Usefulness of Failed Electrical Cardioversion for Early Recurrence After Catheter Ablation for Atrial Fibrillation as a Predictor of Future Recurrence

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Early recurrence of atrial arrhythmia (ERAA) during a blanking period after catheter ablation (CA) for atrial fibrillation (AF) does not always result in subsequent AF recurrence. We investigated whether failed electrical cardioversion (ECV) during the blanking period was associated with recurrence. A total of 1,240 consecutive patients who underwent first-time CA for AF at our institution between March 2012 and March 2016 were investigated. Among the 517 patients (42%) who experienced ERAA, 262 underwent ECV. Failure or success of ECV was defined according to the current expert consensus statement. Failed ECV was defined as failure to terminate AF and/or relapse into AF within 30 seconds after transient sinus rhythm conversion by ECV with a shock energy of 270 J in this study. Of the patients, 254 (97%) with restored sinus rhythm were included, and 8 who experienced sustained AF afterward and discontinued the rhythm-control strategy were excluded. We divided the 254 patients into the following 2 groups on the basis of failed or successful ECV: failed-ECV (n = 105; at least 1 failed ECV but experienced successful ECV at a later date nevertheless) and successful-ECV (n = 149, no failed ECV) groups. At the median follow-up period of 610 days after CA, the recurrence rate was higher in the failed-ECV group than in the successful-ECV group (76.2% vs 45.6%, log-rank $p < 0.001$). After adjustment for baseline differences, failed ECV was found to be a significant predictor of recurrence in the multivariate model ($p < 0.001$). In conclusion, failed ECV for ERAA was an independent predictor of future recurrence. **(Am J Cardiol 2019;123:794−800)**

Catheter ablation (CA) for atrial fibrillation (AF) is an effective nonpharmacological treatment for maintaining sinus rhythm (SR).[1] Early recurrences of atrial arrhythmia (ERAA) are defined as recurrences within blanking period (BP) of 90 days after CA. Though ERAA are one of predictors of recurrences after the BP,[2,3] they are believed to relate to transient inflammation of atrial myocardium due to CA.[4] Therefore, the current expert consensus statement recommends that ERAA should not be considered as ablation failure, and repeat CA should not be performed within the BP.[5] Previous study reported that an aggressive strategy of electrical cardioversion (ECV) for ERAA to restore SR reduced AF recurrence after CA.[6] However, it is still unknown that whether response to ECV for ERAA was associated with ablation outcome. Therefore, this study aimed to investigate impact of failed ECV for ERAA on recurrence after the BP.

Methods

This retrospective single-center observational study was performed at Sakurabashi Watanabe Hospital, Osaka, Japan. From March 2012 to March 2016, 1,240 consecutive patients (57%, paroxysmal AF; n = 705) underwent first-time radiofrequency CA for AF. In them, 517 patients (41.7%) experienced ERAA, which was defined as atrial tachyarrhythmia lasting >30 seconds during a BP of 90 days after CA. A rhythm-control approach with ECV or pharmacological cardioversion for ERAA was strongly recommended. Basically, an intravenous infusion of antiarrhythmic drugs (AADs) before ECV was performed except in patients with current oral administration of AADs, as simultaneous prescription of multiple AADs was discouraged at our institution. If an intravenous infusion of AADs was ineffective or not applicable, we performed ECV to restore the SR. We performed ECV using a biphasic external defibrillator (TEC-7511, Nihon Kohden, Tokyo, Japan). The sternal and apical paddles were placed to the right of the upper sternal border below the clavicle and to the left of the nipple with the center of the electrode in the midaxillary

