Factors Associated with Silent Cerebral Events During Atrial Fibrillation Ablation in Patients on Uninterrupted Oral Anticoagulation

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Abstract

Introduction: Silent cerebral events (SCEs) are related to the potential thromboembolic risk in atrial fibrillation (AF) ablation. Peri-procedural uninterrupted oral anticoagulation (OAC) reportedly reduced the risk of SCEs, but the incidence still remains. Methods and Results: AF patients undergoing catheter ablation were eligible. All patients took non-vitamin K antagonist oral anticoagulants (NOACs, n=248) or vitamin K antagonist (VKA, n=37) for peri-procedural OAC (>4 weeks) without interruption during the procedure. Brain magnetic resonance imaging was performed within 2 days after the procedure to detect SCEs. Clinical characteristics and procedure-related parameters were compared between patients with and without SCEs. SCEs were detected in 66 patients (23.1%, SCE[+]) but were not detected in 219 patients (SCE[-]). Average age was higher in SCE[+] than in SCE[-] (66±10 years vs. 62±12 years, $p<0.05$). Persistent AF prevalence, CHADS2/CHA2DS2-VASc scores, serum NT-ProBNP levels, left-atrial dimension (LAD), and spontaneous echo contrast prevalence in transesophageal echocardiography significantly increased in SCE[+] vs. SCE[-]. SCE[+] had lower baseline activated clotting time (ACT) before heparin injection and longer time to reach optimal ACT (>300 sec) than SCE [-] (146±27 sec vs. 156±29 sec and 44±30 sec vs. 35±25 sec, $p<0.05$, respectively). In multivariate analysis, LAD, baseline ACT, and time to reach the optimal ACT were predictors for SCEs. The average values of the ACT parameters were significantly different among NOACs/VKA. Conclusion: LAD and intra-procedural ACT kinetics significantly affect SCEs during AF ablation. Different anticoagulants have different impacts on ACT during the procedure, which should be considered when estimating the risk of SCEs.

Introduction

Catheter ablation is a common intervention for atrial fibrillation (AF) but there are concerns about serious complications, with clinically apparent cerebral thromboembolisms being the most worrisome. Although the incidence of cerebral thromboembolisms is very low (<1%),[1] recent studies suggest that they are only the tip of the iceberg.[2,3]

A silent cerebral event (SCE) is defined as an acute new brain lesion in a patient without clinically apparent neurological deficit. SCEs are detected by brain magnetic resonance imaging (MRI). The lesions are usually small, but typical to cerebral thromboembolisms; they are frequently observed in asymptomatic patients who have undergone AF ablation. Although the small number of SCEs does not cause neurocognitive dysfunction, the greater volume and/or larger number of SCE lesions are reportedly related to neuropsychological decline.[4] SCE incidence may be a surrogate marker for the potential thromboembolic risk under specific ablation procedure and peri-procedural OAC. Thus, strategies to reduce SCE might be beneficial.

The uninterrupted use of non-vitamin K antagonist oral anticoagulants (NOACs) became the practical standard for the peri-procedural OAC and reportedly reduced the risk of SCEs when compared to the use with interruption during the procedure.[4] However, a recent meta-analysis demonstrated that the incidence of SCEs remains at around 16% even in the uninterrupted OAC.[5] Exploring the risk factors of SCEs may contribute to further reduction of potential thromboembolic risk in the era of uninterrupted OAC for AF ablation.

Therefore, we sought factors associated with SCEs during AF ablation in patients on uninterrupted OAC for the peri-procedural period.

Methods

Study Population

This is a non-randomized single center retrospective study of AF patients undergoing catheter ablation at Fujita Health University from January 2015 to September 2019. Written informed consent was obtained from all patients undergoing catheter ablation for AF. Among them, patients on uninterrupted OAC who underwent brain MRI within 2 days after the catheter ablation were enrolled. Baseline demographics/clinical information (AF type, past history, comorbidities, medications, etc.) was obtained; CHADS2 and CHA2DS2-VASc scores were calculated. Laboratory examinations (creatinine and brain natriuretic peptide, etc.) and transthoracic echocardiography (ejection fraction and left atrial dimension, etc.) were performed before catheter ablation. Transesophageal echocardiography (TEE) was performed one day before the procedure, and patients with left atrial appendage thrombus detected by TEE were excluded. Patients with creatinine clearance (CrCl, calculated by Cockcroft-Gault formula) <15 mL/min and those on hemodialysis were excluded from the study. Patients with mechanical valves was also excluded.

