

ORIGINAL ARTICLE

Impact of factor Xa inhibitors on outcomes of atrial tachyarrhythmia recurrence following catheter ablation for atrial fibrillation: comparison with warfarin

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Abstract

Background: Factor Xa inhibitors (FXaIs) have been reported to exhibit antifibrotic effects. However, their impact on the outcomes of atrial fibrillation (AF) ablation remains unknown. This study aimed to investigate the association between freedom from atrial tachyarrhythmia recurrence and oral anticoagulant (OAC) therapy following AF ablation.

Methods: This single-center retrospective study comprised consecutive 1,702 patients who underwent AF catheter ablation in our hospital between January 2014 and September 2021. Arrhythmia recurrence was defined as documented atrial tachyarrhythmias lasting for >30 s after the 3-month blanking period, and the recurrence rate within 12 months following ablation was compared between patients who were administered FXaIs and warfarin (WF).

Results: Overall, 1,321 patients (916 men; mean age, 64 ± 10 years; 947 paroxysmal and 374 persistent) who continued OAC therapy following ablation were finally followed up for 12 months. Of them, 1,222 (93%) and 99 (7%) patients were administered FXaIs and WF, respectively. During the follow-up period of 324 ± 80 days, 115 recurrences in FXaI (33, 48, and 34 in rivaroxaban, edoxaban, and apixaban, respectively) and 13 in WF were noted. The 12-month freedom from recurrence in FXaI and WF groups was 90.0% and 85.6%, respectively, with no significant difference (P=0.21). In multivariate analysis, FXaI treatment was not an independent factor that predicts atrial tachyarrhythmia recurrence compared with WF treatment (hazard ratio, 0.66; 95% confidence interval, 0.37–1.20; P=0.17).

Conclusions: Regarding atrial tachyarrhythmia recurrence following AF ablation for 12 months, no significant difference was observed between FXaIs and WF treatment as post-ablation OAC therapy.

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Key words: Atrial fibrillation; Catheter ablation; Factor Xa inhibitors; Warfarin; Fibrosis.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. AF induces structural and electrical remodeling¹⁾, which promotes interstitial fibrosis and consequently provides substrates for AF²⁾. Furthermore, AF is associated with thromboembolic events, including

cerebrovascular stroke; oral anticoagulant (OAC) therapy is required for patients with AF who have risk factors for these events³⁾. Maintenance of sinus rhythm (SR) following catheter ablation (CA) for AF is associated with a reduction of the risk of such events⁴⁾, and ablation therapy is a well-established AF treatment⁵⁾. According to the expert consensus statement, OAC therapy with

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warfarin (WF) or direct oral anticoagulants (DOACs) including factor Xa inhibitors (FXaIs) is recommended for at least 3 months post-CA for AF⁶⁾. Although FXaIs have been reported to possess antifibrotic effects in basic research⁷⁻¹⁰⁾, the effect of these FXaIs on SR maintenance following CA has not been investigated in the clinical setting. Dabigatran, a selective direct thrombin inhibitor, has also been reported to have antifibrotic effects¹¹⁾. However, in the present study, we focused on the effects of FXaIs which have been more frequently reported in the basic research area. Here, we aimed to investigate the differences in the recurrence rate among the types of post-ablation OAC therapy, especially with focus on FXaIs compared with WF, in patients who underwent CA for AF.

Methods

Study population

The study cohort included 1,702 consecutive patients who underwent de novo CA for AF in Hirosaki University Hospital between January 2014 and September 2021. The exclusion criteria included patients who were administered dabigatran before and after CA, had long-standing persistent atrial fibrillation (LPRAF), lost to follow-up, atrial tachyarrhythmia recurrence within the 3-month blanking period, and interrupted anticoagulant medication or passed away within 12 months following CA. This study was approved by the ethics committee of the Hirosaki University Graduate School of Medicine (Reference no. 2023-035), and an exemption of informed consent was granted.

