Adverse Clinical Events during Long-Term Follow-Up
After Catheter Ablation of Atrial Fibrillation
Comparison to a Non-Ablation Patient Group

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Summary

Pulmonary vein isolation (PVI) of atrial fibrillation (AF) can reduce the AF burden and, potentially, reduce the long-term risk of strokes and death. However, it remains unclear whether anticoagulants can be stopped after PVI because of post-ablation AF recurrence in some patients. This study aimed to investigate the discontinuation rate of anticoagulants and long-term incidence of strokes after PVI.

We enrolled 512 consecutive Japanese patients with AF (mean age, 63.4 ± 10.4 years; 123 women; 234 with non-paroxysmal AF; CHADS2 score/CHA2DS2-VASC score, 1.32 ± 1.12/2.21 ± 1.54) who underwent PVI between 2012 and 2015. During a 28.0 ± 17.1-month follow-up, anticoagulants were terminated in 230 (44.9%) of the 512 patients, AF recurred in 200 (39.1%), and 10 (1.95%) suffered from a stroke. Death occurred in 5 (0.98%) patients. Although the incidence of strokes, by a Kaplan-Meier analysis, was similar, the incidence of death was lower (Hazard ratio 0.37, 95% confidence interval 0.12-0.93, \( P = 0.041 \)) in the AF ablation group than the control group without ablation after 1:1 propensity score matching (the control data was derived from 2,986 patients in the SAKURA AF Registry, a large-cohort AF registry).

Anticoagulants were discontinued in nearly half the patients who underwent AF ablation; of these, 39.1% experienced AF recurrences, 1.95% suffered from strokes, and 0.98% died, but the risk of death after AF ablation appeared to be lower than that in a propensity score-matched control group without ablation during long-term follow-up.

(Int Heart J 2019; 60: 812-821)

Key words: Atrial fibrillation ablation, Oral anticoagulant termination, Stroke, Mortality

Atrial fibrillation (AF) worsens the quality of life and increases the risk of a stroke, heart failure, or death. Pulmonary vein (PV) isolation (PVI) is reportedly a more effective therapy for relief from symptoms and AF recurrences than antiarrhythmic drugs (AADs).\(^1\)\(^-\)\(^3\) PVI can better reduce AF recurrences than AADs; thus, it might have beneficial effects on clinical outcomes, including ischemic strokes, heart failure, and death. If PVI really cures AF in some patients, oral anticoagulants (OACs) can be ceased without clinically relevant events related to AF occurring after AF ablation. Nonetheless, despite ablation technology advancements, the one-year recurrence rates of paroxysmal and non-paroxysmal AF are reportedly ~20% and over 30%, respectively, and these rates gradually increase during long-term follow-up.\(^6\)\(^-\)\(^7\) Therefore, it remains unclear whether anticoagulants can be terminated after PVI or whether PVI can reduce long-term clinically relevant events that are related to AF. Therefore, we sought to investigate the anticoagulant discontinuation rate and its impact on the long-term incidence of strokes, major bleeding, and death after AF ablation. To verify ablation’s beneficial effects on post-ablation clinical events, we compared the incidences of strokes, major bleeding, and death between patients who underwent AF ablation and a control group of patients without AF ablation whose data were obtained from the SAKURA AF Registry (UMIN Clinical Trials Registry: UMIN000014420).\(^8\)\(^-\)\(^10\)

Methods

Study population: This study consisted of 512 consecu-
tive patients (age, 63.4 ± 10.4 years; 123 women) who underwent an initial catheter ablation of AF at Nihon University Itabashi Hospital or Nihon University Hospital between February 2012 and December 2015. Paroxysmal AF (lasting < 7 days) was present in 278 patients; non-paroxysmal AF (lasting ≥ 7 days) was present in 234. All patients gave informed consent for catheter ablation of AF. The study protocol was approved by the institutional review boards of Nihon University Itabashi Hospital and Nihon University Hospital.

**Ablation protocol:** All AADs were discontinued one week before the procedure. The ablation protocol was performed as described previously. All procedures were performed under conscious sedation with propofol and/or dexmedetomidine. During the procedure, the activated clotting time was kept above 300 seconds by heparin after the transseptal puncture. An extensive encircling PVI was performed with a single or double circular catheter method, in which two 20-pole circular-shaped catheters (Lasso, Biosense Webster, Diamond Bar, CA, USA) were placed in the ipsilateral superior and inferior PVs. The ablation catheters were 3.5-mm-tip irrigation catheters (NAVISTAR THERMOCOOL, Biosense Webster) or 4-mm-tip irrigation catheters (Safire BLU Duo, St. Jude Medical, St. Paul, MN, USA). From October 2013, a 3.5-mm-tip irrigation catheter incorporating contact force (SMART TOUCH, Biosense Webster) was used. After the PVI, acute PV reconnections were evaluated on 3D voltage maps; thereafter, any dormant PV conduction was provoked by intravenous injections of 30 mg of adenosine triphosphate. If an acute PV reconnection or dormant PV conduction was evident, touch-up ablation was performed.

The cryoballoon ablation technique was also described previously using the Arctic Front Advance cryoballoon (Medtronic Minneapolis, MN). The PVI was started from the left superior PV, and ablation then proceeded in the order of the left inferior, right inferior, and right superior PV. Each PV was generally ablated once, but twice if necessary. In some patients with dormant conduction or residual PV potentials, touch-up ablation was performed with a 4-mm-tip irrigation catheter (Safire BLU Duo).

