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ORIGINAL ARTICLE

Effect of Catheter Ablation for Atrial Fibrillation in Heart Failure With Mid-Range or Preserved Ejection Fraction

— Pooled Analysis of the AF Frontier Ablation Registry and Hokuriku-Plus AF Registry —

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on behalf of the AF Ablation Frontier Registry and the Hokuriku-Plus AF Registry Investigators

Background: A recent randomized trial demonstrated that catheter ablation for atrial fibrillation (AF) in patients with heart failure with reduced ejection fraction (EF) is associated with a reduction in death or heart failure. However, the effect of catheter ablation for AF in patients with heart failure with mid-range or preserved EF is unclear.

Methods and Results: We screened 899 AF patients (72.4% male, mean age 68.4 years) with heart failure and left ventricular EF ≥40% from 2 Japanese multicenter AF registries: the Atrial Fibrillation registry to Follow the long-teRm Outcomes and use of aNTIcoagulants aftER Ablation (AF Frontier Ablation Registry) as the ablation group (525 patients who underwent ablation) and the Hokuriku-Plus AF Registry as the medical therapy group (374 patients who did not undergo ablation). Propensity score matching was performed in these 2 registries to yield 106 matched patient pairs. The primary endpoint was a composite of cardiovascular death and hospitalization for heart failure. At 24.6 months, the ablation group had a significantly lower incidence of the primary endpoint (hazard ratio 0.32; 95% confidence interval 0.13–0.70; P=0.004) than the medical therapy group.

Conclusions: Compared with medical therapy, catheter ablation for AF in patients with heart failure and mid-range or preserved EF was associated with a significantly lower incidence of cardiovascular death or hospitalization for heart failure.

Key Words: Atrial fibrillation; Cardiovascular death; Catheter ablation; Heart failure

Atrial fibrillation (AF) is one of the most common arrhythmias and is associated with a wide range of adverse events, including cardiovascular death, heart failure,[1] worsening renal function,[2] sudden cardiac death,[3,4] and thromboembolism.[5] AF and heart failure are both highly prevalent diseases that frequently occur together, leading to a poor prognosis.[1] Moreover, these diseases share a common risk profile with several coinciding cardiovascular risk factors promoting the odds of developing both AF and heart failure separately from each

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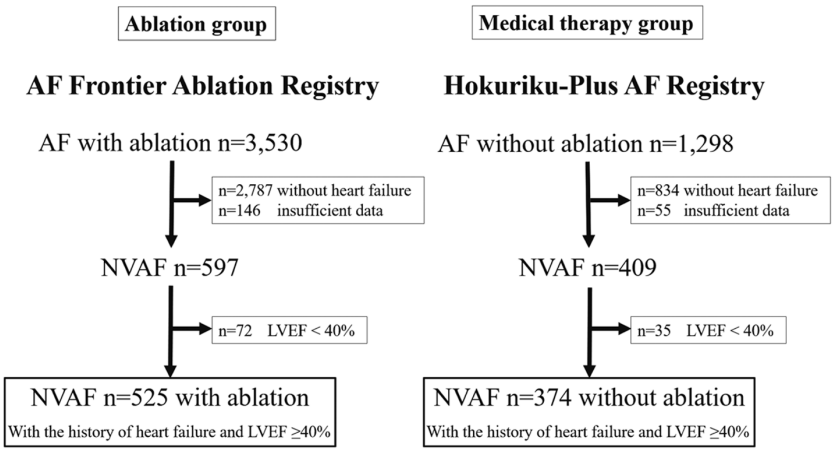

Figure 1. Flowchart of the study selection process from the 2 registries. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; NVAF, non-valvular atrial fibrillation.

other.[6] The presence of AF is associated with adverse outcomes in patients with heart failure, and maintaining sinus rhythm seems to improve prognosis in patients with AF and heart failure.[7] However, compared with rate control, pharmacological rhythm control does not improve the prognosis of patients with heart failure and AF.[8] A recent report showed that catheter ablation for AF resulted in a significant reduction in all-cause mortality and hospitalization, and a greater improvement in left ventricular systolic function than medical therapy.[9] In addition, the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial reported that catheter ablation for AF with heart failure and severe systolic dysfunction (left ventricular ejection fraction [LVEF] ≤35%) was associated with a reduction in mortality or heart failure.[10] However, the clinical outcomes of catheter ablation for AF in heart failure with mid-range ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) have not been fully evaluated. Thus, the aim of the present study was to investigate the effect of catheter ablation for AF in patients with HFmrEF or HFpEF on clinical outcomes using pooled data from 2 Japanese multicenter cohorts: the Atrial Fibrillation registry to Follow the long-teRm Outcomes and the use of aNTIcoagulants aftER Ablation (AF Frontier Ablation Registry)[11–14] and the Hokuriku-Plus AF Registry.[15–18]

