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Assessment of Long-Term Use Versus Discontinuation of Direct Oral Anticoagulant After Catheter Ablation for Atrial Fibrillation—RYOUMA Registry Subanalysis

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ABSTRACT

Background: The relationship between oral anticoagulant (OAC) status after catheter ablation (CA) for atrial fibrillation (AF) and the risks of ischemic stroke or major bleeding events is still unknown.

Methods: This is a subanalysis of the RYOUMA registry, a prospective multicenter observational study of Japanese patients who underwent CA for AF in 2017–2018.

Results: Of the 2844 patients, the rate of DOAC continuation was 48.1%, 69.6%, and 80.9% in patients with a CHADS2 score of 0–1, 2, and 3–6, respectively. Among the patients taking DOACs with a CHADS2 score of 0–1 and 2, the incidence rates of major bleeding were significantly higher than those of ischemic stroke or systemic embolic events (SEEs) (1.3%/year [95% CI, 0.6–2.1] vs. 0.3%/year [95% CI, 0.0–0.7], $p = 0.019$; 1.8%/year [95% CI, 0.6–3.0] vs. 0.2%/year [95% CI, 0.0–0.6], $p = 0.018$, respectively). However, there was no difference between the incidence rates of major bleeding events and ischemic stroke or SEEs in patients taking DOACs with a CHADS2 score of 3–6 (1.6%/year [95% CI, 0.2–3.0] vs. 1.0%/year [95% CI, 0.0–2.1], $p = 0.474$).

Conclusions: In patients with a CHADS2 score of 2, those who continued taking DOACs had a higher incidence rate of major bleeding events compared to ischemic stroke/SEEs, similar to those with a CHADS2 score of 0–1. Conversely, in patients with a CHADS2 score of 3–6, the incidence rates of both ischemic stroke/SEEs and major bleeding were similarly high.

Trial Registration: The study was registered as UMIN000026092 (University Hospital Medical Information Network-Clinical Trial Registry)

1 | Introduction

Catheter ablation (CA) is an effective therapeutic strategy for atrial fibrillation (AF) (Tzeis et al. 2024; Hindricks et al. 2021; Nogami et al. 2021). Periprocedural oral anticoagulation (OAC) is crucial for preventing periprocedural thromboembolism; nonetheless, the optimal long-term anticoagulation after successful AF ablation remains controversial. Current guidelines and consensus statements (Tzeis et al. 2024; Hindricks et al. 2021; Nogami et al. 2021); however, recommend continuation of OAC based on clinical risk scoring, irrespective of procedural outcome. In Japanese guidelines (Nogami et al. 2021), continuation of OAC after AF ablation is recommended for all patients for at least 3 months. After 3 months post-ablation, interruption of OAC should be considered in the patients with a CHADS2 score of 0. Patients with a CHADS2 score of 1 may also be considered for the interruption of OAC, considering the balance between the risk of thromboembolism and bleeding events. On the other hand, for patients with a CHADS2 score of ≥ 2, continuation of OAC beyond 3 months post-ablation is recommended, considering the risk of ischemic stroke when atrial arrhythmias recur (class IIa). However, our previous report of the RYOUMA registry (Real world ablation therapY with anti-cOagUlants in Management of Atrial fibrillation) revealed that over half of the patients continued OAC therapy at 1 year after CA, and there are some patients with the continuation of OAC beyond 3 months despite a CHADS2 score of 0 or 1, as well as those with discontinuation of OAC with a CHADS2 score of ≥ 2 (Figure S1) (Nogami et al. 2022). Therefore, in this subanalysis, we examined the characteristics of patients who either continued or discontinued DOAC therapy after AF ablation in relation to their CHADS2 score. Furthermore, we evaluated the risk of stroke and major bleeding following CA in patients with and without guideline-recommended anticoagulation therapy.

2 | Methods

2.1 | Study Design

The RYOUMA registry is a prospective multicenter observational study, and study design and primary outcome results have been reported previously (Nogami et al. 2022). All patients with non-valvular AF planning their first CA were eligible for inclusion. In this subanalysis, patients using warfarin or not using OAC before CA were excluded.

Baseline data were collected before the CA procedure. Thromboembolic risk was stratified using the CHADS2 score (congestive heart failure; hypertension; age ≥ 75 years; diabetes; previous stroke or transient ischemic attack (TIA) [doubled]) (Gage et al. 2001) and the CHA2DS2-VASc score (congestive heart failure; hypertension; age ≥ 75 years [doubled]; diabetes; previous stroke, TIA or thromboembolism [doubled]; vascular disease; age 65–74 years; and female) (Lip et al. 2010). Bleeding risk was evaluated using the HAS-BLED score (uncontrolled hypertension; renal dysfunction; liver dysfunction; prior stroke; previous bleeding; age > 65 years; labile international normalized ratio; and aspirin use or alcohol consumption) (Pisters et al. 2010). However, information on the factor "L," lability of the international normalized ratio, was not calculated because this factor is inappropriate for patients taking DOACs. Bleeding risk was considered high if the HAS-B(L)ED score was ≥ 3. The OAC status after CA was obtained at any serious adverse events (SAEs) or on the day of the last follow-up.

All patients were classified into three groups according to their CHADS2 score (0–1, 2 and 3–6), as the Japanese guidelines recommend using the CHADS2 score (Class I) over the CHA2DS2-VASc score (Class IIb). Baseline characteristics and clinical outcomes were compared among these three groups, along with their DOAC status.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the research protocol was approved by all applicable participating sites. All patients provided written informed consent before participating in the study. The study was registered as UMIN000026092 (University Hospital Medical Information Network-Clinical Trial Registry). The study protocol also received approval from the ethical committee at each study site before the initiation of the registry (University of Tsukuba Hospital: H28-219).

