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ORIGINAL ARTICLE

A novel protocol for initial heparin administration during catheter ablation for atrial fibrillation in patients taking direct oral anticoagulants

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Abstract
Thromboembolism and bleeding complications remain a major limitation of the catheter ablation (CA) for atrial fibrillation (AF). This study aimed to evaluate the association between achieving target activated clotting time (ACT) and clinical factors, and to develop an appropriate protocol for early achievement of target ACT in patients with direct oral anticoagulants (DOACs). At the initiation cohort, 190 patients (127 males, age 68 ± 9) taking DOACs who underwent CA for AF were studied. All patients underwent transthoracic echocardiography/transesophageal echocardiography/blood sampling before the CA. The ACTs were measured before heparin administration (pre-ACT) and in 30 min (30-min ACT) after initial heparin administration (100 U/kg +3000 U). At the validation cohort, the indicator obtained from the first study was reassessed in the subsequent 138 patients (94 males, age 68 ± 10). At the initiation cohort, 30-min ACT reached the target ACT in 79/190 patients (42%). Univariate analysis showed that longer pre-ACT, elevated aPTT, higher PT-INR, antiplatelet medication, and dabigatran were associated with achieving the target 30-min ACT. On multivariate analysis, only longer pre-ACT was independently associated with achieving the target 30-min ACT ($P = 0.0396$, the optimal cutoff value; 130 s). As a novel protocol, we added 2000 U of initial heparin dose (total 100 U/kg +5000 U) in patients with low pre-ACT (< 130); then, the achievement rate to target 30-min ACT improved from 41.6 to 80.5% without increasing bleeding complications. Our novel protocol of initial heparin administration based on pre-ACT is useful for an appropriate systemic anticoagulation in patients taking DOACs during the CA for AF.

Keywords Direct oral anticoagulants · Heparin · Atrial fibrillation · Catheter ablation

Introduction

Catheter ablation (CA) is useful as a rhythm control therapy in patients with atrial fibrillation (AF), and has been widely performed. The periprocedural thromboembolism (TE) is a rare, but often devastating complication. The risk of periprocedural TE remains significant, reaching 0.25–3% in previous studies [1, 2]. Periprocedural management of anticoagulation in patients undergoing CA is important to prevent complications and the use of systemic anticoagulation with heparin has become widely recognized.

The current guidelines recommend performing CA for AF with uninterrupted oral anticoagulant and maintaining the target activated clotting time (ACT ≥ 300 s) for preventing periprocedural thromboembolism/bleeding complications [3]. These guidelines are based on the previous studies including warfarin-treated patients. Recently, direct oral anticoagulant (DOAC) such as dabigatran, rivaroxaban, apixaban, and edoxaban have been approved for long-term anticoagulation [4]. Their safety and efficacy of anticoagulation in patients with non-valvular AF have been demonstrated. Previous studies have reported that DOAC-treated patients required a higher heparin dose and a longer time to reach the target ACT than those in warfarin-treated patients [5, 6]. However, there are few data about DOAC-treated patients. In other words, the target ACT is evidence based for warfarin-treated patients. Therefore, specific data on DOAC in the setting of CA for AF might be needed. This study aimed to evaluate the association between achieving

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target ACT within 30 min and clinical/biological factors, and to develop an appropriate protocol for early achievement of target ACT in patients with DOAC.

Methods

Intravenous heparin was administered at an initial bolus dose of 100 U/kg in patients taking warfarin. Based on our experience, this initial bolus dose of 100 U/kg was insufficient to achieve target ACT in patients taking DOACs. Approximately, 70% of patients taking DOACs did not reach target ACT measured 30 min after an initial bolus dose of 100 U/kg. Therefore, heparin was administered at 100 U/kg + 3000 U in patients taking DOACs in our center.

Patient population

This retrospective study included 246 consecutive patients with non-valvular AF who underwent CA at the Hyogo College of Medicine between September 2015 and February 2017. From this initial population, patients taking warfarin ($n = 48$), patients not taking anticoagulant ($n = 3$), or patients with renal deficiency (creatinine clearance < 30 mL/min, $n = 15$) were excluded. The remaining 190 patients taking DOACs (22 dabigatran, 103 rivaroxaban, 48 apixaban, 17 edoxaban, 127 males, 68 ± 9 years, 95 non-paroxysmal AF) were included in retrospective study analyzes (the initiation cohort). The choice of anticoagulants agents depended on the clinician's preference. The dose of DOACs was adjusted according to patient characteristics (renal function, age, weight, or past history). Blood samples were obtained in the morning before CA, and all patients underwent transthoracic echocardiography within 48-h before the CA procedure using a Prosound F75 (Hitachi Aloka Medical, Tokyo, Japan) with a 3.88-MHz transducer probe. The clinical/biological variables, and echocardiographic findings (left atrial diameter, left ventricular dimension during end diastole, left ventricular ejection fraction, *E* wave, *E*/*e'* ratio, and deceleration time) were retrospectively assessed. All patients underwent TEE within 48 h of the CA procedure using an iE33 (Philips Medical System, Andover, MA, USA) with a 4-MHz Omniplane probe to exclude patients with left atrial thrombus from our study. No complications from any of the echocardiographic procedures were reported. All patients were above 18 years and provided written informed consent to the procedures. The research protocol was approved by the appointed local ethics committee.

