Current Status and Clinical Outcomes of Oral Anticoagulant Discontinuation After Ablation for Atrial Fibrillation in Japan
—Findings From the AF Frontier Ablation Registry—

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Background: The safety of discontinuing oral anticoagulant (OAC) after ablation for atrial fibrillation (AF) in Japanese patients has not been clarified.

Methods and Results: A study based on the Atrial Fibrillation registry to Follow the long-teRm Outcomes and use of aNTIcoagulants aftER Ablation (AF Frontier Ablation Registry) was conducted. Data were collected from 3,451 consecutive patients (74.1% men; age, 63.3±10.3 years) who had undergone AF ablation at any of 24 cardiovascular centers in Japan between August 2011 and July 2017. During a 20.7-month follow-up period, OAC therapy was discontinued in 1,836 (53.2%) patients; 51 patients (1.5%) suffered a stroke/transient ischemic attack (TIA), 71 (2.1%) suffered major bleeding, and 36 (1.0%) died. Patients in whom OAC therapy was discontinued were significantly younger than those in whom OACs were continued, and their CHA2DS2-VASc scores were significantly lower. The incidences of stroke/TIA, major bleeding, and death were significantly lower among these patients. Upon multivariate adjustment, stroke events were independently associated with relatively high baseline CHA2DS2-VASc scores but not with OAC status.

Conclusions: Although the incidences of stroke/TIA, major bleeding, and death were relatively low among patients for whom OAC therapy was discontinued, stroke/TIA occurrence was strongly associated with a high baseline stroke risk rather than with OAC status. Thus, discontinuation of OAC therapy requires careful consideration, especially in patients with a high baseline stroke risk.

Key Words: Ablation; Anticoagulant drugs; Atrial fibrillation; Mortality; Stroke

Atrial fibrillation (AF) affects quality of life and increases the risks of stroke, heart failure, and death.1 Pulmonary vein isolation (PVI) is reported to be more effective than antiarrhythmic drug (AAD) therapy for relief of symptoms and freedom from AF recurrence,2,3 and thus might yield improved clinical outcomes in terms of ischemic stroke, heart failure, and death. For patients in whom PVI is truly curative, it should be possible to discontinue oral anticoagulants (OACs) without fear that an AF-related clinical event will occur. Despite

Received July 3, 2019; revised manuscript received September 12, 2019; accepted September 17, 2019; J-STAGE Advance Publication released online October 16, 2019 Time for primary review: 22 days
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advancements in ablation technologies and strategies, however, the reported 1-year paroxysmal and non-paroxysmal AF recurrence rates are approximately 20% and >30%, respectively, and the rates increase gradually over the long term. Therefore, it remains unclear whether anticoagulant therapy can be safely terminated after PVI. Several current guidelines suggest that OAC discontinuation is limited to patients with a low CHADS2 score, and this has been confirmed by several clinical reports. Although most of the reported clinical data has been collected in Western countries, the findings may be applicable to Japanese patients, because the incidence of adverse clinical events among Japanese patients with AF appears to be lower than that among Western patients. Therefore, we conducted a registry-based observational study to investigate the rate at which anticoagulation therapy is terminated after AF ablation among patients in Japan and the relationship between discontinuation and the long-term incidences of stroke, major bleeding, cardiovascular events, and death.

Methods

Study Population
The study began with a review of the records of 3,530 consecutive patients who had undergone catheter ablation for AF at any of 24 cardiovascular centers in Japan between August 2011 and July 2017. All patients were listed in the Atrial Fibrillation registry to Follow the long-term Outcomes and use of ANTicoagulants after Ablation (AF Frontier Ablation Registry) (UMIN Clinical Trials Registry: UMIN000026849). The intended follow-up for each patient was a minimum of 12 months. Of the total patients, 79 were lost to follow-up, leaving 3,451 patients for inclusion in the study. Patients consented to the use of their anonymized clinical data for research purposes by the opt-out method, and the study protocol was approved by the institutional review boards of the 24 hospitals where patients were treated.