2.2 | Follow-Up and Clinical Outcomes

The primary outcomes assessed in this subanalysis were SAEs during the 1-year follow-up period. SAEs included ischemic stroke, systemic embolic events (SEEs), major bleeding, all-cause death, cardiovascular deaths, cardiovascular adverse events, and intracranial hemorrhage. These events were evaluated by an event adjudication committee. Major bleeding events were defined according to the criteria of the International Society on Thrombosis Hemostasis (Schulman and Kearon 2005). When SAEs occurred during the follow-up period, case report forms (CRFs) were promptly submitted and evaluated by an event adjudication committee. We also collected follow-up data at 1, 3, 6, and 12 months after the ablation procedure. All AEs, including SAEs, clinically relevant non-major bleeding, and AF recurrence, were reported. The recurrence of AF was defined as any documented AF episode lasting over 30 s. All SAEs were evaluated by an event adjudication committee. Even in the absence of any adverse events, CRFs were collected by the clinical research coordinator. The timing and frequency of 24-h Holter monitor and/or 2-week event monitor implementation were left to the discretion of each attending physician.

2.3 | Statistical Analysis

Continuous variables were presented as the median and interquartile ranges (IQRs). Categorical variables were summarized using *n* (%). Baseline characteristics were compared using the chi-squared test for categorical variables and Wilcoxon's rank sum test for continuous variables. The cumulative event rates during the follow-up period were estimated using the Kaplan–Meier method. The survival curves were compared using a log-rank test. For each endpoint, the incidence rate of the event and 95% confidence intervals (CIs) were estimated. The incidence rates of the event were compared using risk difference.

Cox proportional hazard regression analysis was used to assess the predictors in each factor of the CHADS2 score for ischemic stroke/SEEs. Statistical significance was defined as a two-tailed $p < 0.05$. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Patients Characteristics

The patient flow diagram is presented in Figure 1. For this subanalysis, a total of 2844 patients were included. Baseline patient characteristics are summarized in Table 1. The median age was 68.0 years, and 70.9% were men, with 64.0% of patients having paroxysmal AF. Among all patients, 35.7% had a CHADS2 score of ≥ 2, and 32.1% had a HAS-B(L)ED score of ≥ 3. Types of DOACs included dabigatran (13.3%), rivaroxaban (27.6%), apixaban (26.9%), and edoxaban (32.2%).

In the previous report from the RYOUMA registry, the rate of OAC continuation in patients with DOAC was reported to decrease as the CHADS2 score decreased (Figure S1) (Nogami et al. 2022). The baseline characteristics according to the CHADS2 score categories and DOAC continuation status are shown in Table 2. The rate of DOAC continuation was 48.1%, 69.6%, and 80.9% in patients with a CHADS2 score of 0–1, 2, and 3–6, respectively. Among patients with a CHADS2 score of 0–1, those with DOAC continuation were older (67.0 years [IQR, 60.0–71.0] vs. 63.0 years [IQR, 54.0–69.0], $p < 0.001$), had a lower proportion of males (70.6% vs. 76.4%, $p = 0.005$), lower body weight (65.2 kg [IQR, 56.6–74.2] vs. 66.5 kg [IQR, 59.2–74.5], $p = 0.037$), lower creatinine clearance (CrCl) (78.9 mL/min [IQR, 64.5–98.6] vs. 86.1 mL/min [IQR, 70.3–105.6], $p < 0.001$), a lower proportion of paroxysmal AF (59.0% vs. 70.6%, $p < 0.001$), a higher rate of anti-arrhythmic drug (AAD) use (75.7% vs. 67.2%, $p < 0.001$), and a higher rate of AF recurrence (12.6% vs. 6.5%, $p < 0.001$) compared to those with DOAC discontinuation. The median scores of CHADS2, CHA2DS2-VASc, and HAS-B(L)ED were also higher in those with DOAC continuation compared to DOAC discontinuation (1.0 [IQR, 0.0–1.0] vs. 0.0 [IQR, 0.0–1.0], $p < 0.001$; 2.0 [IQR, 1.0–2.0] vs. 1.0 [IQR, 0.0–2.0], $p < 0.001$; and 2.0 [IQR, 1.0–2.0] vs. 1.0 [IQR, 1.0–2.0], $p < 0.001$, respectively). Among patients with a CHADS2 score of 0–1, a higher CHA2DS2-VASc score and AF recurrence are independent factors for DOAC continuation. In contrast, among patients with a CHADS2 score of 2, there were no significant differences between those with DOAC continuation and discontinuation. Among patients with a CHADS2 score of 3–6, the only observed difference was in the prevalence of malignancy.

3.2 | Clinical Outcomes

In this study, 2630 out of 2844 patients (92.5%) completed the one-year follow-up period. In terms of the primary endpoint, adjudicated ischemic stroke/SEEs occurred in seven patients, major bleeding events occurred in 31, and all-cause death occurred in 12 during the 1-year post-ablation period starting from postoperative day 30. Among the seven patients with ischemic stroke/SEEs, two had atherothrombotic or lacunar infarction, three had hemorrhagic infarction, and two had cardioembolic infarction. Of the 31 patients with major bleeding events, eight patients had intracranial hemorrhage, and 23 patients had other bleeding. Details of major bleeding events are shown in Table S1, and details of all-cause deaths and DOAC status are shown in Table S2. The cumulative event rates of ischemic stroke/SEEs and major bleeding events at 1 year were 0.26% (95% CI, 0.12–0.54) and 1.14% (95% CI,