Peri-procedural Oral Anticoagulation

All patients were treated with NOACs or VKA for [?]4 weeks before AF ablation (dabigatran 150 mg/110 mg b.i.d., rivaroxaban 15 mg/10 mg q.d., apixaban 5 mg/2.5 mg b.i.d., edoxaban 60 mg/30 mg q.d., warfarin q.d.). Approved dose criteria were specific to each NOAC according to the patient's renal function, weight, age, and concomitant medications, as indicated in approved package inserts (PIs).[6,7] In patients on VKA, a target international normalized ratio (INR) was set to 2.0-3.0 but the therapeutic intensity was lowered (PT-INR 1.6-2.6) in elderly patients ([?]70 years).[8] The quality of VKA control was evaluated by monitoring the PT-INR and calculating the time in therapeutic range (TTR).[9] In all patients, the initial choice/dose of anticoagulants was decided by the physicians/cardiologists who first diagnosed AF; the anticoagulants were continued before ablation without change, interruption, and heparin bridging. NOACs and VKA were used without interruption during the procedure. Once-daily drugs (rivaroxaban and edoxaban) were administered in the morning and the catheter ablation was scheduled in the afternoon. Inappropriate dose reduction was defined as the low dose treatment due to physician's decision/preference that did not follow the PIs in each drug. A proton pump inhibitor was prescribed in all patients to minimize the risk of esophageal injury.

Ablation Procedure

In paroxysmal AF patients, pulmonary vein isolation (PVI) was performed using either cryo-balloon ablation (CBA, single short freezing for 180 sec in each PV) or radiofrequency catheter ablation (RFCA) in the first session. RFCA was selected in patients with common PV or large PV ostium (>28mm) based on the LA/PV anatomy evaluated by cardiac-computed tomography imaging before the procedure. In persistent AF patients, only RFCA was used for PVI in the first session. In all patients, only the PVI strategy was used for the first AF ablation and no additional linear ablation in the LA was performed; only cavotricuspid isthmus ablation was permitted for documented typical atrial flutter. In the second session for both types of AF, the incomplete line of PVI was repaired with RFCA if necessary, and additional linear ablation at the roof and bottom between left and right PV (posterior wall isolation) and superior vena cava isolation were performed.

The CBA procedure was achieved using electro-anatomical mapping (EnSite NavX, Abbott, St. Paul, MN,

USA) and fluoroscopic guidance to position the cryo-balloon catheter. In the RFCA procedure, PVI was achieved using a focal "point-by-point" catheter approach, delivering radiofrequency energy to the cardiac tissue with irrigation tip catheters (THERMOCOOL SMARTTOUCH® SF, Biosense Webster, Diamond Bar, CA, USA [target contact force: 10-20g, RF time: 30-60 sec, irrigation flow rate: 8 ml/min for [?]30W, 15 ml/min for >30W, power control mode], or FlexAbility™, Abbott, St Paul, MN, USA [RF time: 30-60 sec, irrigation flow rate: 10 ml/min for <38, 13 ml/min for [?]38, temperature control mode]). RFCA lesion sets encircled the PV antra using electro-anatomical mapping (CARTO3, Biosense Webster, Diamond Bar, CA, USA or EnSite NavX, Abbott, St. Paul, MN, USA) and fluoroscopy guidance.

All procedures were performed under sinus rhythm; internal (3-35J) or external (50-220J) electrical cardioversion was performed with gradually increasing shock intensity to restore sinus rhythm when AF was observed before/during the procedure.

