Clinical Outcomes of Off-Label Underdosing of Direct Oral Anticoagulants After Ablation for Atrial Fibrillation
Subanalysis of the AF Frontier Ablation Registry

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Summary

Direct oral anticoagulants (DOACs) are sometimes prescribed at off-label under-doses for patients who have undergone ablation for atrial fibrillation (AF). This practice may be an attempt to balance the risk of bleeding against that of stroke or AF recurrence.

We examined outcomes of 1163 patients who continued use of a DOAC after ablation. The patients were enrolled in a large (3530 patients) multicenter registry in Japan. The study patients were classified as 749 (64.4%) appropriate standard-dose DOAC users, 216 (18.6%) off-label under-dose DOAC users, and 198 (17.0%) appropriate low-dose DOAC users.

Age and CHA2DS2-VASc scores differed significantly between DOAC dosing regimens, with patients given an appropriate standard-dose being significantly younger (63.3 ± 9.4 versus 64.8 ± 9.5 versus 73.2 ± 6.8 years, P < 0.0001) and lower (2.1 ± 1.5 versus 2.4 ± 1.6 versus 3.4 ± 1.4, P < 0.0001) than those given an off-label under-dose or an appropriate low-dose. During the median 19.0-month follow-up period, the AF recurrence rate was similar between the appropriate standard-dose and off-label under-dose groups but relatively low in the appropriate low-dose group (42.5% versus 41.2% versus 35.4%, P = 0.08). Annualized rates of thromboembolic events, major bleeding, and death from any cause were 0.47%, 0.70%, and 0.23% in the off-label under-dose group, while those rates were 0.74%, 0.73%, and 0.65% in the appropriate standard-dose, and 1.58%, 2.12%, and 1.57% in the appropriate low-dose groups.

In conclusion, the clinical adverse event rates for patients on an off-label under-dose DOAC regimen after ablation, predicated on careful patient evaluations, was not high as seen with that of patients on a standard DOAC dosing regimen.

Key words: Anticoagulation, Catheter ablation, Bleeding, Stroke, Mortality

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trial fibrillation (AF) is known to increase the risks of stroke, heart failure, and death. Over the past decade, pulmonary vein isolation (PVI) has been shown to be more effective than antiarrhythmic drug (AAD) therapy for freedom from recurrence of AF. An important question now is how to manage oral anticoagulants (OACs) after PVI. Theoretically, in cases in which PVI is truly curative, OACs can be stopped, but analysis of real-world data obtained from a Japanese patient registry showed that OACs were continued for about half of the patients under consideration of their risk for stroke and/or AF recurrence. The decision on whether or not to use an OAC after ablation is made at the physician’s discretion, but not without an understanding of the patient’s preference. One concern pertains to use of direct OACs (DOACs); overdosing can lead to stroke. However, a decrease in the AF burden achieved by PVI may lessen the risk of such clinical events even if OACs are discontinued or inappropriately reduced. The effects of post-AF ablation off-label dosing of DOACs on clinical outcomes remain unclear. Thus, we conducted a registry-based substudy in which we compared clinical outcomes of post-PVI use of DOACs administered at an appropriate standard-dose, appropriate low-dose, or off-label under-dose, focusing especially on the outcomes of off-label underdosing.

Methods

Patient selection and division of patients into groups: We began with a review of the records of 3530 consecutive patients who had undergone catheter ablation of AF at any of 24 cardiovascular centers in Japan between August 2011 and July 2017. All 3530 patients had been enrolled 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: UMIN0000026849). Seventy-nine of the total patients were lost to follow-up, leaving, for possible inclusion in the study, a total of 3451 patients who had been followed up for at least 12 months. Of those 3451 patients, 2698 were DOAC users. One thousand one hundred and sixty-three patients who continued DOACs were included in the substudy described herein, with the exclusion of 39 given an off-label over-dose and 31 an unknown dose. The patients had consented, by the opt-out method, to the use of their anonymized clinical data for research purposes, and the study protocol was approved by the institutional review board of each of the 24 hospitals where patients were treated.

For the purpose of the study, patients were divided into groups according to whether they had been treated after the ablation procedure under an appropriate standard-dose DOAC regimen (n = 749 [64.4%]), appropriate low-dose DOAC regimen (n = 198 [17.0%]), or off-label under-dose DOAC (n = 216 [18.6%]) regimen. The three dosing regimens are defined below.

Data collection: Data contained in the AF Frontier Ablation Registry had been obtained through a review of patients’ hospital charts and entered into an Excel spreadsheet by each patient’s physician or by the clinical research coordinator at each institution. The spreadsheets were sent to our hospital. Data obtained included (but was not limited to) the following: Patients’ clinical characteristics at the time of enrollment, such as age, sex, body mass index (BMI), type of AF, comorbidities (e.g., hypertension, diabetes, history of stroke/transient ischemic attack [TIA]); DOAC type and dosage and antiplatelet drug use after ablation, laboratory test results (hemoglobin [Hb] concentration; creatinine clearance [CrCl]); transthoracic echocardiography-derived left ventricular ejection fraction and left atrial diameter; and the ablation method (radiofrequency or cryoballoon ablation).

