Conclusions

We demonstrated that the rate of patients reaching the target ACT after an initial heparin injection was significantly lower in the DG and AG than in the WG and RG regardless of the session start time. Furthermore, the average time required to reach the target ACT was significantly longer in the DG and AG than in the WG and RG.

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CLINICAL PERSPECTIVES

New oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban, have been used during the periprocedural period of atrial fibrillation (AF) ablation with the enhancement of use for nonvalvular AF; however, there is still controversy regarding the most suitable method between interrupted and uninterrupted NOACs. Meanwhile, close monitoring of intraoperative activated clotting time (ACT) is crucial to prevent complications during the periprocedural period. At present, some reports have demonstrated differences in the change in ACT between NOACs and warfarin. However, there are few data about ACTs in patients receiving uninterrupted NOACs during the procedure. In the present study, the time required to reach the target ACT was significantly longer in the dabigatran group and apixaban group than in the warfarin group and rivaroxaban group regardless of the session start time. Moreover, the incidence of bleeding or thromboembolic complications was equivalent among the anticoagulant groups. These findings would be useful for patients with uninterrupted NOAC use during the periprocedural period of AF ablation.