In both ablation methods, if restoration of sinus rhythm was not obtained after the PVI, additional linear left atrial (LA) ablation, such as creating a mitral isthmus line and LA roof line, was performed, and the residual potentials, including complex fractionated atrial electrocardiograms in the LA, were ablated whenever appropriate. Electrical cardioversion was performed when AF/atrial tachycardia was sustained even after additional LA ablation. A tricuspid valve isthmus ablation and superior vena cava isolation were also performed whenever necessary.

**Comparison with a non-ablation group:** We compared the patients enrolled in this study protocol who underwent AF ablation (ablation group) with a group of patients who did not undergo AF ablation (non-ablation group). Data from patients in the non-ablation group were collected from the SAKURA AF Registry (UMIN Clinical Trials Registry: UMIN000014420). The study design, data collection method, and patients’ clinical characteristics were reported previously. Patients were eligible for inclusion in the registry if they had nonvalvular AF diagnosed on a 12-lead electrocardiogram (ECG), 24-hour Holter ECG, or event-activated ECG recording, were aged ≥ 20 years, or had started on, or were already being treated with, any anticoagulant drug for stroke prophylaxis. Recruitment began in September 2013 and ended in December 2015. Among 3,268 AF patients enrolled in this Registry from 63 institutions (2 cardiovascular centers, 13 affiliated hospitals or community hospitals, and 48 private clinics) in the Tokyo area, 1,578 were treated with warfarin and 1,690 with any of 4 other direct oral anticoagulants (DOACs). The non-ablation group was comprised of patients with no history of ablation at the registry enrollment or during the present study’s follow-up period.

**Post-ablation follow-up and study endpoints:** In the ablation group, all AADs and OACs were resumed after the ablation procedure during the 3-month post-ablation blanking period. Thereafter, discontinuing OACs or administering AADs in patients without an arrhythmia recurrence depended on the physicians’ decision. Follow-up data after ablation was retrospectively obtained by hospital chart reviews and/or telephone contact with patients, relatives, and/or referring physicians. All patients underwent routine follow-up examinations at our outpatient clinic 2 weeks and 1 month after the ablation and at 1-to-3-month intervals thereafter for at least 6 months. Twenty-four-hour Holter recordings were scheduled between 3 and 6 months after the ablation. An ECG event recorder was used if patients reported any cardiac symptoms. Any documented AF episodes lasting longer than 30 seconds on the standard ECG, event-activated ECG, or 24-hour Holter recording was considered a recurrence. The primary endpoint of interest in the present study was the occurrence of a stroke (ischemic stroke, hemorrhagic stroke, or transient ischemic attack [TIA]). Major bleeding was 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 and was specified as the safety endpoint. Cardiovascular death or death from any other cause was also recorded. The net clinical outcome (composite of strokes/systemic embolic events, major bleeding, or death from any cause) was also considered a study endpoint.

**Statistical analysis:** Categorical variables are presented as the number and percentage and were compared with the chi-square test or Fisher’s exact test when appropriate. Continuous variables are presented as the mean ± standard deviation, or median with the interquartile range, and were compared using the Student t-test or Wilcoxon rank sum test.

A multivariable analysis, using a logistic regression model with clinically relevant variables, was conducted to identify the independent factors of discontinuation of a post-ablation OAC. Clinical events between the patients with discontinuation of OACs (OAC-off group) and without discontinuation of OACs (OAC-on group), and between the other two groups, such as those with and without AF recurrence, etc., were analyzed by a Fisher’s exact test. To reduce the effect of any potential confounding factors in this observational study, we performed a rigorous adjustment for the differences in the characteristics at
enrollment between the ablation and non-ablation groups using propensity score matching. The covariates entered into the propensity score were the clinically relevant factors, including the components of the CHA2DS2-VASc score (age, sex category, body mass index [BMI], paroxysmal AF [versus non-paroxysmal AF], congestive heart failure, hypertension, diabetes, history of a stroke/TIA, vascular disease, warfarin [versus DOAC], antiplatelet drug use, and creatinine clearance). The propensity score-matched pairs were created from ablation and non-ablation groups based on the nearest neighbor pair-matching algorithm with a 0.3 caliper width. A matching ratio of 1:1 was used. We used the Kaplan-Meier method to estimate the cumulative event rates and assessed the differences with a log-rank test. A Cox hazard model was performed to identify the relative risk of clinical events between the ablation and non-ablation groups. A P value of <0.05 was considered statistically significant. Statistical analyses were performed using JMP 12 (SAS Institute Inc., Cary, NC, USA) software.

Results

Clinical characteristics: The clinical characteristics of patients with and without OAC discontinuation are summarized in Table I. The mean age in the present study population was 63.4 ± 10.4 years, 76% of the patients were male, and 278 (54%) had paroxysmal AF. The LA diameter was 39.9 ± 6.8 mm, and left ventricular (LV) ejection fraction 65.8 ± 9.8%. The mean CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes, and a stroke/TIA) and CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, a stroke/TIA, vascular disease, age 65-74 years, and sex category. *Comparison between the two groups was by a Student t-test or Wilcoxon rank sum test or chi-squared test, as appropriate.