Ablation protocol: All AADs were discontinued one week before ablation was performed. Generally, OACs were continued, but this varied from institution to institution. The ablation procedure was performed according to each institution’s particular protocol but generally as previously described. Extensive encircling PVI was performed with an irrigated-tip contact force (CF)-sensing catheter or irrigated-tip standard non-CF-sensing catheter guided by a 3-dimensional mapping system. In some patients, adenosine triphosphate was injected intravenously after PVI to provoke dormant PV conduction at the physician’s discretion. If acute PV reconnection or dormant PV conduction was observed, touch-up ablation was performed.

Cryoballoon ablation was performed with an Arctic Front Advance cryoballon (Medtronic, Minneapolis, MN, USA), as described previously. 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 LA substrate modification by linear LA ablation (e.g., mitral isthmus line ablation, LA roofline ablation, or LA box isolation by creation of a roof line and a floor line) and/or electrogram-based ablation targeting complex fractionated atrial electrograms or low-voltage areas, was performed, as appropriate. Electrocardioversion was performed when sustained AF or atrial tachycardia was recorded after the additional LA ablation. Cavo-tricuspid isthmus ablation and/or superior vena cava isolation was also performed when necessary.

Post-ablation follow-up: Each patient underwent electrocardiography or cardiology follow-up examination at their hospital’s outpatient clinic, and such examination was generally conducted at 3, 6, 9, and 12 months, then once or twice per year thereafter. Whether or not medications were prescribed after the ablation procedure was at the electrophysiologist’s or cardiologist’s discretion and generally based on the patient’s clinical characteristics and/or preference, with each patient visiting his or her local physician for routine follow-up examinations. Patients’ AAD and OAC therapies were continued during the three-month post-ablation blanking period. For patients in whom the arrhythmia did not recur, the AAD and OAC therapies were discontinued. Twenty-four-hour Holter recordings were obtained 3-6 months after the ablation procedure. A cardiac event recorder was used for any patient who reported cardiac symptoms. Any AF or atrial tachycardia lasting > 30 seconds, recorded by standard electrocardiog-
raphy (ECG), 24-hour Holter monitoring, or event-activated ECG was considered a recurrence.

**Definitions:** Administration of a DOAC at an appropriate standard-dose or appropriate low-dose was defined as administration according to a standard regimen or a low-dose regimen, respectively. Administration of the following drugs at the following dosages were considered appropriate low-dose drug regimens: dabigatran at 110 mg (b.i.d.) for patients with CrCl 30-50 mL/minute, age ≥ 70 years, or a history of bleeding; rivaroxaban at 10 mg (o.d.) for patients with CrCl of 15-50 mL/minute; apixaban at 2.5 mg (b.i.d.) for patients with any 2 of the following: age ≥ 80 years, body weight < 60 kg, and serum Cr ≥ 1.5 mg/dL, and edoxaban at 30 mg (o.d.) for patients with CrCl 15-50 mL/minute or body weight < 60 kg.9) Off-label low-dose use of any of these drugs was defined as administration of a DOAC at a low-dose despite the standard dosage criteria being met. Intentional overdosing (off-label standard-dose therapy) was defined as administration of a DOAC at a standard-dose despite the low-dose criteria being met. Dabigatran was considered contraindicated for patients with CrCl < 30 mL/minute, and the other DOACs were considered contraindicated for patients with CrCl < 15 mL/minute.

**Outcomes of interest:** The primary outcome of interest was occurrence of a thromboembolic event (ischemic stroke, TIA, or systemic embolic event), hemorrhagic stroke, cardiovascular event (hospitalization for heart failure, myocardial infarction/unstable angina, or another cardiovascular disorder), or death (cardiovascular death, stroke-related death, or death from any other cause). Major bleeding, defined as a reduction in the Hb concentration of at least 2 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ, was specified as the safety endpoint. Net clinical events (NCE), i.e., a composite of thromboembolic event, major bleeding, and death was also taken as a study endpoint.

**Statistical analysis:** Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as the number and percentage of patients. Between-group differences in continuous variables were evaluated by one-way analysis of variance, and between-group differences in categorical variables were analyzed by chi-square test. Annualized rates of each clinical event were expressed as events per 100 patient-years. Kaplan-Meier curves for freedom from AF and for the cumulative incidences of thromboembolic events, major bleeding, cardiovascular events, death from any cause, and NCE were drawn, and between-group differences in freedom from AF were analyzed by log-rank test. All statistical analyses were performed with JMP 13 software (SAS Institute Inc., Cary, NC, USA), and P < 0.05 was considered statistically significant.