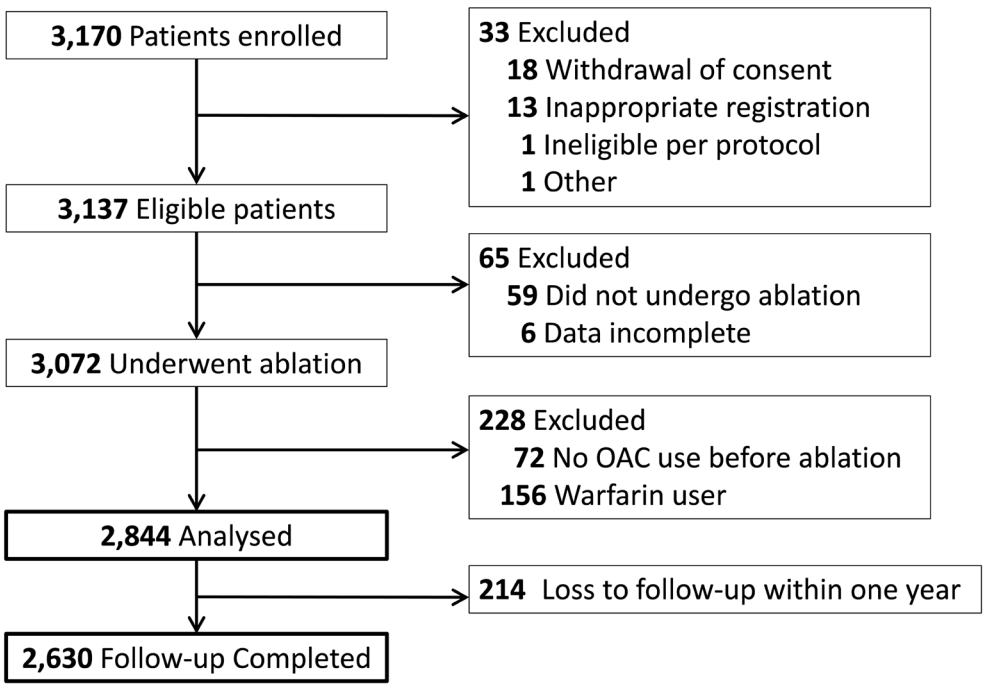

FIGURE 1 | Patient flow diagram. OAC, oral anticoagulant.

TABLE 1 | Baseline demographic and clinical characteristics of study patients.

	n **= 2844**
Age, median [IQR], years	68.0 [60.0–73.0]
Male sex, *n* (%)	2016 (70.9)
Body weight, median [IQR], kg	64.9 [56.9–73.7]
BMI, median [IQR], kg/m^2	23.8 [21.8–26.3]
Creatinine clearance, median [IQR], mL/min	76.9 [61.4–96.0]
AF type	
Paroxysmal, *n* (%)	1821 (64.0)
Persistent, *n* (%)	711 (25.0)
Long-standing persistent, *n* (%)	312 (11.0)
$CHADS_2$ score, median [IQR]	1.0 [0.0–2.0]
$CHADS_2$ score ≥ 2, *n* (%)	1016 (35.7)
$CHADS_2$ score ≥ 1, *n* (%)	2062 (72.5)
CHA_2DS_2-VASc score, median [IQR]	2.0 [1.0–3.0]
CHA_2DS_2-VASc score ≥ 3, *n* (%)	1191 (41.9)
CHA_2DS_2-VASc score ≥ 2, *n* (%)	1856 (65.3)
HAS-B(L)ED score, median [IQR]	2.0 [1.0–3.0]
HAS-B(L)ED score ≥ 3, *n* (%)	914 (32.1)
Comorbidity, *n* (%)	
Hypertension	1722 (60.5)
Diabetes	483 (17.0)
Heart disease	756 (26.6)
Kidney disease	229 (8.1)
Hemodialysis	2 (0.1)
Hepatic disorder	176 (6.2)
Cerebrovascular disease	314 (11.0)
Thromboembolism	98 (3.4)
Dementia	15 (0.5)
Antiplatelets use, *n* (%)	247 (8.7)
Type of DOACs, *n* (%)	
Dabigatran	377 (13.3)
Rivaroxaban	784 (27.6)
Apixaban	766 (26.9)
Edoxaban	917 (32.2)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DOAC, direct-acting oral anticoagulant; IQR, interquartile range.

0.80–1.61), respectively (Figure 2). The number of each SAE, categorized by CHADS2 score, was presented in Table 3, distinguishing between those taking DOAC and those not taking DOAC at any SAEs or on the day of the last follow-up. All seven patients who experienced ischemic stroke/SEEs were on DOACs: three patients with a CHADS2 score of 0–1, one patient with a CHADS2 score of 2, and three patients with a CHADS2 score of 3–6. No cases of ischemic stroke/SEEs were observed in patients not taking DOACs. Among patients taking DOACs, the incidence rates of major bleeding events were significantly higher than those of ischemic stroke/SEEs in the patients with a CHADS2 score of 0–1 (1.3%/year [95% CI, 0.6–2.1] vs. 0.3%/year [95% CI, 0.0–0.7], $p = 0.019$) and in patients with a CHADS2 score of 2 (1.8%/year [95% CI, 0.6–3.0] vs. 0.2%/year [95% CI, 0.0–0.6], $p = 0.018$) (Figure 3A). On the other hand, among patients with a CHADS2 score of 3–6, there was no difference between the incidence rate of major bleeding and ischemic stroke/SEEs (1.6%/year [95% CI, 0.2–3.0] vs. 1.0%/year [95% CI, 0.0–2.1], $p = 0.47$). Among patients not taking DOACs, the incidence rates of major bleeding were very low in those with a CHADS2 score of 0–1 (0.4%/year [95% CI, 0.0–0.8]) and with a CHADS2 score of 2 (0%/year), although in those with a CHADS2 score of 3–6, that was very high (6.0%/year [95% CI, 0.0–12.6]) (Figure 3B). In terms of all-cause mortality, for patients with a CHADS2 score of 3–6, the mortality rate was higher compared to patients with a CHADS2 score of 0–1 or 2. The number of major bleeding events, categorized as intracranial hemorrhage or other major bleeding based on CHADS2 scores, is shown in Table S3. Among the eight patients who experienced intracranial hemorrhage, six were on DOACs: five had a CHADS2 score of 0–1, and one had a CHADS2 score of 2. Two patients were not taking DOACs and had a CHADS2 score of 3–6. One patient with cerebral hemorrhage, who was taking DOACs and had a CHADS2 score of 2, died as a result of the hemorrhage.