Anticoagulant regimen during periprocedural period

The anticoagulant regimen during periprocedural period is shown in Fig. 1. On the procedure day, DOACs were not administered before the procedure. All DOACs were started at least four weeks before the CA. On the procedure day, patients taking dabigatran or apixaban received only the evening dose, whereas patients taking rivaroxaban or edoxaban received a single dose in the evening. The right femoral vein was used for catheter insertion. In the absence of a patent foramen oval, atransseptalpuncture was performed using the Brockenbrough technique. After two transseptal punctures, three long sheaths (SL0, St. Jude Medical, St. Paul, MN, USA) were introduced into both superior PVs. Two 20-polar circumferential catheters (Lasso, Biosense Webster, Diamond Bar, CA, USA) were placed transseptally at the antrum of the target PVs. CA for AF was performed as described previously [7].

The anticoagulant regimen during the procedure is shown in Fig. 2. Unfractionated heparin (initial heparin administration: 100 U/kg + 3000 U) was administered immediately after a transseptal puncture during procedures. A continuous heparinized saline infusion was not administered. ACT (Hemochron Response Whole Blood Coagulation System, ITC, Edison, NJ, USA) was measured before heparin administration (pre-ACT), 30 min (30-min ACT) after initial

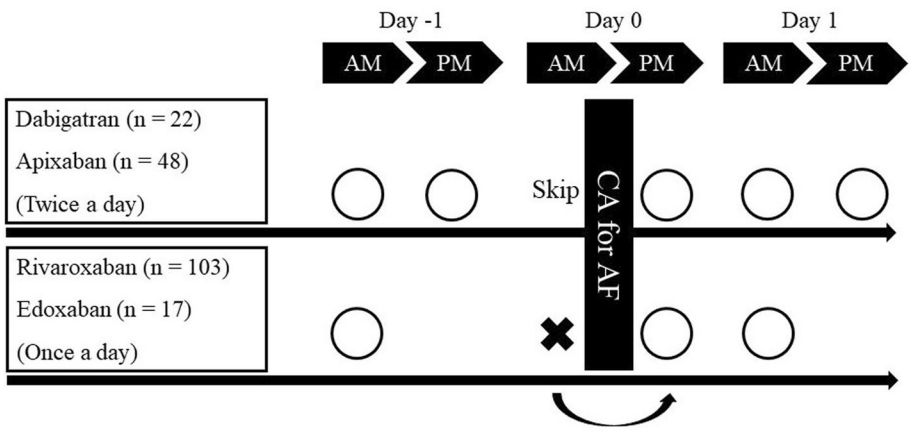


Fig. 1 The anticoagulation regimens during periprocedural period in the four DOACs groups. *AF* atrial fibrillation, *CA* catheter ablation, *DOACs* direct oral anticoagulants

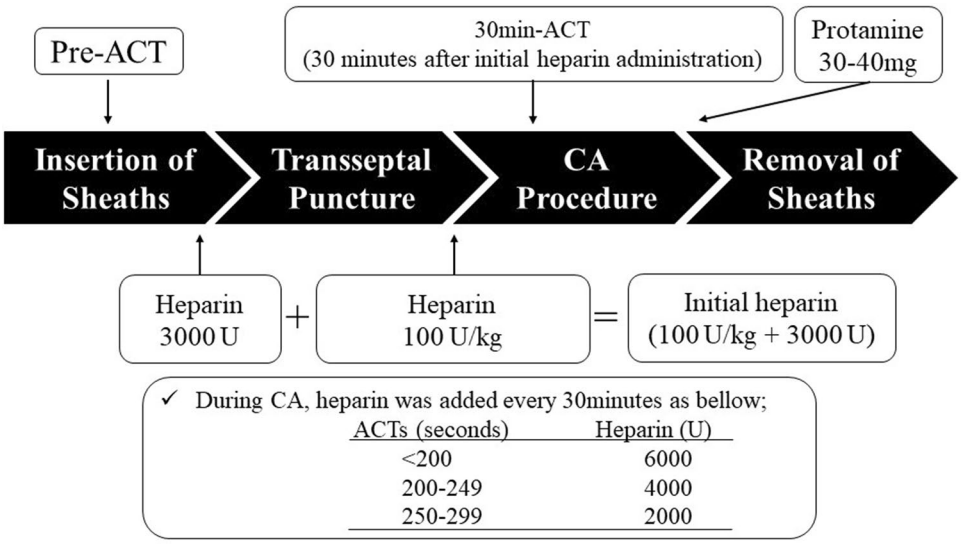


Fig. 2 The anticoagulation regimens and measurement of ACT during procedure period. *ACT* activated clotting time, *CA* catheter ablation