Data Collection
Patients’ characteristics and pre-ablation (baseline) and follow-up data were obtained through a review of their hospital charts. The anonymized patient data were collected in the Excel form by physicians or the clinical research coordinator at each institution, and included patients’ characteristics such as sex, age, body mass index (BMI), type of AF; number of ablation sessions (1, 2, 3 or >3 sessions); any comorbidity (hypertension, diabetes, history of a stroke/transient ischemic attack [TIA]); use of an OAC, including the type (warfarin vs. direct OAC [DOAC]), use of an antiplatelet drug; and laboratory test results (hemoglobin concentration and creatinine clearance [CrCl]); trans thoracic echocardiography-derived left atrial diameter (LAd) and left ventricular ejection fraction (LVEF), and the ablation method (radiofrequency [RF], cryoballoon or hot balloon). Follow-up variables included OAC discontinuation, AF recurrence after a blanking period of 3 months, occurrence of any adverse clinical event during the follow-up period, and whether AAD use had been discontinued by the end of the follow-up period.

Ablation Protocol
All AADs were discontinued 1 week before ablation. Generally, OACs were continued, but this varied from institution to institution, and the procedure itself was performed according to each institution’s particular protocol but generally as previously described. Extensive encircling PVI was guided by a circular mapping catheter or multiple-electrode catheter and a 3D mapping system. The ablation catheter was an irrigated-tip contact force (CF) sensing catheter or irrigated-tip standard non-CF sensing catheter, depending on the hospital’s preference or type of catheter available at the time of the procedure. In some patients, adenosine triphosphate was injected intravenously after PVI to provoke dormant PV conduction (performed at the physician’s discretion). If acute PV reconnection or dormant PV conduction was evident, touch-up ablation was performed.

Cryoballoon ablation was performed with an Arctic Front Advance cryoballoon (Medtronic, Minneapolis, MN, USA), as described previously. Each PV was encircled once (but twice if necessary). Any touch-up ablation required for dormant conduction or residual PV potentials was performed with a standard irrigated-tip catheter. Regardless of the ablation method, if sinus rhythm was not restored after PVI, additional linear LA ablation (e.g., mitral isthmus line or LA roof line ablation) was performed, and the residual potentials, including complex fractionated atrial ECGs in the LA, were ablated, as appropriate. Electrical cardioversion was performed when sustained AF/atrial tachycardia was recorded after additional LA ablation. Tricuspid valve isthmus ablation and superior vena cava isolation were also performed when necessary.

Post-Ablation Follow-up
All patients underwent routine follow-up examinations at their hospital’s outpatient clinic. AAD and OAC therapies were generally continued during the 3-month post-ablation blanking period. Thereafter, for patients in whom the arrhythmia did not recur, OAC and AAD therapies were discontinued. The post-ablation medications depended on the physician’s discretion, generally based on the patient’s characteristics or preferences. 24-hour Holter recordings were obtained 3–6 months after ablation. An ECG event recorder was used for any patient who reported cardiac symptoms. Any documented AF episode >30s in duration on the standard ECG recording, event-activated ECG recording, or 24-hour Holter recording was considered a recurrence.

Study Endpoints
The primary study endpoint was discontinuation of OAC therapy after ablation. There were 2 secondary endpoints: occurrence of a stroke (ischemic stroke or hemorrhagic...
stroke) or a TIA (efficacy endpoint) and occurrence of major bleeding (defined as a reduction in the hemoglobin concentration of at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ) (safety endpoint). Cardiovascular events, including hospitalization for heart failure, myocardial infarction/unstable angina or other cardiovascular events, and death from any cause (cardiovascular death, stroke-related death, and non-cardiovascular death) were assessed.

**Statistical Analysis**
Categorical variables are presented as the number and percentage.
Results

Clinical Characteristics

Clinical characteristics are shown for the total study patients and per study group in Table 1. The total male:female ratio was 2,558:893 and mean age 63.3±10.3 years. The AF was paroxysmal (lasting <7 days) in 2,157 (62.5%) patients, persistent (lasting ≥7 days to 12 months) in 1,036 (30.0%), and long-lasting persistent (lasting ≥12 months) in 258 (7.5%). Mean CHADS2 and CHA2DS2-VASc scores were 1.2±1.1 and 2.1±1.5, respectively. Standard RF ablation was performed in 1,523 (44.1%) patients, CF-based RF ablation in 1,678 (48.6%), cryoballoon ablation in 248 (7.1%), and hot balloon ablation in 2 (0.1%). Patients’ mean LAd was 40.0±6.6 mm and LVEF was 63.6±9.6%. Of the total 3,451 patients, 3,038 (88.0%) underwent a single AF ablation procedure, and the remaining 413 (12.0%) underwent ≥1 additional ablation procedures. During the post-ablation blanking period, warfarin was used by 711 (20.6%) patients, and DOACs were used by 2,698 (78.0%) patients, but the OAC type in 42 patients (1.2%) was not reported.
Outcomes and OAC Discontinuation/Continuation During Follow-up

