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Uninterrupted Direct Oral Anticoagulant and Warfarin Administration in Elderly Patients Undergoing Catheter Ablation for Atrial Fibrillation

A Comparison With Younger Patients

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ABSTRACT

OBJECTIVES The goal of this study was to evaluate the efficacy and safety of uninterrupted direct oral anticoagulant (DOAC) use and uninterrupted warfarin administration in elderly patients undergoing catheter ablation for atrial fibrillation (AF).

BACKGROUND There is limited knowledge regarding the uninterrupted use of oral anticoagulant agents in elderly patients undergoing catheter ablation for AF.

METHODS This retrospective study included 2,164 patients (n = 325 ≥75 years of age and n = 1,839 <75 years of age) who underwent catheter ablation for AF. All the patients received uninterrupted oral anticoagulant agents during the procedure. We investigated the occurrences of periprocedural events and compared these between the DOAC and warfarin groups of the elderly and younger groups.

RESULTS Major bleeding events (3.1% vs. 1.3%; p = 0.023) and minor bleeding events (9.2% vs. 5.0%; p = 0.002), except for thromboembolic events (0% vs. 0.8%; p = 0.248), were significantly higher in the elderly group than in the younger group. No significant differences in thromboembolic and bleeding events were found between the DOAC and warfarin groups of both the elderly and younger groups. Adverse complications did not differ between the groups after adjustment using propensity score matching analysis. Multivariate analysis revealed that lower body weight (odds ratio: 0.96; p = 0.010) and antiplatelet drug use (odds ratio: 2.21; p = 0.039) were independent predictors of adverse events in the elderly group.

CONCLUSIONS The periprocedural bleeding risk during the use of uninterrupted oral anticoagulants was higher in the elderly group than in the younger group. This area needs more attention for these patients in whom caution is required. (J Am Coll Cardiol EP 2018;4:592–600) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Catheter ablation for atrial fibrillation (AF) is a well-established treatment for drug-refractory AF, and its efficacy and outcomes are acceptable, resulting in an increasing number of patients undergoing catheter ablation in clinical practice (1). Although the catheter ablation procedure is a safe and less invasive technique, there are a few periprocedural complications that must be recognized, such as bleeding and thromboembolic events, during such a procedure (2,3).

To reduce fatal thromboembolic complications, the administration of uninterrupted vitamin K antagonists during catheter ablation is feasible without increasing bleeding events, compared with the administration of interrupted vitamin K antagonists using low-molecular-weight heparin bridging (4). Direct oral anticoagulants (DOACs) have recently been introduced, and many patients receiving DOACs are scheduled to undergo catheter ablation treatment for AF. Although a strict consensus regarding periprocedural DOAC management during the catheter ablation procedure is lacking, recent reports have suggested equivalent safety and efficacy profiles for uninterrupted use of DOAC and uninterrupted use of vitamin K antagonists (5–14). These data were supported by a recent prospective, randomized controlled study showing similar outcomes during catheter ablation for AF between periprocedural uninterrupted dabigatran and warfarin (15). However, the involved population of these studies consisted of middle-aged (approximately 60 years of age) patients with AF. There are no data regarding the safety and efficacy of uninterrupted DOAC and warfarin use in elderly individuals during catheter ablation for AF.

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With the advancing age of the population, the number of elderly patients undergoing catheter ablation for AF is increasing. Because elderly patients with AF have more comorbidities than younger patients with AF, performing catheter ablation for AF in elderly patients with administration of anticoagulant drugs requires careful attention to the risk of periprocedural complications (16). It is unclear whether uninterrupted DOAC and warfarin use for elderly patients with AF during the ablation procedure provide similar efficacy and safety outcomes compared with the results observed in younger patients with AF.

The present study was conducted to evaluate the safety and efficacy of periprocedural uninterrupted DOAC and warfarin administration in patients ≥75 years of age undergoing catheter ablation for AF and to compare them with those in patients <75 years of age.

METHODS

STUDY POPULATION. The study population was retrospectively analyzed from a catheter ablation database at Nagoya University Hospital, Nagoya, Japan. This study was approved by our institutional ethics committee. All consecutive patients who underwent catheter ablation for AF between January 2008 and June 2017 in Nagoya University Hospital were initially assessed. Patients who were lost to follow-up within 30 days after ablation were excluded.