heparin administration, and every 30 min subsequently. The additional heparin was administered at 6000, 4000, or 2000 U for ACTs of < 200, 200–249, or 250–299 s, respectively. The Homochron Response clot detection module contains 2 test wells into which disposable unitized coagulation test tubes can be inserted. It uses disposable flip-top non-evacuated glass test tubes containing a precision magnet for clot detection and Celite-based reagents, which activate the coagulation process. Immediately after completion of the CA procedure, protamine (30–40 mg) was administered intravenously just before removal of all sheaths (Fig. 2). We assessed the following factors; (1) initial heparin dose (2) total heparin dose (3) pre-ACT (before insertion of sheath) (4) 30-min ACT (30 min after initial heparin administration) (5) final ACT (before removal of sheath) (6) time to reach target ACT (> 300 s), and (7) time in target range.

Complications

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 were classified as thromboembolic complications after intracranial 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 after the ablation procedure.

Statistical analysis

Continuous variables (e.g., age) are presented as mean value ± standard deviation and were compared using one-way analysis of variance (ANOVA). Categorical variables (e.g., gender) were compared using the chi-square test or Fisher's exact test. A P value < 0.05 was considered statistically significant. The variables that were found to be significant in univariate analysis were entered into a multivariate analysis.

Analysis of the area under the receiver-operating characteristic (ROC) curve was performed. An optimal cut-off value was determined by considering values that yielded the greatest sensitivity and specificity by calculating the Youden index [8]. All analyzes were performed with the statistical software JMP pro version 10 software (SAS, Cary, NC, USA) and Microsoft Excel.

Results

Patient population

Among 246 patients screened, 190 patients were enrolled in the initiation cohort based on the inclusion and exclusion criteria. Of the 190 patients, 79 patients (42%) achieved a target 30-min ACT (30-min ACT ≥ 300 s). The patients were divided into two groups based on 30-min ACT (Fig. 3, 30-min ACT < 300 group, $n = 111$, and 30-min ACT ≥ 300 group, $n = 79$).

Baseline characteristics of the patients are listed in Table 1. Patients in the 30-min ACT ≥ 300 group had significantly higher PT-INR and elevated aPTT than patients in the 30-min ACT < 300 group. Baseline medication therapy is listed in Table 1. Patients in the 30-min ACT ≥ 300 group

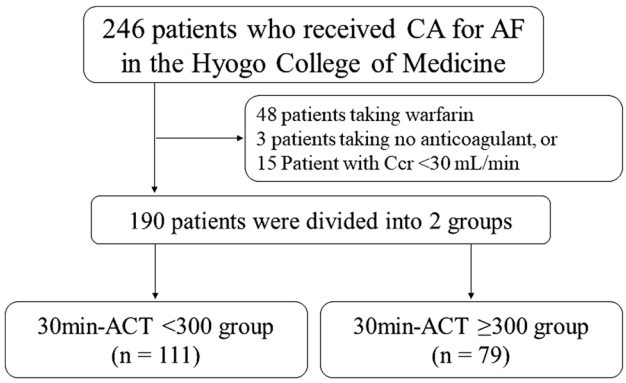


Fig. 3 Flow chart of the initial cohort patients. *ACT* activated clotting time, *AF* atrial fibrillation, *CA* catheter ablation, *Ccr* creatinine clearance

had a significantly higher proportion of antiplatelet and larger dose of dabigatran than patients in the 30-min ACT < 300 group. Table 2 lists the echocardiographic findings of the study groups. The parameters, including left atrial diameter, left ventricular dimension during end diastole, left ventricular ejection fraction, *E* wave, *E*/*e'* ratio, and deceleration time, did not differ between the two groups.

Procedural and ACT findings

Procedural findings are listed in Table 2. Of the 190 patients included in the initiation cohort, 160 patients (84%) underwent their first CA for AF. All patients had successful pulmonary vein isolation. Procedural time and other procedural characteristics, including cavotricuspid isthmus ablation, superior vena cava isolation, box isolation, and CA for atrial tachycardia, did not differ between the two groups. ACT findings are listed in Table 2. Patients in the 30-min ACT ≥ 300 group had a significantly smaller total heparin dose, longer pre-ACT, elevated 30-min ACT, higher final ACT, shorter time to achieve target ACT, and a larger time in target range than patients in the 30-min ACT < 300 group.