During the final follow-up (median 20.7 [12.7–33.2] months), 2,405 (69.7%) of the 3,451 patients were arrhythmia-free, with 565 (23.5%) of these patients still taking an AAD. Kaplan-Meier freedom rate from AF recurrence among patients who underwent 1 ablation procedure was 78.4% at 1 year and 69.8% at 2 years, whereas that among patients who underwent ≥2 ablation procedures was 76.0% at 1 year and 65.0% at 2 years. OACs were discontinued in 1,836 (53.2%) patients (discontinuation group) at 5.4 (3.1–11.0) months after ablation. The OAC discontinuation rate increased predominantly in 43.3% at 1 year but thereafter increased modestly to 56.2% at 2 years (Figure 1A). The OAC discontinuation rate decreased gradually without a tipping point as the CHADS2 and CHA2DS2-VASc scores increased (Figure 1B,C, Table 1). As shown in Table 1, male sex was more prevalent in the OAC discontinuation group than in the OAC continuation group, patients in the OAC discontinuation group were significantly younger than those in the OAC continuation group, and BMI was significantly lower in this group. Antiplatelet drugs use was less prevalent, and the baseline hemoglobin concentration and CrCl were higher in this group. Also higher in this group were the prevalence of paroxysmal AF, the percentage of patients who required only 1 ablation session, the percentage of patients without a comorbidity, and the percentage of patients in whom AF did not recur during the follow-up period (P<0.05 for all). CHADS2 and CHA2DS2-VASc scores were lower, LVEF was greater, and LAd smaller in this group than in the OAC continuation group. DOAC use was greater in this group, as was non-use of AAD by the time of the final follow-up examination (P<0.05 for all).

By the time of the final follow-up examination, stroke/TIA had occurred in 51 (1.5%) of the total patients, major bleeding had occurred in 71 (2.1%), there was a cardiovascular event in 106 (3.1%), and 36 (1.0%) patients had died. Cardiovascular events consisted of 23 (0.7%) cases of myocardial infarction/unstable angina, 44 (1.3%) hospitalizations for heart failure, and 39 (1.1%) other cardiovascular events. Deaths comprised 5 (0.1%) cardiovascular deaths, 4 (0.1%) stroke-related deaths, and 27 (0.8%) non-cardiovascular deaths. The overall incidence of clinical adverse events, including stroke/TIA, major bleeding, cardiovascular events, and death was significantly lower in the OAC discontinuation group than in the OAC continuation group (P<0.05 for all) (Figure 2). In the OAC discontinu-
advance group 18 patients suffered a stroke/TIA, and these patients were significantly older than those in the same group who did not suffer a stroke/TIA (n=1,818) (69.7±10.9 years vs. 61.3±10.3 years, P<0.001). In addition, their CHADS2 (1.7±10.3 years, P<0.001) and CHA2DS2-VASc scores were higher (3.0±1.3 vs. 1.6±1.3, P=0.001). In the OAC discontinuation group, AF recurrence was more prevalent among these patients than among those who did not suffer a stroke/TIA (n=1,818) (69.7±10.9 years, P<0.001) and CHA2DS2-VASc scores were higher (3.0±1.3 vs. 1.6±1.3, P=0.001). Similarly, patients in this group who suffered major bleeding (n=29) were significantly older than those who did not (n=1,807) (71.8±7.3 years vs. 61.2±10.3 years, P=0.001), and their CHADS2 scores (1.7±1.4 vs. 0.9±0.9, P<0.001) and CHA2DS2-VASc scores were higher (2.9±1.8 vs. 1.6±1.3, P<0.001). AF recurrence tended to be more prevalent among these patients than among those who did not suffer major bleeding (31.0% [9/29] vs. 17.9% [324/1,807], P=0.09).

