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ORIGINAL ARTICLE

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Comparison of direct oral anticoagulants and warfarin regarding midterm adverse events in patients with atrial fibrillation undergoing catheter ablation

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Abstract

Background: Oral anticoagulants, including direct oral anticoagulants (DOACs), are usually required in atrial fibrillation (AF) patients who are at a high risk of thromboembolism (TE), even if they had undergone catheter ablation (CA). Although several studies have reported the safety and efficacy of DOACs around CA in AF patients, there are only limited data regarding the midterm incidence of TE and bleeding complications post-CA among AF patients treated with warfarin or DOACs.

Methods: We studied 629 AF patients (mean age: 65.3 ± 10.3 years; 442 men) undergoing CA, to calculate the midterm incidence of TE and bleeding complications associated with warfarin or DOACs.

Results: In total, 292 patients used warfarin and 337 used DOACs (dabigatran: 90 patients; rivaroxaban: 137; and apixaban: 110). At baseline, the CHA2DS2-VASc and HAS-BLED scores were similar between the 2 groups. During a median follow-up period of 7 months, no TE complications occurred. The warfarin group had a significantly higher bleeding event rate than did the DOACs group (all bleeding complications: 32 [11.0%] vs 15 [4.5%], respectively, $P = .002$). The rate of all bleeding complications was significantly higher in the warfarin group than in the DOACs group (10.1% vs 3.7%, respectively, at 10 months; $P = .024$). In Cox proportional hazards modeling, DOAC use was significantly associated with a decreased risk of bleeding (adjusted hazard ratio: 0.497; 95% confidence interval: 0.261-0.906, $P = .022$).

Conclusions: Direct oral anticoagulant use in AF patients undergoing CA may be associated with a similar risk of TE as warfarin but is associated with a lower risk of bleeding.

KEYWORDS
atrial fibrillation, catheter ablation, complication, direct oral anticoagulants, warfarin

1 | INTRODUCTION

Catheter ablation (CA) is an established treatment for patients with drug-refractory atrial fibrillation (AF).[1–3] Several studies have reported that CA for AF reduced the risk of thromboembolism (TE), including stroke. Anticoagulation therapy discontinuation could be considered in some AF patients who undergo CA.[4] However, AF patients with a high risk of TE or a history of stroke should continue using anticoagulant drugs, even if they have undergone CA for AF.[4,5]

Recently, the use of direct oral anticoagulants (DOACs) is increasing as a substitute for warfarin in patients with AF,[6] and several large clinical studies have evaluated the safety and efficacy of DOACs around CA for AF.[7–11] However, the data are limited regarding adverse events with the long-term use of DOACs in patients requiring continuous anticoagulant drugs after CA for AF.

The purpose of this study was to compare the midterm incidence of TE and bleeding complications after CA among AF patients receiving postprocedural treatment with warfarin or DOACs.

2 | METHODS

2.1 | Subjects

We identified consecutive patients who underwent radiofrequency CA between January 2013 and July 2015 at the Japanese Red Cross Musashino Hospital. All patients were required to have at least one filled prescription for an oral anticoagulant (OAC). Patients who continued taking an OAC for at least 4 weeks prior to CA and at least 4 weeks afterward were included in this study, because we aimed to examine the relationship between adverse events and the OAC status in patients with AF after CA. Neither the type of AF (paroxysmal, persistent, or permanent) nor the number of AF ablation sessions (1st, 2nd, 3rd, or 4th) was considered when we selected patients. We obtained clinical data including the drug dosage and results of laboratory examinations from the patients' medical records. A total of 731 AF patients were identified as consecutive patients who underwent CA in this study. We excluded 102 AF patients with the following conditions from this study: those with 2 or more OACs, those with an overdose of DOACs, those in whom CA was performed without of the use of an OAC, those in whom CA was performed less than 4 weeks after DOAC was started, those in whom an OAC was changed immediately after CA, and those in whom follow-up data for more than 4 weeks after CA was unavailable. Therefore, 629 AF patients were included in the current analysis. This study was approved by the institutional review board of the Japanese Red Cross Musashino Hospital, and this study complied with the ethical principles of the Declaration of Helsinki and the Japanese Ethical Guideline for Medical and Health Research Involving Human Subjects. All participants were notified that they would be included in the study, and we explained to them that they were free to opt out of participation at any time.

