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Original Article

Association between oral anticoagulants continuation on thromboembolism and bleeding events in patients with $CHADS_2$ score 0–2 points after catheter ablation for persistent atrial fibrillation

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ABSTRACT

Background: Guidelines state that oral anticoagulants (OACs) should be continued after catheter ablation for atrial fibrillation (AF) based on thromboembolic risk stratification, regardless of procedural results. However, whether OACs could be discontinued in low-thromboembolic-risk patients remains unclear.
Methods: This was a retrospective follow-up study from the EARNEST-PVI (NCT03514693) trial, which compared the efficacy of pulmonary vein isolation (PVI)-alone and PVI-plus strategies for persistent AF ablation. A total of 427 patients with $CHADS_2$ score of ≤2 points were divided into two groups: OAC continuation throughout the overall period (group C, $n = 205$) and OAC discontinuation within 1 year after ablation (group D, $n = 222$). The incidence of thromboembolic and bleeding events was analyzed.
Results: AF recurrence (33 % vs. 17 %, $p < 0.001$), thromboembolic events (1.39 % vs. 0 % per year, $p = 0.005$), and overall bleeding event rates (7.54 % vs. 3.32 % per year, $p = 0.003$) were higher in group C than in group D. There was no significant difference in major bleeding event rates between the C and D groups (0.51 % vs. 0.67 % per year, $p = 0.686$). However, a higher number of overall bleeding events, including major and clinically relevant non-major events, was observed in group C (adjusted hazards ratio: 2.04, 95 % confidence interval: 1.14–3.65, $p = 0.016$).
Conclusions: Thromboembolic events and overall bleeding events were fewer in the OAC discontinuation group compared with the OAC continuation group. Discontinuation of OACs might be considered in patients with low $CHADS_2$ score after catheter ablation of persistent AF.

Introduction

Regarding management of patients with atrial fibrillation (AF), previous guidelines recommend oral anticoagulants (OACs) based on thromboembolic risk stratification such as $CHAD_2$ and CHA_2DS_2-VASc

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score [1–3]. Several studies have demonstrated that persistent AF (PerAF) is associated with a higher risk of stroke than is paroxysmal AF [4–7], and the latest Japanese guidelines focus update recommends the HELT-E_2S_2 risk score, which considers PerAF as a stroke risk [8].

Catheter ablation reduces the burden of AF even in patients with PerAF [9]. Patients with low $CHADS_2$ scores (≤2) after catheter ablation may have as low an incidence of thromboembolism as those on OACs, but a higher incidence of major bleeding [10]. Meanwhile, the current guidelines recommend OAC continuation post-ablation when the $CHADS_2$ score is ≥2 points regardless of the procedural results and type of AF [3]. In the real world, OAC has occasionally been continued even in low-risk patients ($CHADS_2$ score ≤ 1) based on the discretion of the attending physician. The risk-benefit balance of OAC in patients maintaining sinus rhythm after PerAF ablation may warrant reconsideration.

The Effect of Extensive Ablation on Recurrence in Patients with Persistent AF Treated with Pulmonary Vein Isolation (EARNEST-PVI) trial was a prospective multicenter randomized controlled trial that focused on the efficacy of additional ablation to pulmonary vein isolation (PVI) for PerAF ablation [11]. In the current study, we conducted a retrospective follow-up study from the EARNEST-PVI trial using extended prognostic data, including thromboembolic and bleeding events, 5 years after ablation. We investigated the association between OAC continuation and thromboembolic and bleeding events in patients with a $CHADS_2$ score of ≤2 points.

Methods

Study design

The EARNEST-PVI trial, which was registered at ClinicalTrials.gov (NCT03514693), was a prospective, multicenter, randomized, open-label, non-inferiority trial involving patients with PerAF who underwent initial catheter ablation procedures. The study design has been previously described [12]. Patients were enrolled between March 2016 and September 2017 at eight experienced centers. This study was conducted by the Osaka Cardiovascular Conference Arrhythmia Investigators. After obtaining written informed consent to participate, patients eligible for the trial were randomized to undergo either PVI alone or in combination with additional ablation. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki and was approved by the ethics committee of each participating center.