Anticoagulation during Procedure

Baseline activated clotting time (ACT) was measured before an initial bolus injection of unfractionated heparin (UFH). Then, a bolus of UFH (80-120 IU/kg) was administered. ACT was measured every 10-20 minutes after the first UFH shot, and additional UFH boluses (20-60 IU/kg) were administered before trans-septal puncture in order to reach optimal ACT (>300 sec) for AF ablation.[10] The time from the baseline ACT measurement and the amount of UFH to achieve the optimal ACT were calculated. During the procedure, ACT was measured every 20-30 minutes; additional UFH boluses were intermittently administered to maintain the ACT >300 sec. All left atrial sheaths were regularly flushed with heparinized saline to avoid clot formation within the sheaths. The total amount of UFH required for the procedure was also calculated. After the procedure, UFH was neutralized with protamine sulfate

Brain MRI

Brain MRI was performed within 2 days after the procedure using a 1.5 Tesla (T) scanner (Achieva 1.5T Nova Dual; Philips Healthcare, Best, The Netherlands) with an 8-channel brain coil, or a 3 T scanner (Ingenia 3T; Philips) with a dS head coil, or a Vantage Titan 3T (Canon Medical Systems Corporation, Otawara, Japan) with a 16- or a 32-channel coil to defect SCEs. In each patient, axial diffusion-weighted imaging was performed using single-shot, spin-echo, echo planar imaging with two b values of 0 and 1000 sec/mm^2 and three diffusion directions. Other scan parameters were as follows: repetition time/echo time 3600-5100/83-98 msec, 112-176x128-256 matrix, 288-512x288-512 reconstruction matrix, 220x220 mm field of view, slice thickness 5.0mm, slice gap 1.0 mm, and 1-4 excitations. The apparent diffusion coefficient map (ADC-map) was obtained to prevent the over-detection of T2 shine-through effects on diffusion-weighted imaging.

The definition for diagnosing SCE was based on the detection of new hyperintense lesions of the diffusion-weighted MRI with hypointense findings of the ADC-map according to a neuroimaging expert's recommendation.[11] MRI images were independently evaluated by certified radiologists in a blinded manner. A neurological examination was performed on hospital admission and after the ablation procedure by certified neurologists or certified physicians blinded to the MRI findings. The neurological dysfunction was evaluated using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS).

Statistical Methods

Continuous variables, represented as mean +- standard deviation, were compared using unpaired t -tests or one-way analysis of variance, as appropriate. Categorical data, expressed as frequencies and percentages, were compared using chi-square tests. All tests were 2-sided, and a p value <0.05 was considered to be statistically significant. The statistical analyses were performed using JMP11 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Two hundred eighty-five AF patients treated with NOACs (dabigatran 150 mg/110 mg b.i.d.: n=74/11, rivaroxaban 15 mg/10 mg q.d.: n=54/5, apixaban 5 mg/2.5 mg b.i.d.: n=43/5, edoxaban 60 mg/30 mg q.d.: n=33/23) or VKA (n=37) for [?]4 weeks before catheter ablation were eligible. Table 1 summarizes patients' characteristics. NOACs were prescribed at appropriate doses in 234 patients (95%) whereas at inappropriate doses in 14 patients (5%). The average of TTR and PT-INR on the day of the procedure in patients treated with VKA were 73+-37% and 2.1+-0.4, respectively.

Comparison of Clinical Characteristics between Patients with and without SCEs

Sixty-six patients (23.1%) had SCEs (SCE[+]) and the remaining 219 patients did not (SCE[-], Table 1). Average age was significantly higher in SCE[+] than SCE[-]. The prevalence of persistent AF, $CHADS_2$/CHA_2DS_2-VASc scores, the prevalence of stroke/TIA, and serum NT-ProBNP levels were higher in SCE[+] than in SCE[-]. In transthoracic echocardiography, left-atrial dimension (LAD) was significantly larger in SCE[+] than SCE[-]. In TEE, spontaneous echo contrast (SEC) were more frequently observed in SCE[+] than in SCE[-]. During the procedure, SCE[+] had lower baseline ACT values before UFH injection and longer time to reach optimal ACT (> 300 sec) than SCE [-]. The amount of UFH to reach the optimal ACT and the total amount of UFH for the entire procedure were comparable between SCE[+] and SCE[-] (Table 1).

Risk Factors for SCEs

Significant univariate factors were age, persistent AF, $CHADS_2$/CH_2ADS_2-VASc score, serum NT-ProBNP levels, LAD, spontaneous echo contrast, baseline ACT before first UFH injection, and time to reach the optimal ACT (> 300 sec), all of which were directed to multivariate analysis. $CHADS_2$ score (> 2 points or <2 points) and CH_2ADS_2-VASc score (> 3 points or <3 points) were considered as categorical data based on the clinical risk stratification of thromboembolism. LAD was also considered as categorical data with a clinical cut-off value of 40 mm. After adjusting for age and gender, multivariate logistic analysis demonstrated that LAD, and the baseline ACT, and the time to reach the optimal ACT were significant risk factors for SCEs (Table 2).