2.2 | Baseline characteristics and OAC status

We collected baseline data, including demographics (age, sex, and body mass index), type of AF, the ratio of the first AF ablation session, duration of AF history, comorbidities, CHA2DS2-VASc score, HAS-BLED score, echocardiographic parameters, and brain natriuretic peptide level. The CHA2DS2-VASc score was calculated for each patient, with a total possible score of 0 to 9 points (1 point for congestive heart failure, 1 for hypertension, 1 for diabetes, 2 for ischemic stroke or transient ischemic attack [TIA], 1 for vascular disease, 1 for age 65 to 74 years, 2 for age ≥75 years, and 1 for female sex). The HAS-BLED score was calculated for each patient, with a total score of 0 to 9 points (1 point for hypertension, 1 for abnormal renal function, 1 for abnormal liver function, 1 for stroke history, 1 for bleeding history, 1 for a labile international normalized ratio [INR], 1 for age ≥65 years, 1 for use of an antiplatelet drug, and 1 for alcohol dependence).

In the current analysis, antiplatelet drugs used were aspirin, clopidogrel, ticlopidine, and cilostazol. The OAC status included warfarin and 3 DOACs: dabigatran, rivaroxaban, and apixaban. The prothrombin time-INR (PT-INR) of warfarin users was measured before CA. When analyzing the administration of warfarin, we determined that the optimal therapeutic range of the PT-INR was 1.6-2.6 for age ≥70 years and 2.0-3.0 for age <70 years, according to the Guidelines for Pharmacotherapy of Atrial Fibrillation.[12–14] We selected the DOAC dose based on the manufacturer's label recommendations. The appropriate standard dose and indicated reduced dose were defined as administration according to a standard- or reduced-dose regimen, respectively. For example, the standard dose of rivaroxaban was 15 mg/day for patients with a creatinine clearance level ≥50 mL/min. The definition of a reduced-dose regimen for each DOAC is as follows. Dabigatran is suggested for patients with any one of the following: age ≥70 years, creatinine clearance level of 30-50 mL/min, history of major bleeding, and the use of p-glycoprotein inhibitors. Rivaroxaban should be reduced in patients with a creatinine clearance level of 15-49 mL/min, and apixaban should be reduced in patients with any 2 of the following: body weight ≤60 kg, age ≥80 years, and serum creatinine level ≥1.5 mg/dL.

2.3 | Follow-up strategy

Follow-up data were obtained at routine or additional visits at our institution. The patients were followed from 4 weeks after CA until the end of the follow-up period (September 2016) or until the OAC was discontinued, the OAC was changed, or the next CA session was performed for recurrent AF. The OAC was discontinued at 3 to 6 months after CA in AF recurrence-free patients without the risk factors of TE. TE and bleeding complications were evaluated in patients in the warfarin and DOACs groups during the follow-up period.

2.4 | Efficacy and safety endpoints

The efficacy endpoint was evaluated in terms of the incidence of TE complications, including TIA and symptomatic cerebral infarction. Patients with silent cerebral infarction as seen on magnetic resonance imaging were not included in this study. The safety endpoint was evaluated in terms of major and minor bleeding complications. The major bleeding complications were defined as fatal bleeding, symptomatic bleeding at a critical site, bleeding causing a decrease in the hemoglobin level of ≥2 g/dL, or bleeding requiring transfusion.[15] Minor bleeding complications were defined as bleeding that did not require invasive treatment, and these complications included epistaxis, hematuria, bloody stool, bloody sputum, hematoma, subcutaneous hemorrhage, subconjunctival hemorrhage, intraoral hemorrhage, and pericardial effusion.[16]

2.5 | Statistical analysis

All continuous variables in the warfarin and DOACs groups are summarized as the mean ± standard deviation or median and interquartile range. Differences in the clinical characteristics between the 2 groups were analyzed using the Mann-Whitney *U* test, Chi-squared test, or Fisher's exact test, as appropriate. A Kaplan-Meier analysis was used to summarize the midterm incidence of all bleeding complications in patients in the 2 groups, and the incidence of events was compared between the 2 groups using the log-rank test. A Cox proportional hazard model was used to evaluate the association between the use of DOACs and all bleeding complications. The results of the Cox proportional hazards modeling were given as a hazard ratio (HR) and 95% confidence interval (CI). We used the HAS-BLED score as an adjustment variable in a multivariate Cox proportional analysis for the midterm incidence of all bleeding complications, because the HAS-BLED score is frequently used in clinical practice to assess the individual bleeding risk of patients with AF.[17] All analyses were performed with JMP software version 12.2.0 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

