Circulation Reports
Circ Rep 2020; 2: 707 – 714
doi:10.1253/circrep.CR-20-0111

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Prognostic Significance of Post-Procedural Left Ventricular Ejection Fraction Following Atrial Fibrillation Ablation in Patients With Systolic Dysfunction

Kyoichiro Yazaki, MD; Koichiro Ejima, MD, PhD; Shohei Kataoka, MD; Satoshi Higuchi, MD; Miwa Kanai, MD; Daigo Yagishita, MD; Morio Shoda, MD, PhD; Nobuhisa Hagiwara, MD, PhD

Background: Atrial fibrillation (AF) ablation is associated with a good prognosis; nevertheless, the effect of post-procedural systolic function on a patient's prognosis remains uncertain.

Methods and Results: Of 1,077 consecutive patients undergoing AF ablation, the prognosis of 150 patients with abnormal left ventricular ejection fraction (LVEF; <50%) was evaluated. Patients were categorized as having reduced LVEF (rEF; LVEF <40%), mid-range ejection fraction (mrEF; 40%≤LVEF<50%), or preserved LVEF (pEF; LVEF ≥50%). Post-procedural LVEF, evaluated 3 months after the procedure, was post-rEF in 28 patients (19%), post-mrEF in 49 (33%), and post-pEF in 73 (49%). During the median follow-up of 31 months, the cumulative ratios of the composite outcome (heart failure hospitalization or death) in the post-rEF, post-mrEF, and post-pEF groups were 18%, 5%, and 2%, respectively, at 1 year and 50%, 13%, and 4%, respectively, at 3 years (P<0.0001). The post-rEF group had a 4.5- to 5.0-fold higher risk of the outcome compared with the post-pEF group, whereas the post-mrEF group showed no risk after adjusting for confounders, including age ≥65 years, preprocedural LVEF category, and recurrence of atrial tachyarrhythmia.

Conclusions: Patients with post-mrEF had a comparable prognosis to those with post-pEF over a relatively long follow-up, whereas those with post-rEF had the poorest outcome of the 3 groups, regardless of preprocedural LVEF status.

Key Words: Atrial fibrillation; Catheter ablation; Death; Heart failure hospitalization; Left ventricular ejection fraction

Atrial fibrillation (AF) is often associated with impaired left ventricular ejection fraction (LVEF) and poor prognosis due to the absence of atrioventricular synchrony, a deficiency of atrial kick, irregularity, or tachycardia.[1] Several randomized control studies have reported that AF ablation is associated with a good prognosis and significant LVEF improvement.[2,3] In addition, several studies have reported predictors of LVEF improvement after AF ablation in heart failure patients.[4–6] Nevertheless, the definition of LVEF improvement varies among studies, meaning that the relationship between LVEF improvement and prognosis is not clear. Therefore, the aim of the present study was to investigate the relationship between post-procedural LVEF (3 months after the procedure) and prognosis in patients who underwent AF ablation.

Methods

Study Population

This retrospective observational study screened 1,077 consecutive patients undergoing radiofrequency catheter ablation for AF (**Figure 1**). Of patients undergoing circumferential pulmonary vein isolation (PVI) between August 2009 and May 2019, 195 who had impaired LVEF (<50%) were enrolled in the present study. Patients who underwent cardiac resynchronized therapy after the procedure, those who were followed up for <6 months after the procedure, and those who did not receive echocardiographic evaluations 3 months after the index procedure were excluded. AF ablation was indicated based on previous expert consensus statements.[7–9] Within the 1 month prior to each session, patients underwent 3-dimensional cardiac computed

Received October 22, 2020; accepted October 23, 2020; J-STAGE Advance Publication released online November 27, 2020 Time for primary review: 1 day

Department of Cardiology, Tokyo Women's Medical University School of Medicine, Tokyo (K.Y., K.E., S.K., S.H., M.K., D.Y., M.S., N.H.); Clinical Research Division for Heart Rhythm Management, Department of Cardiology, Tokyo Women's Medical University, Tokyo (K.E., M.S.), Japan

N.H. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Koichiro Ejima, MD, PhD, Department of Cardiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: koichiro@qf6.so-net.ne.jp

ISSN-2434-0790

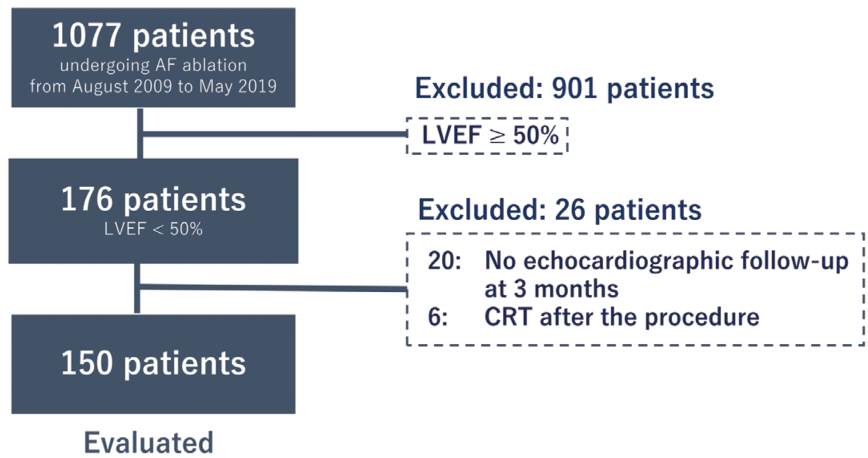

Figure 1. Study flowchart. AF, atrial fibrillation; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction.