Comparison of Intra-procedural ACT Kinetics between Oral Anticoagulants

We compared the intra-procedural ACT kinetics between oral anticoagulants (Figure 1). Dabigatran had the highest baseline ACT value among all the agents (175+-32 sec). Edoxaban (155+-20 sec) showed the lower baseline ACT value than dabigatran but had the highest value among factor Xa inhibitors. The baseline ACT values were statistically comparable among rivaroxaban (143+-18 sec), apixaban (136+-25 sec), and warfarin (145+-21 sec, Figure 1A).

Rivaroxaban (41+-25 sec) and apixaban (45+-28 sec) showed the significantly longer time to reach the optimal ACT than edoxaban (29+-22 sec) and warfarin (27+-16 sec). Dabigatran (35+-25 sec) also showed the longer time than edoxaban and warfarin but the difference did not reach statistical significance (Figure 1B). These suggest that the intra-procedural ACT kinetics varies among oral anticoagulants, which potentially affects the incidence of SCEs in each anticoagulant.

Comparison of SCE Incidence between Oral Anticoagulants

Figure 2 showed the incidence of SCEs in each anticoagulant. Warfarin and apixaban had higher incidence of SCEs than the other drugs although the difference did not reach statistical significance.

We assumed that there may be differences in clinical characteristics between patients with different oral anticoagulants, which may also affect the incidence of SCEs. We compared the patient-dependent factors associated with SCEs identified by univariate/multivariate analyses among the five anticoagulants. Age, the prevalence of persistent AF, $CHADS_2$/CHA_2DS_2-VASc scores, and LAD were significantly different among the anticoagulants (Table 3). Apixaban and warfarin were prescribed in the more elderly patients with the higher $CHADS_2$/CHA_2DS_2-VASc scores. On the other hand, edoxaban tended to be prescribed in those with the lower risks in the patient's factors, which may also contribute to the incidence of SCE (Table 3).

Discussion

The major findings of this study are as follows. The incidence of SCEs remains at 23.1% in patients on uninterrupted OAC for AF ablation. In multivariate analysis, LAD, baseline ACT before UFH injection, and time to reach optimal ACT were significant risk factors for SCEs. Finally, the average values of the baseline ACT and the time to reach the optimal ACT were significantly different between patients with different oral anticoagulants. Intra-procedural ACT kinetics affect the incidence of SCEs and vary among anticoagulants in patients on uninterrupted OAC, which should be considered when estimating the risk of SCEs.

Comparison with Previous Studies

SCE is potentially associated with unfavorable neuropsychological outcomes. Previous studies demonstrated that the uninterrupted OAC minimized the risk of SCEs during AF ablation compared to interrupted OAC;[4] expert consensus and guidelines first recommend the use of NOACs or VKA without interruption during the procedure.[12] However, recent studies have reported that the incidence of MRI-detected SCEs still hovers at 2% to 27.2 % in patients on uninterrupted OAC for AF ablation.[5,13-17] In the present study, the SCE incidence remains at 23.1% in total, and was almost similar to or even higher than the incidence in the previous studies.

Different protocols of intra-procedural UFH administration may affect the incidence of SCEs despite of the same ACT target (>300 sec) during the procedure. Kirchhof et al. have reported that the SCEs at postprocedural MRI were identified in 84 out of 323 patients on uninterrupted apixaban or VKA (26.0%); a bolus of UFH (100 IU/kg, based on body weight) was first administered prior to transseptal puncture, as in the present study.[13] On the other hand, Di Biase et al. have demonstrated that the SCEs were detected in only 2 out of 86 patients on uninterrupted rivaroxaban (2.3%); the designated amount of UFH was first injected (10,000/8,000 IU in male/female, irrespective of body weight) before transseptal puncture.[15] The amount of the first UFH shot seems to be higher in the previous study by De Biase et al. than in the present study (4000-6000IU, based on Japanese body weight), which likely shortens the time to reach the optimal ACT. UFH boluses were intermittently administered during the procedure in the previous and the present studies, however the transseptal sheaths were also continuously infused with UFH saline in the previous study by De Biase et al.,[15] which may advantage keeping ACT levels constant and avoiding clot formation within the sheaths.