On multivariate analysis, only longer pre-ACT ($P = 0.0009$, odds ratio 1.014 for each 1 s increase in pre-ACT, 95% confidence interval 1.001–1.020) was independently associated with achieving the target 30-min ACT ≥ 300 (Table 3).

Moreover, we investigated pre-ACT, achievement rate to the target 30-min ACT, and total amount of heparin by DOAC (direct thrombin inhibitor/BID: dabigatran, Xa-inhibitor/QD: rivaroxaban or edoxaban, Xa-inhibitor: apixaban). Patients who took direct thrombin inhibitor presented prolonged pre-ACT (151 ± 24 s vs. 122 ± 20 s, 130 ± 29 s), higher achievement rate to the target 30-min ACT (64% vs. 33%, 50%), fewer total amount of heparin (170 ± 28 unit/kg vs. 206 ± 43 unit/kg, 198 ± 37 unit/kg) than Xa-inhibitor/QD and Xa-inhibitor/BID.

Major bleeding complications occurred in 3/190 patients (1.6%) in the initiation cohort. Pericardial effusion occurred in two patients (one patient taking rivaroxaban 10 mg/day, pre-ACT 322s, one patient taking apixaban 10 mg/day, pre-ACT 256s). These patients with pericardial effusion required pericardiocentesis and hemodynamic function was subsequently restored. One patient taking dabigatran 220 mg/day (pre-ACT 318s) experienced hematoma at the femoral puncture site. This patient required surgical intervention. There were no thromboembolic events.

Novel protocol for achieving target ACT

We then developed a novel protocol to improve the rate of achieving the target 30-min ACT (> 300 s). We calculated the optimal cut-off value of pre-ACT (130 s) using the ROC curve analysis. Eighty of 190 patients showed pre-ACT > 130 in initial cohort, and 64 of those 80 patients (80%) had reached the target 30-min ACT (> 300). Therefore, we defined the following new protocol to raise the achievement rate of the target 30-min ACT in patients with pre-ACT < 130. The initial heparin dose was set as "100 U/kg + 5000 U" in patients with pre-ACT < 130 and "100 U/kg + 3000 U" in patients with pre-ACT > 130. We then investigated the achievement rate of the target 30-min ACT using the new protocol in consecutive 138 patients (47 dabigatran, 29 rivaroxaban, 38 apixaban, 24 edoxaban, 94 males, 68 ± 10 years, 62 non-paroxysmal AF) (the validation cohort). All patients had the CA performed for non-valvular AF in our center between April 2017 and February 2018 (Fig. 4). All patients were divided into two groups (pre-ACT < 130 s; 62 patients, pre-ACT ≥ 130 s; 76 patients). The distribution of pre-ACT based on the previous protocol and the novel protocol is described in Fig. 5. The achievement rate of target 30-min ACT improved from 41.6 to 80.5%. Moreover, the time to reach target 30-min ACT based on our novel protocol was significantlyshorter than that of the previous protocol (38.6 ± 20.2 min vs. 68.3 ± 49.7 min, $P < 0.0001$). The time in target range also improved (previous protocol: 43.0 ± 30.5%, novel protocol: 73.8 ± 24.9%, $P < 0.0001$).

In the validation cohort, major bleeding complications occurred in 1/138 patients (0.7%). One patient taking dabigatran 220 mg/day (pre-ACT 333s) experienced hematoma at the femoral puncture site. This patient required surgical intervention. Pericardial effusion occurred in two patients (one patient taking apixaban 10 mg/day, pre-ACT 350s, one patient taking apixaban 5 mg/day, pre-ACT 414s). These patients were defined as minor bleeding complications because pericardial effusion did not require pericardiocentesis. There were no thromboembolic events.