**Results**

**Patients’ clinical characteristics:** Clinical characteristics of the 1163 DOAC users are shown in Table I. Age differed significantly between the three groups of patients, with those in the appropriate low-dose group being significantly older than those in the off-label under-dose group and those in the appropriate standard-dose group (73.2 ± 6.8 versus 64.8 ± 9.5 versus 63.3 ± 9.4 years, respectively; P < 0.0001). Female sex was more prevalent (23.0% versus 34.3% versus. 50.0%, P < 0.0001), BMI was significantly lower (24.7 ± 3.7 versus 24.2 ± 3.4 versus 22.7 ± 3.1; P < 0.0001), and CHA2DS2-VASc scores were significantly higher (2.1 ± 1.5 versus 2.4 ± 1.6 versus 3.4 ± 1.4; P < 0.0001) in the appropriate standard-dose versus off-label under-dose versus appropriate low-dose group. Paroxysmal AF was also more prevalent in the appropriate standard-dose versus off-label under-dose versus appropriate low-dose group (23.0% versus 34.3% versus 50.0%, respectively; P = 0.001). Patients’ medical histories, regardless of the dosing regimen, were similar. CrCl was significantly lower in the appropriate low-dose versus appropriate standard-dose versus off-label under-dose group (53.0 ± 16.6 versus 76.7 ± 23.8 versus 73.3 ± 22.3 mL/minute, respectively; P = 0.0001). Off-label under-dose prescribing was more prevalent among dabigatran users and edoxaban users (29.5% [84/284] and 19.5% [25/128], respectively) than among rivaroxaban users and apixaban users (13.8% [51/370] and 14.7% [56/381], respectively). Cryoballoon ablation was performed in 49 (6.5%) of the appropriate standard-dose, 21 (9.7%) of the off-label under-dose, and 12 (6.1%) of the appropriate low-dose groups, respectively (P = 0.26). Additional LA substrate modification was performed comparatively infrequently in the off-label under-dose group (n = 83 [38.4%]) versus in the standard-dose group (n = 338 [45.1%]) and low-dose group (n = 94 [47.5%]) (P = 0.12).

**AF recurrence during follow-up, per DOAC dosing regimen:** During the follow-up period (median 19.0 [11.3-25.7] months), 477 (41.0%) of the 1163 patients were AF-free. Five hundred and forty-one (46.5%) of the patients were still taking an AAD. Three hundred and eighteen (42.5%) patients in the appropriate standard-dose group, 70 (35.4%) in the appropriate low-dose group, and 89 (41.2%) in the off-label under-dose group suffered AF recurrence. The Kaplan-Meier curves for freedom from AF recurrence are shown in Figure 1. Freedom from AF recurrence was more common in the appropriate low-dose group than in the appropriate standard-dose group (P = 0.02 by log-rank test) but did not differ significantly between the appropriate standard-dose and off-label under-dose groups (P = 0.44 by log-rank test).

**Clinical outcomes, per DOAC dosing regimen:** During follow-up, a thromboembolic event occurred in 17 (1.5%) patients, major bleeding in 20 (1.7%) of the patients, and 15 (1.4%) of the patients died (Table II). Kaplan-Meier curves for thromboembolic events, major bleeding, and death from any cause, and NCE are shown per group (i.e., per dosing regimen) in Figures 2, 3. Annualized rates of a thromboembolic event, major bleeding, death from any cause, and NCE in the off-label under-dose group were 0.47%, 0.70%, 0.23%, and 1.19%, respectively. Although three patients who took 150 mg of dabigatran and three patients who took 15 mg of edoxaban were included in the off-label under-dose group, those patients did not have any clinical events. Those rates in the appropriate standard-dose group were 0.74%, 0.73%, 0.65%, and
Table 1. Clinical Characteristics of the Total Study Patients and as Grouped Per Dosing Regimen