Methods

Study Population

The study population was enrolled from 2 Japanese multicenter registries. The first was the AF Frontier Ablation Registry, which is a multicenter population-based cohort study whose study design has been described in detail previously.[11–14] Briefly, 3,530 consecutive patients who underwent catheter ablation for AF at 24 cardiovascular centers between August 2011 and July 2017 were recruited. The data over a median follow-up of 1.6 years included the presence of AF recurrence after catheter ablation and the occurrence of death, stroke, major bleeding, and hospitalization for heart failure. The second registry was the Hokuriku-Plus AF Registry, which is a multicenter population-based prospective cohort study. A detailed study design of the Hokuriku-Plus AF Registry has been published previously.[15–18] Briefly, 1,396 non-valvular AF patients were recruited from 19 institutions in the Hokuriku and Yokohama areas (3 cardiovascular centers, 15 affiliated hospitals or community hospitals, and 1 private clinic). Baseline enrollment was performed between January 2013 and May 2014, and follow-up examinations and the occurrence of adverse events, including death, hospitalization for heart failure, stroke, or bleeding, were conducted every year from baseline to 5 years of follow-up. The Hokuriku-Plus AF Registry included 1,298 (93%) patients with AF and without a history of catheter ablation for AF.

The AF Frontier Ablation Registry was approved by the

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Table 1. Baseline Characteristics of All Patients and Propensity Score-Matched Patients in the Ablation and Medical Therapy Groups

	Total patients				Propensity score-matched patients			
	Entire cohort (n=899)	Ablation group (n=525)	Medical therapy group (n=374)	P value	Entire cohort (n=212)	Ablation group (n=106)	Medical therapy group (n=106)	P value
Age (years)	68.4±11.6	63.7±10.8	75.0±9.1	<0.0001	72.9±9.2	73.2±7.5	72.6±10.7	0.61
Male sex	651 (72.4)	386 (73.5)	265 (70.9)	0.41	142 (67.0)	70 (66.0)	72 (67.9)	0.88
Follow-up period (months)	33.3±21.4	22.9±14.3	47.8±21.3	<0.0001	29.3±20.9	27.0±19.8	31.6±21.8	0.11
SBP (mmHg)	124±18	125±18	123±18	0.23	126±18	128±18	124±18	0.10
BMI (kg/m^2)	23.8±4.0	24.0±3.7	23.4±4.3	0.01	23.5±3.9	23.6±3.7	23.4±4.1	0.69
Persistent or permanent AF	574 (63.9)	272 (51.8)	302 (80.8)	<0.0001	164 (77.4)	82 (77.4)	82 (77.4)	1.00
Hypertension	525 (58.4)	271 (51.6)	254 (67.9)	<0.0001	144 (67.9)	78 (73.6)	66 (62.3)	0.11
Diabetes	220 (24.5)	97 (18.5)	123 (32.9)	<0.0001	69 (32.6)	31 (29.3)	38 (35.9)	0.38
Prior stroke or TIA	98 (10.9)	45 (8.6)	53 (14.2)	0.01	31 (14.6)	18 (17.0)	13 (12.3)	0.44
Prior bleeding	14 (1.6)	5 (1.0)	9 (2.4)	0.10	1 (0.5)	1 (0.9)	0 (0.0)	1.00
Vascular disease	163 (18.1)	60 (11.4)	103 (27.5)	<0.0001	54 (25.5)	24 (22.6)	30 (28.3)	0.43
CHA_2DS_2-VASc score	3.49±1.72	2.94±1.59	4.27±1.60	<0.0001	4.17±1.57	4.32±1.52	4.03±1.62	0.18
Hemoglobin, (g/dL)	13.6±1.9	14.0±1.6	13.0±2.0	<0.0001	13.2±1.9	13.0±1.8	13.4±2.1	0.16
AST (IU/L)	27.3±17.3	27.9±20.0	26.5±12.5	0.23	27.8±17.3	28.9±20.8	27.0±12.9	0.33
Ccr (mL/min)	64.5±26.9	69.3±25.2	57.4±27.7	<0.0001	56.6±27.2	55.7±21.5	57.5±31.9	0.63
Hypertrophic cardiomyopathy	57 (6.3)	29 (5.5)	28 (7.5)	0.27	21 (9.9)	12 (11.3)	9 (8.5)	0.65
LA diameter (mm)	44.4±8.1	42.2±7.1	47.6±8.4	<0.0001	45.4±7.5	45.7±7.2	45.1±7.9	0.52
LVEF (%)	64.5±10.9	61.3±9.6	68.8±10.9	<0.0001	64.1±10.2	64.4±9.5	63.7±10.9	0.62
HFpEF	800 (89.0)	449 (85.5)	351 (93.8)	<0.0001	187 (88.2)	94 (88.7)	93 (87.7)	1.00
HFmrEF	99 (11.0)	76 (14.5)	23 (6.2)	<0.0001	25 (11.8)	12 (11.3)	13 (12.3)	1.00
Any OAC use	871 (96.9)	525 (100.0)	346 (92.5)	<0.0001	212 (100.0)	106 (100.0)	106 (100.0)	1.00