This study was a secondary retrospective analysis conducted on the patient population from the primary study registered at ClinicalTrials.gov (NCT03514693). Although the primary study pre-specified its outcomes as listed in the ClinicalTrials.gov registration, the outcomes analyzed in this manuscript include additional variables that were not pre-specified in the registration. These additional outcomes were retrospectively collected from the clinical records of the enrolled patients.

The participants were individuals with PerAF, defined as a sustained episode of AF lasting from 7 days to <5 years, who were recruited from eight experienced centers. The exclusion criteria were: (1) age < 20 or ≥ 80 years; (2) sinus rhythm at enrollment; (3) left atrial diameter > 50 mm in the parasternal long axis on echocardiography; (4) AF with mitral stenosis or prosthetic heart valve; (5) valvular AF and history of cardiac surgery; (6) hemodialysis; (7) prior catheter ablation; (8) left ventricular ejection fraction ≤30 %; and (9) New York Heart Association functional class 3 or 4.

Prior to the ablation procedure, comprehensive clinical data, including patient history, blood tests, 12-lead electrocardiogram (ECG), and transthoracic echocardiography, were collected. Thromboembolic risk was stratified using the $CHADS_2$ [13,14], CHA_2DS_2-VASc [15,16], and HELT-E_2S_2 scores [4]. Bleeding risk was evaluated using the HAS-BLED [17] and ORBIT scores [18].

Among the 512 enrolled patients, data of 497 were included in the main analysis in the EARNEST-PVI trial. Out of the 497 patients (Fig. 1), we excluded 70 in the current study; 63 with $CHADS_2$ ≥ 3 points, 6 with follow-up duration within 90 days after the procedure, and 1 having an uncertain event date. Finally, 427 patients were included in the study.

Data collection and post-ablation anticoagulation strategy

Scheduled follow-up visits were conducted 1, 3, 6, 9, and 12 months after the initial ablation procedure and every year thereafter. At each follow-up visit, ECG and medication evaluations were performed. A 24-h Holter ECG was performed at 6 and 12 months. The patients were allowed to visit the clinic or hospital on unscheduled days, and

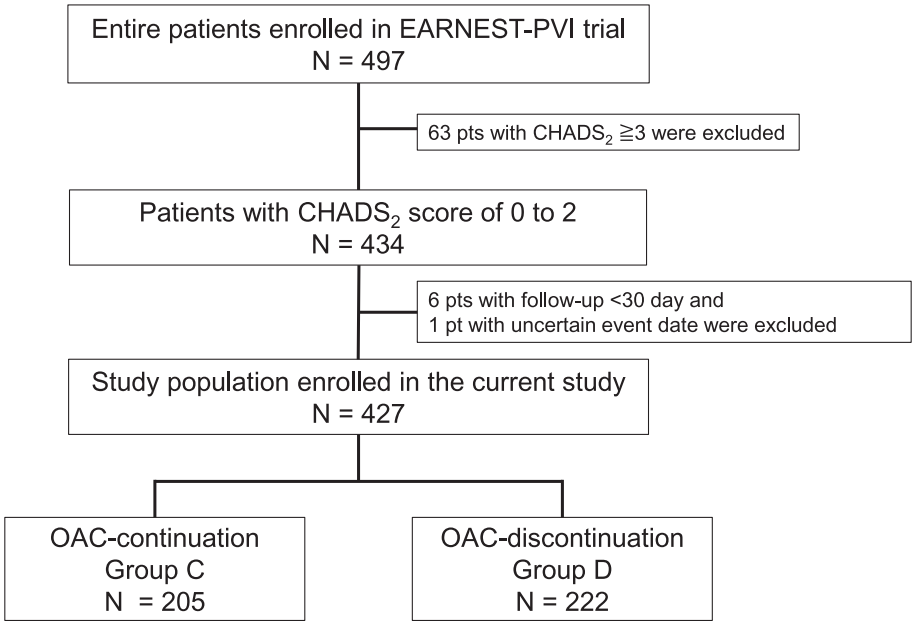

Fig. 1. The study flow chart.
OAC, oral anticoagulant.

symptom-triggered tests were used for heart rhythm monitoring when necessary. Recurrent AF was defined as episodes lasting >30 s, as documented by 12-lead ECG or other appropriate tests.

The post-procedure OAC strategy involved resuming OAC therapy the day after the procedure for at least 3 months. Thereafter, the decision to continue or discontinue OAC was made at the discretion of the cardiovascular physicians of the participating hospitals by referring to $CHADS_2$ score [1–3].