|                      | Total patients (n = 1163) | Appropriate standard dose (n = 749) | Off-label under-dose (n = 216) | Appropriate low dose (n = 198) | P value* |
|----------------------|--------------------------|-----------------------------------|-------------------------------|-------------------------------|----------|
| Age (years)          | 65.3 ± 9.8               | 63.3 ± 9.4                        | 64.8 ± 9.5                    | 73.2 ± 6.8                    | < 0.0001 |
| Female sex           | 345 (29.7%)              | 172 (23.0%)                       | 74 (34.3%)                    | 99 (50.0%)                    | < 0.0001 |
| Height (cm)          | 164.8 ± 9.3              | 166.7 ± 8.7                       | 164.3 ± 9.1                   | 158.3 ± 8.8                   | < 0.0001 |
| Weight (kg)          | 66.3 ± 13.4              | 69.0 ± 13.4                       | 65.7 ± 12.3                   | 57.0 ± 10.0                   | < 0.0001 |
| BMI (kg/m²)          | 24.3 ± 3.7               | 24.7 ± 3.7                        | 24.2 ± 3.4                    | 22.7 ± 3.1                    | < 0.0001 |
| AF type              |                          |                                   |                               |                               |          |
| Paroxysmal           | 664 (57.1%)              | 402 (53.7%)                       | 128 (59.3%)                   | 134 (67.7%)                   | 0.01     |
| Persistent           | 380 (32.7%)              | 263 (35.1%)                       | 64 (29.6%)                    | 53 (26.8%)                    | 0.05     |
| Long-standing persistent | 119 (10.2%)          | 84 (11.2%)                        | 24 (11.1%)                    | 11 (5.6%)                     | 0.04     |
| Medical history      |                          |                                   |                               |                               |          |
| Hypertension         | 724 (62.3%)              | 459 (61.3%)                       | 135 (62.5%)                   | 130 (65.7%)                   | 0.52     |
| Diabetes             | 240 (20.6%)              | 153 (20.4%)                       | 38 (17.6%)                    | 49 (24.8%)                    | 0.20     |
| Heart failure        | 193 (16.6%)              | 114 (15.2%)                       | 37 (17.1%)                    | 42 (21.2%)                    | 0.14     |
| Vascular disease     | 126 (10.8%)              | 73 (9.8%)                         | 30 (13.9%)                    | 23 (11.6%)                    | 0.22     |
| Stroke/TIA           | 144 (12.4%)              | 89 (11.9%)                        | 27 (12.5%)                    | 28 (14.1%)                    | 0.70     |
| Major bleeding       | 19 (1.6%)                | 11 (1.5%)                         | 5 (2.3%)                      | 3 (1.5%)                      | 0.68     |
| CHADS2 score         | 1.4 ± 1.2                | 1.3 ± 1.1                         | 1.4 ± 1.2                     | 1.9 ± 1.2                     | < 0.0001 |
| HAS-BLED score       | 2.4 ± 1.6                | 2.1 ± 1.5                         | 2.4 ± 1.6                     | 3.4 ± 1.4                     | < 0.0001 |
| Hemoglobin           | 14.1 ± 1.6               | 14.3 ± 1.5                        | 13.9 ± 1.6                    | 13.4 ± 1.6                    | < 0.0001 |
| CrCl                  | 72.1 ± 24.1              | 76.7 ± 23.8                       | 73.3 ± 22.3                   | 53.0 ± 16.6                   | < 0.0001 |
| Echocardiographic variables |              |                                   |                               |                               |          |
| LVEF (%)             | 63.5 ± 10.2              | 63.3 ± 9.9                        | 62.9 ± 10.5                   | 64.7 ± 10.9                   | 0.15     |
| LAD (mm)             | 41.5 ± 6.6               | 41.5 ± 6.6                        | 41.9 ± 6.6                    | 41.2 ± 6.5                    | 0.51     |
| Ablation             |                          |                                   |                               |                               |          |
| Radiofrequency ablation | 1081 (92.9)             | 700 (93.5%)                       | 195 (90.3%)                   | 186 (93.9%)                   | 0.26     |
| Cryoballoon ablation | 82 (7.1)                 | 49 (6.5%)                         | 21 (9.7%)                     | 12 (6.1%)                     | 0.26     |
| LA substrate modification | 515 (44.3%)          | 338 (45.1%)                       | 83 (38.4%)                    | 94 (47.5%)                    | 0.13     |
| Post-ablation antiplatelet use | 93 (80%)               | 53 (7.1%)                         | 20 (9.3%)                     | 20 (10.1%)                    | 0.29     |
| Post-ablation DOAC therapy |              |                                   |                               |                               |          |
| Dabigatran           | 284 (24.4%)              | 118 (15.8%)                       | 84 (38.4%)                    | 82 (41.4%)                    | < 0.0001 |
| Rivaroxaban          | 370 (31.8%)              | 280 (37.4%)                       | 51 (23.6%)                    | 39 (19.7%)                    | < 0.0001 |
| Apixaban             | 381 (32.8%)              | 303 (40.5%)                       | 56 (25.9%)                    | 22 (11.1%)                    | < 0.0001 |
| Edoxaban             | 128 (11.0%)              | 48 (6.4%)                         | 25 (11.6%)                    | 55 (27.8%)                    | < 0.0001 |

Values are shown as the mean ± standard deviation or n (%). AF indicates atrial fibrillation; BMI, body mass index; CHADS2, 1 point for congestive heart failure, hypertension, age ≥ 75 years and diabetes, 2 points for stroke; CHA2DS2-VASc, 1 point for congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years and sex category, 2 points for age ≥ 75 years and stroke; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HAS-BLED, uncontrolled hypertension (baseline systolic blood pressure > 160 mmHg), abnormal renal function (serum creatinine ≥ 2.26 mg/dL)/liver function (chronic hepatic disease [e.g., cirrhosis] or aspartate aminotransferase and/or alanine aminotransferase > 3 x normal range), stroke, prior major bleeding, elderly (age ≥ 65 years), drugs (antiplatelet drugs or nonsteroidal anti-inflammatory drugs)/high alcohol use, Labile INR (over-dosing shown by baseline PT-INR in warfarin users); LAD, left atrial diameter; LVEF, left ventricle ejection fraction; and TIA, transient ischemic attack. *obtained by ANOVA or chi-square test, as appropriate.