Table 1 Baseline characteristics and medication therapy before the catheter ablation

	30 min-ACT < 300 group ($n=111$)	30 min-ACT ≥ 300 group ($n=79$)	*P* value
Age (years)	67 ± 10	69 ± 8	0.07
Male, *n* (%)	74 (67%)	53 (67%)	0.9514
Non-paroxysmal AF, *n* (%)	55 (50%)	40 (51%)	0.8833
Total AF duration (months)	37 ± 49	22 ± 32	0.0196
Height (m)	1.65 ± 0.09	1.65 ± 0.09	0.7697
Weight (kg)	65 ± 13	66 ± 12	0.7452
BMI (kg/m^2)	24 ± 3	24 ± 3	0.7513
BSA (m^2)	1.71 ± 0.20	1.72 ± 0.18	0.7155
Prior CHF, *n* (%)	18 (16%)	9 (11%)	0.348
Hypertension, *n* (%)	63 (57%)	47 (59%)	0.7065
Dyslipidemia, *n* (%)	35 (32%)	30 (38%)	0.3562
DM, *n* (%)	21 (19%)	16 (20%)	0.8189
Prior stroke/TIA, *n* (%)	16 (15%)	8 (10%)	0.3682
$CHADS_2$ score	1.4 ± 1.2	1.3 ± 1.1	0.7296
CHA_2DS_2-VASc score	2.5 ± 1.5	2.7 ± 1.5	0.3294
HAS-BLED score	1.3 ± 1.0	1.5 ± 1.0	0.2881
Structural heart disease, *n* (%)	29 (26%)	79 (20%)	0.8999
Labolatory data			
CRP (mg/dL)	0.199 ± 0.641	0.106 ± 0.240	0.2225
BNP (pg/mL)	142 ± 171	124 ± 128	0.4155
Serum creatinine (mg/dL)	0.82 ± 0.26	0.79 ± 0.23	0.3903
Ccr (mL/min)	89 ± 23	93 ± 23	0.2759
Uric acid (mg/dL)	6.0 ± 1.3	5.9 ± 1.4	0.5351
Hemoglobin (g/dL)	13.9 ± 1.6	13.4 ± 1.5	0.0547
PT-INR	1.10 ± 0.07	1.14 ± 0.09	0.0063
aPTT (s)	33.4 ± 3.3	36.9 ± 10.8	0.0013
Medication therapy			
Beta blocker, *n* (%)	71 (64%)	42 (53%)	0.1351
ACE inhibitor, *n* (%)	10 (9%)	7 (9%)	0.9719
ARB, *n* (%)	31 (28%)	23 (29%)	0.8582
Calcium blocker, *n* (%)	36 (32%)	32 (41%)	0.2525
Statin, *n* (%)	30 (27%)	27 (34%)	0.2891
Antiplatelet, *n* (%)	8 (7%)	14 (18%)	0.0256
PPI, *n* (%)			
AAD, *n* (%)	47 (42%)	25 (32%)	0.1341
Amiodarone, *n* (%)	11 (10%)	5 (6%)	0.381
Dabigatran, *n* (%)	8 (7%)	14 (18%)	0.0256
300 mg/day, *n* (%)	3 (3%)	7 (9%)	0.0962
220 mg/day	5 (5%)	7 (9%)	0.2417
Rivaroxaban, *n* (%)	68 (61%)	35 (44%)	0.0208
15 mg/day	53 (48%)	27 (34%)	0.0619
10 mg/day	15 (14%)	8 (10%)	0.5094
Apixaban, *n* (%)	24 (22%)	24 (30%)	0.1709
10 mg/day	19 (17%)	17 (22%)	0.4454
5 mg/day	5 (5%)	7 (9%)	0.2417
Edoxaban, *n* (%)	11 (10%)	6 (8%)	0.6184
60 mg/day	5 (5%)	3 (4%)	1
30 mg/day	6 (5%)	3 (4%)	0.7375

Values are given as no. (%) or mean ± SD

AAD antiarrhythmic drug, *ACE* angiotensin converting enzyme, *ACT* activated clotting time, *AF* atrial fibrillation, *aPTT* activated partial thromboplastin time, *ARB* angiotensin receptor blocker, *BNP* brain natriuretic peptide, *BMI* body mass index, *BSA* body surface area, *Ccr* creatinine clearance, *CHF* congestive heart failure, *CRP* C-reactive protein, *DM* diabetes mellitus, *PPI* proton pump inhibitor, *PT-INR* prothrombin time international normalized ratio, *TIA* transient ischemic attack