We included 629 consecutive AF patients in the analyses. There were no cases in which OAC was discontinued within 4 weeks after CA due to bleeding complications in this study. The patients' clinical characteristics are shown in Table 1. Among the 629 patients (mean age: 65.3 ± 10.3 years; 442 men), 292 (46.4%) patients took warfarin and 337 (53.6%) patients took a DOAC (dabigatran: n = 90 [26.7%], rivaroxaban: n = 137 [40.7%], or apixaban: n = 110 [32.6%]). The patients in the warfarin group were significantly older than those in the DOACs group, and there was a higher ratio of patients with paroxysmal AF in the warfarin group than in the DOACs group. The incidence of heart failure, as well as the brain natriuretic peptide level, was higher in the warfarin group than in the DOACs group. The CHA2DS2-VASc score and HAS-BLED score were similar between the 2 groups; however, creatinine clearance was lower in the warfarin group than in the DOACs group.

3.2 | OAC management

Among the 337 patients who were prescribed a DOAC, 54 dabigatran users, 19 rivaroxaban users, and 17 apixaban users were prescribed a reduced dose. Additionally, 38 patients (11.3% of all DOAC patients) were prescribed off-label under dose or non-suggested-dose DOACs and most of the under dose DOACs user were included in the dabigatran group. The mean PT-INR in the warfarin group was 2.01 ± 0.45, and 61.6% of warfarin users had a PT-INR within the optimal therapeutic range. On the contrary, 34.9% had a PT-INR below the therapeutic range and 3.4% had a PT-INR above the therapeutic range. Antiplatelet drugs were used in 25 warfarin users (8.6%) and 20 DOACs users (5.9%), and there was no significant difference in the co-use of antiplatelet drugs between the 2 groups (Table 2).

3.3 | Clinical endpoints

Table 3 shows the clinical outcomes. In the warfarin group, no TE complications occurred during the follow-up period, whereas all types of bleeding complications occurred in 32 patients (11.0%). Major bleeding complications occurred in 6 patients (2.1%), and minor bleeding complications occurred in 26 (8.9%). In the DOACs group, no TE complications occurred during the follow-up period, whereas all types of bleeding complications occurred in 15 patients (4.5%). Major bleeding complications occurred in 4 patients (1.2%) and minor bleeding complications occurred in 12 (3.6%). When the rates of TE complications were compared between the warfarin and DOAC groups, no significant differences were found. However, patients in the warfarin group had a significantly higher rate of minor bleeding complications than did those in the DOACs group (8.9% vs 3.6%, respectively, $P = .005$). All types of bleeding complications occurred more frequently in the warfarin group than in the DOACs group (11.0% vs 4.5%, respectively, $P = .002$).

Figure 1 shows the rate of all bleeding complications after the ablation procedure according to the anticoagulant drug status. The rate of all types of bleeding complications at 10 months after CA was 10.1% in the warfarin group and 3.7% in the DOACs group. The Kaplan-Meier analysis showed that the rate of all types of bleeding complications was significantly higher in the warfarin group than in the DOACs group during a median follow-up period of 7 months (range: 4-14 months) after CA (log-rank; $P = .024$).

Table 4 shows the results of the multivariate Cox proportional analysis for all bleeding complications. DOACs use was significantly associated with a decreased risk of all bleeding complications (adjusted HR: 0.497; 95% CI: 0.261-0.906, $P = .022$).