2.14%, respectively, while those in the appropriate low-dose group were 1.58%, 2.12%, 1.57%, and 4.56%, respectively.

Discussion

Our major findings were as follows. Firstly, under-dose DOAC therapy was applied in 18.6% of the patients given a DOAC after AF ablation. Age of patients differed significantly between groups, i.e., between DOAC dosing regimens, with patients given an appropriate standard-dose being significantly younger than those given an off-label under-dose or an appropriate low-dose; CHA2DS2-VASc scores also differed, being significantly low in the appropriate standard-dose group. Secondly, the AF recurrence rate was similar between the appropriate standard-dose and off-label under-dose groups but relatively low in the appropriate low-dose group. Thirdly, annualized rate of NCE (including thromboembolic events, major bleeding, and death) appeared to be not high in the off-label under-dose group as seen with that in the appropriate standard-dose group.

Clinical characteristics of off-label under-dose DOAC users: There have been no reports of outcomes of post-PVI off-label under-dose DOAC use in Japan. Physicians choose off-label underdosing on the basis of several factors, and the risk of a bleeding event is taken into consideration. An analysis of data from the Fushimi AF Registry, which is a well-known registry of AF patients in Japan, most of whom have not undergone ablation, revealed off-label underdosing in 29% of dabigatran users, 26% of apixaban users, and 21% of rivaroxaban users.10 In addi-
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POST-ABLATION OFF-LABEL ANTICOAGULANT DOSING

Figure 1. Kaplan-Meier curves showing the freedom from recurrence of atrial fibrillation among patients in the appropriate standard-dose (Standard-dose), appropriate low-dose (Low-dose), and off-label under-dose (Under-dose) DOAC users.

Table II. Incidence of Major Clinical Events among the Total Study Patients and among Patients as Grouped per Dosing Regimen

| Event Type                | Total Patients (n = 1163) | Appropriate standard dose (n = 749) | Off-label under-dose (n = 216) | Appropriate low dose (n = 198) |
|---------------------------|---------------------------|------------------------------------|-------------------------------|------------------------------|
|                           | Total patient-years (%) | Events per 100 patient-years (%)  | Total patient-years (%)       | Events per 100 patient-years |
| Death                     | 15 (1.4)                  | 0.73 (0.41-1.21)                   | 8 (1.1)                       | 0.65 (0.28-1.28)             | 1 (0.5)                       | 0.23 (0.01-1.29)              | 6 (3.0)                       | 1.57 (0.58-3.41)              |
| Cardiovascular            | 0 (0)                     | 0                                  | 0 (0)                         | 0                            | 0                            | 0                             | 1 (0.5)                       | 0.26 (0.01-1.45)              |
| Stroke                    | 2 (0.2)                   | 0.10 (0.01-0.35)                   | 1 (0.1)                       | 0.08 (0.002-0.45)            | 0 (0)                        | 0                             | 0 (0)                         | 0                            |
| Other                     | 13 (1.1)                  | 0.64 (0.34-1.09)                   | 7 (0.9)                       | 0.57 (0.23-1.17)             | 1 (0.5)                      | 0.23 (0.01-1.29)              | 5 (2.5)                       | 1.31 (0.42-3.05)              |
| Thromboembolic event      | 17 (1.5)                  | 0.84 (0.49-1.34)                   | 9 (1.2)                       | 0.74 (0.34-1.40)             | 2 (0.9)                      | 0.47 (0.06-1.69)              | 6 (3.0)                       | 1.58 (0.58-3.43)              |
| Ischemic stroke           | 14 (1.2)                  | 0.69 (0.38-1.16)                   | 7 (0.9)                       | 0.57 (0.23-1.18)             | 2 (0.9)                      | 0.47 (0.06-1.69)              | 5 (2.5)                       | 1.32 (0.43-3.08)              |
| TIA                       | 3 (0.3)                   | 0.15 (0.03-0.43)                   | 2 (0.3)                       | 0.16 (0.02-0.59)             | 0 (0)                        | 0                             | 1 (0.5)                       | 0.26 (0.01-1.45)              |
| Systemic embolism         | 0 (0)                     | 0                                  | 0 (0)                         | 0                            | 0                            | 0                             | 0                             | 0                            |
| Hemorrhagic stroke        | 3 (0.3)                   | 0.15 (0.03-0.43)                   | 3 (0.4)                       | 0.24 (0.05-0.71)             | 0 (0)                        | 0                             | 0 (0)                         | 0                            |
| Major bleeding            | 20 (1.7)                  | 0.98 (0.60-1.52)                   | 9 (1.2)                       | 0.73 (0.34-1.39)             | 3 (1.4)                      | 0.70 (0.14-2.05)              | 8 (4.0)                       | 2.12 (0.91-4.18)              |
| Intracranial              | 7 (0.6)                   | 0.34 (0.14-0.71)                   | 4 (0.5)                       | 0.33 (0.09-0.83)             | 0 (0)                        | 0                             | 3 (1.5)                       | 0.79 (0.16-2.30)              |
| NCE                       | 48 (4.1)                  | 2.39 (1.76-3.17)                   | 26 (3.5)                      | 2.14 (1.40-3.14)             | 5 (2.3)                      | 1.19 (0.39-2.77)              | 17 (8.6)                      | 4.56 (2.66-7.31)              |