In the present study, 2,164 patients (n = 325 ≥75 years of age [elderly group] and n = 1,839 <75 years of age [younger group]) were analyzed. Patients who had >1 catheter ablation procedure during the study period were treated as multiple samples in this cohort. The indications for catheter ablation for AF were in compliance with the latest guidelines (17). Before the procedure, informed, written consent was obtained from all patients according to our hospital guidelines. This study was performed in compliance with the Declaration of Helsinki principles.

PERIPROCEDURAL ANTICOAGULANT MANAGEMENT. The patients were administered DOAC or warfarin at least 3 weeks before the ablation procedure. The choice of DOAC or warfarin was made according to the attending physician. The DOACs included apixaban, rivaroxaban, dabigatran, and edoxaban. Each DOAC was prescribed in accordance with the drug package insert. In our institution, dabigatran was available as of March 2011, and rivaroxaban, apixaban, and edoxaban were introduced in April 2012, February 2013, and December 2014, respectively. The warfarin dosage was adjusted to maintain a target international normalized ratio of 2.0 to 3.0 (or 1.6 to 2.6 in those ≥70 years of age) according to the guideline (18).

The aforementioned anticoagulant drugs were continued during the procedure. No heparin bridging was performed. On the procedure day, apixaban and dabigatran were prescribed in the morning and evening as usual; rivaroxaban and edoxaban were administered only in the morning. No patients were prescribed rivaroxaban and edoxaban in the evening the day before ablation. This approach implied that the last dose was taken the morning of the procedure day. After the procedure, the anticoagulant drugs were continuously administered as usual.

CATHETER ABLATION PROCEDURES. Patients who were scheduled for catheter ablation treatment were admitted the day before the procedure. At admission,

ABBREVIATIONS AND ACRONYMS

ACT = activated clotting time
AF = atrial fibrillation
DOAC = direct oral anticoagulant
PV = pulmonary vein

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baseline blood testing, echocardiography, and electrocardiography were performed. Transesophageal echocardiography was performed in all patients to confirm the absence of atrial thrombus. A heparin bolus of 80 to 100 IU/kg was administered immediately after insertion of all sheaths.

The radiofrequency ablation procedure was performed as described previously (19). After transseptal puncture using intracardiac echocardiography, two 8-F sheaths and an 8.5-F steerable sheath were introduced into the left atrium. Using a circular mapping catheter placed on the ostium of each pulmonary vein (PV) atrium, encircling PV isolation was performed with a 3.5-mm tip, open-irrigated ablation catheter. All ablation procedures were performed by using a three-dimensional electroanatomic mapping system (CARTO, Biosense Webster, Inc., Irvine, California). The radiofrequency energy output was titrated to 25 to 35 W at a flow rate of 17 to 30 ml/min with a maximum temperature of 42°C. For the most part, paroxysmal AF and early persistent AF had PV isolation alone; however, in patients with prolonged persistent AF or atrial tachycardia, additional linear ablation and complex fractionated electrogram ablation were applied. If the rhythm of the patients did not convert to sinus rhythm at the end of ablation, external cardioversion was performed.

Cryoballoon ablation was available for patients with paroxysmal AF from July 2014. The attending physician determined whether radiofrequency or cryoballoon application should be performed for the patients with paroxysmal AF. For the cryoballoon ablation procedure, a 12-F steerable sheath was introduced into the left atrium. The second-generation 28-mm cryoballoon system (Arctic Front Advance, Medtronic, Minneapolis, Minnesota) was advanced and placed on the ostium of each PV by using an inner circular mapping catheter. After confirmation of PV ostium occlusion with the cryoballoon using a contrast medium, a 180-s cycle freeze ablation was repeated until electrical isolation of the PV was achieved. All procedures were performed by using a three-dimensional electroanatomic mapping system (EnSite NavX, St. Jude Medical, Inc., St. Paul, Minnesota).

Another balloon technology (i.e., hot balloon ablation procedure [Toray Industries, Inc., Tokyo, Japan]) has been introduced and available since April 2016 in Japan (20). The balloon was placed into the target PV ostium while advancing the guidewire through a catheter lumen into the PV. Thereafter, all PVs were ablated in order.