Table I. OAC-off Group and OAC-on Group Patient Characteristics

|                        | Total (n = 512) | OAC-off (n = 230) | OAC-on (n = 282) | P value* |
|------------------------|---------------|------------------|------------------|---------|
| Age (years)            | 63.4 ± 10.4   | 61.4 ± 10.7      | 65.1 ± 9.9       | < 0.001 |
| ≥ 65 years             | 273 (53)      | 101 (44)         | 172 (61)         | 0.193   |
| ≥ 75 years             | 71 (14)       | 24 (10)          | 47 (17)          | 0.288   |
| Female                 | 123 (24)      | 48 (21)          | 75 (27)          | 0.130   |
| Body mass index (kg/m²)| 24.0 ± 3.6    | 23.4 ± 3.5       | 24.5 ± 3.6       | < 0.001 |
| Paroxysmal AF          | 278 (54)      | 144 (63)         | 134 (48)         | 0.001   |
| Comorbidities          |               |                  |                  |         |
| Hypertension           | 304 (59)      | 126 (55)         | 178 (63)         | 0.050   |
| Diabetes               | 109 (21)      | 37 (16)          | 72 (26)          | 0.008   |
| History of a stroke/TIA| 63 (12)       | 15 (7)           | 48 (17)          | < 0.001 |
| Heart failure          | 67 (13)       | 19 (8)           | 48 (17)          | 0.003   |
| Vascular disease       | 56 (11)       | 20 (9)           | 36 (13)          | 0.139   |
| CHA2DS2 score          | 1.32 ± 1.12   | 1.03 ± 0.98      | 1.56 ± 1.18      | < 0.001 |
| CHA2DS2-VASc score ≥ 3 | 225 (44)      | 52 (23)          | 173 (61)         | < 0.001 |
| Echocardiography       |               |                  |                  |         |
| Left ventricular ejection fraction (%) | 65.8 ± 9.8   | 66.7 ± 9.5       | 65.0 ± 10.0      | 0.061   |
| Left atrial diameter (mm) | 39.9 ± 6.8   | 37.4 ± 6.2       | 41.9 ± 6.5       | < 0.001 |
| Comorbidities          |               |                  |                  |         |
| Warfarin               | 130 (25)      | 60 (26)          | 73 (26)          | 0.105   |
| Dabigatran             | 71 (14)       | 31 (13)          | 40 (14)          |         |
| Rivaroxaban            | 95 (19)       | 54 (23)          | 41 (15)          |         |
| Apixaban               | 163 (32)      | 65 (28)          | 98 (35)          |         |
| Edoxaban               | 50 (10)       | 20 (9)           | 30 (11)          |         |
| Antiarrhythmic drug    | 225 (44)      | 52 (23)          | 173 (61)         | < 0.001 |
| Antiplatelet drug      | 33 (6)        | 9 (4)            | 24 (9)           | 0.031   |
| Follow-up hospital     |               |                  |                  |         |
| Itabashi Hospital      | 321 (63)      | 166 (72)         | 155 (55)         | < 0.001 |
| Creatinine clearance (minutes/mL) | 70 ± 26     | 70 ± 28          | 69 ± 24          | 0.658   |
| AF recurrence          | 200 (39)      | 42 (18)          | 158 (56)         | < 0.001 |

Values are shown as the mean ± SD or n (%). OAC indicates oral anticoagulant; AF, atrial fibrillation; TIA, transient ischemic attack; CHA2DS2, congestive heart failure, hypertension, age ≥75 years, diabetes, and a stroke/TIA; and CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, a stroke/TIA, vascular disease, age 65-74 years, and sex category. *Comparison between the two groups was by a Student t-test or Wilcoxon rank sum test or chi-squared test, as appropriate.

Clinical outcomes: During the follow-up period of 28.0 ± 17.1 months, AF recurred in 200 (39.1%) of the 512 patients. The event-free rate from recurrent atrial tachyarrhythmias after the initial procedure was 70.2% at 1 year and 60.8% at 2 years. At the final follow-up assessment, the prevalence of arrhythmia-free patients was 60.9%, with 27.8% (87/312) on AADs. OACs were discontinued in the 230 (44.9%) patients comprising the OAC-off group.
at 12.2 ± 9.9 months after ablation. Anticoagulant termination was associated with a younger age (P < 0.001), lower BMI (P < 0.001), no prior history of diabetes mellitus (P = 0.008), no prior heart failure (P = 0.003), no prior stroke/TIA (P < 0.001), small LA diameter (P < 0.001), no use of AADs (P < 0.001) and antiplatelet drugs (P = 0.031), and no AF recurrence (P < 0.001). A multivariate logistic regression analysis revealed that a young age (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.93-0.98, P < 0.001), lower BMI (OR 0.93, 95% CI 0.87-1.00, P = 0.040), no history of a prior stroke/TIA (OR 2.44, 95% CI 1.17-5.10, P = 0.017), small LA diameter (OR 0.94, 95% CI 0.90-0.98, P = 0.003), and no AF recurrence (OR 4.15, 95% CI 2.53-6.81, P < 0.001) remained as significant factors for termination of anticoagulation (Table II).

The details of the stroke and major bleeding events that occurred are summarized in Table III. The difference in the patient characteristics for strokes, major bleeding, and all-cause mortality are shown in Table IV. Stroke events occurred in 10 patients (1.95%) at a median follow-up time of 19.4 (5.4-41.9) months after the ablation: 3 patients (1.30%, annual incidence: 0.54 per 100 patient-years [95% CI 0.10-0.88]) in the OAC-off group versus 7 (2.48%, annual incidence: 1.11 per 100 patient-years [95% CI 0.34-1.45]) in the OAC-on group (P = 0.523). Also, there was no difference in the incidence of strokes between the patients with versus without AF recurrence (2.00% [4/200] versus 1.92% [6/312], P > 0.999). Only a CHA2DS2-VASc score of ≥ 3 was associated with the incidence of a stroke (4.06% [8/197] versus 0.63% [2/315], P = 0.016), but there were no significant associations with the other covariables, including age, sex, BMI, paroxysmal AF, LA diameter, LV ejection fraction, use of antiplatelet drugs, and creatinine clearance. Major bleeding occurred in 10 (1.95%) patients at a median follow-up of 9.9 (1.7-24.0) months after the ablation: 1 patient (0.43%, annual incidence: 0.18 per 100 patient-years [95% CI 0.02-0.57]) in the OAC-off group versus 9 (3.19%, annual incidence: 1.42 per 100 patient-years [95% CI 0.47-1.71]) in the OAC-on group (P = 0.027).