Ablation procedure

All patients had taken OACs for at least 4 weeks before CA for AF and undergone preprocedural transthoracic echocardiography and cardiac computed tomography (CT). In all patients, pulmonary vein (PV) isolation (PVI)

was performed with radiofrequency (RF) ablation until June 2014 and subsequently with either cryoballoon (CB) or RF ablation after July 2014. When the CT image revealed that the PV ostium had smaller diameter than the CB, the CB was used for patients with paroxysmal atrial fibrillation (PAF) after June 2014 and for those with persistent atrial fibrillation (PRAF) after November 2020. Otherwise, RF was used for PVI. After RF PVI was successfully achieved, intravenous isoproterenol was administered to induce non-PV triggers. Additional RF energy applications were delivered to isolate the SVC and eliminate its origin when a non-PV trigger was identified in the superior vena cava (SVC) and atria. After PVI was achieved using RF for PRAF, failure to terminate AF required extensive additional ablation, including a left atrial (LA) roof line, LA posterior wall isolation¹²⁾, sites with continuous fractionated atrial electrogram¹³⁾ and/or low voltage¹⁴⁾, and sites with fractionated signal areas during SR¹⁵⁾, based on the discretion of the operators. Additional cavotricuspid isthmus ablation for atrial flutter was also performed in some patients who had CB ablation.

Follow-up and post-ablation OAC therapy

All patients were evaluated in the outpatient clinic with clinical review, including 12-lead electrocardiogram (ECG) and/or 24-h Holter ECG at 1, 3, 6, and 12 months following the index procedure. Based on the prior consensus statement⁶⁾, a 3-month blanking period was used following the procedure. After the blanking period during follow-up, recurrence was defined as atrial tachyarrhythmias including AF, atrial flutter, and atrial tachycardia lasting for >30 s or complaints similar to those before the procedure. FXaI (rivaroxaban, apixaban, and edoxaban) or WF administration was continued either 12 months during follow-up or atrial tachyarrhythmia recurrence. Regarding the selection of OACs, we continued the prescription from the physician

who referred patients to us. If Vaughan Williams class I or III antiarrhythmic drugs (AADs) were administered within the blanking period, their continuation was left to the discretion of the attending physician. Beta-blockers (BBs) were continued if they were administered for other indications (hypertension and ischemic heart disease). BBs for heart rate control could be started if they are required.

Statistical analysis

Categorical variables were expressed as frequencies (percentages). Continuous variables were expressed as means \pm standard deviations for normally distributed data, and as medians with interquartile ranges for nonnormally distributed data. Continuous variables between the two groups were compared using an unpaired t-test or the Mann-Whitney U test. For comparisons of more than three groups, the Kruskal-Wallis test was used, and if a significant difference was noted, the Steel-Dwass test was performed as a post-hoc test. To examine temporal trends in OAC prescriptions over time, the Cochran-Armitage trend test was used. Using the Kaplan-Meier method, the event-free rate was estimated, and the differences were assessed using the log-rank test. To identify variables potentially associated with atrial tachyarrhythmia recurrence, univariate Cox regression analysis was used; multivariate analysis was further performed after adjusting for age, sex, and variables with $P < 0.05$ shown in the univariate analysis. Each FXaI treatment was compared with WF as a reference in univariate and multivariate analyses. The adjusted hazard ratio (HR) with 95% confidence intervals (CIs) was presented. Data were analyzed using JMP Windows version 16.0 (SAS Institute, Cary, NC, USA). P values of <0.05 were considered statistically significant.

Results

Patients' characteristics

Of 1,702 patients, 381 (22% of the study population) were excluded; 165 were administered with dabigatran, 126 had LPRAF, 55 were lost to follow-up, 6 interrupted OACs due to hemoptysis ($n = 1$) or by themselves ($n = 5$), and 3 died from cerebral infarction ($n = 1$), cerebral hemorrhage ($n = 1$), and an unexpected accident ($n = 1$). Atrial tachyarrhythmia recurrence within the blanking period developed in 26 patients. Finally, a total of 1,321 patients were enrolled in this study (Figure 1).