During the entire procedure, activated clotting time (ACT) was monitored every 20 to 30 min after the bolus infusion. The target range of ACT between 300 and 350 s was maintained by additional heparin infusion. At the end of the procedure, protamine (30 to 50 mg) was administered to reverse the effect of heparin, and all sheaths were removed.

OUTCOMES. The patients remained hospitalized under continuous rhythm monitoring for 3 days after the procedure. It was arranged for all the patients to come to the follow-up visit at the outpatient clinic in our hospital 1 month after discharge, and they were queried regarding any occurrence of complications and treatment in other institutions. If the patients experienced any problem and events before the follow-up visit, they were recommended to visit the hospital or emergency department.

Thromboembolic events were defined as symptomatic cerebral infarction and transient ischemic attack. In case of suspected cerebrovascular events, magnetic resonance imaging was performed after ruling out intracranial hemorrhage by using head computed tomography, and the diagnosis was confirmed by a neurologist. Bleeding events were defined as any bleeding of puncture site hematoma, gastrointestinal bleeding, vascular complications, and pericardial effusion. Major bleeding events were classified as any bleeding requiring blood transfusion, surgical intervention, or pericardial effusion with tamponade requiring drainage. Other bleeding complications, puncture site hematoma or bleeding, and pericardial effusion that did not require an invasive treatment were defined as minor bleeding events. Major adverse events were defined as any thromboembolic events and bleeding events. Periprocedural complications were considered from the start of ablation session to 30 days after the procedure. All the complication events were evaluated by using the patients' medical record in our hospital. The adverse events were reviewed and confirmed by 2 independent researchers.

STATISTICAL ANALYSIS. Comparison of the differences in the baseline characteristics was analyzed by using Student's *t*-test, and categorical variables were compared by using the chi-square test or Fisher exact test. The prognostic value of each factor was first evaluated by using a univariate logistic regression analysis. Factors with p values <0.05 in the univariate analysis were entered into a multivariate logistic regression model using a forward stepwise method to identify independent predictors. For a propensity score matched analysis, the propensity score was calculated with a multivariable logistic regression model using DOAC as the dependent variable and including the baseline factors. Thereafter,

1:1 nearest-neighbor greedy matching was performed. A p value <0.05 was considered statistically significant.

RESULTS

BASELINE PATIENT CHARACTERISTICS. Among the total population, most patients (87%) underwent radiofrequency catheter ablation; however, 263 and 12 patients underwent cryoballoon and hot balloon ablation procedures, respectively. The baseline characteristics and examination results in the elderly and younger patients are shown in Table 1. In the elderly group, the mean age was 78.1 years (58% male). A total of 238 patients (73%) presented with paroxysmal AF. The mean $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category) scores were 2.2 ± 0.9 and 3.7 ± 1.1. DOACs and warfarin were prescribed in 186 and 139 patients. The number of patients under the therapeutic range in the warfarin group was 29 (21%). A total of 114 (61%) patients received a reduced dosage of DOACs. Comparing the elderly and younger patients, there were significant differences in several characteristics and examination results.

COMPARISON OF PERIPROCEDURAL COMPLICATIONS BETWEEN THE ELDERLY AND YOUNGER GROUPS. During the periprocedural period, major bleeding and minor bleeding events occurred in 10 and 30 patients in the elderly group, respectively. No thromboembolic events were observed. Compared with the younger group, the elderly group had a significantly higher number of major bleeding events (3.1% vs. 1.3%; p = 0.023) and minor bleeding events (9.2% vs. 5.0%; p = 0.002), except for the thromboembolic events (0% vs. 0.8%; p = 0.248) (Figure 1). Details of the periprocedural complications in the elderly and younger patients are reported in Table 2. Of note, the elderly patients had a significantly higher occurrence of bleeding hematoma requiring blood transfusion (1.2% vs. 0.1%; p = 0.002) (a major bleeding event) and of puncture site bleeding or hematoma (8.3% vs. 4.1%; p = 0.001) (a minor bleeding event) compared with the younger patients (Figure 2). In addition, the risk of major bleeding events for the elderly patients was higher than for the younger patients among the warfarin group (4.3% vs. 1.3%; p = 0.025), whereas