An old age (69.4 ± 6.7 years versus 63.3 ± 10.4 years, P = 0.041) and CHA2DS2-VASc score ≥ 3 were modestly associated with the incidence of major bleeding events (3.55% [7/197] versus 0.95% [3/315], P = 0.050), but there were no associations with any other covariable. All-cause death occurred in 5 (0.98%) patients: 1 from cardiovascular causes and 4 from non-cardiovascular causes. There were no clear associations between the covariables and death.

Comparison between the ablation group and non-ablation group: From the 512 patients who underwent ablation in this study, and the 2,986 who did not, 436 well-balanced patient pairs were obtained after propensity score matching. As summarized in Table V, there were no significant differences in any of the patient characteristics. Kaplan-Meier curves for strokes, major bleeding events, and death are shown for the ablation and non-ablation groups in the Figure. There were no significant differences in the incidence of strokes (Hazard ratio [HR] 0.65, 95% CI 0.23-1.66, P = 0.382 by log-rank test) and major bleeding events (HR 1.17, 95% CI 0.43-3.21, P = 0.751) between the two groups, but the ablation group had a significantly lower incidence of all-cause death (HR 0.37, 95% CI 0.12-0.93, P = 0.041) and tended to have a lower composite net clinical event rate (HR 0.58, 95% CI 0.31-1.03, P = 0.066) than the non-ablation group. The rate of cardiovascular deaths tended to be lower (0.2% [1/436: 1 death due to aortic dissection] versus 1.6% [7/436: 4 deaths due to heart failure, 2 due to strokes, and 1 due to sudden cardiac death], P = 0.069), but the rate of non-cardiovascular death did not significantly differ between the ablation and non-ablation groups (0.9% [4/436: 1 cancer-related death, 1 death from pneumoniae, 1 unknown cause, and 1 death from multi-organ failure] versus 2.5% [11/436: 6 cancer-related deaths, 3 deaths from pneumoniae, 1 fatal bleeding, and 1 death due to a car accident], P = 0.115). Therefore, the incidence of deaths due to strokes was equivalent between the ablation and non-ablation group patients (0% versus 0.5%, P = 0.499).

Table II. Major Determinants for Terminating Oral Anticoagulants using a Multivariate Logistic Regression Analysis

| Variable                        | Odds ratio (95% CI) | P value |
|---------------------------------|--------------------|--------|
| Age (+ 1 year)                  | 0.96 (0.93-0.98)   | < 0.001|
| Body mass index (+ 1 kg/m²)     | 0.93 (0.87-1.00)   | 0.040  |
| Paroxysmal AF                   | 0.86 (0.54-1.38)   | 0.541  |
| No hypertension                | 0.92 (0.57-1.48)   | 0.741  |
| No diabetes                    | 1.20 (0.68-2.13)   | 0.531  |
| No heart failure                | 1.47 (0.72-3.02)   | 0.290  |
| No history of a stroke/TIA     | 2.44 (1.17-5.10)   | 0.017  |
| Left atrial diameter (+ 1 mm)   | 0.94 (0.90-0.98)   | 0.003  |
| No use of antiarrhythmic drugs  | 4.72 (2.85-7.81)   | < 0.001|
| No use of antiplatelet drugs    | 3.10 (1.21-8.00)   | 0.019  |
| No AF recurrence                | 4.15 (2.53-6.81)   | < 0.001|

95% CI indicates 95% confidence interval; AF indicates atrial fibrillation; and TIA, transient ischemic attack.
Table III. Details of Stroke or Major Bleeding Events