The major determinants of stroke/TIA and major bleeding are shown in Table 2. Age, CHA2DS2-VASc score, and LAd were positively related to the incidence of stroke/TIA (hazard ratio [HR] for per year increase in age: 1.06; HR per 1-point increase in CHA2DS2-VASc: 1.44; and HR per millimeter increase in LAd: 1.06). Long-lasting-AF (vs. paroxysmal AF), hypertension, heart failure, vascular disease, and OAC continuation were shown to be significantly associated with the incidence of stroke/TIA but not with AF recurrence after ablation. On multivariate Cox hazard analysis, long-lasting-AF (HR: 3.07 [95% confidence interval (CI): 1.31–6.63] vs. paroxysmal AF) and CHA2DS2-VASc score (HR: 1.31 [95% CI: 1.06–1.60]) remained significant predictors for the incidence of stroke/TIA. Age and CHA2DS2-VASc score were positively related to the incidence of a major bleeding event (HR per year increase in age: 1.10; HR per 1-point increase in CHA2DS2-VASc: 1.43). BMI, hemoglobin concentration, and CrCl were inversely related to the occurrence of a major bleeding event. Use of antiplatelet drugs and OAC continuation were significantly associated with the occurrence of a major bleeding event. Multivariate Cox hazard model revealed age (HR: 1.06 [95% CI: 1.02–1.11] per year increase) as a significant predictor of a major bleeding event.

**Table 2. Univariate and Multivariate Cox Hazard Models for Predicting Stroke/TIA and Major Bleeding Events**

|                        | Stroke/TIA | Major bleeding |
|------------------------|------------|----------------|
|                        | Univariate | Multivariate   | Univariate | Multivariate   |
| Age (+1 year)          |            |                |            |                |
| HR (95% CI) P value    | 1.06 (1.03–1.10) 0.003 | 1.03 (0.99–1.07) 0.16 | 1.10 (1.06–1.13) <0.001 | 1.06 (1.02–1.11) 0.020 |
| Female                 |            |                |            |                |
| HR (95% CI) P value    | 0.94 (0.48–1.72) 0.85 | 0.91 (0.84–0.97) 0.007 | 0.95 (0.88–1.03) 0.26 |                |
| BMI (+1 kg/m²)         |            |                |            |                |
| HR (95% CI) P value    | 1.00 (0.92–1.00) 0.92 |                | 0.91 (0.84–0.97) 0.007 |                |
| AF type                |            |                |            |                |
| Paroxysmal             | Ref.       | Ref.           | Ref.       |                |
| Persistent             | 1.07 (0.54–2.00) 0.64 | 0.91 (0.45–1.73) 0.76 | 1.05 (0.62–1.73) 0.85 |                |
| Long-standing persistent| 3.38 (1.55–6.76) 0.003 | 3.07 (1.31–6.63) 0.012 | 0.82 (0.25–2.03) 0.70 |                |
| Ablation sessions ≥2   | 1.54 (0.63–3.24) 0.32 |                | 0.40 (0.10–1.07) 0.07 |                |
| Comorbidities          |            |                |            |                |
| Hypertension           |            |                |            |                |
| HR (95% CI) P value    | 2.01 (1.11–3.85) 0.020 |                | 1.14 (0.71–1.86) 0.56 |                |
| Diabetes               |            |                |            |                |
| HR (95% CI) P value    | 1.73 (0.89–3.16) 0.11 |                | 2.08 (1.21–2.82) 0.009 |                |
| Heart failure          |            |                |            |                |
| HR (95% CI) P value    | 2.17 (1.15–3.90) 0.019 |                | 1.74 (0.99–2.93) 0.05 |                |
| Stroke/TIA             |            |                |            |                |
| HR (95% CI) P value    | 2.09 (0.91–4.22) 0.08 |                | 1.07 (0.42–2.28) 0.87 |                |
| Vascular disease       |            |                |            |                |
| HR (95% CI) P value    | 2.46 (1.20–4.64) 0.016 |                | 2.43 (1.30–4.25) 0.007 |                |
| CHA2DS2-VASc           | 1.44 (1.24–1.68) <0.001 | 1.31 (1.06–1.60) 0.015 | 1.43 (1.25–1.63) <0.001 | 1.03 (0.84–1.25) 0.78 |
| Echocardiography variables |        |                |            |                |
| LVEF (+1%)             | 0.99 (0.96–1.02) 0.40 |                | 1.01 (0.98–1.04) 0.48 |                |
| LAd (+1 mm)            | 1.06 (1.02–1.10) 0.006 | 1.04 (0.99–1.08) 0.12 | 1.01 (0.98–1.05) 0.42 |                |
| Post-ablation therapy  |            |                |            |                |
| Warfarin (vs. DOAC)    | 1.40 (0.76–2.51) 0.28 |                | 1.47 (0.87–2.42) 0.15 |                |
| Antiplatelet therapy   | 1.15 (0.40–2.63) 0.78 |                | 2.91 (1.55–5.08) 0.002 | 1.79 (0.91–3.31) 0.09 |
| AAD use                | 1.25 (0.69–2.39) 0.45 |                | 1.39 (0.98–1.96) 0.07 |                |
| Hb (mg/dL)             | 0.85 (0.71–1.01) 0.07 | 0.73 (0.63–0.85) <0.001 | 0.88 (0.75–1.04) 0.15 |                |
| CrCl (mL/min)          | 0.99 (0.98–1.00) 0.11 | 0.97 (0.96–0.98) <0.001 | 1.00 (0.98–1.01) 0.57 |                |
| AF recurrence          | 1.34 (0.76–2.34) 0.31 |                | 1.56 (0.96–2.51) 0.07 |                |
| OAC discontinuation    | 0.44 (0.24–0.78) 0.004 | 0.74 (0.39–1.35) 0.32 | 0.53 (0.33–0.86) 0.010 | 0.75 (0.45–1.23) 0.26 |