TABLE 1 Comparison of Baseline Characteristics Between the Elderly and Younger Groups

	Age ≥75 yrs (n = 325)	Age <75 yrs (n = 1,839)	p Value
Age, yrs	78.1 ± 2.7	60.5 ± 10.2	<0.001
Male	188 (58)	1,415 (77)	<0.001
Body weight, kg	57.7 ± 11.2	66.8 ± 12.6	<0.001
Body mass index, kg/m^2	23.1 ± 3.9	24.3 ± 4.7	<0.001
Duration of AF, yrs	3.5 ± 5.3	3.9 ± 4.5	0.218
Paroxysmal AF	238 (73)	1,235 (67)	0.030
Symptoms	259 (80)	1.320 (72)	0.003
Medications			
No. of antiarrhythmic drugs	0.8 ± 0.8	0.8 ± 0.8	0.517
Antiplatelet drug	58 (18)	214 (12)	0.002
Comorbidities			
Hypertension	206 (63)	803 (44)	<0.001
Diabetes mellitus	55 (17)	247 (13)	0.094
Heart failure	59 (18)	235 (13)	0.009
Stroke	28 (8.6)	139 (7.6)	0.510
History of maze procedure	4 (1)	17 (1)	0.528
Echocardiographic data			
Left atrial diameter, mm	40.3 ± 6.5	39.5 ± 6.8	0.047
Left ventricular ejection fraction, %	61.9 ± 9.7	60.6 ± 9.6	0.027
$CHADS_2$ score	2.2 ± 0.9	0.9 ± 1.0	<0.001
CHA_2DS_2-VASc score	3.7 ± 1.1	1.6 ± 1.4	<0.001
HAS-BLED score	2.0 ± 0.8	1.1 ± 1.0	<0.001
Laboratory data			
Creatinine clearance, ml/min	54.1 ± 17.7	89.4 ± 35.2	<0.001
B-type natriuretic peptide levels, pg/dl	161.4 ± 283.3	88.7 ± 180.1	<0.001
Ablation procedures			
Radiofrequency ablation	275 (85)	1,564 (85)	0.841
Repeat ablation	115 (35)	554 (30)	0.059
Oral anticoagulant agents			
Dabigatran			
150 mg*	5 (1.5)	117 (6.4)	
110 mg*	41 (13)	170 (9.2)	
Rivaroxaban			
15 mg†	12 (3.7)	172 (9.4)	
10 mg†	24 (7.4)	20 (1.1)	
Apixaban			
5 mg*	52 (16)	411 (22)	
2.5 mg*	37 (11)	41 (0.8)	
Edoxaban			
60 mg†	3 (0.9)	20 (1.1)	
30 mg†	12 (3.7)	19 (1)	
Warfarin	139 (43)	896 (49)	0.048
International normalized ratio	2.0 ± 0.5	2.1 ± 0.6	0.379
Under the therapeutic range	29 (21)	410 (46)	<0.001

Values are mean ± SD or n (%). *Twice daily. †Once daily.

AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, and drugs/alcohol concomitantly.

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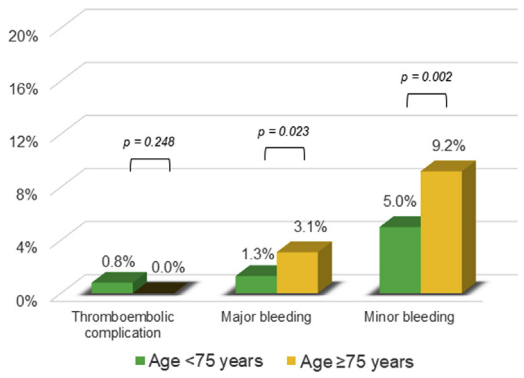
FIGURE 1 Comparison of the Periprocedural Complications Between the Elderly and Younger Groups



the risk of minor bleeding events was higher in the elderly patients among the DOAC group (9.7% vs. 4.9%; p = 0.010) (Online Figure 1).