Table 2 Echocardiographic and procedural findings

	30 min-ACT < 300 group ($n=111$)	30 min-ACT ≥ 300 group ($n=79$)	*P* value
TTE findings			
Left atrial diameter (mm)	42 ± 6	43 ± 7	0.3941
E wave (cm/s)	79 ± 25	79 ± 25	0.9718
LVDd (mm)	49 ± 6	49 ± 5	0.9291
DcT (ms)	187 ± 61	191 ± 53	0.5764
E/*e'* ratio	12 ± 6	12 ± 5	0.9884
LVH, *n* (%)	15 (14%)	9 (11%)	0.6645
LVEF (%)	65 ± 11	65 ± 11	0.8964
Procedural findings			
1st session, *n* (%)	93 (84%)	67 (85%)	0.8484
PV isolation, *n* (%)	111 (100%)	79 (100%)	1
CTI block, *n* (%)	91 (82%)	62 (78%)	0.5481
SVC isolation, *n* (%)	24 (22%)	12 (15%)	0.2649
Additional procedure, *n* (%)	8 (7%)	8 (10%)	0.4751
Procedure time (min)	149 ± 50	150 ± 37	0.7954
RF time (min)	33 ± 17	32 ± 14	0.7581
RF energy (103 J)	49.8 ± 22.7	49.9 ± 26.4	0.992
Initial heparin dose (U)	9298 ± 1522	9490 ± 1537	0.3953
Total heparin dose (U)	13,900 ± 3546	11,712 ± 2428	< 0.0001
Total heparin dose (U/kg)	214 ± 42	179 ± 32	< 0.0001
Pre-ACT (s)	122 ± 23	134 ± 27	0.0009
30 min-ACT (s)	270 ± 25	333 ± 34	< 0.0001
Final ACT (s)	292 ± 36	305 ± 32	0.0091
Time to target ACT (min)	69 ± 30	32 ± 7	0.0172
Time in target range (%)	28 ± 24	64 ± 26	< 0.0001

Values are given as no. (%) or mean ± SD

ACT activated clotting time, *CTI* cavo tricuspid isthmus, *DcT* deceleration time, *LVDd* left ventricular diameter during end diastole, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *PV* pulmonary vein, *RF* radio frequency, *SVC* superior vena cava, *TTE* transthoracic echocardiography

Table 3 Univariate and multivariate analyzes

	Univariate analysis	Multivariate analysis	
	P value	*P* value	Odds ratio (95% CI)
Pre-ACT	0.0009	0.0396	1.014* (1.001–1.020)
PT-INR	0.0063	0.612	
aPTT	0.0013	0.0847	
Antiplatelet	0.0256	0.0964	
Dabigatran	0.0256	0.4442	

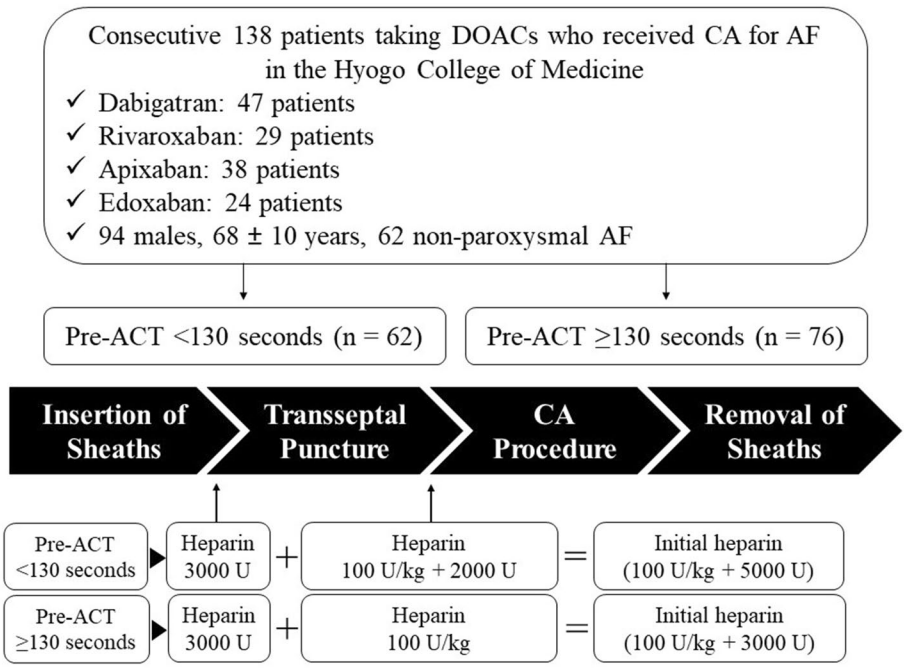
ACT activated clotting time, *aPTT* activated partial thromboplastin time, *CI* confidence interval, *PT-INR* prothrombin time international normalized ratio

[a]For each 1 s increase in pre-ACT

Discussion

The objective of this study was to evaluate the association between achieving target ACT and clinical factors, and to develop an appropriate protocol for early target ACT achievement in patients taking DOACs using a single-center database. Univariate analysis showed that longer pre-ACT, elevated aPTT, higher PT-INR, antiplatelet medication, and dabigatran were associated with achieving the target 30-min ACT. On multivariate analysis, only longer pre-ACT was independently associated with achieving the target 30-min ACT ($P=0.0396$, the optimal cutoff value; 130 s). Next, we developed a novel protocol for achieving the target 30-min ACT based on pre-ACT (the optimal cut-off value; 130 s). The rate of target 30-min ACT achievement improved from 41.6 to 80.5% using this novel protocol. This study showed that our novel protocol is useful for achieving target 30-min ACT without increasing complications.