tomography and transthoracic echocardiography. Transesophageal echocardiography was performed in patients with persistent AF and those with paroxysmal AF with a high $CHADS_2$ score (>2 points).

This study was conducted in accordance with institutional guidelines and the principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board of Tokyo Women's Medical University (ID: 4190-R). All patients provided written informed consent prior to study participation.

Catheter Ablation Protocol

A detailed description of the catheter ablation protocol has been published previously.[10] Wide circumferential PVI consisted of a point-by-point radiofrequency application using an image of the 3-dimensional mapping system (CARTO 3; Biosense Webster, Diamond Bar, CA, USA) with 2 long sheaths, 1 circular multielectrode catheter, and a 3.5-mm open-irrigated tip catheter (ThermoCool, ThermoCool SF, or ThermoCool STSF; Biosense Webster) as the ablation catheter. From February 2013, empirical superior vena cava isolation was routinely performed. The main goal of ablation was complete isolation of the thoracic vein (pulmonary vein and superior vena cava). Atrial overdrive pacing was induced by infusion of isoproterenol and the absence of dormant conduction was confirmed by infusion of ATP infusion; these procedures were conducted for a minimum of 20 min after isolation of the ipsilateral pulmonary vein pair. If other atrial tachyarrhythmias (ATA) or non-pulmonary vein foci were triggered, they were targeted for elimination as much as possible.

Echocardiographic Evaluation

In all patients, transthoracic echocardiography was performed in the left lateral decubitus position using an ultrasound system. All images were stored digitally, and relevant parameters were then measured according to the recommendations of the American Society of Echocardiography.[11] Left atrial and left ventricular (LV) volumes were measured using the modified Simpson's method. LV filling pressures were calculated by dividing the standard E-wave by the early diastolic mitral annular velocity (e'), resulting in a measurement of early diastolic mitral flow velocity (E)/e' at the septal wall, using color-coded tissue Doppler imaging with a 4-chamber view. In general, patients also underwent several other tests, including magnetic resonance imaging, myocardial scintigraphy, coronary angiography, myocardial biopsy, and, occasionally, genetic tests to identify structural heart diseases (SHDs) such as, coronary artery disease, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease, congenital heart disease, or other cardiomyopathies, as the cause of cardiac dysfunction based on the current heart failure management guidelines.[12]

Follow-up

Patients were routinely followed up without the use of antiarrhythmic drugs (AADs) after the index procedure. Patients visited the outpatient clinic 1, 3, 6, 9, and 12 months after the index procedure and every 6 months thereafter. Echocardiography was routinely performed at 3, 6, and 12 months until LVEF was improved. The LVEF 3 months after the procedure was regarded as the post-procedural LVEF. In addition, ATA recurrence was evaluated prior to the echocardiographic evaluation to assess the effect of ATA recurrence on changes in LVEF. Medical records were reviewed for patient admissions or deaths during the follow-up period. The primary outcome was the composite of all-cause death and heart failure hospitalization (HFH). ATA recurrence was assessed using 24-h ambulatory electrocardiography monitoring every 3 months in the first year and every 6 months thereafter. In addition, a portable electrocardiograph (HCG-801R; Omron, Kyoto, Japan) was used for patients with frequent symptoms without a documented electrocardiogram and 2–3 daily pulse checks were made in asymptomatic patients. Recurrence was defined as symptomatic and/or documented ATA on 12-lead electrocardiography, 24-h ambulatory electrocardiography monitoring, or portable electrocardiography after a 2-month blanking period.

In accordance with the recent heart failure management guidelines,[13] patients were categorized into 3 groups based on LVEF: reduced LVEF (rEF; LVEF <40%), mid-range EF (mrEF; 40%≤LVEF<50%), and preserved LVEF (pEF;