Grouping

The grouping and follow-up schemata are shown in Fig. 2. The patients were allocated into two groups: the OAC-continuation group (group C), which comprised patients who continued OAC therapy for at least 1 year after ablation and the OAC-discontinuation group (group D), which comprised patients who discontinued OAC therapy within 1 year after ablation. In this trial, the average time to disruption of OAC in all patients who discontinued OAC was 0.98 years; therefore, the boundary between group C and group D was set at 1 year in this study. The patients in group C who had disrupted OAC therapy for >1 year after ablation were censored at the time of discontinuation. The follow-up period began on day 90 post-ablation in group C and on the date of OAC disruption in group D.

Endpoints

The primary endpoints were thromboembolic events (fatal or non-fatal ischemic stroke and systemic embolism) and major or clinically relevant non-major (CRNM) bleeding events during the follow-up period. Major bleeding was defined according to the International Society of Thrombosis and Hemostasis criteria (a reduction in hemoglobin of ≥2 g/dL, transfusion of ≥2 units packed red cells, symptomatic bleeding in a critical site or organ, or death) [19]. CRNM bleeding was defined as clinically relevant events such as epistaxis, hematuria, blackish feces or melena, hemoptysis, or other bleeding events that were not defined as major bleeding. An independent clinical events committee adjudicated all clinical events detailed in the medical records, considering only the first event of each type if the patient experienced multiple events during the follow-up period.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median and interquartile range, and comparisons were made using Student's *t*-test, Mann–Whitney *U* test, as appropriate. Categorical variables are expressed as the number and percentage of patients; differences between patients classified into groups C and D were analyzed using the chi-square test or Fisher's exact test.

The incidence of major outcome events was calculated by dividing the number of events by the person-years at risk. Survival distributions for each group were calculated using the Kaplan–Meier method. In addition, thromboembolic events (ischemic stroke or systemic embolism) and major and CRNM bleeding events between the two groups during the observation period were compared using either the log-rank test or Gehan generalized Wilcoxon method for time-to-event analysis.

Cox regression models were used to identify risk factors independently associated with the endpoints, with adjusted hazard ratios for OAC continuation, age, sex, body mass index (BMI), and use of antiplatelet agents. Propensity score-matching analysis was conducted for sensitivity analysis. Propensity scores were generated using a logistic regression model that included age, sex, BMI, antiplatelet medication use, HAS-BLED score, and anemia. Nearest neighbor matching without replacement was employed with a ratio of 1:1, using a caliper width of 0.2 times the propensity score logit standard deviation. All analyses were performed using JMP17 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Within 1 year after ablation, 222 patients had discontinued OAC and were assigned to group D. The number of OAC continuations and discontinuations in each $CHADS_2$ and HAS-BLED score among the entire