To eliminate the influence of antiplatelet therapy, we analyzed the subgroup not receiving antiplatelet therapy ($n = 2597$) (Table S4). Among patients taking DOACs with a CHADS2 score of 0–1 or 2, the incidence rates of SAEs were similar to the overall patient trend, and the incidence rates of major bleeding events were significantly higher than those of ischemic stroke/SEEs (CHADS2 score 0–1: 1.3%/year [95% CI, 0.5–2.0] vs. 0.3%/year [95% CI, 0.0–0.7], $p = 0.031$; CHADS2 score 2: 1.8%/year [95% CI, 0.5–3.1] vs. 0.3%/year [95% CI, 0.0–0.7], $p = 0.032$, respectively). However, among patients with a CHADS2 score of 3–6, the incidence rate of major bleeding events was the same as that of ischemic stroke/SEEs (1.3%/year [95% CI, 0.0–2.7] vs. 1.3%/year [95% CI, 0.0–2.7]) (Figure S2). Among patients not taking DOACs, the trend was the same as in the overall population, but the incidence of major bleeding and overall mortality decreased.

In the CHA2DS2-VASc score classification and HAS-B(L)ED score classification, identifying a group with a low thromboembolic risk but a high bleeding risk (as in patients with a CHADS2 score of 2) among individuals taking DOACs proved challenging (Figures S3 and S4).

SAEs by the individual CHADS2 factors are depicted in Figure S5 and Table S5. Among patients who continued taking DOACs, those with "S" factor have a higher incidence rate of ischemic stroke/SEEs (1.0%/year [95% CI, 0.0–2.3]) compared to patients with other CHADS2 factors (0.3%–0.5%/year). However, due to the low number of events, statistical

TABLE 2 | Baseline characteristics according to the $CHADS_2$ score categories and DOAC continuation status.

$CHADS_2$ score	0–1			2			3–6		
DOAC status	Continued *N* = 880	Discontinued *N* = 948	*p* Continued versus Discontinued	Continued *N* = 441	Discontinued *N* = 193	*p* Continued versus Discontinued	Continued *N* = 309	Discontinued *N* = 73	*p* Continued versus Discontinued
Age, median [IQR], years	67.0 [60.0–71.0]	63.0 [54.0–69.0]	$p < 0.001$	72.0 [66.0–77.0]	70.0 [63.0–77.0]	$p = 0.109$	75.0 [69.0–78.0]	75.0 [71.0–80.0]	$p = 0.154$
Male sex, *n* (%)	621 (70.6)	724 (76.4)	$p = 0.005$	283 (64.2)	129 (66.8)	$p = 0.517$	210 (68.0)	49 (67.1)	$p = 0.890$
Body weight, median [IQR], kg	65.2 [56.6–74.2]	66.5 [59.2–74.5]	$p = 0.037$	63.6 [56.2–72.2]	62.8 [56.8–75.1]	$p = 0.586$	62.3 [55.0–71.0]	61.5 [54.0–70.9]	$p = 0.500$
BMI, median [IQR], kg/m^2	23.9 [21.7–26.3]	23.7 [21.7–25.8]	$p = 0.237$	24.0 [22.0–27.2]	24.3 [21.6–26.7]	$p = 0.691$	23.8 [21.9–26.6]	23.7 [21.3–25.9]	$p = 0.450$
Creatinine clearance, median [IQR], mL/min	78.9 [64.5–98.6]	86.1 [70.3–105.6]	$p < 0.001$	70.1 [54.4–86.20]	71.8 [57.1–92.8]	$p = 0.188$	63.9 [50.1–76.3]	56.7 [48.9–78.7]	$p = 0.192$
AF type									
Paroxysmal, *n* (%)	519 (59.0)	669 (70.6)	$p < 0.001$	275 (62.4)	124 (64.2)	$p = 0.677$	184 (59.5)	50 (68.5)	$p = 0.277$
Persistent, *n* (%)	239 (27.2)	200 (21.1)		119 (27.0)	46 (23.8)		92 (29.8)	15 (20.5)	
Long-standing persistent, *n* (%)	122 (13.9)	79 (8.3)		47 (10.7)	23 (11.9)		33 (10.7)	8 (11.0)	
AAD use, *n* (%)	666 (75.7)	637 (67.2)	$p < 0.001$	331 (75.1)	133 (68.9)	$p = 0.108$	238 (77.0)	60 (82.2)	$p = 0.338$
AF recurrence, *n* (%)	111 (12.6)	62 (6.5)	$p < 0.001$	43 (9.8)	12 (6.2)	$p = 0.146$	28 (9.1)	7 (9.6)	$p = 0.889$
$CHADS_2$ score, median [IQR]	1.0 [0.0–1.0]	0.0 [0.0–1.0]	$p < 0.001$	2.0 [2.0–2.0]	2.0 [2.0–2.0]	$p = 1.000$	3.0 [3.0–4.0]	3.0 [3.0–4.0]	$p = 0.838$
CHA_2DS_2-VASc score, median [IQR]	2.0 [1.0–2.0]	1.0 [0.0–2.0]	$p < 0.001$	3.0 [3.0–4.0]	3.0 [3.0–4.0]	$p = 0.169$	5.0 [4.0–5.0]	5.0 [4.0–6.0]	$p = 0.426$
HAS-B(L)ED score, median [IQR]	2.0 [1.0–2.0]	1.0 [1.0–2.0]	$p < 0.001$	2.0 [2.0–3.0]	2.0 [2.0–3.0]	$p = 0.768$	3.0 [3.0–4.0]	3.0 [2.0–5.0]	$p = 0.457$
Comorbidity, *n* (%)									
Hypertension	454 (51.6)	386 (40.7)	$p < 0.001$	372 (84.4)	165 (85.5)	$p = 0.714$	280 (90.6)	65 (89.0)	$p = 0.683$