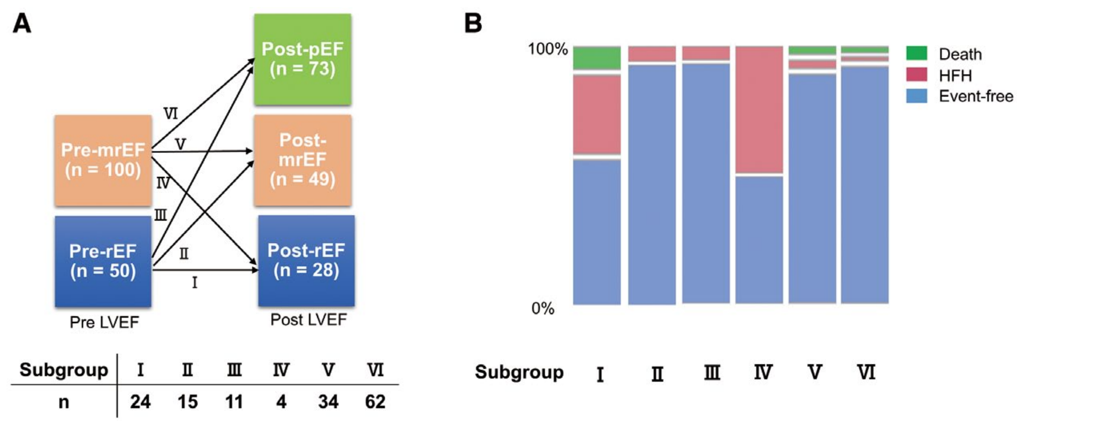

Figure 2. Left ventricular ejection fraction (LVEF) transition subgroups and their prognoses. (**A**) Distribution and transition of LVEF before (Post-) and after (Pre-) the procedures, as indicated by the roman numerals corresponding to each subgroup. The figure shows the number of patients in each subgroup. mrEF, mid-range LVEF; pEF, preserved LVEF; rEF, reduced LVEF. (**B**) Rate of outcomes (i.e., death and heart failure hospitalization [HFH]) in the 6 subgroups.

LVEF ≥50%). In patients with pre- and post-procedural LVEF data, values are reported as pre- or post-rEF, pre- or post-mrEF, and pre- or post-pEF.

Statistical Analysis

Continuous variables are expressed as mean±SD or as the median with interquartile range (IQR). Student's t-test and the Wilcoxon test were used to compare continuous variables between the groups. Categorical variables are summarized as percentages. Fisher's exact test was used to evaluate the significance of differences in categorical variables. The incidence of the primary outcome was assessed using the Kaplan-Meier method, and the significance of differences among groups were compared using the log-rank test with Bonferroni correction. Pre- and post-procedural LVEF were compared using the paired t-test. A Cox proportional hazards model was used to evaluate the predictors of the primary outcome in univariate and multivariate analyses, using 3 models that included relevant covariates: Model 1 included age ≥65 years, post-procedural LVEF category, and pre-rEF; Model 2 did. ATA recurrence, pre-rEF, and post-procedural LVEF category; and Model 3 did age ≥65 years, ATA recurrence, and post-procedural LVEF category.

All analyses were performed using JMP® 13 (SAS Institute, Cary, NC, USA), and 2-sided $P<0.05$ was considered significant.

Results

Baseline Characteristics

Of the 176 patients with LVEF <50%, 20 did not have echocardiographic data at 3 months after the index procedure (although all received at least 1 echocardiographic evaluation within 1 year) and 6 underwent cardiac resynchronization therapy after the procedure. These 26 patients were excluded from the study and the remaining 150 patients (mean age 60±10 years, 87% men) were selected for evaluation. None of the patients experienced paroxysmal AF, and the mean preprocedural LVEF was 41%. In all, 93, 51, and 6 patients required 1, 2, and 3 sessions, respectively.

At 1 and 5 years after the single procedure, sinus rhythm was maintained in 50% and 34% of patients, respectively, without AADs and in 75% and 65% of patients, respectively, with AADs. At 1 and 5 years after the final procedure, this proportion increased to 73% and 62%, respectively, of those without AADs and to 88% and 80%, respectively, of those using AADs. Six patients (5%) had persistent AF despite the use of AADs during the follow-up period (i.e., the combination of catheter ablation and medical therapy failed to maintain sinus rhythm). The ATA recurrence rate did not differ significantly between pre-mrEF and pre-rEF patients after the single and final procedures ($P=0.84$ and 0.05, respectively, log-rank test). Procedure-related complications were observed in 2 patients: 1 experienced transient ischemic attack immediately after the procedure, and the other had intra-abdominal hematoma due to wire perforation, which recovered without blood transfusion.

Results of Catheter Ablation and LVEF Transition

After AF ablation, sinus rhythm was maintained in 86 patients (57%) 3 months after the index procedure. Overall, the mean LVEF increased significantly from 41±8% to 49±9% ($P<0.0001$); however, this absolute change was limited in patients who had ATA recurrence regardless of an absolute change (Δ) in heart rate (ΔLVEF, 5±8% vs. 11±7% [$P<0.0001$]; median [IQR] Δheart rate, 3.5 [−9, 19.5] vs.12 [−3, 14] beats/min [$P=0.12$]). The distribution of the patients according to post-procedural LVEF was 28 (19%) post-rEF, 49 (33%) post-mrEF, and 73 (49%) post-pEF. Details of LVEF transition before and after AF ablation are shown in **Figure 2A**. After categorizing all patients into 6 subgroups according to the transition (for detailed characteristics, see the **Supplementary Table**), 4 patients with pre-mrEF experienced a decrease to post-rEF, whereas the remaining patients in the post-rEF subgroup had previously been categorized in the pre-rEF subgroup. The primary outcome was observed mostly in patients in the post-rEF subgroup ($P<0.0001$; **Figure 2B**).