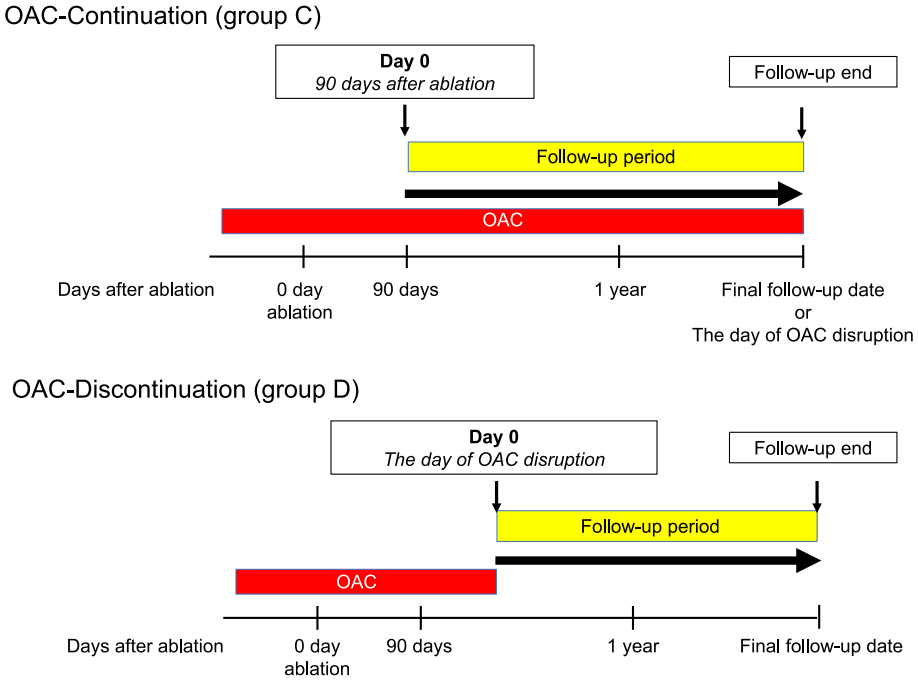

Fig. 2. Definition of the groupings and follow-up period in each group.
OAC, oral anticoagulant.

EARNEST-PVI study population is shown in Fig. 3. The percentages in group C for $CHADS_2$ score 0, 1, and 2 points were 0:30 %, 1:51 %, and 2:65 %, respectively. Table 1 presents the baseline characteristics of group C and D (Online Tables 1 to 3 summarize a comparison between groups C and D including patients with a $CHADS_2$ score of 0 to 2 points). The patients in group C were significantly older than those in group D (66.4 ± 8.5 years vs. 61.9 ± 9.2 years, $p < 0.001$) and were more likely to have hypertension, diabetes, vascular disease, and to be taking antiplatelet medications. The variations in $CHADS_2$ scores of 1 and 2 are shown in Online Fig. 1. Group C exhibited a higher recurrence rate within 1 year than did group D (33 % vs. 17 %, $p < 0.001$). Group C had a higher $CHADS_2$ score (1.15 ± 0.71 vs. 0.76 ± 0.72, $p < 0.001$) and HAS-BLED score (1.5 ± 1.1 vs. 1.1 ± 0.9, $p < 0.001$) than did group D. We also confirmed crossover of OAC during the follow-up period (Online Fig. 2).

Thromboembolic events and bleeding events

The median follow-up duration was 3.2 (1.8–3.7) and 3.0 (2.2–3.5) years in groups C and D, respectively ($p = 0.065$). Of the total, eight patients experienced thromboembolic events with an incidence rate of 0.68 per 100 patient-years (Online Table 4). The eight patients who experienced thromboembolic events were in group C, with an incidence rate of 1.39 per 100 patient-years; no patients experienced a thromboembolic event in group D (the Gehan generalized Wilcoxon method, $p = 0.005$; Fig. 4A). The incidence of thromboembolism stratified by the $CHADS_2$ score is shown in Online Fig. 3. Three patients in group C experienced major bleeding, while four patients in group D experienced major bleeding (Fig. 4B). The incidence of major bleeding was not different between groups C and D (0.51 vs. 0.67 per 100 patient-years, $p = 0.686$). The incidence of major bleeding stratified by the $CHADS_2$ score is shown in Online Fig. 4. As shown in Fig. 4C, 39 patients in group C experienced overall bleeding events, including major and CRMN, as well as 19 patients in group D. The incidence of overall bleeding was higher in group C than in group D (7.54 vs. 3.32 per 100 patient-years, $p = 0.003$). Regarding the multivariable analysis after adjustment for age, sex, BMI, and antiplatelet medication status, OAC continuation was associated with overall bleeding events (hazard ratio: 2.04, 95 % confidence interval: 1.14–3.65, $p = 0.016$; Table 2). Using the Kaplan–Meier analysis after propensity score matching, the incidence of overall bleeding events was higher in group C than in group D (log-rank test, $p = 0.0499$; Fig. 4D). Standardized mean differences (SMDs) before and after matching are shown in Online Tables 5 and 6. The incidence of overall bleeding stratified by the $CHADS_2$ score is shown in Online Fig. 5. We performed an analysis that excluded censoring due to OAC discontinuation in group C and compared the event rates between the two groups. The results showed no significant differences (Online Fig. 6). In this analysis, the results were consistent across all outcomes except for overall bleeding in the propensity score-matched cohort. An analysis including cases in which OACs were discontinued in group C showed a trend toward increased overall bleeding, although the difference was not statistically significant.

Discussion

We investigated the association of OAC continuation with thromboembolic and bleeding events in patients with a $CHADS_2$ score of ≤2 points after PerAF ablation. The main findings of this study were: (1) after PerAF ablation, patients with $CHADS_2$ score of ≤2 points in the OAC-discontinuation group did not develop thromboembolism; (2) the incidence of major bleeding was equivalent between the OAC-continuation and -discontinuation groups; and (3) OAC continuation was associated with the risk of overall bleeding events.