Current guidelines have established CA of AF as an important therapeutic strategy. In recent research, Marrouche et al. demonstrated that the CA for AF patients with heart failure is useful to reduce rate of a composite end point of all-cause death and hospitalization for worsening heart



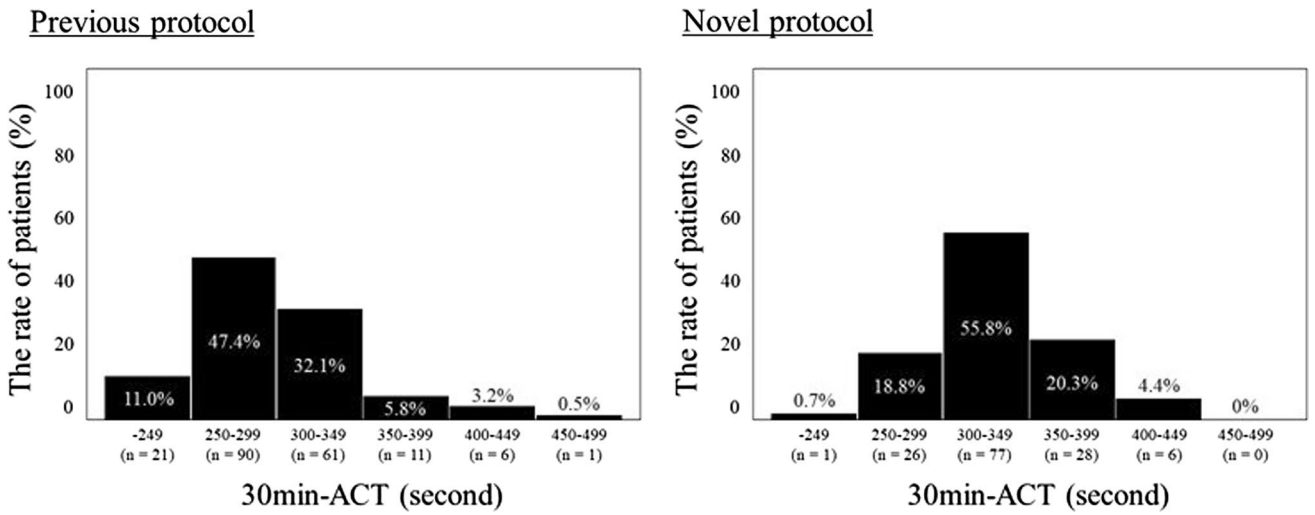


Fig. 4 Flow chart of the validation cohort patients and novel heparin protocol. *ACT* activated clotting time, *AF* atrial fibrillation, *CA* catheter ablation, *DOACs* direct oral anticoagulants

Fig. 5 The distribution of 30-min ACT in previous protocol (left) and novel protocol (right). *ACT* activated clotting time

failure compared with medical therapy [9]. Thus, the indications of CA have recently been extended. However, TE and bleeding complications remain a major limitation.

The current guidelines also suggest systemic anticoagulation with heparin to maintain an ACT of more than 300 s to reduce the risk of TE events associated with the CA procedure [3]. With the development of CA procedures such as cryo-balloon ablation, procedural times have become shorter [10]. Therefore, it is necessary to achieve target ACT earlier. Previously, intravenous heparin was administered at an initial bolus dose of 100 U/kg in patients taking warfarin [11]. However, there is no standard protocol for heparin administration during the CA in patients taking DOAC. In our center, the initial bolus dose of 100 U/kg was insufficient in patients taking DOAC. Our preliminary study showed that approximately 70% patients taking DOAC did not reach 30-min ACT. Previous studies have reported heparin requirements and ACT in patients anticoagulated with DOAC and warfarin. Their findings showed that those treated with DOAC required a higher dose of heparin and a longer time to reach the target ACT than those receiving warfarin [5, 6]. Yamaji et al. investigated differences in ACT and initial heparin dosage during the CA for AF patients taking edoxaban and uninterrupted warfarin [12]. Their study indicated

that edoxaban required a higher initial dose to achieve the target ACT, and edoxaban had a lower baseline ACT compared with warfarin. They also evaluated the adequate initial heparin dosage in patients taking DOAC (dabigatran, apixaban, and rivaroxaban) [13]. Their results indicated that initial bolus heparin dosages of 120 (achievement rate of target ACT; 77%) or 130 U/kg (achievement rate; 90%) for dabigatran, and 130 U/kg for rivaroxaban (achievement rate; 73%) and apixaban (achievement rate; 73%), were sufficient. In our study, direct thrombin inhibitor-treated patients presented prolonged pre-ACT, higher achievement rate to the target 30-min ACT, and fewer total amount of heparin than Xa-inhibitor-treated patients. Thus, the kind of DOAC might impact on ACT and heparin dose. However, multivariate analysis showed that taking DTI was not significant in our study. Therefore, we believe that pre-ACT is more important than the kind of DOAC. Our initial cohort included only 22 direct thrombin inhibitor-treated patients. Further investigations including larger number of patients may be necessary.