Follow-up

During the median follow-up of 31 months, the primary

Table 1. Characteristics at Baseline and During Follow-up Among the 3 LVEF Categories After the Procedure

Variables	Post-rEF (n=28)	Post-mrEF (n=49)	Post-pEF (n=73)	P value
Mean age (years)	61±11	61±10	60±10	0.55
Men	28 (100)	39 (80)	63 (86)	0.04
Paroxysmal AF	12 (43)	17 (35)	31 (42)	0.65
History of AF (months)	28 [9–96]	33 [6–84]	24 [9–72]	0.64
Total no. sessions	1.4±0.6	1.3±0.5	1.5±0.6	0.28
History of HF hospitalization	5 (18)	14 (29)	21 (29)	0.50
Known structural heart disease	20 (71)‡‡‡	24 (49)‡	19 (26)	<0.0001
Ischemic cardiomyopathy	3 (11)	4 (8)	3 (4)	
Non-ischemic cardiomyopathy	13 (46)	10 (20)	12 (16)	
Hypertrophic cardiomyopathy	3 (11)	8 (16)	3 (4)	
Congenital heart disease	1 (4)	1 (2)	1 (1)	
Medications				
β-blockers	22 (79)	35 (73)	42 (58)	0.08
ACEI/ARBs	22 (79)‡‡	27 (56)	34 (47)	0.02
MCR antagonist	17 (61)‡‡‡	10 (21)**	13 (18)	<0.0001
Heart rate (beats/min)				
Before the procedure	89±26	84±25	84±23	0.57
After the procedure	76±16	71±13	72±12	0.33
ATA recurrence	16 (57)‡	23 (47)	25 (34)	0.09
Antiarrhythmic drug	16 (57)‡‡‡	12 (25)**	13 (18)	0.0003
Preprocedural echocardiographic parameters				
LAVI (mL/m²)	53±22‡	49±21	44±15	0.09
LVEF (%)	31±8‡‡‡	42±7***	44±76	<0.0001
E/e'	13±5	10±5*	11±5	0.06
LVDd (mm)	61±9‡‡‡	50±9***	51±6	<0.0001
LVDs (mm)	52±10‡‡‡	39±8***	38±7	<0.0001
LVEDV (mL)	194±64‡‡‡	143±32***	132±33	<0.0001
LVESV (mL)	136±56‡‡‡	84±24***	74±24	<0.0001

Unless indicated otherwise, data are given as the mean ± SD, n (%), or as the median [interquartile range]. *P<0.05, **P<0.01, ***P<0.001 compared with patients with reduced left ventricular ejection fraction (LVEF) after the procedure (post-rEF); †P<0.05, ††P<0.01, †††P<0.0001 compared with patients with mid-range LVEF after the procedure (post-mrEF); ‡P<0.05, ‡‡P<0.01, ‡‡‡P<0.001 compared with patients with preserved LVEF after the procedure (post-pEF). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ATA recurrence, recurrence of atrial tachyarrhythmia (before LVEF evaluation); E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; HF, heart failure; LAVI, left atrial volume index; LVDd, left ventricular (LV) end-diastolic dimension; LVDs, LV end-systolic dimension; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MCR, mineralocorticoid receptor.

outcomes occurred in 18 (12%) patients: 11 HFHs (7%) and 7 all-cause deaths (5%; n=3 cardiac issues, n=2 any malignancies, and n=2 other issues). No significant differences were found in the type of AF, history of AF, or prevalence of known SHD, including ischemic or non-ischemic cardiomyopathy, hypertrophic cardiomyopathy, or congenital heart disease, between patients who experienced the outcome and those who did not.

Differences in Clinical Characteristics Among the 3 LVEF Categories

Table 1 shows the differences in characteristics among the 3 categories of post-procedural LVEF. No differences were noted in the type of AF, history of AF, or history of HFH for AF; however, SHD was more frequently observed in patients in the post-rEF group. Standard drugs for heart failure, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, mineralocorticoid receptor antagonists, or AADs, were more frequently used in the post-rEF group. ATA tended to recur more frequently after the single procedure in the post-rEF group. The distribution of recurrence type, including paroxysmal and persistent AF and paroxysmal and persistent atrial tachycardia, did not differ significantly among the 3 groups (P=0.31). The left atrial volume index (LAVI) and E/e' did not differ significantly among the 3 groups.

In the Kaplan-Meier curve analysis using Bonferroni correction, a significant difference was found in the incidence of the outcome between the post-rEF and post-mrEF (P=0.0003) and post-rEF and post-pEF (P<0.0001) groups, but not between the post-mrEF and post-pEF groups. The cumulative ratios of the outcomes in the post-rEF, post-mrEF, and post-pEF groups were 18%, 5%, and 2%, respectively, 1 year after the procedure and 50%, 13%, and 4%, respectively, 3 years after the procedure (**Figure 3A**). Similar findings were noted among the 3 groups with regard to the incidence of HFH (**Figure 3B**). Nevertheless, there was no significant difference in mortality rate among the 3 groups (**Figure 3**).