Unless indicated otherwise, data are given as the mean±SD or n (%). AF, atrial fibrillation; AST, aspartate aminotransferase; BMI, body mass index; Ccr, creatinine clearance; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant; SBP, systolic blood pressure; TIA, transient ischemic attack.

Institutional Review Board (IRB) of Nihon University Itabashi Hospital, the Clinical Research Judging Committee, and the IRBs of participating hospitals. The Hokuriku-Plus AF Registry was approved by the Ethics Committee for Medical Research of Kanazawa University Graduate School of Medical Science and by the participating hospitals. All participants provided written informed consent.

The selection flow of the study population is shown in **Figure 1**. Heart failure was diagnosed if patients had symptoms of heart failure or received treatment for heart failure or the presence of severe left ventricular systolic dysfunction (LVEF <40%). Patients with heart failure were categorized into 3 groups based on ejection fraction (EF): heart failure with reduced EF (HFrEF; LVEF <40%), HFmrEF (LVEF 40–49%), and HFpEF (LVEF ≥50%).[19] Using data from the AF Frontier Ablation and Hokuriku-Plus AF registries, we created 2 groups: (1) patients with HFmrEF or HFpEF who underwent ablation for AF (ablation group); and (2) patients with HFmrEF or HFpEF who were treated without ablation (medical therapy group).

We used propensity score matching to adjust for baseline differences between the groups. The propensity scores accounted for age, sex, body mass index, follow-up period, type of AF (paroxysmal AF vs. persistent AF that lasted >7 days), CHA_2DS_2-VASc score, use of any oral anticoagulant, serum hemoglobin level, serum creatinine clearance, left atrial diameter, and LVEF by means of logistic regression analysis. One-to-one propensity score matching was performed to compare the outcomes between the 2 groups using a 0.05 caliper, equal to 0.2 of the standard deviation of the propensity score logit.

Risk Factor Definitions

The CHA_2DS_2-VASc stroke risk score was recorded as the baseline stroke risk. The components of the CHA_2DS_2-VASc score included congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack (TIA; doubled), vascular disease, age 65–74 years, and female sex. The criteria for diagnoses of congestive heart failure, hypertension, diabetes, and vascular disease have been reported previously.[20] Regarding examination findings, creatinine clearance was estimated using the Cockcroft-Gault formula.[21] Echocardiographic data were collected at the time of registry entry. Left atrial diameter was recorded in the parasternal window.

Ablation Procedure

The details of the ablation procedure in the AF Frontier Ablation Registry have been described previously.[11–14] Briefly, pulmonary vein isolation (PVI) was performed using a radiofrequency ablation catheter or cryoablation catheter. The ablation procedure was guided by a circular mapping catheter or multi-electrode catheter. Some patients were injected intravenously with adenosine triphosphate after

Table 2. Events Outcomes and Annual Event Rates in the Propensity Score-Matched Cohort

	Total cohort (n=212)	Ablation group (n=106)	Medical therapy group (n=106)	HR	95% CI	P value (Cox regression)
Cardiovascular death or HF hospitalization	32 (6.3)	7 (3.0)	25 (9.1)	0.32	0.13–0.70	0.004
Cardiovascular death	14 (2.7)	1 (0.4)	13 (4.7)	0.10	0.01–0.45	0.001
Hospitalization for HF	25 (4.9)	6 (2.6)	19 (6.9)	0.36	0.13–0.86	0.02
Stroke or TIA	15 (2.9)	6 (2.6)	9 (3.3)	0.77	0.26–2.13	0.61
Major bleeding	18 (3.5)	8 (3.4)	10 (3.6)	1.01	0.38–2.58	0.98

Unless indicated otherwise, values show the total number of events during follow-up, with the incidence per 100 person-years in parentheses. The association between catheter ablation for atrial fibrillation and each endpoint was analyzed using the Cox regression hazard model and the log-rank test. CI, confidence interval; HF, heart failure; HR, hazard ratio; TIA, transient ischemic attack.