Patients' characteristics are shown in Table 1. Of the enrolled patients, 1,222 (93%) and 99 (7%) were administered with FXaIs and WF, respectively. The mean age of all patients was 64 ± 10 years, 69% were men, the proportion of PAF was 72%, and the mean CHADS₂ score was 0.7 ± 0.9 . No significant differences in these variables were noted between the two groups. Conversely, the WF group had a significantly higher serum creatinine level than the FXaI group (2.0 ± 2.5 vs. 0.9 ± 0.4 mg/dL, $P < 0.0001$), and AADs were twice more administered in the WF group than those in the FXaI group (27% vs. 14%, $P = 0.0008$). Treatment with angiotensin II receptor blocker (ARB) did not differ between the two groups. CB balloon ablation was less performed in the WF group than in the FXaI group (21% vs. 35%, $P = 0.004$). Regarding transthoracic echocardiography, no difference in left ventricular ejection fraction (LVEF) was observed between the two groups. The WF group had significantly higher left atrial volume index (LAVI) and E/e' than the FXaI group (39 [30–53] vs. 35 [27–43] mL/m², $P = 0.0005$ and 11 [8–17] vs. 9 [7–12], $P < 0.0001$, respectively).

Of 1,222 patients who were administered with FXaIs, 422 (35%), 444 (36%), and 356 (29%) were administered with rivaroxaban, edoxaban, and apixaban, respectively. The patients'

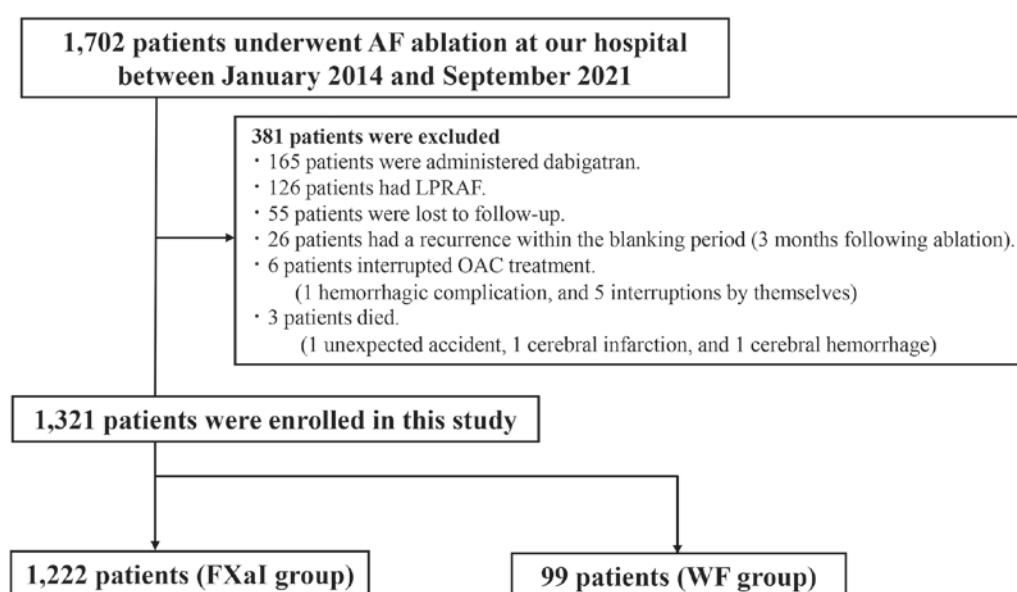


Figure 1 Patient selection for this study. The study participants are shown in the flow chart. AF, atrial fibrillation; FXaI, factor Xa inhibitor; LPRAF, long-standing persistent atrial fibrillation; OAC, oral anticoagulant; WF, warfarin

Table 1. Baseline characteristics of the study patients.