DETAILED COMPLICATIONS AND THEIR TREATMENTS. Regarding the major bleeding events in the elderly group, 5 patients developed cardiac tamponade requiring drainage. Among them, 2 patients (80-year-old and 81-year-old men) receiving DOACs had restored stable hemodynamic condition after puncture drainage and protamine infusion. The DOACs (apixaban and dabigatran) were discontinued for only 2 to 3 days after the occurrence of complications.

TABLE 2 Comparison of the Detailed Periprocedural Complications Between the Elderly and Younger Groups

	Age ≥75 yrs (n = 325)	Age <75 yrs (n = 1,839)	p Value
Thromboembolic complications	0 (0)	14 (0.8)	0.248
Cerebral infarction	0 (0)	10 (0.5)	0.376
Transient ischemic attack	0 (0)	4 (0.2)	0.999
Major bleeding complications	10 (3.1)	23 (1.3)	0.023
Cardiac tamponade	5 (1.5)	15 (0.8)	0.209
Vascular complications	1 (0.3)	3 (0.2)	0.479
Arteriovenous fistula requiring surgery	0 (0)	2 (0.1)	0.999
Bleeding hematoma requiring blood transfusion	4 (1.2)	1 (0.1)	0.002
Pericardial effusion requiring blood transfusion	0 (0)	1 (0.1)	0.999
Gastrointestinal bleeding requiring blood transfusion	0 (0)	1 (0.1)	0.999
Minor bleeding complications	30 (9.2)	92 (5)	0.002
Puncture site bleeding or hematoma	27 (8.3)	75 (4.1)	0.001
Pericardial effusion without tamponade	1 (0.3)	6 (0.3)	0.999
Arteriovenous fistula	1 (0.3)	4 (0.2)	0.557
Vascular pseudoaneurysm	1 (0.3)	5 (0.3)	0.999
Continuous hematuria	0 (0)	1 (0.1)	0.999
Continuous bloody phlegm	0 (0)	1 (0.1)	0.999
Major adverse events	40 (12)	129 (7)	0.001

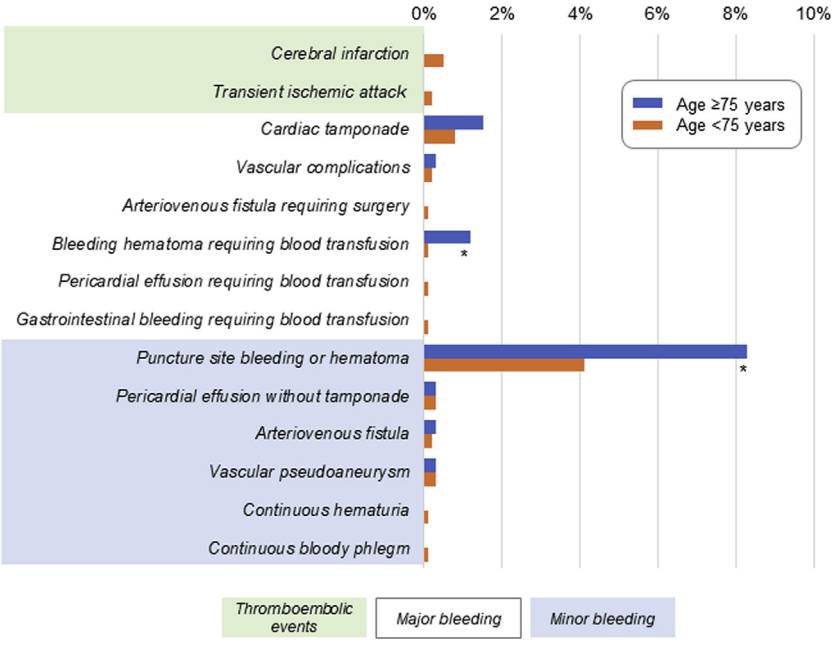
Values are n (%).