PVI to expose dormant conduction between the pulmonary vein and left atrium. Touch-up ablation was performed when acute pulmonary vein reconnection or dormant conduction occurred. Additional linear ablations, such as tricuspid valve isthmus linear ablation, mitral isthmus linear ablation, and left atrial roof linear ablation, were performed at the physician's discretion. Residual potentials, including complex fractionated atrial electrograms in the left atrium, were ablated as appropriate.

Study Endpoints and Post-Catheter Ablation Follow-up

The primary endpoint of this analysis was the composite of cardiovascular death and hospitalization for heart failure. Secondary endpoints were cardiovascular death, hospitalization for heart failure, stroke/TIA, and major bleeding. Cardiovascular death included death caused by heart failure or vascular disease and sudden cardiac death. Stroke was defined as a sudden onset of focal deficit lasting >24 h and was further categorized as ischemic or hemorrhagic. Major bleeding included intracranial hemorrhage, bleeding requiring transfusion, and bleeding with a reduction in the hemoglobin concentration of >2 g/dL. The AF-free interval after catheter ablation was also assessed in the catheter ablation group. AF recurrence was defined as any documented episode of atrial tachyarrhythmia lasting >30 s after a blanking period of 3 months postoperatively. We divided the ablation group into 2 subgroups: (1) the successful ablation group, which was free from AF after ablation; and (2) the unsuccessful ablation group, which had episodes of AF recurrence during follow-up.

Statistical Analysis

Continuous variables are presented as the mean±SD and categorical variables are presented as percentages. Continuous variables were compared using Student's t-test for paired data, and categorical variables were compared using Fisher's exact test. Adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CIs) of each variable associated with adverse events were calculated by the Cox proportional hazard model. To investigate differences between groups in the cumulative ratio for adverse events, the occurrence of adverse events is presented using Kaplan-Meier survival curves and compared using the log-rank test. Two-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using JMP Pro version 14 (SAS Institute, Cary, NC, USA) or EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add frequently used statistical functions in biostatistics.[22]

Results

Baseline Characteristics

Of the 3,530 patients in the AF Frontier Ablation Registry who underwent catheter ablation, 2,787 without heart failure and 146 without sufficient data were excluded. Of the 1,298 patients in the Hokuriku-Plus AF Registry who had no history of ablation for AF, 834 without heart failure and 55 without sufficient data were excluded. In addition, we excluded patients with HFrEF from these 2 registries. Accordingly, 525 AF patients who underwent ablation from the AF Frontier Ablation Registry and 374 AF patients who received medical therapy from the Hokuriku-Plus AF Registry and had HFmrEF or HFpEF were included in this analysis (**Figure 1**).

The baseline clinical characteristics of all patients (n=899) and those in the ablation (n=525) and medical therapy (n=374) groups are presented in **Table 1**. As expected, there were many significant differences in baseline characteristics between the ablation and medical therapy groups, including age, follow-up period, body mass index, type of AF, CHA_2DS_2-VASc score, serum hemoglobin concentration, serum creatinine clearance, left atrial diameter, LVEF, and rate of anticoagulation therapy. After propensity score matching, 106 patients with a well-matched baseline were identified in each group (**Table 1**). No significant differences were observed in any of the baseline characteristics assessed. In the propensity-matched cohort, the mean duration of follow-up was 29.3±20.9 months (median 24.6 months; interquartile range 12.2–45.1 months), the mean age was 72.9±9.2 years, 67.0% of patients were male, and 77.4% had persistent AF. The mean CHA_2DS_2-VASc score was 4.17±1.57, and creatinine clearance was 56.6±27.2 mL/min. The left atrial diameter and LVEF were 45.4±7.5 mm and 64.1±10.2%, respectively. All patients received anticoagulation therapy at baseline.

Primary Endpoint

During a median follow-up of 24.6 months, the composite primary endpoint (cardiovascular death or hospitalization for heart failure) occurred in significantly fewer patients in the ablation than medical therapy group (7 patients [3.0/100 person-years] vs. 25 patients [9.1/100 person-years]; HR 0.32; P=0.004, Cox regression; **Table 2**). The Kaplan-Meier curve demonstrated a significantly lower incidence of the primary endpoint in the ablation than medical therapy group (P=0.005, log-rank test; **Figure 2A**).

Secondary Endpoints

One patient in the ablation group and 13 patients in the medical therapy group died of cardiovascular causes (0.4 vs. 4.7/100 person-years; P=0.001). Hospitalization for heart failure occurred in significantly fewer patients in the ablation than medical therapy group (2.6 vs. 6.9/100 person-years; P=0.02). Stroke/TIA occurred in 6 patients in the ablation group and in 9 patients in the medical therapy group (2.6 vs. 3.3/100 person-years; P=0.61); major bleeding occurred in 8 patients in the catheter ablation group and in 10 patients in the medical therapy group (3.4 vs. 3.6/100 person-years; P=0.98; **Table 2**). Kaplan-Meier curves showing a comparison of secondary endpoints of cardiovascular death and hospitalization for heart failure in the 2 groups are shown in **Figure 2B**,**C**; these curves demonstrated a significantly lower incidence of both cardiovascular death and hospitalization for heart failure in the ablation than medical therapy group (P=0.003 and P=0.02, respectively).

