Long-term prognosis of patients undergoing radiofrequency catheter ablation for atrial fibrillation: Comparison between heart failure subtypes based on left ventricular ejection fraction

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INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) frequently coexist. AF occurs in over half of individuals with HF and HF occurs in over one-third of those with AF.[1] In patients with HF, AF is a major risk factor for a poor prognosis.[2] European Society of Cardiology (2016) guidelines classify HF into three subtypes based on left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF), LVEF of <40%; HF with mid-range EF (HFmrEF), 40% ≤LVEF <50%; and HF with preserved EF (HFpEF), LVEF of ≥50%.[3] The effect of LVEF on the prognosis of HF is controversial. Many reports state that HFrEF and HFpEF have similar mortality rates,[4,5] whereas others report patients with HFrEF have higher mortality rates than those with HFpEF,[6] although this difference is small.[7] Sartipy et al.[8] demonstrated HF patients with AF have a worse prognosis than those without AF, regardless of HF subtype. Furthermore, the detection and treatment of AF are important in all patients with HF.

Radiofrequency catheter ablation (RFCA) can reduce the frequency of AF and is widely accepted as a standard treatment, resulting in prolonged arrhythmia-free survival, improved quality of life, and lower risk of stroke.[9,10] Furthermore, RFCA for AF improved the prognosis of patients with HF[11]; however, the responsible factors have not yet been fully identified.

Here, we compared the long-term prognosis of patients undergoing RFCA for AF according to HF subtype.

METHODS

Study design and setting

The present study was a sub-analysis of the Kansai plus atrial fibrillation (KPAF) registry, a physician-initiated, non-company-sponsored, all-case registration, multicentre study of RFCA for AF, including two prospective randomised trials, UNDER-ATP[12] and EAST-AF,[13] and observational trials (ClinicalTrials.gov: NCT01477983). One observational study has already been published.[14] The KPAF registry and our sub-analysis study were approved by the institutional review board of each participating centre and conducted according to the principles of the Declaration of Helsinki.

Consent

Written informed consent to participate in the KPAF registry was obtained from all participants. Consent to participate in our sub-analysis study was obtained using an opt-out procedure. The full methodology of the KPAF registry is described in detail elsewhere.[12,13]

Study population

The KPAF registry enrolled patients from 26 cardiovascular centres, mostly located in the Kansai region of Japan, who underwent first-time RFCA for AF between November 2011 and March 2014. The age range of 5010 eligible patients was 19–90 years. Paroxysmal AF was defined as transient AF terminating spontaneously or after introducing antiarrhythmic drugs (AADs) within one week of onset. Persistent AF was defined as AF lasting from one week to one year and long-lasting AF as AF lasting for more than one year. Early rhythm control (ERC) was defined as AF diagnosed ≤12 months before RFCA.

The inclusion criterion was HF diagnosed by cardiologists at each institution plus a documented history of HF. HF was defined as a syndrome characterised by symptoms such

as shortness of breath at rest, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea and/or fatigue, signs of fluid retention such as pulmonary congestion or ankle swelling, and objective evidence of abnormalities of cardiac structure or function at rest. Echocardiography was performed before RFCA, and HF was classified as HFrEF (<40%), HFmrEF (40%–49%), and HFpEF (≥50%) LVEF. The exclusion criterion was a lack of transthoracic echocardiography baseline data. We sub-analysed 656 patients with HF (HFrEF n=98, HFmrEF n=107, HFpEF n=451). A flowchart of the present study is shown in *Figure 1*.

Ablation procedure

All ablation procedures were performed according to KPAF registry guidelines.[12,13] Briefly, the standard methods of pulmonary vein (PV) isolation at participating centres included extensive encircling PV isolation using a three-dimensional mapping system (CARTO, Biosense-Webster, Diamond Bar, CA, USA; EnSite NavX, St Jude Medical, St Paul, MN, USA). Decisions concerning additional ablation, including tricuspid valve isthmus ablation, continuous fractionated atrial electrogram ablation, left atrium (LA) linear ablation, and ganglionated plexi ablation, were at the discretion of the operator and/or the attending cardiologist. Generally, AADs were continued or started after early recurrence. Repeat procedures were permitted for recurrence beyond the 3 months post-index procedure.

Clinical evaluation at baseline and follow-up

At baseline, patients' demographic data, cardiovascular histories, coronary risk factors, and medications were recorded. Symptoms of HF were evaluated using the New York Heart Association (NYHA) classification. Blood samples were collected, and echocardiography performed before RFCA. Creatinine clearance (CCr) was calculated according to Cockcroft's

formula. The modified Simpson method and/or Teichholz method was used to measure LVEF, the former being preferred. We devised the following protocol to accurately detect recurrence of atrial tachyarrhythmias. The participating patients: 1) attended outpatient departments of participating facilities for follow-up 3, 6, 12, 24, 36, 48, and 60 months after discharge, undergoing 12-lead electrocardiogram (ECG) at every visit and 24-hour Holter monitoring at 6, 12, 24, 36, 48, and 60 months; 2) received a mobile ECG self-monitoring system (HCG-801, Omron Healthcare, Kyoto, Japan) on discharge and were instructed to record their ECG when they had cardiac symptoms, including palpitations and dyspnoea; and 3) visited outpatients when their symptoms persisted. Echocardiography was performed at 3, 6, 12, 24, 36, 48, and 60 months.