	All patients (n=1,321)	FXaI (n=1,222)	WF (n=99)	P-value
Age (year)	64 ± 10	64 ± 10	64 ± 11	0.80
Male	916 (69)	839 (69)	77 (78)	0.052
BMI (kg/m ²)	24 (22-26)	24 (22-26)	23 (21-26)	0.16
Serum Cr (mg/dL)	0.9 ± 0.8	0.9 ± 0.4	2.0 ± 2.5	<0.0001
Type of AF				
Paroxysmal	947 (72)	877 (72)	70 (71)	0.82
Persistent	374 (28)	345 (28)	29 (29)	
Past medical history				
Hypertension	339 (26)	322 (26)	17 (17)	0.036
Diabetes mellitus	103 (8)	98 (8)	5 (5)	0.26
Previous stroke / TIA	107 (8)	102 (8)	5 (5)	0.22
CHADS ₂ score	0.7 ± 0.9	0.7 ± 0.9	0.7 ± 0.8	0.59
HCM	38 (3)	36 (3)	2 (2)	0.58
Drugs				
Beta-blocker	755 (57)	697 (57)	58 (59)	0.76
AADs	195 (15)	168 (14)	27 (27)	0.0008
ARB	304 (23)	278 (23)	26 (26)	0.43
Inappropriate under dose of FXaI	–	97 (8)	–	–
Ablation procedure				
Cryoballoon ablation	449 (34)	428 (35)	21 (21)	0.004
Additional ablation	184 (14)	165 (14)	19 (19)	0.13
Transthoracic echocardiography				
LVEF (%)	65 (59-70)	65 (59-70)	65 (53-71)	0.54
LAVI (mL/m ²)	35 (28-44)	35 (27-43)	39 (30-53)	0.0005
E/e'	9 (8-12)	9 (7-12)	11 (8-17)	<0.0001

Dates are presented as mean ± standard deviation, median (interquartile ranges), or n (%). AADs indicates antiarrhythmic drugs; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; Cr, creatinine; FXaI, factor Xa inhibitor; HCM, hypertrophic cardiomyopathy; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; TIA, transient ischemic attack; WF, warfarin.

Table 2. Characteristics of the study patients categorized by each FXaI

	Rivaroxaban (n=422)	Edoxaban (n=444)	Apixaban (n=356)	P-value
Age (year)	62 ± 11	65 ± 10	66 ± 10	<0.0001
Male	313 (74)	313 (70)	213 (60)	<0.0001
BMI (kg/m ²)	24 (22-27)	24 (22-26)	24 (22-26)	0.43
Serum Cr (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.6	0.68
Type of AF				
Paroxysmal	315 (75)	300 (68)	262 (74)	0.047
Persistent	107 (25)	144 (32)	94 (26)	
Past medical history				
Hypertension	120 (28)	106 (24)	96 (27)	0.30
Diabetes mellitus	36 (9)	26 (6)	36 (10)	0.07
Previous stroke / TIA	37 (9)	37 (8)	28 (8)	0.90
CHADS ₂ score	0.7 ± 0.9	0.7 ± 0.9	0.7 ± 0.9	0.36
HCM	16 (4)	12 (3)	8 (2)	0.42
Drugs				
Beta-blocker	237 (56)	268 (60)	192 (54)	0.17
AADs	55 (13)	62 (14)	51 (14)	0.86
ARB	103 (24)	89 (20)	86 (24)	0.23
Inappropriate under dose of FXaI	29 (7)	42 (9)	26 (7)	0.33
Ablation procedure				
Cryoballoon ablation	114 (27)	183 (41)	131 (37)	<0.0001
Additional ablation	48 (11)	66 (15)	51 (14)	0.27
Transthoracic echocardiography				
LVEF (%)	66 (60-71)	64 (57-68)	64 (59-70)	<0.0001
LAVI (mL/m ²)	34 (26-41)	35 (28-44)	35 (29-44)	0.02
E/e'	9 (7-11)	9 (7-12)	10 (8-12)	0.0009

Dates are presented as mean ± standard deviation, median (interquartile ranges), or n (%). Abbreviations are shown in Table 1.

characteristics categorized by each FXaI are summarized in Table 2. Briefly, patients with rivaroxaban were younger, more men, and had less CB ablation than those with edoxaban and apixaban. Furthermore, the rivaroxaban group had higher LVEF, lower LAVI, and lower E/e' than the edoxaban and apixaban groups. No significant differences in CHADS₂ scores were observed among the three groups.

Prescription rate of OAC

The prescription rate of OACs during the study period is shown in Figure 2. As the study progressed, the proportion of patients with WF decreased (24 [21%], 23 [15%], 11 [6%], 15 [8%], 6 [3%], 9 [5%], 6 [3%], and 5 [5%] in 2014, 2015, 2016, 2017, 2018, 2019, 2020, and 2021, respectively); in the opposite direction, those with FXaIs increased ($P_{\text{trend}} < 0.0001$).