Different diagnostic criteria determined by brain MRI may also affect the SCE incidence. Guijian et al. reported that SCE incidence was 8% when using the definition of both abnormal diffusion-weighted image and fluid-attenuated inversion recovery (FLAIR) image, but when considering all abnormal diffusion-weighted images, the incidence rose to 27%.[18] We diagnosed SCE using only diffusion-weighted images according to a neuroimaging expert's recommendation, which may increase sensitivity.[11]

Previous studies have reported the risk factors for SCEs, including age, spontaneous echo contrast, complex fractionated atrial electrograms ablation, low left ventricular ejection fraction, perioperative coronary artery imaging, low mean perioperative ACT, electrical/pharmaceutical cardioversion, and arterial hypertension, etc.[19-24]However, these factors were identified in patients taking only VKA, but not NOACs. Kimura et al. demonstrated that the presence of deep and subcortical white matter hyper-intensity and the frequency of cardioversions were associated with SCEs in patients taking rivaroxaban or VKA without interruption during the procedure.[17] In this study, LAD, baseline ACT before UFH injection, and time to reach the optimal ACT were significant risk factors for SCEs. To the best of our knowledge, we first demonstrated that intra-procedural ACT kinetics significantly affect the incidence of SCEs in patients on uninterrupted NOACs/VKA for AF ablation. Nevertheless, the information on this issue is still largely limited.

The ACT kinetics during the procedure are affected by the peri-procedural anticoagulation strategy.[10]Microthrombus can form immediately after a sheath/catheter is inserted into the body. Therefore, it is better for patients to achieve the optimally anticoagulated condition as quickly as possible. The present study demonstrated that different anticoagulants had different impacts on the intra-procedural ACT. Martin et al. demonstrated that at baseline, NOACs prolonged ACT differently; ACT was longer with dabigatran and shorter with

apixaban,[25] being consistent with our results. Dabigatran may have the advantage of decreasing the risk of SCE in terms of baseline ACT prolongation. Martin et al. also demonstrated that ACT prolongation in response to UFH was significantly smaller in rivaroxaban/apixaban than in dabigatran/VKA,[25] which may underlie the longer time needed to reach the optimal ACT in rivaroxaban/apixaban in our study. Modifying the intraprocedural dosing of UFH may decrease the time to reach the optimal ACT and reduce the incidence of SCEs. However, the optimal ACT target (>300 sec) was validated in VKA-treated patients and may not be directly applied to those on NOACs; a specific regimen/monitoring of UFH in each NOAC may be required.

In the present study, apixaban and warfarin had the higher incidence of SCEs than the other anticoagulants although the difference did not reach statistical significance. Accumulating evidence has demonstrated a unique anticoagulation profile in each anticoagulant. In this study, the number of patients was relatively higher in dabigatran group than in the other groups likely because of the favorable outcome of dabigatran in RE-CIRCUIT study.[26] Physicians may use and/or choose an anticoagulant in a patient with a specific clinical background based on the evidence; apixaban and warfarin tended to be prescribed in the more elderly patients who had higher thromboembolic risk in the era of uninterrupted NOACs/VKA.

Limitation

This is a single-center study involving a small number of patients; thus, the statistical power is limited and interpretations should be made with caution. Treatment adherence of NOACs was not carefully evaluated, and poor adherence in some patients could have caused inadequate anticoagulation. The regular dose of rivaroxaban in Japan is different from that in Europe/North America.[27] Acute SCE lesions reportedly regress during the follow-up period, but we did not perform brain MRIs during the chronic phase. Several mechanisms of SCE after AF ablation are proposed rather than microthrombus, such as gaseous emboli and microparticle. The incidence of SCE is affected by multiple factors, and unmeasured procedure-related factors, such as ablation settings (contact force, the number of ablation point, power, irrigation flow rate, etc.), type of ablation catheter, procedure time, and operators, might still affect SCEs, and therefore care should be taken when interpreting the result.