Values are shown as n (%). CI indicates confidence interval; NCE, net clinical events (composite of thromboembolism events, major bleeding, and death from any cause); and TIA, transient ischemic attack.

...tion, analysis of data from the SAKURA AF registry revealed underdosing in 22% of DOAC users.9 We believe the high rates of underdosing of DOACs in Japan reflect the increased risk of major bleeding reported for Asians (versus non-Asians) on warfarin anticoagulation therapy.11,12 Possibly because of ethnicity, for this specific risk of bleeding on warfarin anticoagulant therapy the prevalence of underdosing was slightly higher than that reported for patients enrolled in a European registry.13 We also believe the high reported rates of underdosing were due to patients’ clinical characteristics. Our off-label under-dose group included a slightly greater percentage of women than the appropriate standard-dose group, and CHA2DS2-VASc scores were higher in this off-label under-dose group. Numerous investigators have reported strong association between advanced age, prior stroke/
TIA, high CHADS2, CHA2DS2-VASc, and HAS-BLED scores and occurrence of a thromboembolic event or major bleeding. Moreover, several studies have shown significant association between AF recurrence and stroke/TIA events. Patients in whom the AF recurs after ablation tend to have a higher baseline risk of both stroke and bleeding. Asymptomatic AF recurrence is often observed in these kinds of patients. Physicians might tend to prescribe a DOAC at an under-dose for patients with a relatively high bleeding or stroke risk in an attempt to balance the risk of bleeding against that of stroke or the risk of stroke by future or asymptomatic AF recurrence against the stroke risk of OAC termination after successful ablation.

We also believe the high reported rate of off-label underdosing is based on clinical evidence of the effectiveness of each of the DOACs in relation to the prescribed dosages. Underdosing appears to be more common for patients given dabigatran or edoxaban than for those given apixaban or rivaroxaban. The RE-LY and ENGAGE-AF TIMI48 trials showed the effectiveness of low-dose dabigatran and edoxaban therapies. In fact, these two trials included patients who matched ours in terms of under-dose DOAC use. By contrast, the ROCKET AF and ARISTOTLE trials were under-powered, with too few patients in the low-dose DOAC group to establish superiority, equivalence, or non-inferiority of underdosing compared to appropriate standard dosing. According to current evidence, underdosing of dabigatran or edoxaban may be a good option for patients in need of post-ablation anticoagulation therapy but for whom the risk of bleeding is a concern, especially in patients of low body weight such as Japanese patients with AF. The high reported rates of underdosing might also reflect AF non-recurrence rates. We found no significant difference in AF recurrence between patients given appropriate standard-dose DOAC therapy and those given off-label under-dose DOAC therapy. The exact reasons for DOAC underdosing were not
identified in this study, but our data provide insight into the clinical factors that should be taken into consideration before such a decision is made, with the aforementioned suggesting that physicians selected the various dosing regimens by looking at patients’ clinical characteristics rather than AF recurrence rates.