Predictors of Outcome

Table 2 shows hazard ratios of the outcomes based on univariate analysis. Age ≥65 years, preprocedural LVEF category, LAVI, ATA recurrence before LVEF evaluation,

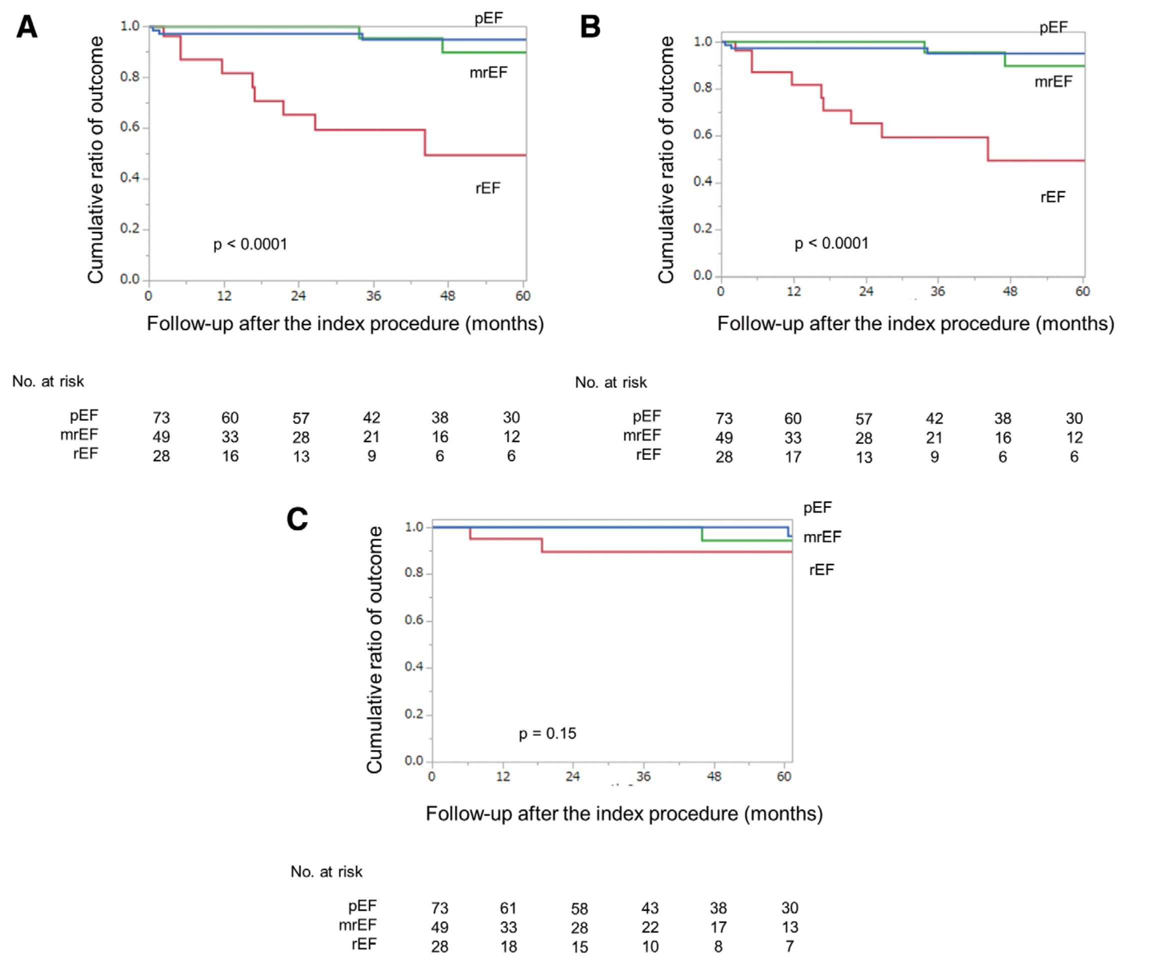

Figure 3. Differences in outcome-free survival rates among the 3 left ventricular ejection fraction (LVEF) categories: reduced LVEF (rEF), mid-range ejection fraction (mrEF), or preserved LVEF (pEF). Kaplan-Meier curves showing differences in the cumulative rate of (**A**) the composite outcome of heart failure hospitalization (HFH) and death, (**B**) HFH, and (**C**) death according to post-procedural LVEF category. AAD, antiarrhythmic drug; PAF/AT, paroxysmal atrial fibrillation/atrial tachycardia; PerAF/AT, persistent atrial fibrillation/atrial tachycardia.

and post-procedural LVEF were significantly associated with the outcome. Multivariate analyses were performed using 3 models that included variables considered to be related to the primary outcome: Model 1 included age ≥65 years, post-procedural LVEF category (post-pEF, post-mrEF, and post-rEF), and pre-rEF; Model 2 included ATA recurrence, pre-rEF, and post-procedural LVEF category; and Model 3 did age ≥65 years, ATA recurrence, and post-procedural LVEF category. In every assessment, post-rEF emerged as an independent predictor of outcomes.