TABLE 1 Comparison of patient clinical characteristics between warfarin and DOACs group

	Total patients (n = 629)	Warfarin (n = 292)	DOACs (n = 337)	*P* value
Age (y)	65.3 ± 10.3	66.4 ± 9.9	64.3 ± 10.6	.013
Male	442 (70.3%)	204 (69.9%)	238 (70.6%)	.835
BMI (kg/m^2)	23.7 ± 3.4	23.6 ± 3.4	23.8 ± 3.3	.612
Paroxysmal AF	354 (56.3%)	125 (42.8%)	229 (68.0%)	<.01
1st session	459 (73.0%)	188 (64.4%)	271 (80.4%)	<.01
Duration of AF history (mo)	5 (2-21)	8.5 (3-36)	4 (1-12.5)	<.01
Hypertension	279 (44.4%)	118 (40.6%)	161 (47.8%)	.069
Diabetes	66 (10.4%)	34 (11.6%)	32 (9.5%)	.381
Heart failure	108 (17.2%)	62 (21.2%)	46 (13.7%)	.012
Stroke	50 (7.9%)	28 (9.6%)	22 (6.5%)	.158
Vascular disease	13 (2.1%)	6 (2.1%)	7 (2.1%)	.989
CHA2DS2-VASc score	2.0 ± 1.4	2.1 ± 1.5	1.9 ± 1.3	.078
HAS-BLED score	1.3 ± 0.9	1.4 ± 1.0	1.3 ± 0.9	.175
Echocardiography				
Ejection fraction (%)	65.8 ± 10.8	65.1 ± 11.7	66.4 ± 10.0	.135
Left atrium diameter (mm)	38.5 ± 6.8	39.5 ± 7.1	37.7 ± 6.4	<.01
CCr (mL/min)	79.5 ± 29.1	74.2 ± 30.3	84.1 ± 27.3	<.01
BNP (pg/mL)	61.3 (27.6-119.2)	78.7 (45.7-147.5)	45.2 (19.5-98.5)	<.01
Duration of OAC use (mo)	7 (4-14)	9 (5-16)	7 (4-13)	<.01

Values are shown as the mean ± standard deviation or median (interquartile range) or n (%).
DOACs, direct oral anticoagulants; BMI, body mass index; AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≧75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years and sex category; HAS-BLED, hypertension, abnormal renal function/liver function, stroke, prior bleeding, elderly (age ≧65 years), use of antiplatelet drugs/alcohol dependence, Labile international normalized ratio; CCr, creatinine clearance; OAC, oral anticoagulant.

In addition, when we analyzed the clinical outcomes of 591 AF patients, excluding those with off-label under dose or non-suggested-dose DOACs, we obtained same results.

4 | DISCUSSION

The main findings of the present study were as follows: (i) there was no significant difference in the CHA2DS2-VASc score and HAS-BLED score (including the rate of combined antiplatelet drugs) between the warfarin and DOACs groups; (ii) there was no significant difference in the prevalence of TE and major bleeding complications between the warfarin and DOACs groups during the follow-up period; (iii) patients in the warfarin group had more minor bleeding complications than did those in the DOACs group, and the rate of all types of bleeding complications was significantly higher in the warfarin group than that in the DOACs group, as assessed with the Kaplan-Meier analysis; and (iv) in a multivariate Cox proportional analysis for all bleeding complications, the use of DOACs was significantly associated with a decreased risk of all types of bleeding complications.

Randomized controlled trials, such as the RE-LY, ROCKET AF, and ARISTOTLE, have reported the efficacy and safety of DOACs compared with warfarin.[6,18–20] A previous meta-analysis reported that DOACs significantly reduced TE, including stroke, compared with warfarin, and were similar to warfarin regarding the occurrence of major bleeding complications.[21] Conversely, DOACs were reported to be associated with an increased risk of gastrointestinal bleeding compared with warfarin.[22] As real-world data, the Fushimi AF Registry study showed that there was no significant difference in the incidence of stroke, TE, and major bleeding complications between warfarin and DOACs.[23] However, the occurrence of minor bleeding complications was not reported in that study.