Thromboembolic risk associated with OAC discontinuation after PerAF ablation

The risk of ischemic stroke in patients with PerAF has recently been reevaluated. A previous study demonstrated that both paroxysmal and PerAF carry similar stroke risks [20], leading to recommendations for OAC use irrespective of the AF type. However, meta-analyses have demonstrated a heightened risk of ischemic stroke in patients with PerAF compared with those with paroxysmal AF [6]. Similarly, a Japanese registry study found a significantly elevated stroke risk in patients with PerAF, regardless of OAC use [5]. An integrated analysis of the Japanese AF registry data [4] revealed that PerAF conferred a 1.59-fold higher risk of stroke than did paroxysmal AF using the newly proposed HELT-E_2S_2 score that incorporated PerAF as a risk factor for stroke. In this retrospective follow-up study from the EARNEST-PVI trial, we found no cases of thromboembolism in the OAC-discontinuation group during a median follow-up of >3 years, suggesting that OAC discontinuation in patients with low $CHADS_2$ score after PerAF ablation might not increase the risk of thromboembolism. Paradoxically, patients in the OAC-continuation group experienced thromboembolic events; however, these results should be interpreted with caution. This could be explained by the fact that the OAC-continuation group

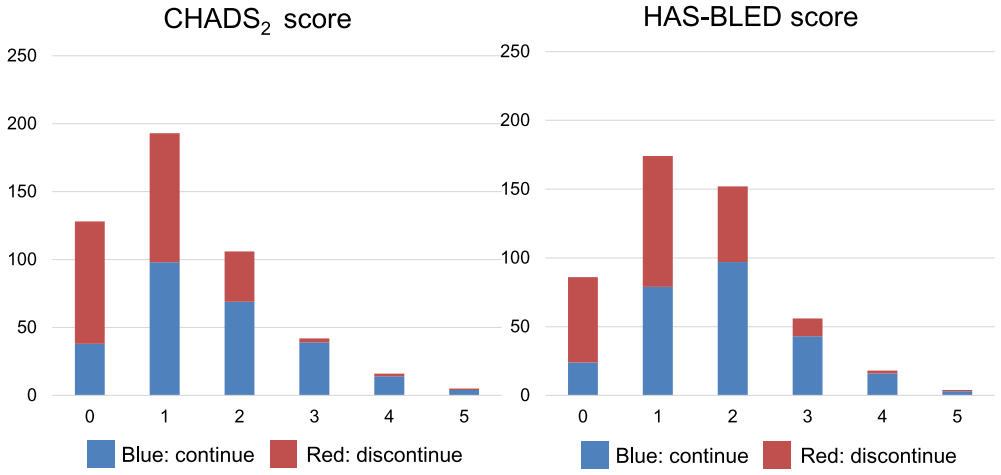

Fig. 3. The number of patients who continued and discontinued OAC in each $CHADS_2$ score and HAS-BLED score among the entire study population of the EARNEST-PVI trial. OAC, oral anticoagulant.