AAD use, antiarrhythmic drug use at final follow-up; BMI, body mass index; CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; LAd, left atrial diameter; other abbreviations as in Table 1.

**Prognostic Performance of Age, CHAD2 and CHA2DS2-VASc Scores for Stroke/TIA and Major Bleeding Events**

The prognostic performance of age and traditional risk scores for stroke/TIA and major bleeding events was investigated (Figure 3). Performance of the CHA2DS2-VASc score for predicting stroke/TIA was best (AUC, 0.70; best cutoff value, ≥3), followed by the CHADS2 score (AUC, 0.69, P=0.45 by DeLong test vs. CHA2DS2-VASc score; best cutoff value, ≥2) and age (AUC, 0.65, P=0.07 vs. CHA2DS2-VASc score; best cutoff value, ≥63 years), and the performance of age for the prediction of major bleeding was best (AUC, 0.73; best cutoff value ≥70 years), fol-
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score tended to be superior to age for prediction of post-ablation stroke/TIA, and age was found to be superior to the CHADS2 and CHA2DS2-VASc scores for prediction of a major bleeding event.

Post-Ablation OAC Discontinuation and Clinical Outcomes

OACs were discontinued within 21 months after ablation in slightly more than 50% of patients included in our study. Discontinuation of OAs beyond 3 months after ablation is reported in 20–80% of patients,9–13,20,21 and observational studies have reported that discontinuation of OACs is dependent on multiple factors, such as ablation success and initial stroke risk, but mainly on the treating physician’s inclination or patient’s preference. In our study, age, male sex, and smaller LAd were associated with OAC discontinuation. A single AF session, absence of comorbidities, and absence of AF recurrence were also associated with OAC discontinuation. Despite the widely varying OAC discontinuation rates documented in previous observational studies, most authors have concluded that OACs can be discontinued in patients judged to be at low risk for a stroke after successful AF ablation,9,13,20,21 and the increased incidence of major bleeding events associated with continuous OAC use outweighs its benefit in terms of stroke prevention. According to current guidelines,6–8 OAC therapy should be

Discussion

Our main findings were as follows. First, OAC use was discontinued at 5.1 (3.1–11.0) months after ablation in 53.2% of the 3,451 AF Frontier Ablation Registry patients included in our study. OAC discontinuation was associated with a younger age, male sex, paroxysmal AF, a single AF session, absence of comorbidities, a smaller LAd, AAD discontinuation by the time of the final follow-up examination, and absence of AF recurrence after ablation. Second, stroke/TIA and major bleeding events occurred in patients with high stroke risk scores, and such events were associated with patients’ baseline clinical characteristics (i.e., CHA2DS2-VASc scores and age), rather than with discontinuation vs. continuation of OAC therapy. Third, the CHA2DS2-VASc score tended to be superior to age for prediction of post-ablation stroke/TIA, and age was found to be superior to the CHADS2 and CHA2DS2-VASc scores for prediction of a major bleeding event.