Comparison of recurrence between the FXaI and WF groups

During the mean observation period of 324 ± 80 days, 115 recurrences in FXaI (33, 48, and 34 in rivaroxaban, edoxaban, and apixaban, respectively) and 13 in WF were noted. The freedom from atrial tachyarrhythmia recurrence for 12 months in the FXaI and WF groups evaluated by the log-rank test was 90.0% and 85.6%, respectively, and no significant difference was observed between the two groups ($P = 0.21$; Figure 3). In univariate Cox regression analysis, diabetes, hypertrophic cardiomyopathy (HCM), and LAVI were significant factors associated with atrial tachyarrhythmia recurrence but not overall FXaI treatment compared with WF treatment (HR, 0.69; 95% CI, 0.39–1.23; $P = 0.21$) (Table 3). In multivariate analysis, diabetes and

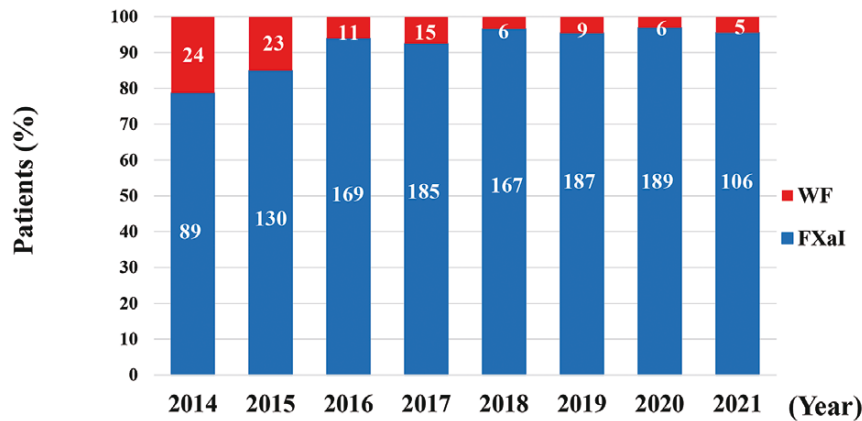


Figure 2 Trends in anticoagulant therapy in this study. The figure shows the proportion of patients who were administered with oral anticoagulants with factor Xa inhibitor (FXaI) and warfarin (WF) each year.

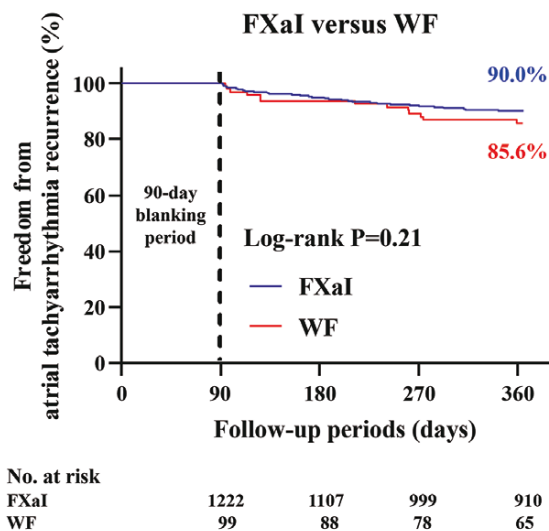


Figure 3 Kaplan-Meier curves demonstrating no significant difference regarding the 12-month freedom from atrial tachyarrhythmia recurrence following catheter ablation for atrial fibrillation in the factor Xa inhibitor (FXaI) versus warfarin (WF) groups.

HCM were independent factors predicting atrial tachyarrhythmia recurrence (HR, 0.31; 95% CI, 0.10–0.96; $P = 0.04$ and HR, 2.41; 95% CI, 1.19–4.87; $P = 0.01$) but not overall FXaI treatment compared with WF treatment (HR, 0.66; 95% CI, 0.37–1.20; $P = 0.17$) (Model 1 in Table 3).

The proportion of patients with WF treatment decreased over time, and this change may have affected the atrial tachyarrhythmia recurrence. Average of the freedom from atrial tachy-

arrhythmia recurrence in all patients was 90.1% from 2014 to 2017 and 89.2% from 2018 to 2021 by the Kaplan-Meier method ($P = 0.42$ by log-rank test), indicating similar recurrence rate between the two study periods. This finding suggests that change in WF treatment over time did not seem to affect the atrial tachyarrhythmia recurrence.