(Continues)

TABLE 2 | (Continued)

$CHADS_2$ score	0–1			2			3–6		
DOAC status	Continued $N=880$	Discontinued $N=948$	*p* Continued versus Discontinued	Continued $N=441$	Discontinued $N=193$	*p* Continued versus Discontinued	Continued $N=309$	Discontinued $N=73$	*p* Continued versus Discontinued
Diabetes	28 (3.2)	27 (2.8)	$p=0.676$	164 (37.2)	67 (34.7)	$p=0.552$	163 (52.8)	34 (46.6)	$p=0.342$
Heart disease	185 (21.0)	104 (11.0)	$p<0.001$	169 (38.3)	80 (41.5)	$p=0.458$	182 (58.9)	36 (49.3)	$p=0.137$
Kidney disease	44 (5.0)	59 (6.2)	$p=0.257$	44 (10.0)	21 (10.9)	$p=0.730$	50 (16.2)	11 (15.1)	$p=0.815$
Hepatic disorder	45 (5.1)	58 (6.1)	$p=0.352$	37 (8.4)	14 (7.3)	$p=0.628$	18 (5.8)	4 (5.5)	$p=0.909$
Cerebrovascular disease	16 (1.8)	11 (1.2)	$p=0.244$	47 (10.7)	19 (9.8)	$p=0.758$	177 (57.3)	44 (60.3)	$p=0.641$
Thromboembolism	20 (2.3)	12 (1.3)	$p=0.101$	21 (4.8)	10 (5.2)	$p=0.822$	25 (8.1)	10 (13.7)	$p=0.135$
Malignancy	65 (7.4)	63 (6.6)	$p=0.535$	66 (15.0)	36 (18.7)	$p=0.245$	41 (13.3)	18 (24.7)	$p=0.015$
Dementia	2 (0.2)	0 (0.0)	$p=0.142$	4 (0.9)	1 (0.5)	$p=0.610$	5 (1.6)	3 (4.1)	$p=0.181$
Antiplatelet use, *n* (%)	44 (5.0)	35 (3.7)	$p=0.169$	57 (12.9)	20 (10.4)	$p=0.363$	74 (23.9)	17 (23.3)	$p=0.905$
Hemoglobin, median [IQR], g/dL	14.2 [13.1–15.2]	14.3 [13.5–15.5]	$p<0.001$	13.7 [12.6–14.9]	13.9 [12.8–14.8]	$p=0.482$	13.7 [12.7–14.7]	13.3 [12.3–14.6]	$p=0.178$
HbA1c (NGSP), median [IQR], %	5.7 [5.5–6.0]	5.7 [5.4–5.9]	$p=0.013$	6.0 [5.7–6.8]	6.0 [5.6–6.5]	$p=0.141$	6.2 [5.8–6.8]	6.1 [5.6–6.6]	$p=0.153$

Abbreviations: AAD, anti-arrhythmic drug; NGSP, national glycohemoglobin standardization program; other abbreviations are as in Table 1.

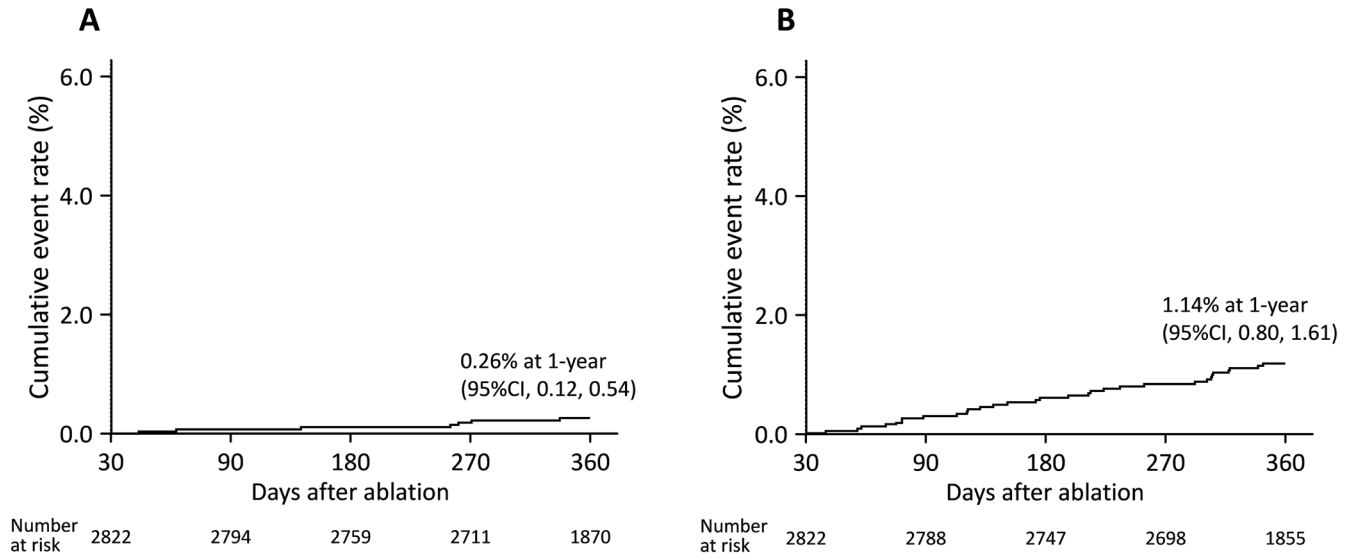

FIGURE 2 | Kaplan–Meier plot of the time to the first serious adverse event. (A) The cumulative event rate of ischemic stroke/SEEs. (B) The cumulative event rate of major bleeding events. SEE, systemic embolic event; other abbreviations as in Figure 1.