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line, respectively. In patients with AF lasting longer than 48 hours or with an unknown onset, we performed a transesophageal echocardiography before ECV to exclude thrombi in the left atrium and left atrial appendage. During electrocardiography and SpO_2 monitoring, a synchronized ECV was performed under sedation with thiamylal sodium, using a step-up method with biphasic shock energies of 100, 150, 200, and 270 J, as required for SR restoration. Failure or success of ECV was defined according to the current expert consensus statement.[5] In this study, failed ECV was defined as into AF within 30 seconds after transient SR restoration by ECV with a shock energy of 270 J, and successful ECV was defined as AF termination and SR restoration for longer than 30 seconds. When patients did not keep SR with shock energies of no more than 200 J and kept SR with 270 J, we defined them as successful ECV. If AF did not terminate with a shock energy of 270 J, the patient's attending physician pretermitted ECV and considered the additional administration of AADs. Any new neurological symptom was checked after ECV.

Among the 517 patients with ERAA, 262 patients (51%, paroxysmal AF; n = 83) underwent ECV. Almost all of them (97%, n = 254) eventually had SR restoration and were included in this study. Eight patients who experienced sustained AF during the BP and discontinued the rhythm-control strategy were excluded. We divided the included patients into the following groups: those who experienced failed ECV at least once during the BP but experienced successful ECV at a later date nevertheless (failed-ECV group; n = 105) and those who experienced only successful ECV (successful-ECV group; n = 149). The end point of this study was the recurrence of atrial tachycardia or AF after BP, which was defined as recurrent atrial tachyarrhythmia lasting >30 seconds beyond 90 days after CA. Patients who continued or started AADs after the BP were considered to have recurrence. We compared the recurrence rate between the groups. The flowchart of the present study is shown in Figure 1. Data analysis was retrospective and based on a review of medical records. This study was approved by the ethical committee of our institution. All patients provided written informed consent for the ablation procedure and use of their clinical data for this retrospective study.

All patients received effective anticoagulation therapy with vitamin K antagonist or direct oral anticoagulants for at least 1 month and underwent transesophageal echocardiography before the CA procedure to exclude thrombi in the left atrium and left atrial appendage. Vitamin K antagonist use was interrupted 1 day before the procedure. Patients administered direct oral anticoagulants were instructed to omit only the dose on the morning of the procedure. All