In the multivariate analysis, the post-rEF group had a 4.5- to 5.0-fold higher risk of the outcome than the post-pEF group. In contrast, there was no significant difference in the risk of outcomes between the post-mrEF and post-pEF groups in either the univariate or multivariate analyses (**Table 3**).

Discussion

Main Finding

In the present study we explored the association between post-procedural LVEF at 3 months and prognosis in patients who underwent AF ablation. First, 43% of patients who experienced ATA recurrence had an attenuated LVEF increase 3 months after the index procedure. Second, patients in the post-rEF subgroups developed the primary outcomes (HFH or death) following AF ablation more commonly than those in the post-mrEF and post-pEF subgroups (who had almost comparable outcomes). Third, the multivariate analysis adjusting for confounders, including pre-LVEF categorization and ATA recurrence, found that post-mrEF patients had comparable outcomes to post-pEF patients, whereas those in the post-rEF subgroup had a 4.5- to 5.0-fold greater risk of the outcomes than those in the post-pEF subgroup.

AF Ablation and LVEF Improvement

It is often difficult to discriminate patients with arrhythmia-induced cardiomyopathy (AIC)[14] from those with organic heart disease due to a reversible condition in the absence of atrial or ventricular arrhythmia. AF is the atrial arrhythmia that most commonly induces AIC, and its treatment by

Table 2. Predictors of Outcome in Univariate Analysis

Variables	HR	95% CI	P value
Age ≥65 years	3.11	1.20–8.40	0.02
Male sex	2.60	0.53–46.83	0.28
Persistent AF	0.41	0.15–1.04	0.06
Known structural heart disease	2.00	0.79–5.28	0.14
History of AF (months)	1.59	0.11–11.29	0.69
ATA recurrence	3.62	1.36–11.29	0.01
History of HF hospitalization	1.69	0.62–4.30	0.29
Pre-rEF	2.94	1.15–7.75	0.02
LAVI (mL/m²)	1.03	1.00–1.05	0.02
LAVI ≥50 mL/m²	1.64	0.63–4.17	0.30
Heart rate (beats/min)			
At baseline	1.00	0.98–1.02	0.92
After the procedure	1.02	0.99–1.06	0.17
Post-procedural LVEF (%)	0.92	0.89–0.96	<0.0001
Post-procedural LVEF category			
Post-pEF	1.00		
Post-mrEF	1.04	0.21–4.28	0.95
Post-rEF	7.61	2.66–24.77	0.0002

CI, confidence interval; HR, hazard ratio; Post-mrEF, patients with mid-range LVEF after the procedure; Post-pEF, patients with preserved LVEF after the procedure; Post-rEF, patients with reduced LVEF after the procedure; Pre-rEF, patients with reduced LVEF before the procedure. Other abbreviations as in Table 1.

Table 3. Predictors of Outcome in the 3 Different Models in Multivariate Analysis

	HR	95% CI	P value
Model 1			
Age ≥65 years	2.78	0.99–8.31	0.05
Pre-rEF	2.12	0.70–6.74	0.18
Post-pEF	1.00		
Post-mrEF	0.97	0.19–4.08	0.96
Post-rEF	4.53	1.33–16.87	0.02
Model 2			
ATA recurrence	2.29	0.80–7.50	0.12
Pre-rEF	1.52	0.52–4.59	0.44
Post-pEF	1.00		
Post-mrEF	0.88	0.18–3.71	0.87
Post-rEF	4.60	1.30–17.52	0.02
Model 3			
Age ≥65 years	2.35	0.80–6.57	0.09
ATA recurrence	2.35	0.84–7.65	0.11
Post-pEF	1.00		
Post-mrEF	0.99	0.20–4.14	0.99
Post-rEF	4.97	1.63–17.06	<0.0001

Abbreviations as in Tables 1,2.

catheter ablation has recently been reported, contributing to a good prognosis in heart failure patients compared with medical treatment.[2] Interestingly, in the present study, patients achieved significant improvements in LVEF after AF ablation, with a 5±8% change in LVEF despite the prior ATA recurrence. This may suggest that the decrease in AF frequency possibly contributed to the improvement in LVEF. We previously reported that the recurrence of persistent AF could be the main factor inhibiting LVEF improvement as compared with paroxysmal AF or sinus rhythm,[15] which partially supports the present findings.