TABLE 3 | Serious adverse events after ablation by $CHADS_2$ score categories (overall patients).

	Events while taking DOACs No. of events (% per Year [95% CI])			Events while taking No DOAC No. of events (% per Year [95% CI])		
$CHADS_2$ score	Ischemic stroke/SEEs	Major bleeding	All-cause death	Ischemic stroke/ SEEs	Major bleeding	All-cause death
0–1 ($n=1828$)	3 (0.3 [0.0–0.7])	12 (1.3 [0.6–2.1])	1 (0.1 [0.0–0.3])	0 NC	3 (0.4 [0.0–0.8])	2 (0.2 [0.0–0.6])
2 ($n=634$)	1 (0.2 [0.0–0.6])	8 (1.8 [0.6–3.0])	2 (0.4 [0.0–1.0])	0 NC	0 NC	2 (1.3 [0.0–3.1])
3–6 ($n=382$)	3 (1.0 [0.0–2.1])	5 (1.6 [0.2–3.0])	2 (0.6 [0.0–1.5])	0 NC	3 (6.0 [0.0–12.6])	3 (5.6 [0.0–11.8])

Abbreviations: NC, not calculated; SEE, systemic embolic eventother abbreviations as in Table 1.

comparison of incidence rates between the patients with "S" factor and those with other factors of a CHADS2 score could not be performed.

4 | Discussion

This is the first prospective study assessing the risk of ischemic stroke and major bleeding events in patients with AF who continued or discontinued DOAC treatment after CA. The main findings of this study are as follows:

1. In patients with a CHADS2 score of 0–1, those who continued taking DOACs were significantly older, had a lower proportion of males, lower body weight, and a lower prevalence of paroxysmal AF, a higher rate of AAD use, and a higher rate of AF recurrence compared to those who discontinued DOACs. Conversely, in patients with a CHADS2 score of 2, there were no significant differences between those continuing DOACs and those discontinuing.
2. In patients with a CHADS2 score of 0–1 and 2, the incidence rate of ischemic stroke/SEEs at 1 year was notably low regardless of DOAC intake.
3. In patients with a CHADS2 score of 2, those who continued taking DOACs had a higher incidence rate of major bleeding events than ischemic stroke/SEEs, similar to those with a CHADS2 score of 0–1.
4. Among patients with a CHADS2 score of 3–6, there was no difference between the incidence rate of major bleeding events and that of ischemic stroke/SEEs in those who continued taking DOACs.

We consider that the differences in patients with a CHADS2 score of 0–1 might be based on risk factors for ischemic stroke/SEEs other than the CHADS2 score and AF recurrence. Japanese guidelines describe low body weight, low CrCl, and persistent AF as risk factors for ischemic stroke/SEEs other than the CHADS2 score. AF recurrence is also likely a significant factor in a physician's decision to continue DOACs in patients