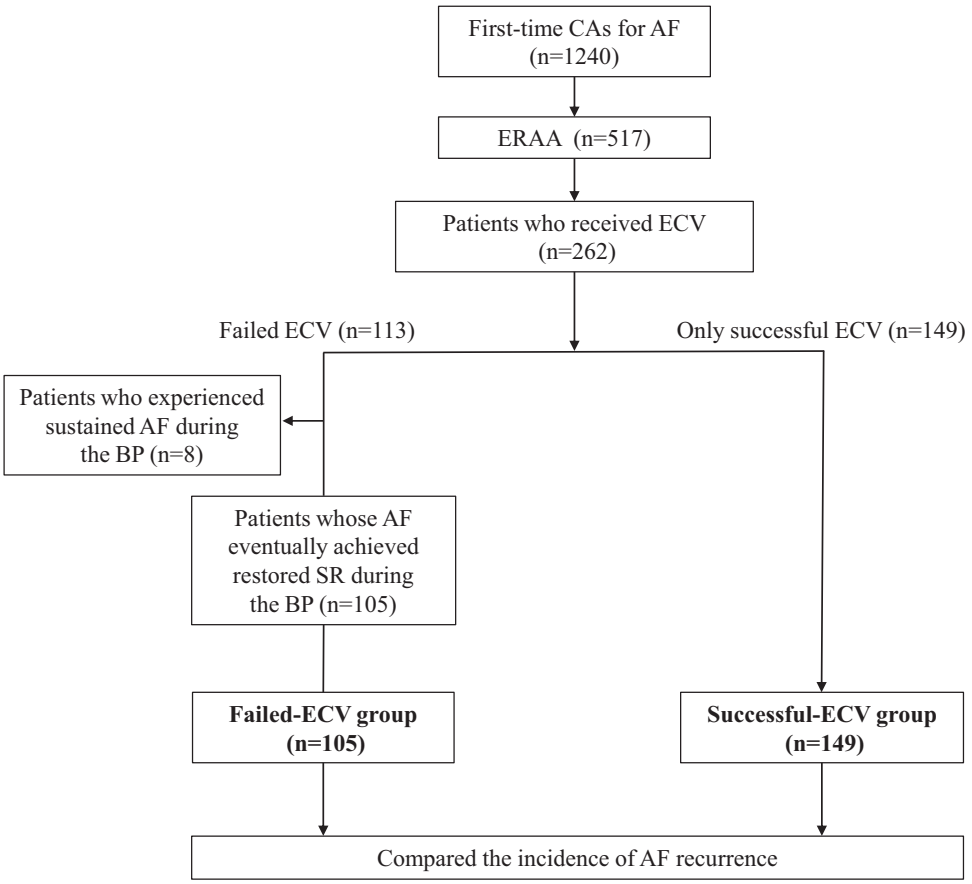

Figure 1. Flowchart of the study.
AF = atrial fibrillation, BP = blanking period, CA = catheter ablation, ECV = electrical cardioversion, ERAA = early recurrence of atrial arrhythmia, SR = sinus rhythm.

AADs were discontinued for at least 5 half-lives before the procedure. Preprocedural evaluations, including electrocardiography, laboratory tests, transthoracic echocardiography, and multidetector computed tomography, were performed in outpatient clinics. Co-morbidities and medications were also evaluated in outpatient clinics, and indications for CA for AF were based on expert consensus.[5]

Detailed electrophysiological studies and CA methods have been described previously.[7] Extensive encircling PV isolation was performed using an open-irrigated ablation catheter (Navistar Thermocool, Biosense-Webster, Diamond Bar, California). We used the single-lasso technique under the guidance of a 3D mapping system (CARTO3, Biosense-Webster, Diamond Bar, California). The end point of PV isolation was the achievement of a bidirectional conduction block between the left atrium and PVs. After the completion of PV isolation, we routinely administered high-dose isoproterenol (4 to 20 μg/min) after a waiting time of at least 20 minutes to examine PV reconnections and/or the presence of non-PV AF triggers, which were defined as ectopies initiating AF originating from non-PV origins. If AF was induced, we performed ECV. After restoration of SR, we investigated the ectopic sites initiating AF. Additional ablation was strongly encouraged against non-PV AF triggers. A cavotricuspid isthmus block line was created if common atrial flutter was detected before or during the procedure with a bidirectional conduction block used as the end point. The superior vena cava was isolated in cases wherein frequent ectopic foci within the superior vena cava or ectopies initiating AF from the superior vena cava were observed. Other additional ablations, such as linear ablation, complex fractionated atrial electrogram ablation, and GP ablation, depended on the operator's judgment. The procedures were performed under mild sedation with pentazocine, dexmedetomidine hydroxyzine, and thiamylal sodium. We strongly recommended the second procedure for the patients with the recurrence. In the second procedure, the methods of electrophysiological studies were similar to those in the first procedure. We searched for the reconnection of PV potentials, identified AF triggers, and attempted to perform ablation on them.

All patients were hospitalized with continuous rhythm monitoring for 3 days after the CA and were seen in our hospital at 1- to 2-month intervals. The patient's attending physician determined the prescription of oral administration of AADs at discharge and at the outpatient clinic as necessary during the BP. We directed patients to check their pulse rate and rhythm 3 times a day and to visit the outpatient clinic if they continuously experienced irregular pulses. An electrocardiogram was obtained at each visit. Transthoracic echocardiography and Holter electrocardiography were performed at 6 months after the CA. In principle, AADs were discontinued at 3 months after the CA procedure except for patients with AF recurrence.