In 2 patients who received warfarin (82-year-old and 83-year-old women), the hemodynamic condition was restored after cardiac tamponade via protamine infusion, blood transfusion, and administration of vitamin K following pericardial puncture drainage. Warfarin was discontinued for 2 to 4 days after the complications. Another 76-year-old man receiving apixaban underwent surgical repair for cardiac tamponade owing to inability to stop bleeding after puncture drainage, protamine infusion, and blood product use. The apixaban was discontinued for 2 days after the procedure. In terms of vascular complication, a 78-year-old man receiving warfarin required endovascular embolic treatment for a bleeding peripheral branch of the femoral artery that was refractory to compression. Three other patients (76-year-old, 83-year-old, and 84-year-old women) who received warfarin, and an 80-year-old woman who received apixaban, required blood transfusions due to anemia related to a puncture site bleeding hematoma. After treatment for the bleeding complications, all patients could be discharged from our hospital without any adverse effect; 1 patient transferred to an extended care hospital owing to decreased daily physical activity after recovery from cardiac tamponade.

Online Table 1 presents additional details of the thromboembolic events and major bleeding events in the younger study group. The mean discontinuation time of oral anticoagulants after the major bleeding events in the elderly and younger groups was 1.4 ± 1.4 days and 3.0 ± 2.9 days, respectively (p = 0.057). In all patients with minor bleeding events in the elderly group, the anticoagulant drugs were continued, except for 1 patient who stopped warfarin for 1 day; 92% of patients in the younger group continued oral anticoagulant use after the minor bleeding events.

COMPARISON OF THE COMPLICATIONS BETWEEN THE DOAC VERSUS WARFARIN GROUPS. Online Table 2 displays a comparison of the demographic and baseline characteristics between the DOAC and warfarin groups in the elderly and younger groups. In the elderly group, there were no significant differences in major bleeding events (2.2% vs. 4.3%; p = 0.336) and minor bleeding events (9.7% vs. 8.6%; p = 0.748) in the DOAC and warfarin groups (Online Figure 2). No significant difference in major and minor bleeding events among the 4 different DOACs was found. In the patients who received rivaroxaban, the morning session without food intake was performed in 9 patients (15 mg in 3 patients). No patients except for 1 with a minor

FIGURE 2 Comparison of the Detailed Complication Rates Between the Elderly and Younger Groups



*p < 0.05.

bleeding event experienced any adverse events. The mean (maximum, minimum) ACT during the procedure in the DOAC and warfarin groups were 309 (352, 267) s and 320 (360, 278) s ($p = 0.012$), respectively. By contrast, in the younger group, there were no significant differences in major adverse events between the DOAC and warfarin groups (Online Figure 2). After adjustment using propensity score matching analyses for DOAC and warfarin groups in the matched 158 elderly and 786 younger patients, no significant differences in the incidence of thromboembolic and bleeding events were observed between the 2 groups of patients.

PREDICTORS OF COMPLICATIONS IN THE ELDERLY GROUP. The predictor of major adverse events in the elderly group was evaluated by using logistic regression analyses (**Table 3**). The univariate logistic regression analyses showed that body mass index, body weight, antiplatelet drug use, and impaired renal function (creatinine clearance <50 ml/min) were significantly associated with adverse events during the procedure. In the subsequent multivariate analysis, lower body weight (odds ratio: 0.96; 95% confidence interval: 0.93 to 0.99; $p = 0.010$), and antiplatelet drug use (odds ratio: 2.21; 95% confidence interval: 1.04 to 4.67; $p = 0.039$) were independent predictors of total events.

DISCUSSION

Thromboembolic events and bleeding complications related to catheter ablation for AF are major concerns, especially in elderly patients. To date, very few studies have focused on these complications in elderly patients during catheter ablation for AF. A recent report from the German ablation registry reported a significantly higher incidence of periprocedural stroke events in patients ≥75 years of age compared with those <75 years of age, although the rate of nonfatal in-hospital complications was similar between the 2 age groups (16). Conversely, among patients ≥65 years of age, age >75 years was the only independent predictor of cerebrovascular events after ablation for AF in another previous study (21). However, oral anticoagulants (warfarin) were interruptedly administered during the ablation in the aforementioned studies. Currently, uninterrupted vitamin K antagonism during the ablation procedure has been widely accepted to reduce stroke events without increasing bleeding compared with interrupted warfarin treatment (4). Recent studies have also reported that perioperative uninterrupted DOAC use was similarly feasible and safe compared with uninterrupted warfarin treatment (5-15). It is unclear whether these results can be applied to elderly