The present study showed that there was no significant difference in the midterm incidence of TE and major bleeding complications between the warfarin and DOACs groups, similar to the result of the Fushimi AF Registry study. Furthermore, the prevalence of major bleeding complications was similar to that in previous studies targeting AF patients who did not undergo CA. Meanwhile, the prevalence of TE complications was lower in our study than that which has been reported in previous studies.[6,18–20,23] We targeted patients undergoing CA for AF, which is why these patients experienced some reduction of TE complications compared with previous studies.[24] We showed that patients in the warfarin group had significantly more minor bleeding complications than did those in the DOACs group. Although minor bleeding complications occur frequently in AF patients who are treated with an OAC, most previous studies concerning the prognosis and management of bleeding have focused on major bleeding,[25–29] and the incidence of minor bleeding complications has rarely been evaluated. The ARISTOTLE trial

TABLE 2 Details of anticoagulation management

	Warfarin (n = 292)	DOACs (n = 337)	*P* value
PT-INR	2.01 ± 0.45		
Within the optimal therapeutic range	180 (61.6%)		
Below the therapeutic range	102 (34.9%)		
Above the therapeutic range	10 (3.4%)		
Dabigatran all user		90 (26.7%)	
300 mg user		36 (10.7%)	
220 mg user		48 (14.2%)	
150 mg user		6 (1.8%)	
Rivaroxaban all user		137 (40.7%)	
15 mg user		118 (35.0%)	
10 mg user		19 (5.6%)	
Apixaban all user		110 (32.6%)	
10 mg user		93 (27.6%)	
5 mg user		17 (5.0%)	
Off-label under dose user		38 (11.3%)	
Dabigatran user		20 (5.9%)	
Rivaroxaban user		8 (2.4%)	
Apixaban user		10 (3.0%)	
Co-use of antiplatelet drug	25 (8.6%)	20 (5.9%)	.203

Values are shown as the mean ± standard deviation or n (%). DOACs, direct oral anticoagulants; PT-INR, prothorombin time-international normalized ratio.

TABLE 3 Comparison of thromboembolic and bleeding complications between warfarin and DOACs group

	Total patients (n = 629)	Warfarin (n = 292)	DOACs (n = 337)	*P* value
All thromboembolic complications	0 (0%)	0 (0%)	0 (0%)	–
Cerebral infarction	0 (0%)	0 (0%)	0 (0%)	
Transient ischemic attack	0 (0%)	0 (0%)	0 (0%)	
All types of bleeding complications	47 (7.5%)	32 (11.0%)	15 (4.5%)	.002
Major bleeding	10 (1.6%)	6 (2.1%)	4 (1.2%)	.386
Gastrointestinal bleeding	4 (0.6%)	2 (0.7%)	2 (0.6%)	
Hemoperitoneum	1 (0.2%)	1 (0.3%)	0 (0%)	
Cerebral bleeding	5 (0.8%)	3 (1.0%)	2 (0.6%)	
Minor bleeding	38 (6.0%)	26 (8.9%)	12 (3.6%)	.005
Epistaxis	4 (0.6%)	1 (0.3%)	3 (0.9%)	
Hematuria	7 (1.1%)	6 (2.1%)	1 (0.3%)	
Bloody stool	10 (1.6%)	6 (2.1%)	4 (1.2%)	
Bloody sputum	2 (0.3%)	1 (0.3%)	1 (0.3%)	
Hematoma	2 (0.3%)	2 (0.7%)	0 (0%)	
Subcutaneous hemorrhage	7 (1.1%)	6 (2.1%)	1 (0.3%)	
Intraoral hemorrhage	3 (0.5%)	3 (1.0%)	0 (0%)	
Subconjuctival hemorrhage	2 (0.3%)	0 (0%)	2 (0.6%)	
Pericardial effusion	1 (0.2%)	1 (0.3%)	0 (0%)	

DOACs, direct oral anticoagulants.

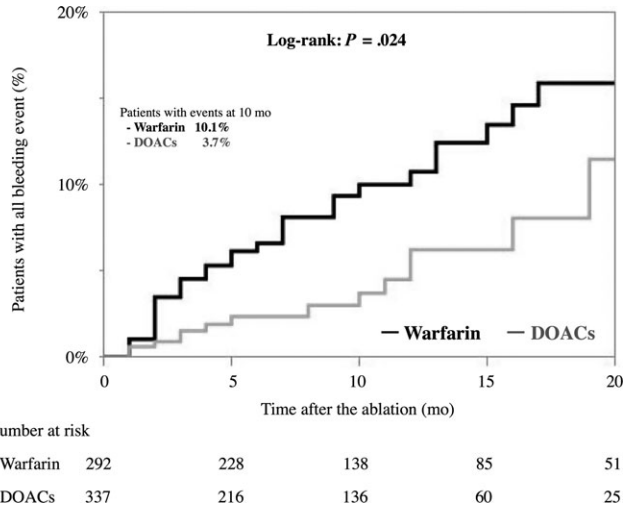

FIGURE 1 Kaplan-Meier curves for all types of bleeding complications after the ablation procedure according to oral anticoagulant status. DOACs, direct oral anticoagulants