Normally and non-normally distributed continuous variables were presented as mean ± standard deviation. Categorical variables were presented as frequency and percentage. Parametric data were compared using Student's t test or the paired Student's t test, whereas nonparametric data were compared using the chi-squared test or Fisher's exact test, as appropriate. Event-free rates were calculated using the Kaplan-Meier method and compared between groups via the log-rank test. All variables were included in a multivariate Cox proportional analysis to clarify significant risk factors and calculate the hazard ratios and 95% confidence intervals (CIs). Hazard ratios with 95% CIs comparing the efficacy of CA between the 2 groups were calculated using a Cox proportional hazards model, and adjusted for covariates, including gender, left atrium diameter, presence of chronic heart failure, oral administration of AADs during the BP, C-reactive protein level, and length of time from CA to the first ECV. All statistical analyses were performed using JMP 12.2.0 (SAS Institute, Cary, North Carolina).

Results

The baseline characteristics and the ECV details are described in Table 1. The prevalence of diabetes mellitus and the prescription rate of bepridil during the BP were higher in the failed-ECV group. One patient with diabetes mellitus received insulin therapy in successful ECV group. We did not observe any significant differences in pharmacological cardioversion using the intravenous infusion of AADs before ECV between the 2 groups. In the failed-ECV group, 5 patients failed to terminate AF and the remaining 100 patients relapsed into AF within 30 seconds after transient SR conversion. Furthermore, SR was restored in 66 patients (63%) by repeat ECV and/or the additional administration of AADs at a later date and the remaining 39 patients (37%) had spontaneous restoration of SR in the outpatient clinic. Among 254 patients who included in this study, 148 patients (58%) experienced recurrence after the BP during a median follow-up period of 610 days (interquartile range 411 to 730) after CA. The annual AF recurrence rate was 35%/year. Kaplan-Meier analysis for recurrence-free survival showed that the recurrence rate was significantly higher in the failed-ECV group than in the successful-ECV group (76.2% vs 46.4%; hazard ratio, 2.56; 95% CI 1.85 to 3.55; log-rank $p < 0.001$; Figure 2). The same significant differences were observed in both the paroxysmal AF and nonparoxysmal AF subgroups (Figure 2). Among these patients who experienced ERAA within 30 days after CA, the recurrence rate was significantly higher in the failed-ECV group (74% vs 45%, $p < 0.001$). Multivariate Cox proportional hazard regression analysis revealed that failed ECV and chronic heart failure were significant positive predictors of future AF recurrences in patients who experienced ERAA (Table 2). A total of 113 patients (43.1%) underwent reablation for AF recurrence. The findings of electrophysiological studies in the reablation are shown in Table 3. The proportion of patients who had AF triggers was significantly higher in the failed-ECV group. The sensitivity and specificity of failed ECV for ERAA to predict future AF recurrence were 0.54 (95% CI 0.49 to 0.58) and 0.76 (95% CI 0.70 to 0.83), respectively. The positive and negative predictive values of failed ECV to predict AF recurrence after BP were 0.76 (95% CI 0.69 to 0.82) and 0.54 (95% CI 0.49 to 0.59), respectively.