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decision to discontinue OAC therapy based mainly on a patient’s characteristics is clinically reasonable. Despite the low incidence of stroke/TIA events among the present patients in whom OAC therapy was discontinued, physicians should be cautious when considering OAC discontinuation, because 35% (18/51) of patients who suffered a stroke/TIA and 40.8% (29/71) of those who suffered major bleeding were part of the OAC discontinuation group. Importantly, those patients were significantly older and their stroke risk scores were higher than those of patients in the same group who did not suffer a stroke/TIA or major bleeding. Furthermore, a CHA2DS2-VASc score \( \geq 3 \), rather than OAC continuation vs. discontinuation, was identified as an independent predictor for each of these clinical events.

There is little data supporting post-AF ablation OAC discontinuation, especially in patients at high risk of stroke/TIA. Numerous investigators have also reported a strong association between advanced age, prior stroke/TIA, high CHADS2, CHA2DS2-VASc, and HAS-BLED scores, and stroke/TIA and major bleeding.\(^9\)\(^{12}\)\(^{20}\)\(^{21}\) Although some recent studies have shown a significant association between AF recurrence and stroke/TIA events,\(^{22}\) our study did not. We cannot say with certainty that AF did not recur asyp-
tomatically in some of the patients who suffered a stroke/TIA. The incidence of asymptomatic AF recurrence increases after ablation, especially among patients at high risk for a stroke/TIA. Therefore, OAC discontinuation in high-stroke risk patients should be carefully considered (or may be unsafe) even if sinus rhythm is thought to be maintained after ablation, because the stroke risk may be high once AF recurs asymptotically.

Comparison of several Japanese AF registries (majority of patients did not undergo ablation) with a similar age and stroke risk score as this study population (62.3±10.3 years, CHADS2: 1.2±1.1 and CHA2DS2-VASc 2.1±1.5) provided further insight into understanding the effect of OAC discontinuation after ablation on the clinical outcomes. Among 3,588 patients (68.±13.5 years) without OAC therapy in the pooled analysis from 3 large Japanese registries, the incidence of strokes was 0.69 and 0.98 events per 100 person-years for those aged <65 years and 65–75 years, respectively. Those events rates seemed higher than that of our OAC discontinuation group (0.4%/year), and therefore, ablation might have beneficial effects on stroke/TIA events in this group even if OACs are discontinued after ablation. In contrast, the incidences of stroke/systemic embolism (SE) and major bleeding events in a warfarin therapy cohort (2,822 patients aged <70 years in the J-Rhythm Registry29) were lower (~0.4%/year and 0.7%/year, respectively) than that in our OAC continuation group (1.1%/year and 1.6%/year, respectively) despite similar ages and stroke risk (61.0±7.0 years and CHADS2: score 1.2±1.0) as our population. In another OAC therapy cohort (1,889 patients aged <75 years in the SAKURA AF registry30), the AF recurrence rate was underestimated. We might have missed patients with asymptomatic recurrence, even though our method of detecting recurrence was that used routinely in Japan. Finally, the follow-up period was relatively short for clarifying stroke/SE and other clinical events. AF recurrence after ablation increases gradually as time passes, and thus, clarifying the association between late recurrence and stroke events will require further prospective long-term studies. Nevertheless, the study included a relatively large number of patients from multiple centers in Japan, and thus we believe that, despite the study limitations, our findings will help physicians judge whether OAC therapy can be discontinued after ablation in Japanese AF patients.

**Conclusions**

In approximately half of our registry patients who underwent AF ablation, OACs were discontinued, and some patients experienced AF recurrence, but neither factor was associated with the occurrence of stroke/TIA or major bleeding after AF ablation. Rather, age and initial stroke risk were related to the stroke/TIA and major bleeding events, suggesting that although OACs should be continued in high-risk patients, OACs can be discontinued in low-risk patients, especially those in a low age category.