Conclusion

The incidence of SCEs remains at 23.1% in patients on uninterrupted OAC for AF ablation. LAD, baseline ACT, and time to reach optimal ACT are significant risk factors for SCE. Intra-procedural ACT kinetics vary among anticoagulants, which should be considered when estimating the risk of SCEs.

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Figure Legends

Figure 1. Comparison of intra-procedural ACT kinetics among oral anticoagulants. A. Baseline ACT before first UFH shot. B. Time to reach optimal ACT >300 sec. ACT, activated clotting time; UFH, unfractionated heparin. A, apixaban; D, dabigatran; E, edoxaban; R, rivaroxaban; W, warfarin.

Figure 2. Comparison of SCE incidence among oral anticoagulants. SCE, silent cerebral event. A, apixaban; D, dabigatran; E, edoxaban; R, rivaroxaban; W, warfarin.

Table 1. Baseline Demographics and Comparison between Patients with and without SCEs

	Total (n=285)	**SCE [-] (n=219)**	**SCE [+] (n=66)**	**P value (SCE[-**
Age, y	63±12	62±12	66±10	0.029
Male, n (%)	208 (73)	158 (72)	50 (76)	0.560
BMI, kg/m^2	23.8±3.6	23.7±3.6	24.1±3.4	0.505
Persistent AF, n (%)	131 (446)	92 (42)	39 (59)	0.015
$CHADS_2$ score, pts	1.2±1.2	1.1±1.1	1.6±1.3	0.003
CHA_2DS_2-VASc score, pts	2.1±1.6	2.0±1.5	2.6±1.7	0.008
CHF, n (%)	79 (28)	58 (26)	21 (32)	0.401
HT, n (%)	121 (43)	90 (41)	31 (47)	0.399
Age [?]65, n (%)	150 (53)	110 (50)	40 (61)	0.137
Age [?]75, n (%)	43 (15)	29 (13)	14 (21)	0.125
DM, n (%)	48 (17)	32 (15)	16 (24)	0.076
Stroke/TIA, n (%)	31 (11)	19 (9)	12 (18)	0.039
Vascular disease, n (%)	13 (5)	8 (4)	5 (8)	0.208
Blood test				
AST, IU/L	22.3±11.3	21.8±10.0	24.2±15.1	0.132
ALT, IU/L	21.5±18.9	21.8±20.7	20.7±10.8	0.689
Cr, mg/dl	0.84±0.2	0.84±0.2	0.86±0.2	0.622
CrCl, ml/min	84.5±29.3	85.5±29.3	81.0±29.5	0.271
NT-ProBNP, pg/ml	529±667	483±686	676±603	0.049
PT-INR	1.52±0.82	1.53±0.06	1.51±0.10	0.912
APTT, sec	42.5±10.1	42.5±8.8	42.7±14.9	0.883
TTE findings				
LVDd, mm	46.8±6.4	46.7±6.5	46.8±6.2	0.929
LVDs, mm	32.1±7.9	32.0±7.7	32.5±8.3	0.684
EF, %	55.8±9.5	55.8±0.6	55.8±1.2	0.984
LAD, mm	38.6±6.9	38.1±7.2	40.4±5.7	0.013
TEE findings				
AF at TEE, n (%)	130 (46)	93 (42)	37 (56)	0.052
SEC, n (%)	56 (20)	32 (15)	24 (36)	<0.001
LAA flow velocity, cm/s	53.2±22.2	54.3±22.3	49.2±22.3	0.101
Oral anticoagulants				
Dabigatran, n (%)	85 (29)	67 (31)	18 (27)	0.307