Impact of AF Recurrence After Catheter Ablation on Primary and Secondary Endpoints

Of the 106 patients in the ablation group, 72 (68%) were free of AF, whereas AF recurrence after ablation occurred in 34 (32%). As indicated in **Table 3**, compared with the successful ablation group, the unsuccessful ablation group had a significantly higher co-occurrence of hypertrophic cardiomyopathy and left atrial enlargement, whereas there were no significant differences between the 2 groups in the mapping tool, the use of a contact force-sensing catheter, and additional procedures other than PVI (left atrial linear ablation, superior vena cava isolation). The incidences of the primary composite endpoint and the secondary endpoint of hospitalization for heart failure showed lower trends in the successful ablation group than in the unsuccessful ablation and medical therapy groups (**Supplementary Figure**).

Discussion

Main Finding

The present pooled analysis of 2 Japanese multicenter registries demonstrated that catheter ablation for AF in patients with HFmrEF or HFpEF was associated with a significantly lower incidence of the composite endpoint of cardiovascular death and hospitalization for heart failure compared with medical therapy. We also found that there was a benefit in cardiovascular death alone in the ablation group.

Effect of AF in Heart Failure According to LVEF

HFpEF and HFmrEF are becoming the most prevalent forms of heart failure.[23,24] In patients with heart failure, AF is progressively more common with increasing EF and is associated with clinical signs and symptoms of heart failure, leading to worse long-term clinical outcomes compared with patients without AF.[25,26]

In addition, AF with HFmrEF or HFpEF is associated with worse outcomes than AF with HFrEF.[27] The hemodynamic adverse effect of AF in HFpEF is more significant because it is associated with increased left atrial stiffness and higher wall stress than in HFrEF.[28] Kaye et al[29] reported that AF patients with HFmrEF or HFpEF had significantly increased pulmonary capillary wedge pressure and a lower cardiac index than patients with sinus rhythm, leading to reductions in the left ventricular stroke work