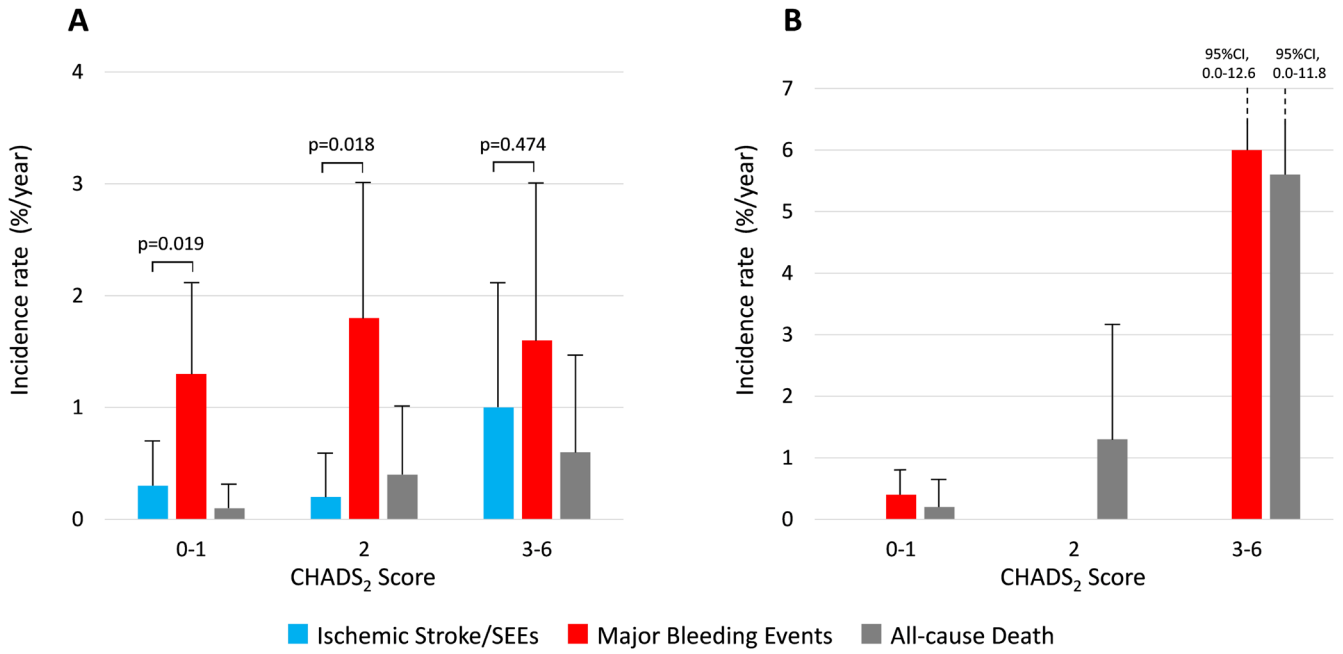

FIGURE 3 | Serious adverse events per year of follow-up after ablation by CHADS2 score categories (overall patients). (A) Events while taking DOACs. (B) Events while not taking DOACs. Error bars denote the upper bound of 95% CIs. DOAC, direct-acting oral anticoagulant; other abbreviations are as in Figures 1 and 2.

even with a low risk of thromboembolism. This might have been more about continuing DOACs in preparation for the second ablation session rather than for preventing thromboembolism in patients with a low risk of thromboembolism.

In this study, ischemic stroke/SEEs occurred in patients who continued taking DOACs, whereas no ischemic stroke/SEEs were observed in those who discontinued taking DOACs. Furthermore, several major bleeding events occurred in patients who discontinued DOACs. This trend appeared paradoxical. The reasons and decision-making processes for discontinuing or continuing DOAC therapy were not elucidated in the entire population of this study; however, each physician likely considered the balance of risks between ischemic stroke/SEEs and major bleeding events. In fact, several patients experienced ischemic stroke/SEEs despite continuing DOAC therapy. These patients were unable to prevent events solely by continuing DOACs and may have required additional preventive measures. Additionally, patients who discontinued DOACs despite having a CHADS2 score of 3–6 might have included those unable to continue due to a higher bleeding risk compared to ischemic stroke/SEEs. Unfortunately, we could not ascertain this reason due to the lack of significant differences in background characteristics between those who continued or discontinued DOACs, except for the presence of malignancy. Nevertheless, physicians who chose to discontinue DOAC therapy for patients with a CHADS2 score of 3–6 likely based their decisions on clear evidence, considering these patients at higher risk for major bleeding events despite their CHADS2 score. Even with the discontinuation of DOAC therapy, we considered that these patients could not prevent major bleeding events due to other risk factors associated with such events.

In this study, the cumulative incidence rate of ischemic stroke/SEEs tended to be lower, while the incidence rate of major bleeding events tended to be higher compared to some previous studies. For example, in the Chinese AF Ablation Registry (Yang et al. 2020), the incidence rates for thromboembolism were 0.54 and 0.86 per 100 patient-years, and the incidence rates for major bleeding events were 0.19 and 0.35 for the Off-OAC (70%) and On-OAC (30%) groups, respectively. Similarly, a Danish study (Karasoy et al. 2015) reported incidence rates for thromboembolism and major bleeding events of 0.60 and 0.73 per 100 patient-years, respectively. Possible reasons for our lower incidence rate of SEEs may be the high quality of AF ablation therapy and the high rate of DOAC continuation in Japan. On the other hand, the higher incidence rate of major bleeding events in our study may be attributed to the continuing DOACs in patients with a lower thromboembolic risk, as well as the difference in the definition of major bleeding events. We used sensitive criteria from the International Society on Thrombosis and Hemostasis and conducted a reliable follow-up in our prospective study.

Recently, a large retrospective analysis from the National Database of Health Insurance Claims and Specific Health Checkups of Japan was reported (Kanaoka et al. 2024). In this analysis, at 6 months after CA, OAC had been discontinued in 29%. There was a higher continuation rate of OAC therapy in the group with higher CHADS2 scores, and continuing OAC therapy was associated with a higher risk of major bleeding in patients with a CHADS2 score ≤ 2 and a lower risk of thromboembolism in patients with a CHADS2 score ≥ 3. While the definition of OAC status after ablation (classified based on the status 6 months after ablation) differs from that of our current study (classified based on the occurrence of any SAEs or on the last follow-up date), the trends of main results are comparable, suggesting that patients with a CHADS2 score ≤ 2 may be considered for the possibility of discontinuation of DOACs. Meta-analyses revealed no significant differences between patients who continued or discontinued OAC therapy regarding

the risk of stroke/SEEs, although OAC continuation was associated with an increased risk of major bleeding (Atti et al. 2018; Liu et al. 2021). A Danish registry (Karasoy et al. 2015) also reported that the rates of thromboembolic events were similarly low among patients who discontinued and continued OAC therapy (0.56 and 0.64%/year, respectively), and continued OAC therapy was significantly associated with serious bleeding risk (hazard ratio 2.05). They concluded that the serious bleeding risk associated with OAC appeared to outweigh the benefits of thromboembolism reduction. However, major bleeding events are rarely life-threatening, whereas stroke events are often life-altering in general. Therefore, the severity of these SAEs and long-term outcomes, including residual disability, should be considered alongside their incidence rates when evaluating clinical outcomes. Unfortunately, this study lacks detailed information on the severity and long-term outcomes. Further research might be needed for optimal OAC therapy for the patients with a CHADS2 score ≤ 2 after CA.

For the patients with a CHADS2 score of 3–6, DOAC continuation after CA had been generally recommended for preventing ischemic stroke regardless of rhythm status. However, the latest expert consensus statement (Tzeis et al. 2024) suggests that the discontinuation of anticoagulation is being considered based on strong patient values and preferences, and left atrial appendage occlusion may be discussed as an alternative approach. The present study showed the incidence rate of major bleeding events was higher and comparable to that of ischemic stroke/SEEs in the patients with a CHADS2 score of 3–6 who continued taking DOACs. Those patients should have a risk of ischemic stroke and also of major bleeding events; the optimal comprehensive management for preventing both events should be considered in the future.