**Clinical outcomes of off-label under-dose DOAC use:** Our study showed a relatively high incidence of NCE among patients in our appropriate low-dose group, but the incidence of NCE or of thromboembolic events, of major bleeding, or of death from any cause in the off-label under-dose group appeared to be similar to that in the appropriate standard-dose group. These outcomes might have been influenced by many factors that contributed to the dosing regimens selected by the patients’ physicians. The increased incidence of NCE in the low-dose group may have been due simply to the patients in this group being at the highest risk of stroke or bleeding, with age, low body weight, and renal dysfunction playing roles. The highest incidence among the patients who were given an appropriately reduced DOAC dose was in line with results of a previously reported AF registry study. A previously reported study of patients given DOAC therapy revealed inappropriate underdosing—inappropriate in terms of patients’ body weight or serum creatinine concentration—to be a risk factor for a recurrent ischemic stroke. In addition, randomized controlled trials have yielded higher incidences thromboembolic events but lower incidences of major bleeding among patients given DOACs at low-doses than among those given DOACs at appropriate standard-doses. Thus, although thromboembolic events in patients receiving underdoses were similar to those receiving appropriate standard-doses, thromboembolic events should theoretically have increased among our off-label under-dose DOAC users because the under-dose regimen tended to be selected for relatively high-risk patients. We cannot overlook the fact that this result could be due to selection bias inherent to registry-based studies, our patients’ individual clinical characteristics, the relatively low body weight of Japanese, and/or the medical system in Japan. Under-dose DOAC users at high risk of stroke might not have been enrolled in the registry because DOAC underdosing has been reported as a strong risk factor for left atrial appendage thrombus before ablation. Analyses of other registry-based data have shown that patients’ baseline stroke/bleeding risks (according to their CHADS₂, CHA₂DS₂-VASc or HAS-BLED scores) were lower in Japanese cohorts than in western cohorts. This trend holds true among patients who undergo AF ablation. Data pertaining to the clinical outcomes of underdosing of DOACs are lacking, especially for patients at low risk for stroke and for patients who are of low body weight, like Japanese. Furthermore, with a Japanese social insurance system that provides for periodic physical examinations, and thus risk factors linked to adverse clinical events are managed, it also provides for such interventions as administration of antihypertensive, lipid- and glucose-lowering medications and thus may increase patients’ awareness of their status and therefore lower their risks for stroke and bleeding, with this system, which is a universal health insurance system, differing from that of other countries. In fact, there are reports of similar incidences of ischemic stroke between off-label under-dose DOAC users in Japan, even in those who did not undergo AF ablation, and appropriate standard-dose users. Moreover, approximately 60% of our patients in the off-label under-dose group had not suffered AF recurrence by three years after ablation. Reduction in the AF burden by PVI might have contributed to observed reduction in the incidence of stroke events. The reduced AF burden associated with ablation therapy was probably not the main contributor to the decreased incidence of stroke in our off-label under-dose group, with the AF recurrence rates being similar between our under-dose group and standard-dose group. Finally, it should be noted that each patient’s DOAC dosing regimen was usually decided upon by the physician who performed the ablation. The slightly lower incidence of additional LA substrate modification in the under-dose group suggests that physicians might have considered the LA substrate to be relatively healthy in this group (in comparison to that in the standard-dose group), and this would have contributed to their post-ablation therapeutic decisions. Although we cannot recommend underdosing of DOACs on the basis of our study results, we can say that DOAC underdosing based on careful medical evaluation does not appear to worsen patients’ prognoses after ablation, with the aforementioned maybe partially explaining the similarity between the off-label under-dose and appropriate standard-dose groups in the risks of thromboembolic events, major bleeding, and NCE despite the slightly increased age and increased stroke risk scores of patients in the off-label under-dose group.

**Study limitations:** Firstly, the study was limited by the unavoidable possibility of a selection bias because of its execution as a retrospective observational study. Further, numerous clinical factors were involved in the occurrence of clinical events after AF ablation. Thus, it was challenging to perform statistical comparisons of the clinical outcomes between the three dose-groups even if a part of the clinical factors were adjusted. Therefore, the rate of each clinical event was expressed as a descriptive result in order to avoid misleading the readers. Secondly, we note that we defined off-label underdosing of DOACs using the criteria for a low-dose regimen. As such, off-label underdosing for dabigatran and edoxaban will differ from off-label underdosing for rivaroxaban and apixaban, with the effectiveness and safety of low-doses of dabigatran and edoxaban having been well established in clinical trials. Thirdly, the patients who took an off-label over-dose or discontinued DOACs after ablation were excluded from our study. The reason why the off-label over-dose users were excluded was that the sample size was too small (n = 39) to assess the clinical outcomes. Nonetheless, as a reference, we showed the outcome data of the off-label over-dose users as follows: the annualized rates of a thromboembolic event; major bleeding; death; and NCE were 2.89%, 2.95%, 0%, and 4.51%, respectively. Those event rates were higher as compared to that in the other DOAC dose groups, which was possibly due to the relatively older patients (71.8 ± 5.3 years) with higher CHA₂DS₂-VASc scores (3.3 ± 1.8) in the off-label over-dose group. Further, we showed previously that patients for
whom DOACs were discontinued, in comparison to those for whom DOACs were continued, were relatively young (60.9 ± 10.4 years), had relatively low CHA2DS2-VASc scores (1.5 ± 1.2), and suffered AF recurrence at a relatively low rate (16.3%), resulting in a relatively low incidence of adverse events. The annual incidences of stroke, major bleeding, and death in the DOAC discontinuation group were 0.4%/year, 0.8%/year, and 0.2%/year, respectively, and were similar to those in the off-label under-dose group. Finally, our evaluation of the effects of the three different DOAC dosing regimens should be considered with caution because of the relatively low overall incidence of clinical events and short follow-up period. Further studies are needed to evaluate specific DOAC dosing regimens in relation to adverse clinical events.