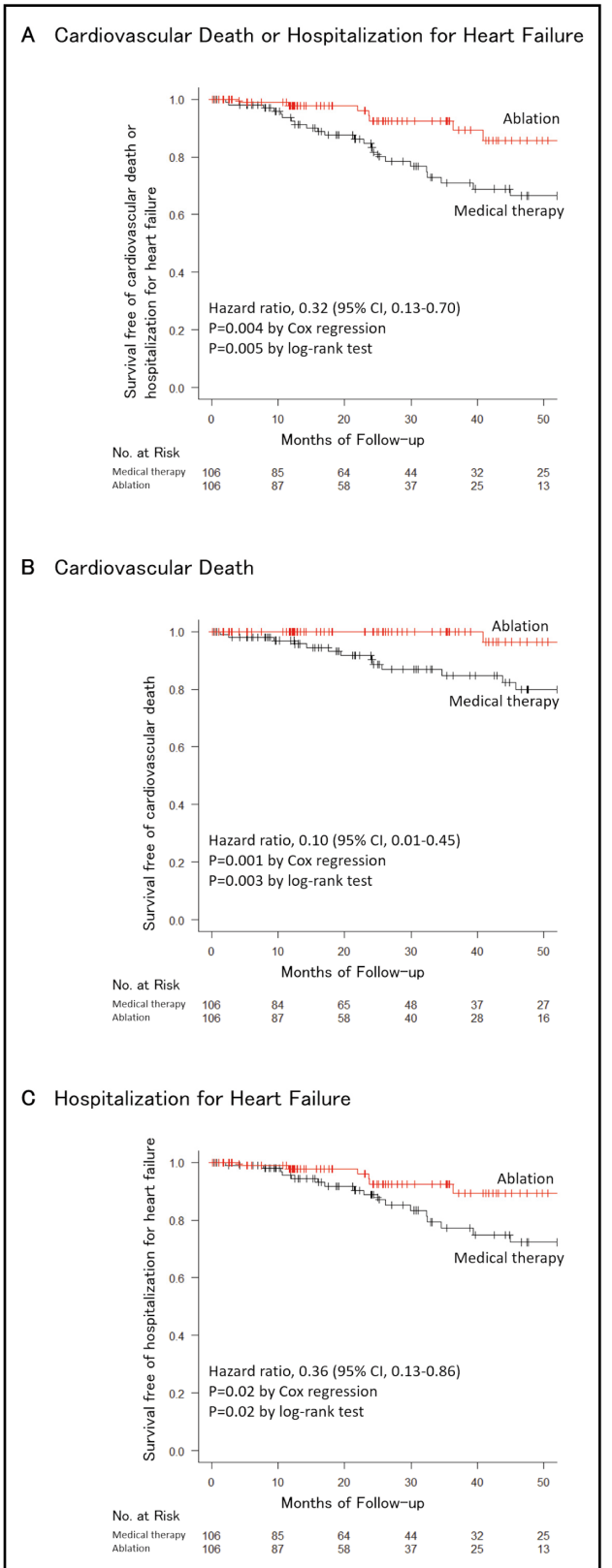

Figure 2. Kaplan-Meier curves comparing freedom from (**A**) the primary endpoint (cardiovascular death or hospitalization for heart failure), (**B**) cardiovascular death, and (**C**) hospitalization for heart failure in the ablation and medical therapy groups. CI, confidence interval.

Table 3. Baseline Characteristics in the Successful and Unsuccessful Catheter Ablation Groups

Variables	Successful CA (n=72)	Unsuccessful CA (n=34)	P value
Age (years)	73.8±7.6	72.0±7.3	0.27
Male sex	48 (66.7)	22 (64.7)	0.83
SBP (mmHg)	126±19	131±18	0.24
BMI (kg/m^2)	23.5±3.8	23.8±3.4	0.70
Persistent or permanent AF	56 (77.8)	26 (76.5)	1.00
CHA_2DS_2-VASc score	4.39±1.53	4.18±1.51	0.51
Hemoglobin (g/dL)	12.9±1.8	13.3±1.7	0.25
AST (IU/L)	29.7±24.1	27.5±11.0	0.61
Ccr (mL/min)	55.9±19.8	55.2±25.0	0.87
Hypertrophic cardiomyopathy	4 (5.6)	8 (23.5)	0.02
LA diameter (mm)	44.6±7.1	47.9±7.0	0.03
Radiofrequency ablation	69 (95.8)	34 (100)	0.55
Contact force-sensing catheter	39 (54.2)	19 (55.9)	1.00
3D mapping system	72 (100)	34 (100)	1.00
CARTO system	53 (73.6)	29 (85.3)	0.22
NAVx system	19 (26.4)	5 (14.7)	0.22
LA linear ablation	33 (45.8)	14 (41.1)	0.68
SVC isolation	16 (22.2)	7 (20.6)	1.00

Unless indicated otherwise, data are given as the mean±SD or n (%). CA, catheter ablation; SVC, superior vena cava. Other abbreviations as in Table 1.

index at rest. In addition, compared with patients with sinus rhythm, the increase in the cardiac index during exercise is significantly blunted in AF patients. These observations imply that eliminating AF by catheter ablation would lead to better clinical outcomes, not only in HFrEF patients but also in HFmrEF and HFpEF patients.

Effect of Catheter Ablation in Heart Failure

The CASTLE-AF trial showed that catheter ablation for AF with heart failure and severe systolic dysfunction reduced death or hospitalization for heart failure, with improvement in EF, compared with medical therapy.[10] However, in HFmrEF or HFpEF, the effectiveness of catheter ablation for AF has not been fully elucidated. Fukui et al[30] and Rattka et al[31] demonstrated that catheter ablation for AF with HFpEF was associated with more favorable clinical outcomes than medical therapy. However, these 2 reports were derived from single-center studies with relatively small sample sizes. The effect of catheter ablation for AF with HFmrEF or HFpEF on hard endpoints has not been evaluated in a multicenter cohort, and current guidelines[32] provide no clear consensus regarding the best management approach. To address this issue, we performed pooled data analysis of 2 large multicenter Japanese registries and demonstrated the association between catheter ablation and a lower incidence of hard endpoints, including cardiovascular death and hospitalization for heart failure. AF results in loss of atrial contraction and, together with increased pressure and volume associated with HFpEF, there is progressive remodeling of the atrium that results in loss of distensibility and a decrease in atrial reservoir function, leading to increased pulmonary capillary wedge pressure and a lower cardiac index.[33] AF can also lead to arrhythmia-induced left ventricular dysfunction, which is induced by extracellular matrix remodeling, cellular remodeling, and defects in calcium ion handling.[34] Therefore, AF results in adverse hemodynamics and leads to an increased risk of heart failure.