| Patient No. | Age (years) | Event type           | Time from ablation (months) | OAC on/off | CHADS2 score | CHADS2 VASC score | AF recurrence | OAC type | If on warfarin, INR value | Permanent injury or deceased |
|-------------|-------------|----------------------|----------------------------|------------|--------------|-------------------|---------------|----------|---------------------------|----------------------------|
| **Stroke Details** |                  |                      |                            |            |              |                   |               |          |                           |                             |
| 26          | 63          | Hemorrhagic stroke   | 62.9                       | On         | 3            | 3                 | +             | WF       | 2.17                      | Hemiparesis                 |
| 61          | 69          | Ischemic stroke      | 22.8                       | On         | 2            | 3                 | +             | Api      | -                         | Deceased                    |
| 68          | 63          | TIA                  | 50.4                       | Off        | 0            | 1                 | -             | Api      | -                         | None                        |
| 85          | 66          | Ischemic stroke      | 39                         | Off        | 2            | 3                 | +             | WF       | N.A.                      | None                        |
| 177         | 65          | Ischemic stroke      | 16                         | Off        | 1            | 2                 | -             | -        | -                         | None                        |
| 204         | 79          | Ischemic stroke      | 32.4                       | On         | 2            | 4                 | +             | Riv      | -                         | Bedridden                   |
| 266         | 70*         | Ischemic stroke      | 1.9                        | On         | 1            | 4                 | +             | Riv      | -                         | Hemiparesis                 |
| 333         | 69          | Ischemic stroke      | 0.3                        | On         | 2            | 3                 | -             | WF       | N.A.                      | None                        |
| 444         | 61*         | Hemorrhagic stroke   | 10.6                       | On         | 3            | 4                 | +             | Edo      | -                         | Dysphagia                   |
| 461         | 75          | Ischemic stroke      | 6.6                        | Off        | 2            | 3                 | -             | Edo      | -                         | Hemispatial Agnosia          |
| Total       |             |                      | 68.0 ± 5.7                 |            | 19.4         | 1.8 ± 0.9         | 3.0 ± 0.9     | 6 (60)   | WF 3 (30)                 |                             |
| **Major bleeding events** |          |                      |                            |            |              |                   |               |          |                           |                             |
| 33          | 75          | Cerebral bleeding    | 45.8                       | On         | 2            | 3                 | +             | Api      | -                         | Gait disturbance            |
| 55          | 55          | Gastrointestinal bleeding | 41.8                     | Off        | 0            | 0                 | +             | -        | -                         | None                        |
| 169         | 67          | Gastrointestinal bleeding | 1                         | On         | 1            | 2                 | +             | WF       | 1.03                      | None                        |
| 202         | 70          | Gastrointestinal bleeding | 9.1                       | On         | 1            | 3                 | +             | WF       | 1.15                      | None                        |
| 239         | 75          | Bleeding in muscles  | 8                          | On         | 3            | 4                 | +             | WF       | 1.12                      | Deceased                    |
| 241         | 74          | Gastrointestinal bleeding | 18                        | On         | 1            | 2                 | -             | WF       | N.A.                      | None                        |
| 252         | 73          | Gastrointestinal bleeding | 13.3                      | On         | 1            | 3                 | -             | WF       | 2.7                       | None                        |
| 266         | 70*         | Cerebral bleeding    | 1.9                        | On         | 1            | 4                 | +             | Riv      | -                         | Hemiparesis                 |
| 404         | 74          | Gastrointestinal bleeding | 0.6                       | On         | 3            | 4                 | +             | Api      | -                         | None                        |
| 444         | 61*         | Cerebral bleeding    | 10.6                       | On         | 3            | 4                 | +             | Edo      | -                         | Dysphagia                   |
| Total       |             |                      | 69.4 ± 6.7                 |            | 9.9          | 1.6 ± 1.0         | 2.9 ± 1.3     | 7 (70)   | WF 5 (50)                 |                             |

Values are shown as the mean ± SD, median (interquartile range) or n (%). N.A indicates not available; Api, apixaban; Edo, edoxaban; Riv, rivaroxaban; WF, warfarin; and the other abbreviations are as in Table I. *Patients experienced both strokes and major bleeding events.

**Discussion**

The main findings regarding the use of anticoagulants and clinical events in patients who underwent ablation in our two hospitals were as follows: First, anticoagulant drugs were discontinued in 230 of the 514 patients 12.2 ± 9.9 months after the ablation. Discontinuation of anticoagulant drugs was independently associated with a younger age, lower BMI, smaller LA diameter, no history of a stroke/TIA, no use of antiarrhythmic and antiplatelet drugs, no AF recurrence, and Itabashi Hospital (versus Nihon University Hospital). Second, during the follow-up period, strokes occurred in 10 patients (1.95%), major bleeding in 10 (1.95%), and all-cause death in 5 (0.98%). The stroke and major bleeding events occurred in patients at a high risk of stroke, but discontinuing OACs was not associated with this risk. Third, between the well-matched patient pairs, the ablation group had a significantly lower incidence of all-cause death, and was likely to have a lower composite net clinical event rate, than the non-ablation group.

**OAC discontinuation and clinical outcomes after ablation:** In our two institutions, OACs were discontinued in 230 (45%) patients at 12.2 ± 9.9 months of follow-up. The discontinuation rate of OACs beyond 3 months after ablation have been reported to range from 50 to 80%.

Based on the results of these observational studies and our study, discontinuing OACs in the clinical setting seems depend upon multiple factors, such as ablation success, initial stroke risk, and physicians’ preference. Despite the widely varying rates of OAC discontinuation, most prior observational studies concluded that OACs can be discon-
largely single-center, retrospective, non-randomized studies. The prior studies were relatively small,
caused by continuous OAC use outweighs its benefit of stroke, the increased incidence of major bleeding events successful AF ablation. 13-19) In patients at a low risk for a
continued in patients with a stroke risk lower than 1% after a stroke, elderly patients, and those treated with DOACs were less prevalent.13-20) Although our study was similarly retrospective, and not randomized, our patients were slightly older, and DOAC users were widespread over 70% of the study patients. The benefits of DOACs over warfarin in

|                                | Yes (n = 10) | No (n = 502) | P value* |
|--------------------------------|-------------|-------------|----------|
| Age (years)                    | 68.0 ± 5.7  | 63.4 ± 10.5 | 0.229    |
| Female                         | 3 (30)      | 120 (24)    | 0.709    |
| Body mass index (m²/kg)        | 24.1 ± 4.0  | 24.0 ± 3.6  | 0.847    |
| Paroxysmal AF                  | 4 (40)      | 274 (55)    | 0.524    |
| Comorbidities                  |             |             |          |
| Hypertension                   | 8 (80)      | 296 (59)    | 0.214    |
| Diabetes                       | 1 (10)      | 108 (22)    | 0.697    |
| History of stroke /TIA         | 2 (20)      | 61 (12)     | 0.484    |
| Heart failure                  | 3 (30)      | 64 (13)     | 0.131    |
| Vascular disease               | 2 (20)      | 54 (11)     | 0.300    |
| CHADS2 score                   | 1.8 ± 0.9   | 1.3 ± 1.1   | 0.071    |
| CHA2DS2-VASe score ≥ 3         | 3.0 ± 0.9   | 2.2 ± 1.5   | 0.041    |
| Creatinine clearance (min)     | 64 ± 13     | 66 ± 10     | 0.920    |
| Left atrial diameter (mm)      | 44 ± 8.5    | 40 ± 7.0    | 0.163    |
| Post-ablation therapy          |             |             |          |
| WF (versus DOAC) **            | 3 (43)      | 69 (26)     | 0.377    |
| Antiarrhythmic drug            | 5 (50)      | 221 (44)    | 0.756    |
| Antiplatelet drug              | 1 (10)      | 32 (6)      | 0.490    |
| Follow-up hospital             |             |             |          |
| Itabashi Hospital (versus Nihon University Hospital) | 7 (70) | 314 (63) | 0.751 |
| Creatinine clearance (minutes/mL) | 66 ± 22 | 70 ± 26 | 0.690 |
| AF recurrence (n = 200)        | 4 (40)      | 196 (39)    | 0.099    |
| OAC-off (n = 230)              | 3 (30)      | 227 (45)    | 0.523    |