Conclusion

Although off-label under-dose DOAC users were older than standard-dose DOAC users and their baseline stroke risk was greater, the incidence of AF recurrence was equivalent between these two groups of patients, as was the prevalence of adverse clinical outcomes. These results suggest that clinical event rates in the post-ablation off-label DOAC underdosing, if performed under careful patient evaluation, may be low, as seen with those achieved under standard DOAC dosing. We note that our findings are not evidence of causality but rather suggest association between post-ablation off-label DOAC under-dosing and acceptable clinical outcomes.

Disclosure

Conflicts of interest: Y.O. has 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. has received research funding from Daiichi-Sankyo. S.S. received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe. A.H. has received accepted remuneration from Nippon Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo. M.K. has received accepted remuneration from Johnson & Johnson K.K., Medtronic Japan, and Boston Scientific Japan and has accepted remuneration from Johnson & Johnson K.K., Medtronic Japan, Bayer Healthcare. H.F. has received lecture fees from Nippon Boehringer Ingelheim and Daiichi-Sankyo. K.K. has received research funding from Biomedica Japan. M.T. serves as a consultant to Medtronic Japan. W.S. has received research funding from Daiichi-Sankyo and Abbott Medical Japan. N.H. has received accepted remuneration from Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Bayer Healthcare, and research funding from Bayer Healthcare, Nippon Boehringer Ingelheim, Daiichi-Sankyo. M.H. has lecture fee from Nippon Boehringer Ingelheim and Bristol-Myers Squibb. K.S. and Y.Y. have received research funding from BIOTRONIK Japan. The other authors have no conflict of interest.

References

1. Odataya A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emmidin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: Systematic review and meta-analysis. BMJ 2016; 354: i4482.
2. 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.
3. Cosedis Nielsen J, Johannessen A, Raatkainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012; 367: 1587-95.
4. Okumura Y, Nagashima K, Arai M, et al. AF Ablation Frontier Registry. Current status and clinical outcomes of oral anticoagulant discontinuation after ablation for atrial fibrillation in Japan - Findings from the AF Frontier Ablation Registry. Circ J 2019; 83: 2418-27.
5. Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol 2016; 68: 2597-604.
6. Ikeda T, Ogawa S, Kitazono T, et al. Outcomes associated with under-dosing of Rivaroxaban for management of non-valvular atrial fibrillation in real-world Japanese clinical settings. J Thromb Thrombolysis 2019; 48: 653-60.
7. Monno K, Okumura Y, Saito Y, et al. Effect of epicardial fat and metabolic syndrome on reverse atrial remodeling after ablation for atrial fibrillation. J Arrhythm 2018; 34: 607-16.
8. 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.
9. Murata N, Okumura Y, Yokoyama K, et al. Clinical outcomes of off-label dosing of direct oral anticoagulant therapy among Japanese patients with atrial fibrillation identified from the SAKURA AF Registry. Circ J 2019; 83: 727-35.
10. Yamashita Y, Uozumi R, Hamatani Y, et al. Current status and outcomes of direct oral anticoagulant use in real-world atrial fibrillation patients - Fushimi AF Registry. Circ J 2017; 81: 1278-85.
11. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among pa-
12. Hori M, Connolly SJ, Zhu J, et al. Dabigatran versus warfarin: Effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke 2013; 44: 1891-6.

13. Ruiz Ortiz M, Muñiz J, Rafa Míquez P, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: Prevalence and associated factors. A subanalysis of the FANTASIA Registry. Europace 2018; 20: 1577-83.

14. 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.

15. 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.

16. 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: 307-14a.

17. Pallisgaard JL, Gislason GH, Hansen J, et al. Temporal trends in atrial fibrillation recurrence rates after ablation between 2005 and 2014: A nationwide Danish cohort study. Eur Heart J 2018; 39: 442-9.

18. 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.

19. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51.

20. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093-104.

21. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-92.

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. Shinoda N, Mori M, Tamura S, Kose S, Kohmura E. Risk of recurrent ischemic stroke with unintended low-dose oral anticoagulant therapy and optimal timing of review. J Stroke Cerebrovasc Dis 2018; 27: 1546-51.

24. Harada M, Koshikawa M, Motoike Y, et al. Left atrial appendage thrombus prior to atrial fibrillation ablation in the era of direct oral anticoagulants. Circ J 2018; 82: 2715-21.

25. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: The Swedish atrial fibrillation cohort study. Eur Heart J 2012; 33: 1500-10.

26. Mansour M, Heist EK, Agarwal R, et al. Stroke and cardiovascular events after ablation or antiarrhythmic drugs for treatment of patients with atrial fibrillation. Am J Cardiol 2018; 121: 1192-9.

27. Arai M, Okumura Y, Nagashima K, et al. Adverse clinical events during long-term follow-up after catheter ablation of atrial fibrillation. Int Heart J 2019; 60: 812-21.

28. Shima A, Tatsumi Y, Ishizaki T, et al. Relationship between outpatient visit frequency and hypertension control: A 9-year occupational cohort study. Hypertens Res 2016; 39: 376-81.