Table 3. Cox regression analyses for atrial tachyarrhythmia recurrence

Variables	Univariate analysis			Multivariate analysis (Model 1)			Multivariate analysis (Model 2)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.02	0.99-1.04	0.06	1.01	0.99-1.03	0.25	1.01	0.99-1.03	0.35
Male	0.78	0.54-1.12	0.17	0.84	0.57-1.23	0.37	0.84	0.57-1.23	0.37
BMI	0.97	0.92-1.02	0.20						
Serum Cr	1.01	0.92-1.24	0.26						
Paroxysmal AF	0.88	0.61-1.28	0.51						
Hypertension	0.76	0.49-1.16	0.20						
Diabetes mellitus	0.28	0.09-0.89	0.03	0.31	0.10-0.96	0.04	0.31	0.10-0.97	0.04
Previous stroke / TIA	0.75	0.37-1.54	0.44						
HCM	2.60	1.32-5.13	0.006	2.41	1.19-4.87	0.01	2.50	1.23-5.06	0.01
Beta-blocker	1.24	0.87-1.77	0.24						
AADs	1.20	0.76-1.90	0.43						
ARB	0.83	0.54-1.28	0.41						
Cryoballoon ablation	1.23	0.86-1.76	0.26						
Additional ablation	1.11	0.69-1.79	0.67						
LVEF	0.99	0.98-1.01	0.18						
LAVI	1.01	1.00-1.03	0.01	1.01	0.99-1.02	0.15	1.01	0.99-1.02	0.16
E/e'	1.02	0.99-1.04	0.07						
FXaI	0.69	0.39-1.23	0.21	0.66	0.37-1.20	0.17			
Each FXaI									
Rivaroxaban	0.57	0.30-1.09	0.09				0.54	0.27-1.05	0.07
Edoxaban	0.79	0.43-1.46	0.46				0.75	0.40-1.40	0.36
Apixaban	0.72	0.38-1.36	0.31				0.69	0.36-1.35	0.28

Overall FXaI treatment was compared with WF as a reference in univariate and multivariate analyses (Model 1). Each FXaI treatment was compared with WF as a reference in univariate and multivariate analyses (Model 2). HR indicates hazard ratio; CI, confidence interval. Other abbreviations are shown in Table 1.

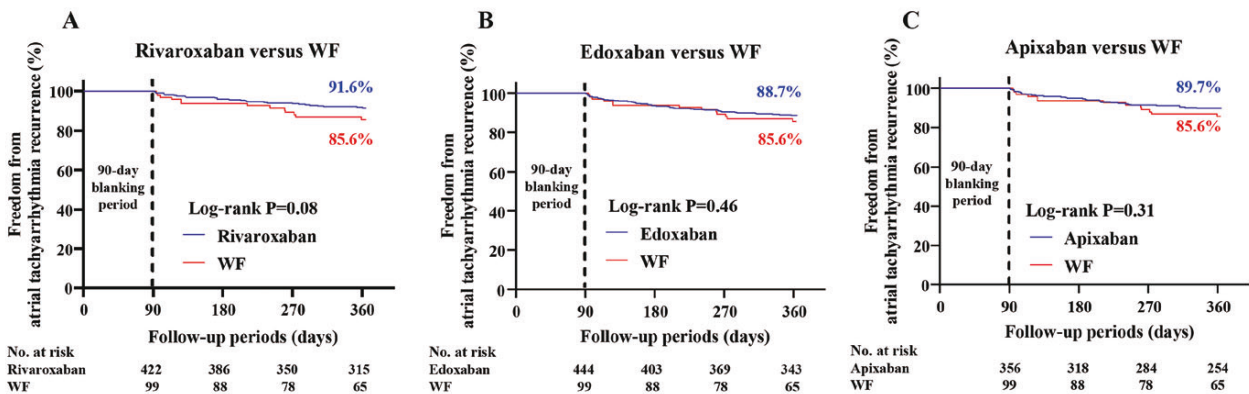


Figure 4 Kaplan-Meier curves demonstrating no significant difference regarding the 12-month freedom from atrial tachyarrhythmia recurrence following catheter ablation for atrial fibrillation in the (A) rivaroxaban versus warfarin (WF) groups, (B) edoxaban versus WF groups, and (C) apixaban versus WF groups.