Values are shown as the mean ± SD or n (%). DOAC indicates direct oral anticoagulant; and the abbreviations are as in Table I. Comparisons between the two groups were by a Wilcoxon rank sum test or Fisher’s exact test, as appropriate. **n = 282 (7 [yes] versus 275 [no] for stroke, 9 [yes] versus 273 [no] for bleeding, 5 [yes] versus 277 [no] for death) taking OACs at the time of the adverse clinical event or at the final follow up.

|                                | Yes (n = 10) | No (n = 507) | P value* |
|--------------------------------|-------------|-------------|----------|
| Age (years)                    | 65.8 ± 8.7  | 65.8 ± 9.2  | 0.946    |
| Female                         | 108 (25)    | 130 (30)    | 0.094    |
| Body mass index (kg/m²)        | 24.1 ± 3.7  | 23.8 ± 3.6  | 0.223    |
| Paroxysmal AF                  | 211 (48)    | 210 (48)    | 0.946    |
| Comorbidities                  |             |             |          |
| CHADS2 score                   | 1.42 ± 1.12 | 1.47 ± 1.11 | 0.505    |
| CHA2DS2-VASe score             | 2.40 ± 1.51 | 2.49 ± 1.49 | 0.384    |
| Hypertension                   | 278 (64)    | 280 (64)    | 0.888    |
| Diabetes                       | 97 (22)     | 112 (26)    | 0.234    |
| History of a stroke/TIA        | 57 (13)     | 60 (14)     | 0.766    |
| Heart failure                  | 60 (14)     | 64 (15)     | 0.698    |
| Vascular disease               | 50 (11)     | 51 (12)     | 0.916    |
| Post-ablation therapy          |             |             |          |
| Warfarin (versus DOAC)         | 119 (27)    | 112 (26)    | 0.591    |
| Antiplatelet drug              | 31 (7)      | 36 (8)      | 0.525    |
| Creatinine clearance (minutes/mL) | 69 ± 26 | 69 ± 25 | 0.783 |
reducing the risk of stroke events and especially of major bleeding in patients with AF have been substantiated in randomized, controlled trials.\textsuperscript{21-24} Therefore, increased DOAC use in our study may have changed the profiles of the stroke and bleeding events in patients for whom OACs were continued after ablation. Nonetheless, the incidence of stroke events was 1.11 per 100 patient-years and 1.42 per 100-person years for major bleeding in the OAC-on group, which was similar to the annual post-ablation event rates reported in the other studies.\textsuperscript{13-20} Unexpectedly, the OAC-off group was not associated with increased stroke events. Rather, the OAC-on group had an increased incidence of strokes and major bleeding events, which was consistent with other studies’ findings.\textsuperscript{13,15,18} In our study, the OAC-on group was independently associated with an older age, history of a stroke/TIA, antiplatelet drug use, larger LA diameter, and AF recurrence. These findings implied that the patients would be at risk of a stroke or bleeding even if they were on an OAC therapy and free from AF. In fact, we found that a CHA2DS2-VASc score of ≥3 was the major determinant for stroke and major bleeding events since AF may not only be causative, but may also be a risk marker for patients at risk of stroke from other mechanisms.\textsuperscript{25} This is supported by several device studies in AF patients that show no temporal relationship between strokes and AF episodes.\textsuperscript{26,27} Although some recent studies have shown that AF recurrence is significantly associated with increased stroke events,\textsuperscript{14,15,18} our study showed no such association. We did not conduct strict continuous monitoring by means of a loop recorder or 2-week Holter monitoring; thus, some patients with stroke events might have had asymptomatic AF recurrences. Asymptomatic AF recurrences increase after ablation and are often observed, especially in patients at high risk of a stroke.\textsuperscript{26} Taken together, our results, and those of the other studies, strongly indicated that the decision to continue long-term post-ablation OAC therapy should depend on the patient’s stroke risk profile and not on the perceived success or failure of ablation, as the current guidelines recommend.\textsuperscript{29-31}