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TABLE 3 Predictors of Major Adverse Events in the Elderly Group

	Major Adverse Events		Univariate Analysis		Multivariate Analysis	
	Yes (n = 40)	No (n = 285)	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yrs	78.4 ± 2.8	78.1 ± 2.7	1.04 (0.92–1.17)	0.557		
Female	20 (50%)	117 (41%)	1.44 (0.74–2.79)	0.285		
Body mass index, kg/m^2	22.0 ± 3.3	23.3 ± 4.0	0.91 (0.82–0.99)	0.048*		
Body weight, kg	52.9 ± 10.8	58.4 ± 11.1	0.95 (0.92–0.99)	0.004*	0.96 (0.93–0.99)	0.010
Duration of AF, yrs	3.7 ± 7.7	3.5 ± 4.8	1.01 (0.95–1.07)	0.784		
Paroxysmal AF	30 (75%)	208 (73%)	1.11 (0.52–2.38)	0.787		
Antiplatelet drug use	13 (33%)	45 (16%)	2.57 (1.23–5.35)	0.012*	2.21 (1.04–4.67)	0.039
DOAC use	22 (55%)	164 (58%)	0.90 (0.46–1.76)	0.761		
Left atrial diameter, mm	42.0 ± 6.5	40.0 ± 6.5	1.05 (0.99–1.10)	0.069		
Left ventricular ejection fraction, %	62.0 ± 9.2	61.9 ± 9.7	1.00 (0.97–1.04)	0.922		
$CHADS_2$ score	2.1 ± 0.9	2.2 ± 0.9	0.85 (0.58–1.26)	0.419		
CHA_2DS_2-VASc score	3.8 ± 1.0	3.7 ± 1.1	1.06 (0.79–1.43)	0.681		
HAS-BLED score	2.1 ± 0.8	2.0 ± 0.8	1.11 (0.73–1.68)	0.624		
Impaired renal function (CrCl <50 ml/min)	25 (63%)	114 (40%)	2.50 (1.26–4.95)	0.009*		
First session for AF	27 (68%)	183 (64%)	1.16 (0.57–2.34)	0.684		
Radiofrequency ablation	35 (88%)	240 (84%)	1.31 (0.49–3.53)	0.590		

Values are mean ± SD or n (%). *Variables included in the multivariate model using a forward stepwise method.
CI = confidence interval; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; OR = odds ratio; other abbreviations as in Table 1.

patients who undergo catheter ablation for AF. Considering that elderly patients with AF are at a higher risk of both thromboembolic and bleeding events during the ablation procedure owing to their higher rate of comorbidities, the administration of uninterrupted anticoagulant drugs during the procedure may be desirable for prevention of stroke; however, this approach requires careful attention to evaluate for increasing risks of bleeding events.

Regarding the stroke events, in patients ≥75 years of age, recent studies reported a stroke event rate of 0.8% to 1.3% during the procedures under interrupted warfarin use (16,22). Metzner et al. (23) reported 2 cases of cerebellar stroke and transient ischemic attack events in 137 procedures among patients ≥75 years of age (the anticoagulant regimen during the ablation was not noted). In contrast, our results showed that there was no symptomatic thromboembolic event in the elderly patients, which suggests that both continuous DOAC and warfarin treatment during ablation procedures may be effective for suppression of thrombi production during the procedure. Moreover, despite more than one-half of the patients with DOAC receiving a reduced dosage due to comorbidities, the effect of uninterrupted DOAC use in elderly patients during catheter ablation was confirmed in the present study. One potential benefit of DOAC administration is its short half-live and rapid onset of action with shorter time to reach therapeutic anticoagulation levels without the need for coagulation monitoring. Considering that 20% of the patients in the warfarin group were in the subtherapeutic anticoagulation range, our results might suggest administration of DOAC as an alternative and feasible therapeutic approach for catheter ablation for elderly patients with AF; furthermore, there may be no need to switch from DOAC to warfarin administration to perform the catheter ablation procedure. However, this retrospective nonrandomized study with a relatively small sample of elderly subjects from a single center does not guarantee the efficacy and safety of uninterrupted use of DOAC during the ablation; further large-scale randomized studies are suggested.