Comparison of recurrence between each FXaI and WF groups

Atrial tachyarrhythmia recurrence for 12 months in each FXaI and WF groups is depicted in Figure 4. Rivaroxaban, edoxaban, and apixaban treatment showed higher 12-month freedom from

atrial tachyarrhythmia recurrence than the WF group (91.6%, 88.7%, and 89.7%, respectively, vs. 85.6%); however, no significant differences were noted ($P = 0.08, 0.46, \text{ and } 0.31$, respectively, by log-rank test). When rivaroxaban, edoxaban, and apixaban were individually analyzed using

univariate Cox regression analysis, no significant difference was observed in all individual FXaIs versus the WF group (Table 3). In multivariate analysis, diabetes and HCM were independent factors predicting atrial tachyarrhythmia recurrence (HR, 0.31; 95% CI, 0.10–0.97; $P = 0.04$ and HR, 2.50; 95% CI, 1.23–5.06; $P = 0.01$). All individual FXaIs did not reach significance; however, rivaroxaban showed the lowest HR among the three FXaIs, with close to significance (HR, 0.54; 95% CI, 0.27–1.05; $P = 0.07$) (Model 2 in Table 3).

Discussion

Major findings

In the present study, no significant differences in atrial tachyarrhythmia recurrence during the 12-month follow-up period were observed between FXaI and WF treatments following CA. Furthermore, although rivaroxaban showed a relatively lower recurrence than WF with close to significance, each individually analyzed FaXI did not show statistical significance compared with WF by multivariate analysis. Conversely, diabetes and HCM were independent factors for predicting atrial tachyarrhythmia recurrence. These findings indicate that atrial tachyarrhythmia recurrence did not differ among the types of post-ablation OAC therapy.

Effects of FXaI on atrial tachyarrhythmia recurrence following CA

FXa not only functions as one of the components of the coagulation cascade but also activates the intracellular signaling cascade through protease-activated receptors (PARs). PAR-1 and PAR-2 are expressed in various cell types, including cardiac myocytes and fibroblasts, and renal podocytes^{7, 16}; PAR signaling activation has been reported to cause pathological fibrotic remodeling and inflammation^{17–19}. Therefore, the protective effects of FXaI on organ damages

have been expected. We previously showed that rivaroxaban exerts protective effects against angiotensin II-induced renal damage, partly through PAR-2 signaling inhibition using an experimental animal model⁷. In clinical setting, Yao et al. showed that dabigatran and rivaroxaban were associated with lower risks of unfavorable renal outcomes, including a 30% decline in the estimated glomerular filtration rate and acute kidney injury (AKI), than WF²⁰. Furthermore, Harel et al. showed that patients with AF aged ≥ 66 years who were prescribed with dabigatran, rivaroxaban, or apixaban were associated with a reduced risk of AKI compared with those prescribed with WF²¹. These experimental and clinical studies indicate that FXaIs exert protective effects against renal damage, partly through PAR signaling inhibition.

In the heart, we and other researchers have shown that FXaIs are involved in cardiac remodeling inhibition by inhibiting the PAR^{9, 10, 22}. Kondo et al. showed that rivaroxaban suppressed stretch-induced PAR-2 upregulation in cardiac fibroblasts and shortened AF duration in mice. They have suggested the potential effects of rivaroxaban in preventing AF substrate progression. Thus, we evaluated our hypothesis that FXaIs may suppress atrial tachyarrhythmia recurrence following CA for AF compared with WF. Our study showed that atrial tachyarrhythmia recurrence during the 12-month follow-up period following CA did not differ between FXaI and WF treatments. However, rivaroxaban among FXaIs showed a relatively lower recurrence than WF with close to significance. Patients with AF treated with rivaroxaban showed higher LVEF and lower LAVI than those treated with edoxaban and apixaban, which may contribute to a relatively lower atrial tachyarrhythmia recurrence following CA. Although the present study did not show favorable effects against AF recurrence, further clinical studies are required

to confirm the effects of FXaIs, including rivaroxaban, on AF recurrence.