Impact of LVEF on Prognosis Following AF Ablation

LVEF has a substantial effect on prognosis in chronic heart failure patients.[16] It also has a key role in the prognosis of heart failure patients undergoing AF ablation. Some large trials have reported the association of AF ablation with LVEF increase and better prognosis than medical treatment.[2,17] Addison et al reported that LVEF normalization after AF ablation was associated with reduced death or HFH rates.[5] Studies have also reported a relationship between poor prognosis and known heart disease,[18] as well as preprocedural late gadolinium enhancement in the left atrium.[5] In contrast to these observations, poor outcomes, even in the presence of LVEF improvement after AF ablation, have been reported. In a previous study, a median increase in LVEF of 8% was observed in patients after AF ablation and a higher post-ablation LVEF was found in 68% of patients; however, approximately 30% of patients either died or, among those with severely reduced LVEF, experienced HFH.[2] In the present study, we recorded a mean increase in LVEF of 9%, and the primary outcome (death or HFH) was observed in 12% of patients, partially consistent with findings of the previous study with a similar follow-up period (31 in the present study vs. 38 months in the previous study). This difference in the rate of the primary endpoint may not be explained by the ATA recurrence rate with or without AADs (33% vs. 35% at 5 years), but rather the difference in preprocedural LVEF severity (31% vs. 41%). Thus, although there is a close relationship between LVEF improvement and good prognosis, the prognostic impact of post-procedural LVEF remains uncertain.

In the present study, we evaluated the prognosis of patients undergoing AF ablation based on the 3 categories of post-procedural LVEF, in accordance with recent guidelines.[13] Considering the LVEF transition from before to after AF ablation, poor outcomes predominantly occurred in those subgroups transitioning from pre-rEF to post-rEF and from pre-mrEF to post-rEF (**Figure 2B**). This suggests an association of rEF with the poorest outcome, which may be due, in part, to the underlying SHDs or difficulty in maintaining sinus rhythm. A previous study reported that the increase in LVEF was limited following AF ablation in the presence of organic heart disease.[18] However, in the present study, SHDs did not affect the outcome rate in univariate analysis. This could underscore the fact that the type of SHD or disease severity may have an important effect on the outcome rate, rather than the mere presence of SHD itself (although this was difficult to assess statistically because of the small number of patients). Most recently, a study suggested that AF had no significant effect on the outcome in heart failure patients with severely impaired LVEF;[19] nevertheless, this did not encourage us to defer AF ablation in this population because a substantial number of patients (26/50) in the pre-rEF group transitioned to the post-mrEF and post-pEF groups after AF ablation. Although an implantable cardiac defibrillator is recommended for primary prevention in patients with an LVEF <35% and heart failure symptoms of New York Heart Association functional class >II, regardless of the kind of underlying heart disease,[20] our data suggest that it is preferable to make this decision after AF ablation because of the high possibility of LVEF improvement.

Characteristics of Patients With mrEF

In contrast with the results of the post-rEF groups, the frequency of the outcome did not differ significantly between the post-mrEF and post-pEF groups, which is partially consistent with our previous results.[21] Using a Japanese registry, the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2 Study) found that mrEF was associated with unplanned HFH but not with death and pEF, concluding that mrEF was an "overlap" transition zone rather than an independent entity.[22] In an acute heart failure study, Cho et al found higher in-hospital mortality and lower long-term survival rates in the rEF than mrEF and pEF groups with non-ischemic etiology.[21] Fonarow et al reported a higher prevalence of heart failure with pEF and similar mortality and rehospitalization rates regardless of LVEF category after discharge.[23] Various conclusions were made regarding the prognosis in heart failure patients in terms of LVEF differences; nevertheless, there was no definite confirmation. In the present study, post-mrEF was not associated with the composite outcome compared with post-pEF in the univariate and multivariate analyses, even after adjusting for several relevant confounders. This suggests that patients in the post-mrEF group had relatively safe and low-risk profiles regardless of preprocedural LVEF.

Comparison With Other Studies With Regard to ATA Recurrence

Several previous studies have similarly the investigated clinical utility of AF ablation in patients with heart failure. The famous Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) randomized control trial demonstrated the superiority of AF ablation to medical therapy in heart failure patients with severe systolic dysfunction.[2] The CASTLE-AF investigators reported a 5-year ATA recurrence rate of 37% following AF ablation.[2] Their strategy consisted of simple PVI with additional approaches being at the operator's discretion (51.7%). Similarly, Black-Maier et al reported the clinical effectiveness of AF ablation in heart failure patients.[24] In that report, the ATA recurrence rate was approximately 33%, regardless of preprocedural LVEF category, following AF ablation. The strategy reported by Black-Maier et al involved substrate modification in the left atria in a non-negligible number of patients.[24] In addition, in both studies, more than 30% of patients used amiodarone to maintain sinus rhythm.[2,24] In contrast, in the present study, ATA recurrence was observed in 65% and 75% of patients at 1 and 5 years after the index procedure, respectively, with or without AADs. Although our strategy, namely PVI and isolation of the superior vena cava without any substrate modifications regardless of the patient's background, was different from that in the previous 2 studies, the freedom-from-ATA rate with or without AADs was not inferior. In addition, the follow-up period in the study of Black-Maier et al was approximately 10 months,[24] significantly shorter than that in the present study, and their data were partially based on the outcomes of multiple procedures, which potentially affected their ATA recurrence rate.