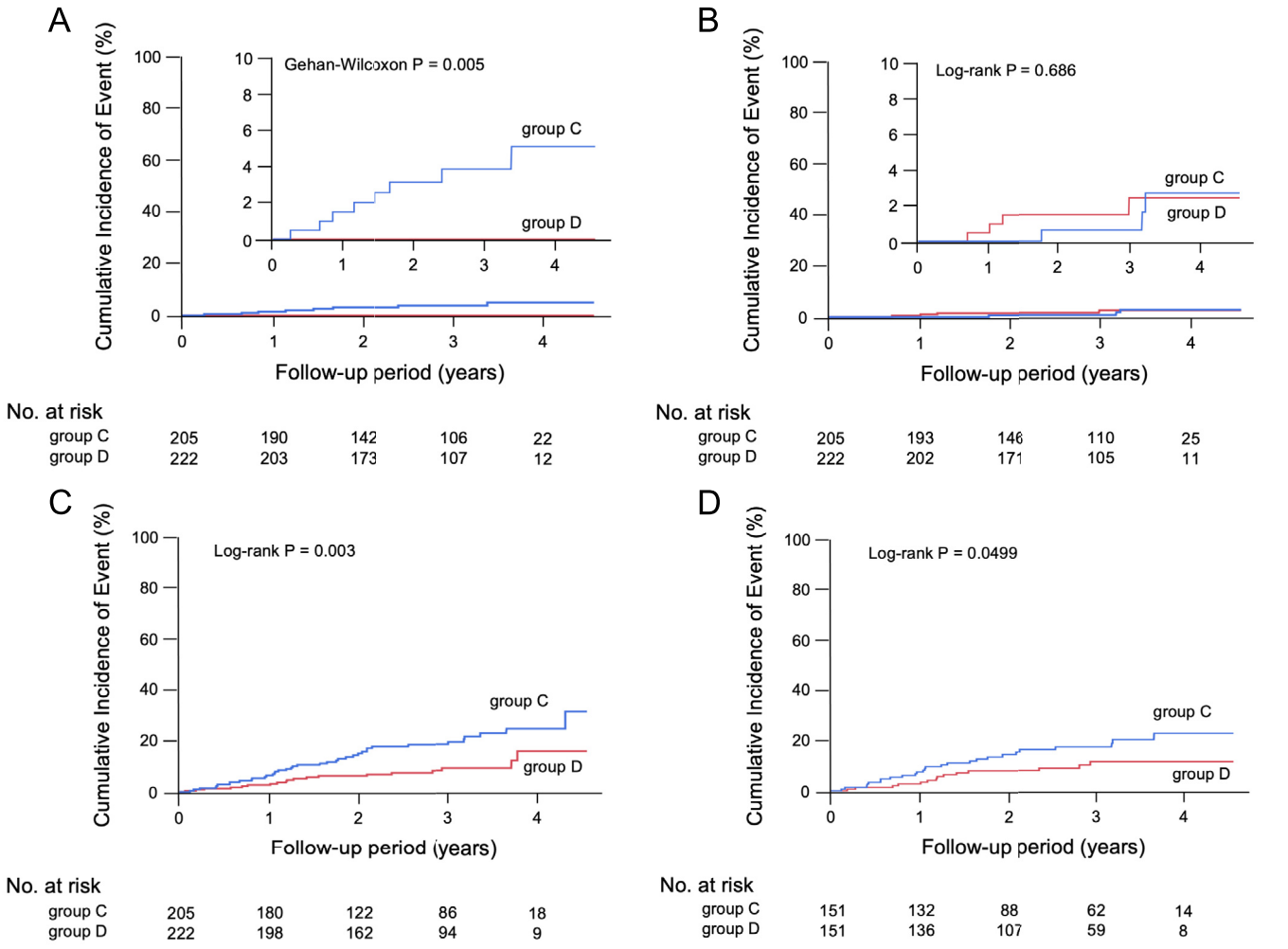

Fig. 4. The incidence of thromboembolism (A), major bleeding (B), overall bleeding (C), and overall bleeding after propensity score matching (D) stratified by OAC continuation. OAC, oral anticoagulant.

had a relatively higher $CHADS_2$ score and more recurrent AF than the OAC-discontinuation group. Although $CHADS_2$ in this study population was <3 points, the impact of AF/atrial tachycardia recurrence might have affected the results. Factors that increase the post-ablation risk of thromboembolism in patients with low $CHADS_2$ scores should be investigated in future studies.

Bleeding risk associated with OAC continuation

Regarding hemorrhagic complications, few studies have compared the risks of major bleeding with and without direct OACs (DOACs). A recent randomized controlled trial of DOAC in subclinical AF has reported a 2.1-fold increase in the risk of major bleeding in the DOAC group versus placebo [21]. In the results after adjusting for variables in the ASSAF-K registry [22], there was no significant difference in major bleeding between DOACs and warfarin, although major bleeding was significantly lower in the absence of OACs compared to warfarin. In the present study, post-ablation OAC continuation in patients with low-$CHADS_2$ score was associated with the incidence of CRNM bleeding; however, there was no significant difference in the occurrence of major bleeding events. A Japanese National Database study found that OACs were significantly associated with the risk of major bleeding in patients with $CHADS_2$ scores of ≤2 points [10]. Considering the incidence of major bleeding in patients with low HAS-BLED scores, the sample size and follow-up duration may have been insufficient in the current study. Although studies on CRNM bleeding with DOACs after ablation are limited, previous research has suggested that the risk of CRNM bleeding may vary depending on the type and dose of DOAC used [23]. In our study, OAC continuation was associated with an increased risk of bleeding, even after adjusting for confounding factors.