Previous reports demonstrated that the major cause of cardiovascular death in the AF population was heart failure.[4] Conversely, another report showed a significant association between AF in heart failure and sudden cardiac death.[35] These previous reports strongly suggest the association between increased AF burden in HFmrEF or HFpEF and worsening heart failure and cardiovascular death. The favorable outcomes in HFmrEF and HFpEF with catheter ablation may be driven mostly by a reduction in the AF burden. Based on previous reports and the results of the present study, catheter ablation for AF may be a preferable treatment to improve clinical outcomes in patients with HFpEF or HFmrEF.

Importance of Successful Sinus Rhythm Maintenance After Catheter Ablation

Compared with medical therapy, catheter ablation is more effective in reducing the AF burden, regardless of the type of AF.[26,36] The CASTLE-AF trial reported that the reduction in death/heart failure was observed with a decrease in AF burden (63.1% and 21.7% in the medical therapy and catheter ablation groups, respectively),[10] suggesting that the reduction in AF burden was important for improving the clinical course of AF in HFrEF. In addition, Sugumar et al[33] reported that successful rhythm control after catheter ablation reversed heart failure symptoms or the adverse hemodynamic state of HFpEF. According to the Japanese multicenter cohort study of patients with AF after catheter ablation, freedom from AF recurrence after catheter ablation was independently associated with a lower risk of cardiac adverse events or death.[13] Reducing AF burden by successful catheter ablation may improve the adverse hemodynamic state, leading to a reduced risk of heart failure or cardiovascular death in the AF population. In the present study with HFmrEF and HFpEF, the incidence of cardiovascular death or hospitalization for

heart failure tended to be lower in the successful than unsuccessful ablation group, which may also support the importance of reducing the AF burden to improve patient outcomes.

Study Limitations

Our study has some limitations. First, it was not free from the intrinsic limitations of retrospective analyses. It is possible that group differences in the baseline characteristics remained after propensity score matching. In particular, information on alcohol intake, smoking, polypharmacy, and frailty was not available, and these characteristics were not adjusted between the 2 groups. Therefore, the causal relationship between the lower incidence of the primary endpoint and catheter ablation is unclear. Second, because we included 11 covariables in the propensity score matching, the sample size of the propensity-matched cohorts became relatively small, which may have produced bias and compromised the statistical power of the study. The question of how to select covariates in propensity score matching is still open. Finally, we did not assess the medical therapy for heart failure, which may have affected the incidence of cardiovascular events.

Conclusions

Catheter ablation for AF in patients with HFmrEF or HFpEF was associated with a significantly lower incidence of cardiovascular death and hospitalization for heart failure compared with medical therapy.

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IRB Information

The AF Frontier Ablation Registry was approved by the Institutional Review Board (IRB) of Nihon University Itabashi Hospital, the Clinical Research Judging Committee (No. RK-161213-06), and the IRBs of participating hospitals. The Hokuriku-Plus AF Registry was approved by the Ethics Committee for Medical Research of Kanazawa University Graduate School of Medical Science (1394-4) and by the participating hospitals.

Data Availability

The deidentified participant data will not be shared.

References

1. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation* 2003; **107:** 2920–2925.
2. Kuronuma K, Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Oiwa K, et al. Worsening renal function, adverse clinical events and major determinants for changes of renal function in patients with atrial fibrillation: A Japanese multicenter registry substudy. *Curr Med Res Opin* 2019; **35:** 2007–2013.
3. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. *Eur Heart J* 2016; **37:** 2882–2889.
4. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, et al. Causes of death in Japanese patients with atrial fibrillation: The Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019; **5:** 35–42.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; **22:** 983–988.
6. Verhaert DVM, Brunner-La Rocca HP, van Veldhuisen DJ, Vernooy K. The bidirectional interaction between atrial fibrillation and heart failure: Consequences for the management of both diseases. *Europace* 2021; **23:** ii40–ii45.
7. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009; **11:** 676–683.
8. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; **358:** 2667–2677.
9. Ravi V, Poudyal A, Lin L, Larsen T, Wasserlauf J, Trohman RG, et al. Mortality benefit of catheter ablation versus medical therapy in atrial fibrillation: An RCT only meta-analysis. *J Cardiovasc Electrophysiol* 2022; **33:** 178–193.
10. 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.
11. Okumura Y, Nagashima K, Arai M, Watanabe R, Yokoyama K, Matsumoto N, et al. Current status and clinical outcomes of oral anticoagulant discontinuation after ablation for atrial fibrillation in Japan: Findings from the AF Frontier Ablation Registry. *Circ J* 2019; **83:** 2418–2427.