Effects of other factors on atrial tachyarrhythmia recurrence following CA

Left atrial dilation and the E/e' index are left ventricular diastolic dysfunction indicators; both have been reported as AF recurrence predictors following CA²³⁻²⁵⁾. Furthermore, low EF has been reported to be one of the predictors for AF recurrence following CA²⁶⁾. In our study, univariate analysis showed that LAVI was significant, E/e' was close to significance, and LVEF was not significant. Multivariate analysis further showed that LAVI did not show significance. The values of these cardiac echocardiographic parameters of our study population were almost within the normal range; therefore, these parameters may have not had a significant impact on atrial tachyarrhythmia recurrence.

HCM has been reported to have a high degree of fibrotic change in the atrium²⁷⁾, and the AF prevalence in HCM has been reported to be as high as 22.5%²⁸⁾. Furthermore, patients with HCM have been reported to have a higher atrial tachyarrhythmia recurrence following CA for AF than those without HCM²⁹⁾. Consistently, our study also showed that HCM was an independent predictor and had the highest HR for atrial tachyarrhythmia recurrence by multivariate analysis.

Diabetes has been reported to be a risk factor for AF recurrence following CA for AF³⁰⁾. However, in our study, diabetes was significantly associated with less atrial tachyarrhythmia recurrence (Table 3). Although the reason for this result is largely unknown, we may speculate an association between diabetes and ARB treatment. Large clinical trials did not show the effectiveness of ARBs in reducing the incidence of recurrent AF³¹⁾. However, a meta-analysis demonstrated that renin-angiotensin system

inhibitors including ARB reduced AF recurrence following CA³²⁾. Although our study showed no associations between ARB treatment and AF recurrence, patients with diabetes were administered with more ARB than those without diabetes (37/103 [36%] vs. 267/1,218 [22%], $P = 0.002$). This association between diabetes and ARB treatment may affect the results, despite a small number of patients with diabetes ($n = 103$, 8%). Furthermore, although we did not recognize the period of diabetes therapy and control status of diabetes, these may also have affected the results.

Administration of FXaI is carefully managed in patients with impaired renal function, and these patients may tend to receive warfarin treatment. Indeed, serum creatinine level in our study was significantly higher in patients with WF than in those with FXaI treatment. Involvement of creatinine on atrial tachyarrhythmia recurrence following CA is still controversial. Impaired renal function is reported to be associated with an increased risk of AF recurrence following CA³³⁾. Other report shows that renal function was not identified as a significant factor for recurrence after CA³⁴⁾. In the present study, creatinine was not an independent predictor for atrial tachyarrhythmia recurrence by the Cox regression analysis. This finding suggests that high serum creatinine level observed in patients with WF treatment may not contribute to the atrial tachyarrhythmia recurrence in our population.

Study limitations

This study had several limitations. First, this study was a retrospective observational study, and 55 patients were lost to follow-up, thereby resulting in selection bias. Second, there was a change in the OAC prescription rate over time owing to the long-term period of over 8 years. As the study period progressed, the number of patients who were administered with FXaIs

increased, and those who were administered with WF decreased. Particularly, the number of overall patients with WF was relatively small, which may have affected the results. Third, advancements in modalities and techniques used for CA over time also contributed to atrial tachyarrhythmia recurrence. Fourth, overall recurrence rate at 1 year following CA in our study was 9.7% (128/1,321). It should be noted that the recurrence rate at 1 year following CA in large European registry including 3,368 patients from 91 hospitals in 26 European countries was 22.2% in experienced high-volume hospitals³⁵. The relatively low recurrence rate in our study may have influenced to the result showing similar recurrence rate between the FXaI and WF groups. Finally, the detection of atrial tachyarrhythmia recurrence may have been underestimated. Despite these limitations, the relatively large number of study participants may have some impact in the clinical practice.

Conclusions

This study investigated the differences in atrial tachyarrhythmia recurrence among the types of OACs following CA for AF. Although some basic research has reported the antifibrotic effects of FXaIs on the myocardium, no significant difference in atrial tachyarrhythmia recurrence was observed between FXaIs and WF during the 12-month follow-up period as post-ablation OAC therapy. To clarify the antifibrotic effects of FXaIs in the clinical setting, further studies are needed.

Conflicts of interest

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