Decision-making for OAC discontinuation after PerAF ablation

Although decision-making for OAC discontinuation after AF ablation is based on the $CHADS_2$ risk score [1–3], post-ablation evidence for OAC discontinuation has not been fully established. In Japan, Okumura et al. conducted a retrospective multicenter observational study after AF ablation to analyze the association between post-ablation OAC discontinuation, stroke, and major bleeding events [24]. Stroke and major bleeding events were more common in the OAC-continuation group than in the OAC-discontinuation group, but were largely influenced by age and $CHADS_2$ score. Although, in our study, we focused on patients with low-$CHADS_2$ scores, our results were consistent with those shown in previous studies wherein the OAC-continuation group had a higher incidence of thromboembolism. In a large retrospective study using the Japanese national database, wherein the risk of stroke and major bleeding events after OAC discontinuation 6 months after ablation were investigated [10], the group with a $CHADS_2$ score of 0–2 and continued OAC did not have reduced ischemic stroke risk but had increased risk of major bleeding. In the group with a $CHADS_2$ score of 3–6, OAC continuation was associated with a reduction in thromboembolism without an increase in major bleeding. The results of our study

Table 1
Baseline patient characteristics.

Variable	Group C ($n = 205$)	Group D ($n = 222$)	*P* value
Follow-up duration, years	3.2 (1.8 - 3.7)	3.0 (2.2 - 3.5)	0.065
PVI-alone group, n (%)	102 (50)	107 (48)	0.748
Age, y.o.	66.4 ± 8.5	61.9 ± 9.2	<0.001
≦65, n (%)	78 (38)	131 (59)	
66 - 74, n (%)	96 (47)	76 (34)	
≧75, n (%)	30 (15)	15 (7)	
Female sex, n (%)	58 (28)	43(19)	0.030
Long-standing PerAF, n (%)	47 (23)	54 (24)	0.734
AF duration before the procedure, days	118 (57 - 333)	142 (69 - 357)	0.254
BMI, kg/m^2	24.9 ± 3.7	24.3 ± 3.6	0.124
Hypertension, n (%)	137 (67)	103 (46)	<0.001
Diabetes, n (%)	36 (18)	17 (8)	0.002
Congestive heart failure, n (%)	29 (14)	28 (13)	0.217
Dyslipidemia, n (%)	96 (47)	95 (43)	0.702
Vascular disease, n (%)	25 (12)	9 (4)	<0.001
History of stroke or TIA, n (%)	3 (2)	6 (3)	0.373
History of systemic TE, n (%)	1 (0)	0 (0)	0.298
Abnormal liver function, n (%)	10 (5)	13 (6)	0.655
Abnormal renal function, n (%)	7 (3)	5 (2)	0.468
eGFR, ml/min/1.73m^2	65.0 ± 13.9	65.4 ± 12.7	0.523
Anemia Hb <13(M), <12(F), n (%)	16 (8)	18 (8)	0.908
LAD, mm	42.8 ± 4.4	40.8 ± 4.8	<0.001
LVEF, %	61.7 ± 10.9	62.4 ± 8.4	0.443
$CHADS_2$	1.15 ± 0.71	0.76 ± 0.72	<0.001
0, n (%)	39 (19)	90 (40)	
1, n (%)	97 (47)	95 (43)	
2, n (%)	69 (34)	37 (17)	
CHA_2DS_2-VASc	2.2 ± 1.1	1.4 ± 1.1	<0.001
CHA_2DS_2-VASc ≧2, n (%)	149 (73)	95 (43)	<0.001
HELT-E_2S_2	1.9 ± 0.6	1.6 ± 0.6	<0.001
HAS-BLED	1.5 ± 1.1	1.1 ± 0.9	<0.001
ORBIT	0.83 ± 0.96	0.62 ± 0.88	0.012
Warfarin, n (%)	19 (9)	–	
DOAC, n (%)	186 (91)	–	
Antiplatelet therapy, n (%)	19 (9)	9 (4)	0.030
AF recurrence within 1 year, n (%)	68 (33)	38 (17)	<0.001