**Acknowledgments**

The authors thank all of the centers that participated in this study and all of the patients who gave consent to participate. We thank Ms. Wendy Alexander-Adams and Mr. John Martin for their encouragement and assistance with the reporting of our findings in English.

**Funding**

This study was supported by a research grant from Bristol-Meyers Squibb.

**Disclosures**

The following authors have potential conflicts of interest: Y.O. received research funding from Bayer Healthcare, Daiichi-Sankyo, Bristol-Meyers Squibb, Nippon Boehringer Ingelheim, Pfizer Japan, TORAy, and Boston Scientific Japan and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, and Bristol-Meyers Squibb. N.M. received research funding from Daiichi-Sankyo. S.S. received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe. A.H. accepted remuneration from Daiichi-Sankyo and Mitsubishi-Tanabe. N.H. accepted remuneration from AstraZeneca, Daiichi-Sankyo, and Bristol-Meyers Squibb. S.K. received research funding from AstraZeneca and Pfizer Japan. S.N. received research funding from Bayer Healthcare, Daiichi-Sankyo, and Bristol-Meyers Squibb.

The authors thank all of the centers that participated in this study and all of the patients who gave consent to participate. We thank Ms. Wendy Alexander-Adams and Mr. John Martin for their encouragement and assistance with the reporting of our findings in English.
Daiichi-Sankyo and Nippon Boehringer Ingelheim, and honoraria for writing promotional material for Bristol-Myers Squibb. W.S. received research funding from Bristol-Myers Squibb, Daiichi-Sankyo, and Nippon Boehringer Ingelheim, and patent royalties/licensing fees from Daiichi-Sankyo, Pfizer Japan, Bristol-Myers Squibb, Bayer Healthcare, and Nippon Boehringer Ingelheim. T.H. serves as a consultant to Medtronic Japan and has received lecture fees from Daiichi-Sankyo. J.N. received a scholarship from the Japanese Heart Rhythm Society and speaking honoraria from Medtronic Japan. K.O. received remuneration from Nippon Boehringer Ingelheim, Daiichi-Sankyo, Johnson & Johnson, and Medtronic Japan. M. Tokuda serves as a consultant to Medtronic Japan. T.Y. received lecture fees from Daiichi-Sankyo and Abbott Medical Japan. K.T. received lecture fees from Daiichi-Sankyo, Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer Japan, Bayer Healthcare, K. Soejima received research funding from Daiichi-Sankyo and Nippon Boehringer Ingelheim, and accepted remuneration from Medtronic Japan, Jonson & Jonson, and Abbott Medical Japan. N.H. accepted remuneration from Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Bayer Healthcare, and research funding from Bayer Healthcare, Nippon Boehringer Ingelheim, Daiichi-Sankyo. M.H. received lecture fee from Nippon Boehringer Ingelheim and Bristol-Myers Squibb. K. Satomi and Y.A. received research funding from BIOTRONIK Japan. Other authors have no conflicts of interest.

References

1. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: Systematic review and meta-analysis. BMJ 2016; 354:14482.

2. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the management of atrial fibrillation: A meta-analysis of randomized, controlled trials. Circ Arrhythm Electrophysiol 2009; 2: 626 – 633.

3. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012; 367:1587 – 1595.

4. Kuck KH, Brugada J, Fürrknranz A, Metzner A, Ouyang F, Chun KR, et al; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016; 374:2235 – 2245.

5. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015; 372:1812 – 1822.

6. Sticherling C, Marin F, Birnie D, Boriani G, Calkins H, Dan GA, et al. Antithrombotic management in patients undergoing electrophysiological procedures: A European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). Europace 2015; 17:1197 –1214.

7. January CT, Wann LS, Alpert JS, Calkins H, Chinarroje JR, Cleveland JC Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64:e1 – e76.

8. Camm AJ, Lip GY, Desingra R, Savelieva I, Atar D, Hohnloser SH, et al; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation – developed with the special contribution of the European Heart Rhythm Association. Europace 2012; 14:1385 –1413.

9. Oral H, Chugh A, Ozyadin M, Good E, Fortino J, Sankaran S, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation 2006; 114:759 – 765.