The ablation procedure’s impact on clinical outcomes: Although several observational studies have compared patients undergoing AF ablation to a matched control population,\textsuperscript{32-34} the data are still limited in Japan. We compared 436 patients undergoing AF ablation with a well-matched cohort of 436 patients who did not undergo AF ablation. The patients who underwent AF ablation gained no statistical benefit in terms of long-term stroke events, but we found a significant beneficial effect of ablation on total mortality. Most prior studies showed that AF ablation may provide a potential protective role from stroke events and all-cause mortality.\textsuperscript{32,34} Bunch \textit{et al.} studied 4,212 ablated patients in Utah and reported a lower long-term risk of stroke events in the ablated group than in the matched control group (HR 0.60, \( P = 0.001 \)) and an even larger mortality benefit from ablation (HR 0.39, \( P = 0.001 \)).\textsuperscript{32,33} In a large study of 361,913 patients with AF in a Swedish database, after propensity score matching followed by
multivariable adjustments, the authors found a lower long-term risk of strokes (HR 0.69, 95% CI 0.51-0.93) and all-cause mortality (HR 0.50, 95% CI 0.37-0.62) in 2,496 ablated patients than in 2,496 well-matched, non-ablated patients.30) Chang et al. also used propensity score matching to balance patient characteristics from data in Taiwan’s National Health Insurance claims database, and 846 ablated patients had a beneficial effect on the stroke risk compared to those without ablation (HR 0.57, 95% CI 0.35-0.94).30) However, they found no survival benefit related to AF ablation (HR 0.88, 95% CI 0.62-1.23).

The mean patient age in our matched ablation group was 66 years, and the CHADS2 and CHA2DS2-VASc scores were 1.4 and 2.4, respectively. In the study by Bunch et al., the age in the ablation group was 65 years, but there was no adjustment for other covariables. In the Swedish database, the age and CHA2DS2-VASc score in the ablation group were 60 years and 1.6, respectively, and the age and CHADS2 score in the Taiwan database were 52 years and only 0.6, respectively. When considering the relatively higher age and risk of strokes in our patients, the stroke event rates in our ablation group were low, which, when annualized, were 0.96% (0.36-2.53%). In our non-ablation group, the stroke rates were even lower, 0.70% (0.21-2.14%), than those in prior studies. As a consequence, the number of stroke events in our two groups was not large enough to perform statistically meaningful comparisons. Nonetheless, our data revealed a beneficial effect on the mortality risk in our ablation patients (HR 0.37, 95% CI 0.12-0.93), despite the relatively low incidence of death in our non-ablation group (0.50% [0.12-1.97%] in the ablation group versus 1.40% [0.63-3.09%] in the non-ablation group). Ablation’s effect on cardiovascular death was greater than on non-cardiovascular death. The nonparallel relation of the ablation effects between the stroke and mortality rates was mainly because the weight of death from strokes was small for overall mortality, i.e., the reduction in the cardiovascular death in the ablation group was due to heart failure, but not to strokes. AF has been associated with an increased oxidative stress, elevated inflammatory status, and endothelial dysfunction.32-35) Therefore, a reduced AF burden after ablation might have provided favorable effects on the cardiovascular condition through the improvement in the hemodynamic and neurohormonal changes, inflammatory state, oxidative stress, or endothelial dysfunction.32-35) The overall incidence of strokes and death in our Japanese cohort was lower than that in the other studies as described above,2-8) which was possibly due to the provision of public health insurance for the entire nation of Japan (which may result in a greater use of OACs, antihypertensives, and/or lipid-lowering drugs) or to racial differences such as a lower burden of vascular disease, less bleeding, and longer longevity compared to patients from Europe and other regions.80)

Although there were some discrepant results, these retrospective registry data should be interpreted with caution. Despite the propensity matching and model adjustment to ensure a balance of comorbidities, medications, and medical service use, some residual confounding factors might still exist because of unmeasured variables. For example, the patients selected for ablation therapy might have been healthier and more likely to undergo medical care; thus, they may have had a greater consciousness of their disease and adhered to their treatment. The primary results in a prospective, randomized controlled trial called the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, were presented at the annual meeting of the Heart Rhythm Society 2018 in Boston. In that trial, 2,204 patients were assigned to medical management or catheter ablation and were followed for about 4 years. Unfortunately, an intention to treat analysis showed that ablation had no beneficial effects on the primary composite endpoint of death, disabling strokes, serious bleeding, cardiac arrest (HR 0.86, 95% CI 0.65-1.15), and all-cause mortality risk compared to the drug group (HR 0.85, 95% CI 0.60-1.21). However, the per-protocol analysis that censored out crossover patients showed a statistically significant 27% relative risk reduction in the primary endpoint among the patients randomized to, and actually treated with, catheter ablation, compared to those randomized to, and exclusively treated with, medical therapy (HR 0.73, 95% CI 0.54-0.99). All-cause mortality in this per-protocol analysis was significantly lower in the ablation group (4.4% versus 7.5% in the non-ablation group [HR 0.60, 95% CI 0.42-0.86]). Taken together, ablation therapy would provide beneficial effects on clinical outcomes driven by AF, but the exact effect may be larger in the real-world cohort than expected in randomized, controlled trials.

**Study limitations:** There were several limitations in this study. First, an observational retrospective study cannot establish causal relationships but only report associations. Therefore, there were several biases in patient selection, as well as diagnostic and therapy/intervention methods. For example, the clinical decision to discontinue or maintain AADs or OAC therapy depended on the physicians’ or patients’ preference. Our study underestimated the arrhythmia recurrence rate and may have missed patients with asymptomatic recurrences, even though our AF recurrence detection method followed the general routine practice in Japan. To minimize these effects, we adjusted for demographic and clinical characteristic imbalances by a multivariate analysis and propensity score matching method to compare our cohort with another general AF population. Despite the adjustment, the possibility of residual confounding factors could not be excluded and, thus, should be considered. Finally, the low incidence of adverse clinical events may have limited the study’s statistical power. Nonetheless, the overall incidence of clinical events seemed similar to that of the other prior observational studies, which may partially reinforce the favorable effect of ablation.