	Total (n=285)	SCE [-] (n=219)	SCE [+] (n=66)	P value (SCE[-
Rivaroxaban, n (%)	59 (21)	46 (21)	13 (20)	
Apixaban, n (%)	48 (17)	32 (15)	16 (24)	
Edoxaban, n (%)	56 (20)	47 (21)	9 (14)	
Warfarin, n (%)	37 (13)	27 (12)	10 (15)	
Low dose in NOACs, n (%)	44 (18)	32 (17)	12 (21)	0.420
IDR in NOACs, n (%)	14 (5)	11 (6)	3 (5)	0.915
Medication				
Beta-blocker, n (%)	147 (52)	110 (50)	37 (56)	0.405
Diuretics, n (%)	53 (18)	41 (19)	12 (18)	0.921
ACEI/ARB, n (%)	79 (27)	57 (26)	22 (33)	0.251
Statin, n (%)	62 (22)	46 (21)	16 (24)	0.580
Antiplatelet, n (%)	21 (7)	17 (8)	4 (6)	0.636
AAD, n (%)	39 (15)	26 (12)	13 (20)	0.118
Procedure				
RFCA, n (%)	181 (71)	134 (68)	47 (80)	0.070
Cryoballoon ablation, n (%)	74 (29)	62 (84)	12 (16)	
Additional linear ablation	52 (18)	37 (17)	15 (23)	0.292
No. of ECV/patients, n	2.6±3.2	2.6±3.1	2.6±3.5	0.953
UFH/ACT kinetics				
Baseline ACT, sec	154±29	156±29	146±27	0.024
Time to reach optimal ACT, sec	37±26	35±25	44±30	0.018
Amount of UFH to reach optimal ACT, IU	6947±2880	6894±2928	7121±2714	0.576
Total amount of UFH, IU	10162±3838	10096±3848	10385±3807	0.595

AAD, anti-arrhythmic drug, ACT: activated clotting time, ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, APTT: activated partial thromboplastin time, AST/ALT: aspartate aminotransferase/alanine aminotransferase, BMI: body mass index, CHF: congestive heart failure, Cr: creatinine, CrCl: creatinine clearance, DM: diabetes mellitus, ECV: electrical cardioversion, EF: ejection fraction, HT: hypertension, IDR: inappropriate dose reduction, LAA: left atrial appendage, LAD: left atrial diameter, LVDd/Ds: left ventricular diastolic/systolic dimension, NOAC, non-vitamin K antagonist oral anticoagulants. PT-INR: prothrombin time-international normalized ratio, RFCA: radiofrequency catheter ablation, SCE, silent cerebral event, SEC: spontaneous echo contrast, TEE: transesophageal echocardiography, TIA: transient ischemic attack, TTE: transthoracic echocardiography, UFH: unfractionated heparin.

Table 2. Risk Factors for LAT

Risk Factor	Odds Ratio	95% CI	P value
Age, 1 year	1.04	1.00-1.07	0.044
Gender, Female	0.90	0.38-2.18	0.809
Type of AF, Persistent AF	1.18	0.37-4.04	0.688
$CHADS_2$ score, [?]2 points	2.22	0.69-7.47	0.181
CHA_2DS_2-VASc score, [?]3 points	1.77	0.51-6.53	0.373
NT-ProBNP, 1 pg/ml	1.00	0.99-1.00	0.676
LAD, [?]40 mm	2.98	1.36-6.77	0.006
SEC	1.81	0.74-4.36	0.188
Baseline ACT, 1IU	0.98	0.97-1.00	0.034
Time to reach optimal ACT (300 sec), 1 min	1.02	1.00-1.03	0.006

ACT: activated clotting time, AF: atrial fibrillation, CI: confidence interval, LAD: left atrial diameter, SEC, spontaneous echo contrast.

Table 3. Comparison of patient-dependent factors associated with SCE risk

Risk Factor	D	R	A	E	W	P value
Age, years	61±12	64±11	68±10	59±14	68±9	<0.001
Persistent AF, n (%)	60 (71)	16 (27)	17 (35)	18 (32)	21 (57)	<0.001
$CHADS_2$ score, pts	1.2±1.2	1.3±1.2	1.6±1.2	0.8±1.0	1.5±1.3	0.003
CHA_2DS_2-VASc score, pts	2.0±1.5	2.2±1.5	2.8±1.7	1.4±1.5	2.4±1.4	<0.001
NT-ProBNP, pg/ml	555±642	633±854	490±492	367±658	590±608	0.326
LAD, mm	40.3±6.2	38.3±7.5	37.6±6.3	37.0±7.8	39.2±6.7	0.043
SEC, n (%)	20 (24)	11 (19)	8 (17)	7 (13)	10 (18)	0.368

AF: atrial fibrillation, LAD: left atrial diameter, SEC: spontaneous echo contrast. A: apixaban, D: dabigatran, E: edoxaban, R: rivaroxaban, W: warfarin.