Table 1
Baseline characteristics

	Electrical cardioversion		
	Failed (n = 105)	Successful (n = 149)	p Value
Variable			
Age, (years)	62.6 ± 1.0	61.7 ± 0.8	0.76
Body mass index, (kg/m^2)	24.5 ± 0.4	24.6 ± 0.3	0.39
Male	78 (74%)	122 (82%)	0.15
Estimated glomerular filtration rate, (ml/min/1.73 m^2)	77.2 ± 2.7	80.5 ± 2.3	0.18
Brain natriuretic peptide (pg/ml)	190 ± 20	164 ± 17	0.84
Left ventricular ejection fraction (%)	63.3 ± 1.0	62.4 ± 0.8	0.77
Left atrium diameter (mm)	40.4 ± 0.6	41.1 ± 0.5	0.19
Type of AF			
Paroxysmal	35 (33%)	48 (32%)	0.85
Persistent	37 (35%)	58 (39%)	
Long-lasting persistent	33 (32%)	43 (24%)	
$CHADS_2$ score			
0, 1	76 (72%)	110 (74%)	0.79
≥2	29 (28%)	39 (26%)	
Comorbidity			
Congestive heart failure	19 (18%)	24 (16%)	0.68
Hypertension	51 (49%)	74 (50%)	0.86
Diabetes mellitus	19 (18%)	13 (9%)	0.03
Previous stroke	3 (3%)	9 (6%)	0.24
Coronary artery disease	12 (11%)	10 (7%)	0.19
Details of the ablation procedure			
Pulmonary vein isolation	105 (100%)	149 (100%)	1.00
Linear ablation of cavo-tricuspid isthmus	34 (30%)	52 (35%)	0.43
Box isolation of left atrium	10 (10%)	16 (11%)	0.75
Linear ablation of mitral isthmus	3 (3%)	7 (5%)	0.45
Complex fractionated atrial electrogram	6 (6%)	5 (3%)	0.37
Superior vena cava isolation	0	3 (2%)	0.07
Nonpulmonary vein AF trigger ablation	6 (6%)	8 (5%)	0.91
Postprocedural factors			
Maximum C-reactive protein value during hospitalization (mg/dl)	2.4 ± 0.3	2.3 ± 0.2	0.65
Administration of medications during the blanking period			
Beta blocker	44 (42%)	50 (33%)	0.18
Antiarrhythmic drug (Class I)	28 (29%)	34 (23%)	0.48
Bepridil	50 (48%)	47 (32%)	0.009
Amiodarone	3 (3%)	3 (2%)	0.69
Details of electrical cardioversion			
Length of time from ablation to first electrical cardioversion (days)	11.0 ± 1.9	19.9 ± 1.6	<0.001
Early recurrence of atrial arrhythmia within 30 days from ablation to the first electrical cardioversion	92 (88%)	117 (79%)	0.06
Length of time from AF recurrence to the electrical cardioversion (hours)			
≤24	83 (79%)	84 (56%)	<0.001
24-48	14 (13%)	24 (16%)	
≥48	8 (8%)	41 (24%)	
Transesophageal echocardiography before electrical cardioversion	8 (8%)	41 (24%)	<0.001
Any oral anticoagulant treatment	105 (100%)	149 (100%)	1.00
Any anti-arrhythmic drug treatment	81 (77%)	84 (56%)	<0.001
Infusion of anti-arrhythmic drug before electrical cardioversion	39 (37%)	44 (29.5%)	0.20
Complication after electrical cardioversion	0	0	1.00

Data are expressed as mean ± standard deviation, n (%).

Discussion

In this study, we investigated the relation between responses to ECV for ERAA and AF recurrence after CA. Failed ECV was an independent predictor of recurrence despite the brief SR restoration, regardless of AF type.

One of the major mechanisms underlying ERAA is the transient inflammation caused by radiofrequency energy delivery to the atrial myocardium,[4] and recent biochemical data have shown that the post-CA inflammatory phase was usually limited within the first month after PV isolation.[8,9] Willems et al reported that the 1-year freedom from AF recurrence was 62.6% in the first month and only 7.8% in the third month in patients with ERAA.[10] These studies indicate that the mechanism behind ERAA occurring within a month after CA might be a relatively transient