**Conclusions**

In nearly half the patients who underwent AF ablation, anticoagulants were discontinued, and some patients experienced AF recurrences, but those factors were not associated with the risk of a stroke and major bleeding after AF ablation. Only the initial stroke risk score was related to stroke and major bleeding events, suggesting that con-
Continuing OACs is safe in high-risk patients regardless of AF recurrence. The propensity score-matched paired-patient comparison of the ablation group with the non-ablation group revealed that AF ablation significantly reduced chronic mortality risk but not the risk of strokes or major bleeding. This finding implied a beneficial prognostic effect of ablation, but it may simply have been a result of an uneven distribution of the prognostic factors not included in the analysis.

Acknowledgments

The authors wish to thank all of the centers listed in the Supplemental Text that participated in this study and all of the patients who provided their 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.

Disclosures

Conflicts of interest: The following authors have potential conflicts of interest: A.H. received research funding from Bayer Healthcare, Daiichi-Sankyo, Otsuka Pharmaceutical, Astellas, Sumitomo Dainippon Pharma, MSD, Nihon Medi-Physics, Bristol-Meyers Squibb, and Johnson & Johnson. N.M. received research funding from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Meyers Squibb, Astellas Pharma, Sanofi, and Takeda Pharmaceuticals. N.M. received research funding from Daiichi-Sankyo, Ono Pharma, and Sumitomo Dainippon Pharma and accepted remuneration from Nihon Medi-Physics, Fujifilm Ri Pharma, and Nihon Biosensors. Y.O. accepted remuneration from Daiichi-Sankyo.

References

1. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005; 93: 2634-40.
2. Pappone C, Angello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF study. J Am Coll Cardiol 2006; 48: 2340-7.
3. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. Circ Arrhythm Electrophysiol 2009; 2: 626-33.
4. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012; 367: 1587-95.
5. Brachmann J, Lewalter T, Kuck KH, et al. Long-term symptom improvement and patient satisfaction following catheter ablation of supraventricular tachycardia: insights from the German ablation registry. Eur Heart J 2017; 38: 1317-26.
6. Kuck KH, Brugada J, Fünkschnau A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016; 374: 2235-45.
7. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015; 372: 1812-22.
8. Okumura Y, Yokoyama K, Matsumoto N, et al. Current use of direct oral anticoagulants for atrial fibrillation in Japan: findings from the SAKURA AF Registry. J Arrhythm 2017; 33: 289-96.
9. Okumura Y, Yokoyama K, Matsumoto N, et al. 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: 2500-9.
10. Okumura Y, Yokoyama K, Matsumoto N, et al. Patient satisfaction with direct oral anticoagulants and warfarin. Int Heart J 2018; 59: 1266-74.
11. Yamaguchi N, Okumura Y, Watanabe I, et al. Impact of sinus node recovery time after long-standing atrial fibrillation termination on the long-term outcome of catheter ablation. Int Heart J 2018; 59: 497-502.
12. Watanabe R, Okumura Y, Nagashima K, 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: 511-9.
13. Oral H, Chugh A, Ozaydin M, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation 2006; 114: 759-65.
14. Neademane K, Schwab MC, Kosaer EM, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol 2008; 51: 843-9.
15. Themistoclakis S, Corrado D, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol 2010; 55: 735-43.
16. Guiot A, Jongnarangsin K, Chugh A, 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.
17. Gaita F, Sardi D, Battaglia 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: 980-6.
18. Karasoy D, Gislason GH, Hansen J, 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: 307-15.
19. Nührich JM, Kuck KH, Andresen D, et al. Oral anticoagulation is frequently discontinued after ablation of paroxysmal atrial fibrillation despite previous stroke: data from the German Ablation Registry. Clin Res Cardiol 2015; 104: 463-70.
20. Ho AC, Hindricks G, Birnie DH, Verma A. Long-term oral anticoagulation for patients after successful catheter ablation of atrial fibrillation: is it necessary? Curr Opin Cardiovasc Med 2015; 30: 1-7.
21. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51.
22. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-91.
23. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus aspirin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-92.
24. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus aspirin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093-104.
25. Bunch TJ, May HT. Atrial fibrillation: a risk factor or risk marker? Eur Heart J 2016; 37: 2890-2.
26. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm 2011; 8: 1416-23.
27. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relation-
ship between subclinical atrial fibrillation and embolic events. Circulation 2014; 129: 2094-9.

28. Hindricks G, Piorowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation 2005; 112: 307-13.

29. Sticherling C, Marin F, Birnie D, 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: 1197-214.

30. January CT, Wann LS, Alpert JS, et al. 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: e1-76.

31. Camm AJ, Lip GY, De Caterina R, et al. 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. Eur Heart J 2012; 33: 2719-47.

32. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011; 22: 839-45.

33. Bunch TJ, May HT, Bair TL, et al. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. Heart Rhythm 2013; 10: 1272-7.

34. 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: 2478-87.

35. Chang CH, Lin JW, Chiu FC, Caffrey JL, Wu LC, Lai MS. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: a nationwide cohort study and propensity score analysis. Circ Arrhythm Electrophysiol 2014; 7: 76-82.

36. Okumura Y, Watanabe I, Nakai T, et al. Impact of biomarkers of inflammation and extracellular matrix turnover on the outcome of atrial fibrillation ablation: importance of matrix metalloproteinase-2 as a predictor of atrial fibrillation recurrence. J Cardiovasc Electrophysiol 2011; 22: 987-93.

37. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. J Interv Card Electrophysiol 2014; 39: 241-9.

38. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010; 304: 1350-7.

**Supplemental File**

Supplemental Text
Please see supplemental files; [https://doi.org/10.1536/ihj.18-517](https://doi.org/10.1536/ihj.18-517)