4.1 | Limitations

This study possesses several limitations. Firstly, it was not a randomized trial. The decision to continue or discontinue anticoagulation after CA was left to the discretion of individual physicians, and the underlying processes or reasons guiding this decision-making remained unknown. Secondly, the findings of this study should be interpreted cautiously due to the low number of events and the small sample size. Multivariate analysis adjusting for clinical risk factors could not be performed because of the limited number of events. Additionally, the relative risk of ischemic stroke/SEEs could not be calculated, as no cases of ischemic stroke/SEEs were observed in patients not taking DOACs. Thirdly, the dosage of each DOAC was not taken into account in this analysis. Off-label overdosing or underdosing may impact the incidence of clinical events. Fourthly, the recurrence rate of AF might not have been sufficiently detected. We did not utilize a 2-week event monitor for all patients, which may have resulted in inadequate detection of asymptomatic AF. The AF recurrence rate in our study was lower than in previous reports. Lastly, a significant limitation is the short follow-up period despite its prospective nature. Our analysis focused on clinical outcomes within 1 year after CA, and long-term outcomes beyond this period were not examined. The latest expert consensus statement (Tzeis et al. 2024) suggests deferral of OAC discontinuation until the completion of 12 months following CA in the intermediate-risk patients to increase the likelihood of selecting patients with truly successful AF elimination. Furthermore, considering that the risk factors for thromboembolism may evolve over time, prolonged patient observation is imperative to assess the necessity of OAC therapy at each time point.

5 | Conclusions

In this subanalysis of a large multicenter prospective registry, the DOAC continuation rate at 1 year after CA was 48.1%, 69.6%, and 80.9% in patients with a CHADS2 score of 0–1, 2, and 3–6, respectively. In patients with a CHADS2 score of 0–1 and 2, the incidence rate of ischemic stroke/SEEs at 1 year after CA was notably low regardless of DOAC intake. In patients with a CHADS2 score of 2, the incidence rate of major bleeding events appeared to be higher than that of ischemic stroke/SEEs among those who continued taking DOACs, resembling the trend observed in patients with a CHADS2 score of 0–1. Conversely, in patients with a CHADS2 score of 3–6, the incidence rates of both ischemic stroke/SEEs and major bleeding events seemed to be comparably high. Further research is needed to evaluate the safety and risks associated with the discontinuation of DOACs after successful CA.

Author Contributions

Conceptualization: Akihiko Nogami. Methodology: Yuka Oda, Akihiko Nogami. Writing – original draft preparation: Yuka Oda. Writing – review and editing: Akihiko Nogami. Statistical analysis: Masahiko Gosho. Funding acquisition: Masayuki Fukuzawa, Atsushi Takita. Resources: Yuki Komatsu, Kyoko Soejima, Itsuro Morishima, Kenichi Hiroshima, Ritsushi Kato, Satoru Sakagami, Fumiharu Miura, Keisuke Okawa, Kikuya Uno, Koichiro Kumagai, Takashi Kurita. Supervision: Tomoko Ishizu, Kazutaka Aonuma.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The study protocol also received approval from the ethical committee at each study site before the initiation of the registry (University of Tsukuba Hospital: H28-219).

Consent

All patients provided written informed consent before participating in the study.

Conflicts of Interest

Akihiko Nogami has received honoraria from Boehringer Ingelheim, DAIICHI SANKYO, Bristol Myers Squibb, Abbott, and Johnson & Johnson; and endowments from Medtronic. Yuki Komatsu has received honoraria from Johnson & Johnson. Kyoko Soejima has received honoraria from Boehringer Ingelheim, DAIICHI SANKYO, Abbott, Medtronic, and Johnson & Johnson. Itsuro Morishima has received honoraria from DAIICHI SANKYO and Abbott. Kenichi Hiroshima has received honoraria from Abbott, Medtronic, Boston, Johnson & Johnson, and Japan Lifeline. Ritsushi Kato has received grant support from Boston Scientific, Abbott, Bayer, and Japan Lifeline. Satoru Sakagami has received honoraria from DAIICHI SANKYO and Johnson & Johnson. Fumiharu Miura has received

honoraria from Medtronic, Abbott, and Biotronik. Keisuke Okawa has received honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, DAIICHI SANKYO, Pfizer, Abbott, Johnson & Johnson, and Medtronic. Masayuki Fukuzawa and Atsushi Takita are employees of DAIICHI SANKYO. Kikuya Uno has received honoraria from Japan Lifeline. Koichiro Kumagai has received honoraria from DAIICHI SANKYO, Boehringer Ingelheim, and Japan Lifeline. Takashi Kurita has received honoraria from Bayer, Boehringer Ingelheim, DAIICHI SANKYO, Bristol-Myers Squibb, Abbott, Medtronic, Japan Lifeline, and Johnson & Johnson. Masahiko Gosho has received honoraria from Pfizer, Ferring Pharma, Merck Biopharma, and AstraZeneca. Tomoko Ishizu has received honoraria from Ono Pharmaceutical, Janssen Pharma, AstraZeneca, and Otsuka Pharmaceutical. Kazutaka Aonuma has received honoraria from Boston Scientific, Japan Lifeline, Nihon Kohden, Biotronik, Toray Industries, Abbott, Boehringer Ingelheim, and Century Medical.

Data Availability Statement

The deidentified participant data and the study protocol will be shared on a request basis for up to 36 months after the publication of this article. Researchers who make the request should include a methodologically sound proposal on how the data will be used; the proposal may be reviewed by the responsible personnel at DAIICHI SANKYO Co. Ltd., and the data requestors will need to sign a data access agreement. Proposals should be directed to akihiko-ind@umin.ac.jp.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.