PVI, pulmonary vein isolation; PerAF, persistent atrial fibrillation; BMI, body mass index, TIA, transient ischemic attack; TE thromboembolism; Hb, hemoglobin; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; DOAC, direct oral anticoagulant.

were consistent with the previous study wherein OAC continuation did not decrease the risk of thromboembolism or increase the risk of bleeding in patients with low-$CHADS_2$ scores [10]. Although the current study enrolled fewer patients than did these two studies, the strength of the current study was the ensured quality of the ablation procedure using contact force-guided ablation and prospectively acquired patient information including AF recurrence and detailed events, which suggests that the results are reliable. Taken together, OAC discontinuation in patients with low $CHADS_2$ score after PerAF ablation should be considered because of the high risk of bleeding. An ongoing randomized controlled trial evaluating post-ablation OAC strategies would provide new evidence [25].

Limitations

The present study has some limitations. First, as a retrospective follow-up study from our multicenter randomized controlled trial, this study was not originally designed to track stroke and major bleeding events, resulting in a limited number of events and insufficient cases for the multivariable analysis. Second, selection bias could have been involved in the decision to continue OAC following the discretion of the attending physician. Hence, the observed significant differences in the recurrence rates of AF and $CHADS_2$ scores between the two groups might have influenced the occurrence of thromboembolic events. Randomized controlled trials are necessary to elucidate the association between post-ablation OAC use and stroke. Third, resumption of anticoagulation therapy was not considered in the OAC-discontinuation group. In clinical practice, OACs are discontinued or resumed based on the medical condition of the patients. Therefore, we categorized the patients based on the discontinuation of anticoagulants within 1 year of ablation. The resumption of OACs while the course of the disease in the discontinuation group may have prevented ischemic stroke, potentially leading to an underestimation of ischemic stroke events.

Table 2
Adjusted Cox regression hazard analysis for overall bleeding event.

	HR (95 % CI)	P value
OAC-continuation	2.04 (1.14 - 3.65)	0.016
Age, y.o.	1.02 (0.99 - 1.06)	0.28
Female sex	0.70 (0.36 - 1.35)	0.29
BMI	0.96 (0.89 - 1.06)	0.36
Antiplatelet therapy	1.75 (0.81 - 3.80)	0.15

OAC, oral anticoagulant; BMI, body mass index.

Conclusions

Our study including patients after PerAF ablation with $CHADS_2$ score of ≤2 points demonstrated that thromboembolic events and overall bleeding events were fewer in the OAC discontinuation group than in the OAC continuation group. Discontinuation of OACs might therefore be considered in patients with low $CHADS_2$ score after catheter ablation of PerAF; however, further studies are warranted to validate these findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2025.04.004.

Ethical approval

The following institutes approved this study: Cardiovascular Center, Sakurabashi-Watanabe Hospital (study number: 17-6); Osaka University Graduate School of Medicine (14377); Kansai Rosai Hospital (15D059g); Osaka General Medical Center (27-2035); Osaka Police Hospital (548); Osaka Rosai Hospital (28-78); Yao Municipal Hospital: (八病H29-5); and Osaka Hospital, Japan Community Healthcare Organization (2016-25).

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Declaration of competing interest

T.O. has received personal fees from Medtronic and Bayer outside the submitted work; N.T. has received personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Medtronic, and Philips outside the submitted work; M.M. has received personal fees from Daiichi Sankyo, Medtronic, Johnson & Johnson, Boston Scientific outside the submitted work; H.M. has received lectures fees from Cook Medical, Philips, and Medtronic, Abbott, Biotronik, Japan Lifeline and Daiichi Sankyo outside the submitted work; Y.E. has received personal fees from Johnson & Johnson and Medtronic, Abbott, and Medtronic outside the submitted work; Y.M. has received a scholarship from the Japanese Heart Rhythm Society, Abbott and Nihon Kohden outside the submitted work; and personal fees from Japan Lifeline, Boston Scientific, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Bayer, Toa Eiyo, AstraZeneca, Ono Pharmaceutical, MEDICAL VIEW, Medtronic, Asahi Kasei ZOLL Medical, Synaptic Medical Japan, and Biotronik outside the submitted work; M.K. has received personal fees from Medtronic, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, and Abbott, and grants from Osaka Heart Club outside the submitted work; K.I. has received

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Data availability

The datasets analyzed during the current study are not publicly available.

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