12. Iso K, Nagashima K, Arai M, Watanabe R, Yokoyama K, Matsumoto N, et al. Clinical outcomes of ablation versus non-ablation therapy for atrial fibrillation in Japan: Analysis of pooled data from the AF Frontier Ablation Registry and SAKURA AF Registry. *Heart Vessels* 2021; **36:** 549–560.
13. Usuda K, Kato T, Tsuda T, Tada H, Niwa S, Usui S, et al. Impact of sinus rhythm maintenance on major adverse cardiac and cerebrovascular events after catheter ablation of atrial fibrillation: Insights from AF Frontier Ablation Registry. *Heart Vessels* 2022; **37:** 327–336.
14. Watanabe R, Nagashima K, Wakamatsu Y, Otsuka N, Yokoyama K, Matsumoto N, et al. Different determinants of the recurrence of atrial fibrillation and adverse clinical events in the mid-term period after atrial fibrillation ablation. *Circ J* 2022; **86:** 233–242.
15. Hayashi K, Tsuda T, Nomura A, Fujino N, Nohara A, Sakata K, et al. Impact of B-type natriuretic peptide level on risk stratification of thromboembolism and death in patients with nonvalvular atrial fibrillation: The Hokuriku-Plus AF Registry. *Circ J* 2018; **82:** 1271–1278.
16. Tsuda T, Hayashi K, Fujino N, Konno T, Tada H, Nomura A, et al. Effect of hypertrophic cardiomyopathy on the prediction of thromboembolism in patients with nonvalvular atrial fibrillation. *Heart Rhythm* 2019; **16:** 829–837.
17. Yamagishi M, Tsuda T, Kato T, Furusho H, Hayashi K. Cost-effectiveness for prevention of thromboembolism by anticoagulants in non-valvular atrial fibrillation: Additional analysis from the Hokuriku-Plus AF Registry. *Heart Vessels* 2019; **34:** 1024–1030.
18. Tsuda T, Hayashi K, Kato T, Usuda K, Kusayama T, Nomura A, et al. Clinical characteristics, outcomes, and risk factors for adverse events in elderly and non-elderly Japanese patients with non-valvular atrial fibrillation: Competing risk analysis from the Hokuriku-Plus AF Registry. *Circ Rep* 2022; **4:** 298–307, doi:10.1253/circrep.CR-22-0012.
19. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure: Digest version. *Circ J* 2019; **83:** 2084–2184.
20. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. *Chest* 2010; **137:** 263–272.
21. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31–41.
22. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; **48:** 452–458.
23. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355:** 251–259.
24. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 study. *Circ J* 2011; **75:** 823–833.
25. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2017; **5:** 565–574.
26. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, et al. Ablation versus drug therapy for atrial fibrillation in heart failure: Results from the CABANA Trial. *Circulation* 2021; **143:** 1377–1390.
27. 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 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018; **39:** 4277–4284.
28. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: Vicious twins. *J Am Coll Cardiol* 2016; **68:** 2217–2228.
29. Kaye DM, Silvestry FE, Gustafsson F, Cleland JG, van Veldhuisen DJ, Ponikowski P, et al. Impact of atrial fibrillation on rest and exercise haemodynamics in heart failure with mid-range and preserved ejection fraction. *Eur J Heart Fail* 2017; **19:** 1690–1697.
30. Fukui A, Tanino T, Yamaguchi T, Hirota K, Saito S, Okada N, et al. Catheter ablation of atrial fibrillation reduces heart failure rehospitalization in patients with heart failure with preserved ejection fraction. *J Cardiovasc Electrophysiol* 2020; **31:** 682–688.
31. Rattka M, Kühberger A, Pott A, Stephan T, Weinmann K, Baumhardt M, et al. Catheter ablation for atrial fibrillation in HFpEF patients: A propensity-score-matched analysis. *J Cardiovasc Electrophysiol* 2021; **32:** 2357–2367.
32. Nogami A, Kurita T, Kusano K, Goya M, Shoda M, Tada H, et al. JCS/JHRS 2021 guideline focused update on non-pharmacotherapy of cardiac arrhythmias. *Circ J* 2022; **86:** 337–363.
33. Sugumar H, Nanayakkara S, Vizi D, Wright L, Chieng D, Leet A, et al. A prospective STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF: STALL AF-HFpEF. *Eur J Heart Fail* 2021; **23:** 785–796.
34. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-induced cardiomyopathies: Mechanisms, recognition, and management. *J Am Coll Cardiol* 2015; **66:** 1714–1728.
35. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vutthikraivit W, et al. Atrial fibrillation is associated with sudden cardiac death: A systematic review and meta-analysis. *J Interv Card Electrophysiol* 2018; **51:** 91–104.
36. Poole JE, Bahnson TD, Monahan KH, Johnson G, Rostami H, Silverstein AP, et al. Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the CABANA Trial. *J Am Coll Cardiol* 2020; **75:** 3105–3118.

Supplementary Files

Please find supplementary file(s);
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