In terms of bleeding complications, we found that elderly patients developed more bleeding complications while undergoing continuous anticoagulant therapy during catheter ablation for AF than did younger patients. This finding was because elderly patients have more comorbidities than younger patients with AF. Compared with the bleeding rates with interrupted anticoagulant use in elderly patients in previous studies (1.3% of the major hemorrhage events from the German ablation registry [16] and 1.5% of major bleeding events in the report by Nademanee et al. [22]), the rate of major bleeding complications (3.1%) was indeed higher in our study in which uninterrupted DOAC and warfarin administration was adopted. However, the temporary discontinuation of the anticoagulant drugs after major

bleeding events lasted only a few days, with all patients maintaining a hemodynamically stable condition. It could be proposed that both uninterrupted DOAC and warfarin use during catheter ablation for AF in elderly patients may be a feasible therapeutic option. Nevertheless, concerns regarding DOAC-related major bleeding events remain because specific commercially available antidotes are not available to-date for DOACs, with the exception of dabigatran (24). Indeed, 1 patient receiving apixaban underwent surgical repair for continuous bleeding of cardiac tamponade. The availability of specific reversal agents for all DOACs in clinical practice could provide a more reliable guarantee for the uninterrupted use of DOACs during catheter ablation for AF in elderly patients.

Although previously reported predictors of periprocedural complications, female sex and persistent AF or atrial tachycardia, were not found to be predictors in our study (13), it is plausible that elderly patients with lower body weight and using antiplatelet drugs are more likely to present with bleeding complications. Careful attention and strict monitoring of those patients who underwent catheter ablation for AF may be required to avoid severe bleeding events.

STUDY LIMITATIONS. This study was retrospectively performed in a single institution, and the sample size was relatively small, especially in the elderly group. Hence, focusing on elderly patients to evaluate the outcomes was, in part, limited. Moreover, because the size of the study was underpowered to detect differences among oral anticoagulant types between the young and elderly patients, the lack of difference may reflect a type II error, thus making these analyses more speculative than definitive. The selections of a DOAC or warfarin and different techniques for catheter AF ablation between the elderly and younger patients were determined by the attending physician. Therefore, some baseline characteristics between the 2 groups were different in this nonrandomized study. Although we performed a propensity score matched analysis, there may be a substantial unknown bias between the 2 treatments. In addition, the researchers evaluated the adverse events without being blinded to the type of anticoagulant drugs used. Although all the complications were reviewed and confirmed by the researchers in this study, some bias regarding outcome calculation might have occurred. Further multicenter randomized, prospective studies with large sample sizes are required to verify these issues.

Moreover, oral bioavailability of ≥15 mg of rivaroxaban is decreased under fasting conditions (25). Rivaroxaban was not used as an uninterrupted regimen completely under morning fasting conditions in the morning session, but it needed to be prescribed in the evening the day before the procedure (11,12); however, most of the elderly patients received a reduce dose of rivaroxaban (10 mg) and had only 1 minor bleeding event with no thromboembolic events in our study. Finally, we evaluated the thromboembolic events based on the patients' reported symptomatic abnormalities. We did not perform magnetic resonance imaging for all patients to detect nonsymptomatic stroke and brain microbleeding events, which could have resulted in an underestimation of the thromboembolic events.

CONCLUSIONS

The rate of periprocedural complications in the uninterrupted DOAC group was similar to that in the uninterrupted warfarin group among elderly patients. However, periprocedural bleeding events during the use of uninterrupted oral anticoagulants in catheter ablation were significantly higher in the elderly group than in the younger group. This outcome highlights the need to monitor such patients more closely during periprocedural ablation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present study shows the efficacy and feasibility of uninterrupted oral anticoagulant use during catheter ablation for AF in elderly patients. Although the rate of periprocedural complications in the uninterrupted DOAC group was similar to that in the uninterrupted warfarin group among elderly patients, the number of periprocedural bleeding events was significantly higher in the elderly group than in the younger group.

TRANSLATIONAL OUTLOOK: Further multicenter randomized, prospective studies with large sample sizes are required to verify the efficacy and feasibility of uninterrupted DOAC and warfarin use during catheter ablation for AF in elderly patients.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.