Previous studies have reported that the prevalence of bleeding complication varies from 0 to 13%.[3, 14–17] In our study, the prevalence of patients with prolonged ACT (> 400) did not differ between the previous protocol and our novel protocol (3.7% vs 4.4%). The prevalence of major bleeding complications was also similar between both protocols (1.6% vs 0.7%). Recent meta-analysis has reported similar safety of DOAC and warfarin in the specific setting of CA for AF. Major bleeding complications occurred 1.1% in uninterrupted DOAC-treated patients [18]. Periprocedural anticoagulation management is critical to balance the risks of thromboembolism and stroke, with the risk of bleeding related to vascular access sites and tamponade. Our findings suggest that our novel protocol based on pre-ACT might strike a good balance. To the best of our knowledge, this is the first study demonstrating the safety and efficacy of a novel protocol based on pre-ACT for achieving target 30-min ACT in patients taking DOACs.

ACT is considered to indicate the function of the entire intrinsic pathway of the coagulation cascade. The ACT has been proven to be a simple, reliable, and reasonably sensitive bedside test of the coagulation mechanism [10]. However, there are no reports that ACT is useful for evaluating the effect of DOACs. Recently, Otuki et al. evaluated the effects of DOACs and warfarin on the coagulation system at the peak concentration time, trough concentration time, and after vascular injury. They demonstrated that the F1 + 2 level (a marker of thrombin generation) at the trough DOAC concentration time was significantly higher in the DOAC groups than in the warfarin group. Kawasugi et al. also studied the effects of DOACs on the thrombin generation assay (a marker of thrombin generation) in ten healthy volunteers [19]. Their study indicated that DOACs significantly decreased thrombin generation 24 h after the DOAC administration (trough concentration time). Their findings suggest that DOAC treatment preserves thrombin generation at the trough concentration time. Thus, these markers, such as the F1 + 2 and the thrombin generation assay, are more useful for evaluating the effect of DOACs than ACT; however, there is an intrinsic delay before these assay results are known. Our study demonstrated that longer pre-ACT was only independently associated with achieving the target 30-min ACT. We believe that the ACT is the most useful marker to predict target ACT achievement at this time. However, previous reports have demonstrated ACT variability [20–22]. Therefore, further investigation is needed to determine a more useful and stable marker.

There are several limitations in our study. First, this is a retrospective study with a small number of patients in a single center. Second, ACT variability may have impacted our results as previous reports have demonstrated its variability [20–22]. The current guidelines recommend the monitoring of anticoagulation activity via ACT. These guidelines were appropriately evidenced based for warfarin-treated patients, and there were few data in DOAC-treated patients. Therefore, more sensitive maker during CA is needed in DOAC-treated patients. However, ACT is a most useful surrogate marker during CA for AF in viewpoints of quickness and simplicity for now.Therefore, we currently have no choice but to use ACT during CA. Third, most of the patients in our study had a low risk of bleeding or stroke. Fourth, in our study, we used heparin protocol with an interruption of DOAC. Therefore, our results can not apply to the patients with an uninterruption of DOAC. Fifth, significant variability in ACT measurement exists based on the type of system used. Currently, the Hemochron system offers two different systems for assessing ACT: the Hemochron Response and the Hemochron Signature Elite. Thenappan et al compared 126-paired samples in 77 patients using these 2 systems [23]. Their study indicated that the Hemochron Response and Hemochron Signature Elite systems differed by > 10% in 33% of the samples and by > 20% in 8% of samples. Moreover, the Hemochron Signature Elite ACT values were usually higher than the Hemochron Response ACT values in the higher therapeutic range of ACT. These findings taken together suggest that ACT in our study might be lower than ACT in previous studies using Hemochron Signature Elite. Finally, different DOACs were used in the first and second studies. Recent studies have shown that patients taking Xa inhibitor require a higher dose of heparin and a longer time to achieve the target ACT than those with dabigatran [5]. Further studies involving patients taking the same DOACs are necessary.

Conclusions

Our novel protocol of initial heparin administration based on pre-ACT is useful for an appropriate systemic anticoagulation in patients taking DOACs during the CA for AF.

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