10. Guiot A, Jongnapasin K, Chugh A, Suwanagool A, Latchamsetty R, Myles JD, et al. Anticoagulant therapy and risk of cerebrovascular events after catheter ablation of atrial fibrillation in the elderly. J Cardiovasc Electrophysiol 2012; 23:36 – 43.

11. Gaia F, Sardi D, Battaglia A, Gallo C, Toso E, Michielon A, et al. Incidence of cerebral thromboembolic events during long-term follow-up in patients treated with transcatheter ablation for atrial fibrillation. Europace 2014; 16:980 – 986.

12. Nührich JM, Kuck KH, Andresen D, Steven D, Spitzer SG, Hofmann E, et al. Oral anticoagulation is frequently discontinued after ablation of atrial fibrillation despite previous stroke: Data from the German Ablation Registry. Clin Res Cardiol 2015; 104:463 – 470.

13. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. J Cardiovasc Electrophysiol 2009; 20: 988 – 993.

14. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: Data from Swedish health registries. Eur Heart J 2016; 37:2478 – 2487.

15. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H; J-RHYTHM Registry Investigators. Beneficial effect of non-vitamin K antagonist oral anticoagulants in patients with non valvular atrial fibrillation: Results of the J-RHYTHM Registry 2. Circ J 2016; 80: 843 – 851.

16. Yamashita Y, Uozumi R, Hamatayani Y, Esato M, Chun YH, Tsuji H, et al. Current status and outcomes of direct oral anticoagulant use in real-world atrial fibrillation patients: Fushimi AF Registry. Circ J 2017; 81:1278 – 1285.

17. Okumura K, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, et al; SAKURA AF Registry Investigators. Three-year clinical outcomes associated with warfarin vs. direct oral anticoagulant use among Japanese patients with atrial fibrillation: Findings from the SAKURA AF Registry. Circ J 2018; 82:2500 – 2509.

18. Monno K, Okumura Y, Saito Y, Aizawa Y, Nagashima K, Arai M, et al. Effect of epicardial fat and metabolic syndrome on reverse atrial remodeling after ablation for atrial fibrillation. J Arrhythm 2018; 34: 607 – 616.

19. Watanabe R, Okumura Y, Nagashima K, Ito K, Takahashi K, Arai M, et al. Influence of balloon temperature and time to pulmonary vein isolation on acute pulmonary vein reconnection and clinical outcomes after cryoballoon ablation of atrial fibrillation. J Arrhythm 2018; 34: 511 – 519.

20. Yagishita A, Takahashi Y, Takahashi A, Fujii A, Kusa S, Fujino T, et al. Incidence of late thromboembolic events after catheter ablation of atrial fibrillation. Circ J 2011; 75: 2343 – 2349.

21. Själander S, Holmquist F, Smith JG, Platovon PG, Keseck M, Svensson PJ, et al. Assessment of use vs. discontinuation of oral anticoagulation after pulmonary vein isolation in patients with atrial fibrillation. JAMA Cardiol 2017; 2: 146 – 152.

22. Karasoy D, Gislonan GH, Hansen J, Johannessen A, Kober L, Hvidtfeldt M, et al. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: Long term follow-up in nationwide cohort of Denmark. Eur Heart J 2015; 36:307 – 314a.

23. Hindricks G, Piorowski C, Tanner H, Kobza R, Gerds-Li JH, Caruccicchio C, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation 2005; 112: 307 – 313.

24. Suzuki S, Takahama T, Okumura K, Atarashi H, Akao M, Ogawa H, et al. Incidence of ischemic stroke in Japanese patients with atrial fibrillation not receiving anticoagulation therapy: Pooled analysis of the Shinken Database, J-RHYTHM Registry, and Fushimi AF Registry. Circ J 2015; 79: 423 – 428.

25. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H; J-RHYTHM Registry Investigators. Use of warfarin in elderly patients with non-valvular atrial fibrillation: Subanalysis of the J-RHYTHM Registry. Circ J 2015; 79: 2345 – 2352.

26. Nishida T, Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, et al; SAKURA AF Registry Investigators. Oral anticoagulant use and clinical outcomes in elderly Japanese patients: Findings from the SAKURA AF Registry. Heart Vessels, doi:10.1007/s00380-019-01446-6.

27. Calkins H, Hindricks G, Cappato R, Kim YH, Saeb EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017; 14: e275 – e444.