reported that nonmajor bleeding, including minor bleeding, was less frequent in patients who were treated with apixaban than in those who were treated with warfarin; moreover, minor bleeding is very important, as it is a frequent clinical complication and often results in adverse outcomes including mortality and major bleeding events.[16] Although we were not able to prove whether the occurrence of minor bleeding was related to adverse outcomes because of the small number of patients who were included, considering this previous report, we consider that the present results are important.

In the present study, the HAS-BLED scores were similar between the 2 groups; however, creatinine clearance was lower in the warfarin group than in the DOACs group. Although creatinine clearance is generally an important factor of bleeding complications, the average value of creatinine clearance was more than 60 mL/min in the 2 groups. Thus, we speculated that the targeted patients in the present study were not at a high risk of bleeding complications in terms of renal function.

In the present study, there were some off-label under dose or non-suggested-dose DOAC users. The Fushimi AF Registry study mentioned that the use of off-label under dose DOAC might have influenced the clinical outcome.[23] However, in our study, only 11% of all DOAC users were prescribed off-label under dose or non-suggested-dose DOACs; moreover, the same result was obtained

TABLE 4 Multivariate Cox proportional analysis

	All types of bleeding complications		
Variables	**HR**	**95% CI**	***P* value**
DOACs use	0.497	0.261-0.906	.022
HAS-BLED score, 1 point increase	1.222	0.91-1.628	.179

HR, hazard ratio; 95% CI, 95% confidence interval; DOACs, direct oral anticoagulants; HAS-BLED, hypertension, abnormal renal function/liver function, stroke, prior bleeding, elderly (age ≧65 years), use of antiplatelet drugs/alcohol dependence, Labile international normalized ratio.

when we analyzed the clinical outcomes of 591 AF patients, excluding those with off-label under dose or non-suggested-dose DOACs. In addition, in the present study, most of the unde dose DOAC users were in the dabigatran group. A reduced dose of dabigatran was proven to be noninferior to warfarin in previous studies.[30] Therefore, the use of an off-label under dose or non-suggested-dose DOAC may have had little influence on the clinical outcomes of the present study.

4.1 | Study limitations

The present study has several limitations. First, this study was a small-scale, retrospective, and observational study at a single institution. Therefore, the Cox proportional hazards modeling might have been biased, and special care should be taken when interpreting the present results. The adjusted HR of the HAS-BLED score was 1.222 (95% CI: 0.91-1.628, $P = .179$), which indicates that the HAS-BLED score showed a 22% increase in bleeding events as a 1-point increase; however, it was not statistically significant, likely due to several reasons. First, the sample size was small and all bleeding events occurred in only 47 patients in the present study. Thus, we may have lacked statistical power. Second, the mean HAS-BLED score of the AF patient group in the present study was 1.3, which was lower than that which has been reported in other studies. A low HAS-BLED score of the participants may result in a low incidence of bleeding events in this study. Second, data on the therapeutic time range in the warfarin group during the follow-up period was not available. Thus, the influences of the quality of warfarin control on clinical events are unknown. Third, adherence to an OAC regimen during the follow-up period is important; however, we did not investigate this factor. Finally, the rate of AF recurrence after CA was not investigated; therefore, the impact of AF recurrence on the clinical outcome, especially TE complications, is not known.

5 | CONCLUSIONS

This retrospective study is one of the first studies to evaluate the midterm follow-up of patients with TE and bleeding events after CA. Furthermore, we found that the risk of TE complications in AF patients undergoing CA was similar among warfarin and DOACs users, whereas the risk of bleeding complications was lower in DOAC users than in warfarin users. DOACs might be suitable for patients requiring continuous OAC administration after CA for AF.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

ETHICAL APPROVAL

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of Japanese Red Cross Musashino Hospital, Approval No. 29081.

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