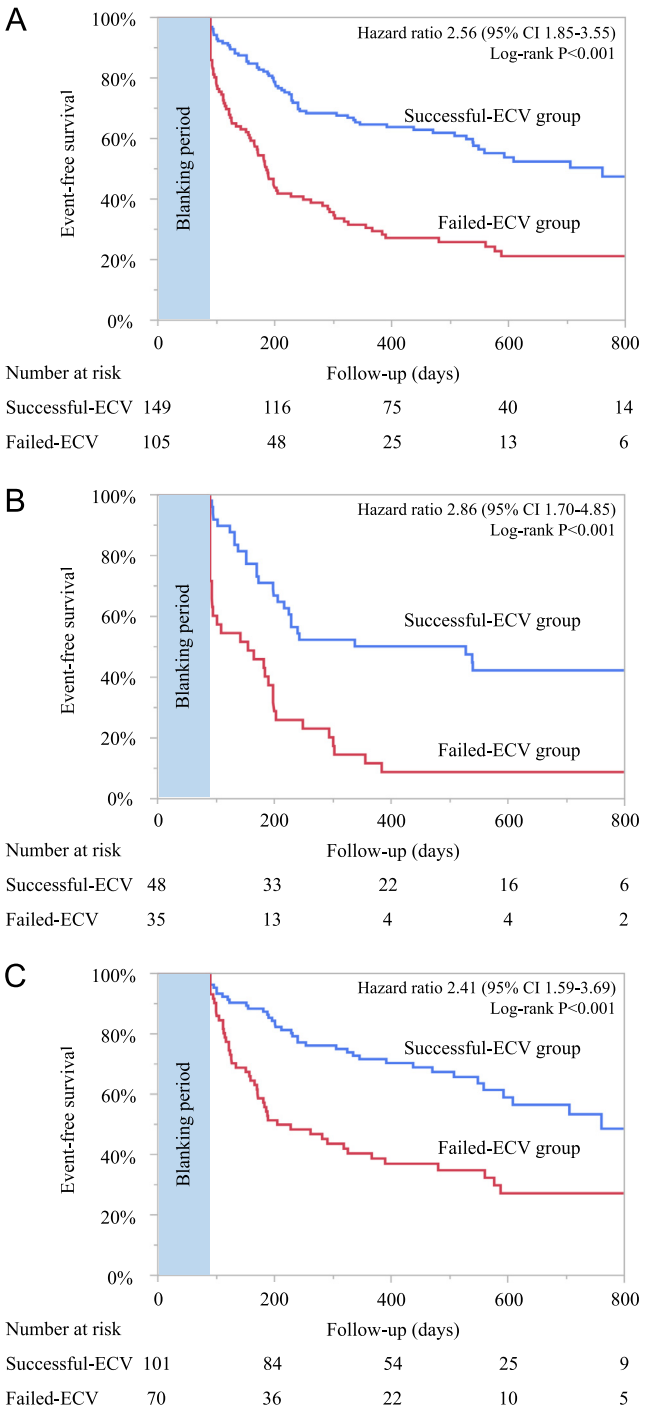

Figure 2. Kaplan-Meier curve for freedom from recurrence after ablation. *(A)* In all patients. *(B)* In paroxysmal AF patients. *(C)* In nonparoxysmal AF patients.
AF = atrial fibrillation, CI = confidence interval, ECV = electrical cardioversion.

phenomenon, whereas occurring beyond 1 month might be because of another mechanism.

The major causes of AF recurrence after BP are residual or reappearing AF triggers and progression of AF substrates.[11–13] In particular, inflammation and oxidative stress of the left atrium are believed to play a role in pathogenesis of AF.[14–17] Furthermore, previous studies have reported that the inflammatory response that develops after CA aggravates the arrhythmogenic activity of PVs.[18,19] In patients who underwent reablation, AF triggers were significantly more frequently observed in the failed-ECV group in this study. Considering the very high recurrence rates in the failed-ECV group, apart from transient phenomena during the BP, one of the mechanisms underlying failed ECV is acceleration of the activity of the residual or reappearing AF triggers because of inflammation after CA.