Study Limitations

First, the present study defined post-procedural LVEF categories based on echocardiographic data 3 months after the procedure, and ATA recurrence was evaluated before the procedure, nearly equivalent to early recurrence, to clearly assess the effectiveness of recurrence on the absolute LVEF change; therefore, LVEF was considered to reflect the results of AF ablation (long-term follow-up reflects the effects of several interventions, such as strengthening drug treatment or disease progression). However, we could not assess longitudinal changes in LVEF, which may have resulted in our overlooking the LVEF trajectory during the late phase. Second, the retrospective observational design and non-negligible number of patients with no echocardiographic follow-up at 3 months could have resulted in selection bias. Third, the low incidence rate of the outcome could statistically underpower this study; nevertheless, we were able to create 3 multivariate models, including 3 variables, comprising the LVEF category and the other 2 confounders. The multivariate analysis of all models showed that post-rEF is an independent predictor of the outcome. This may improve the confidence in our statistical analysis.

Conclusions

In this study, over a relatively long follow-up, post-mrEF and post-pEF patients had comparable prognoses, whereas post-rEF patients had the poorest outcomes among the 3 categories, regardless of preprocedural LVEF. LVEF normalization was not strictly required to avoid poor outcomes. Post-mrEF may be an indicator of good prognosis in patients with systolic dysfunction undergoing AF ablation.

Acknowledgments

The authors thank Editage (www.editage.com) for English language editing.

Disclosures

N.H. is a member of *Circulation Reports*' Editorial Team. The other authors have no conflicts of interest to declare.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

IRB Information

This study was approved by the Institutional Review Board of Tokyo Women's Medical University (ID: 4190-R).

Data Availability

The deidentified participant data will not be shared.

References

1. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016; **133:** 484–492.
2. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018; **378:** 417–427.
3. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008; **359:** 1778–1785.
4. Kim IS, Kim TH, Shim CY, Mun HS, Uhm JS, Joung B, et al. The ratio of early transmitral flow velocity (E) to early mitral annular velocity (Em) predicts improvement in left ventricular systolic and diastolic function 1 year after catheter ablation for atrial fibrillation. *Europace* 2015; **17:** 1051–1058.
5. Addison D, Farhad H, Shah RV, Mayrhofer T, Abbasi SA, John RM, et al. Effect of late gadolinium enhancement on the recovery of left ventricular systolic function after pulmonary vein isolation. *J Am Heart Assoc* 2016; **5:** e003570.
6. Nedios S, Sommer P, Dagres N, Kosiuk J, Arya A, Richter S, et al. Long-term follow-up after atrial fibrillation ablation in patients with impaired left ventricular systolic function: The importance of rhythm and rate control. *Heart Rhythm* 2014; **11:** 344–351.
7. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017; **14:** e275–e444.
8. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) task force on catheter and surgical ablation of atrial fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007; **9:** 335–379.
9. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the Heart Rhythm Society (HRS) task force on catheter and surgical ablation of atrial fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm* 2012; **9:** 632–696.e621.
10. Ejima K, Henmi R, Iwanami Y, Yagishita D, Shoda M, Hagiwara N. Comparison of the efficacy of empiric thoracic vein isolation for the treatment of paroxysmal and persistent atrial fibrillation in patients without structural heart disease. *J Cardiovasc Electrophysiol* 2017; **28:** 266–272.
11. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2019; **32:** 1–64.
12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128:** e240–e327.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37:** 2129–2200.
14. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-induced cardiomyopathies: Mechanisms, recognition, and management. *Am J Coll Cardiol* 2015; **66:** 1714–1728.
15. Kato K, Ejima K, Fukushima N, Ishizawa M, Wakisaka O, Henmi R, et al. Catheter ablation of atrial fibrillation in patients with severely impaired left ventricular systolic function. *Heart Vessels* 2016; **31:** 584–592.
16. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: A meta-analytic approach. *Am J Coll Cardiol* 2010; **56:** 392–406.
17. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014; **7:** 31–38.
18. Prabhu S, Ling LH, Ullah W, Hunter RJ, Schilling RJ, McLellan AJ, et al. The impact of known heart disease on long-term outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction: A multicenter international study. *J Cardiovasc Electrophysiol* 2016; **27:** 281–289.
19. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, et al. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: A report from 14964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018; **39:** 4277–4284.
20. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–237.
21. Cho JH, Choe WS, Cho HJ, Lee HY, Jang J, Lee SE, et al. Comparison of characteristics and 3-year outcomes in patients with acute heart failure with preserved, mid-range, and reduced ejection fraction. *Circ J* 2019; **83:** 347–356.
22. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. *Eur J Heart Fail* 2017; **19:** 1258–1269.
23. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF Registry. *Am J Coll Cardiol* 2007; **50:** 768–777.
24. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018; **15:** 651–657.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-20-0111