The current expert consensus does not recommend early reablation for ERAA.[5] Lellouche et al compared the incidence of AF recurrence between patients with ERAA who underwent early reablation and those who did not. They reported that over 90% of patients with ERAA who did not undergo early reablation experienced recurrence; however, recurrence occurred in only 51% of those who underwent early reablation.[20] This implies that early reablation during the BP would decrease the incidence of AF recurrence. Especially, it is important to predict future recurrence during the BP in patients with severe symptoms. Then, almost 75% of patients with failed ECV during the first month after CA experienced recurrence after the BP in this study. As failed ECV was closely associated with recurrences, we may be able to identify patients with recurrence during the first month to focus on the response to ECV in patients with ERAA, with a reasonably high positive predictive value. They would be suitable candidates for CA within the BP.

Recently, Ebert et al reported that failed ECV with AF within the first 7 days after CA was not associated with AF recurrence,[21] which differed from our findings. However, there were some significant differences between their study and ours. First, we included patients with ERAA within a BP of 3 months, whereas they included patients with ERAA within a BP of only 7 days after CA. The mechanisms underlying ERAA differ depending on the time after CA,[22] and this difference could be crucial. Second, they included 31 patients (17.2%) who underwent reablation. Third, their ablation strategy appeared to be more aggressive than ours; for example, the proportion of patients who underwent linear ablation in left atrium was much higher in their study than in ours (67.8% vs 18.5%). These differences might explain the discrepancy between the 2 studies.

There are several limitations in our study. First, this was a single-center retrospective study. Therefore, the strategies of CA, oral administration of AADs during the BP, and ECV for ERAA were different depending on the patients' attending physician. In particular, the oral administration of AADs during the BP may have influenced our results. Oral AADs suppressed some atrial arrhythmia events. If all patients had not had AADs, our study candidates might have increased. Second, not all patients with ERAA in this study underwent ECV directly, and 83 patients (32.7%) of this study population underwent pharmacological cardioversion using an intravenous administration of an AAD before ECV. Hence, it must have influenced the results of ECV in those patients. Third, we may have underestimated the incidence of AF recurrence, because asymptomatic short-duration AF episodes may have been undetected.

Table 2
Univariate and multivariable analyses of factors associated with AF recurrence after CA

	Univariate		Multivariate	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Gender (female)	1.30 (0.87−1.90)	0.19	1.09 (0.72−1.61)	0.68
Left atrium diameter	0.99 (0.96−1.01)	0.35	0.98 (0.96−1.01)	0.22
Chronic heart failure	1.44 (0.94−2.13)	0.09	1.65 (1.04−2.55)	0.03
Maximum C-reactive protein value during hospitalization	0.92 (0.84−0.98)	0.01	0.93 (0.85−1.00)	0.06
Oral administration of anti-arrhythmic drug during the blanking period	1.09 (0.75−1.62)	0.67	0.89 (0.73−1.70)	0.58
Length of time from ablation to the first electrical cardioversion	1.00 (0.99−1.01)	0.30	1.01 (1.00−1.02)	0.01
Failed electrical cardioversion	2.56 (1.85−3.55)	<0.001	3.05 (2.13−4.39)	<0.001

Table 3
Findings from the reablation procedures

	Electrical cardioversion		p Value
	Failed (n = 63)	Successful (n = 50)	
Type of AF			
Paroxysmal	30 (48%)	21 (42%)	0.62
Persistent	15 (24%)	16 (32%)	
Long-lasting persistent	18 (28%)	13 (26%)	
Findings from the electrophysiological study			
Pulmonary vein reconnection	55 (87%)	45 (90%)	0.55
Identification of AF triggers	18 (28%)	4 (8.0%)	0.008
From pulmonary vein	9 (14%)	3 (6.0%)	0.22
From nonpulmonary vein	9 (14%)	1 (2.0%)	0.04

Data are presented as n (%).

Disclosures

KI has received honoraria from Johnson and Johnson KK, Medtronic, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Daiichi-Sankyo. Other authors (RN, NT, MO, KT, YN, YH, TO, HI, YK, AO, KI, HR, YS, and KF) declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.11.039.

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