Endpoints

The primary endpoint was a composite of all-cause death, hospitalisation for HF, and stroke or systemic embolism after RFCA. The secondary endpoint was recurrence of atrial tachyarrhythmias, with a 90-day blanking period. Atrial tachyarrhythmia recurrence was defined as arrhythmia lasting >30 seconds or requiring repeat ablation, cardioversion, hospital admission, or start of Vaughan Williams class I or III AADs after the blanking period. Repeat ablation was discouraged during the blanking period; thus, if required, recurrent atrial tachyarrhythmias was diagnosed. When repeat ablation was performed within the blanking period of 90 days post-ablation, the patient was considered as having recurrent atrial tachyarrhythmias at Day 91. Cardiovascular (CV) death was defined as death due to HF, sudden cardiac death, myocardial infarction, ischaemic stroke, peripheral vascular disease, or perioperative complications.

Statistical analysis

Categorical variables are expressed as value (percentage) and continuous as mean ± standard

deviation or median and interquartile range with a skewed distribution. Data distribution was analysed using the Shapiro–Wilk W-test. Differences in categorical variables were evaluated using Pearson's χ^2 or Fisher's exact tests, and multiple comparisons were performed using the Benjamini–Hochberg procedure. Differences in continuous variables were evaluated using analysis of variance or Kruskal–Wallis tests based on their distribution. Multiple comparisons were performed using Tukey's or the Steel–Dwass test. Cumulative incidence was evaluated using the Kaplan–Meier method and differences between groups using the log-rank test. Predictors of the primary endpoint were evaluated using univariate and multivariate Cox proportional analysis. Given that primary endpoints occurred in 91 patients, we performed multivariate analysis to adjust for baseline differences, using only 10 variables to avoid overfitting in Cox hazard models. We reviewed published studies to inform our selection of the following 10 variables relevant to our composite endpoint. The following variables were chosen on the basis that they differed significantly among the three groups: age ≥65 years, male sex, paroxysmal AF, CCr <50 mL/min, ischaemic heart disease (IHD), cardiomyopathies, valvular heart disease (VHD), CHA_2Ds_2-VASc score ≥4, recurrent atrial tachyarrhythmias, and HFrEF.

All analyses were performed using JMP 13.0.0 (SAS Institute, Cary, NC, USA). Probability values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Patients' baseline characteristics are summarised in *Table 1*. The proportion of men and patients classified as NYHA class IV was greater in the HFrEF than in the HFpEF group. Patients with HFrEF had a lower prevalence of hypertension than those with HFpEF. Patients

with HFpEF had a higher prevalence of paroxysmal AF than those with HFmrEF. However, the median years since AF diagnosis and the rate of ERC were not significantly different in the three groups.

The prevalence of IHD and cardiomyopathies was higher for patients with HFrEF than those with HFpEF (IHD: 27.6% vs. 10.0%, respectively, $P<0.05$; cardiomyopathies: 36.7% vs. 15.3%, respectively, $P<0.05$). CHA_2DS_2-VASc scores and their distribution were similar among the groups. Patients with HFrEF had a larger mean LA diameter than those with HFpEF (45.9 ± 7.1 mm vs. 42.9 ± 6.7 mm, respectively, $P<0.05$). After ablation, there were no significant differences in the use of AADs among the groups. Class III AADs (including amiodarone, sotalol, and bepridil), β-blockers, and aldosterone antagonists were more frequently used in patients with HFrEF compared with patients with HFpEF. The prevalence of cardiac resynchronisation therapy with defibrillator (CRT-D) was higher for patients with HFrEF than for those with HFpEF (4.1% vs. 0.0%, respectively, $P<0.05$). However, the prevalence of implantable cardioverter defibrillator (ICD) was similar among the groups.

Procedural characteristics and complications

Procedural characteristics and complications are presented in *Table 2*. Successful PV isolation was achieved in 96.3% of patients. There were no significant differences in the utilisation rate of tricuspid valve isthmus ablation, superior vena cava ablation, non-PV foci ablation, complex fractionated electrogram ablation, ganglionated plexus ablation, and LA roofline ablation procedures between the three groups. However, ablation at the mitral isthmus line was more frequently performed in patients with HFrEF compared with those with HFpEF (19.4% vs. 8.2%, respectively, $P<0.05$). The total number of energy applications and total procedure time were both greater in patients with HFrEF compared with patients with HFpEF.

In-hospital HF and protracted low blood pressure (systolic blood pressure <90 mmHg or requiring catecholamines) occurred more frequently in patients with HFrEF compared with patients with either HFmrEF or HFpEF (in-hospital HF: 6.1% vs. 0% and 0.9%, respectively, $P<0.001$; low blood pressure: 8.2% vs. 1.9% and 2.2%, respectively, $P=0.006$). There were no significant differences in rates of other complications, including death, cardiac tamponade, pericardial effusion, pericarditis, and stroke.

Repeat ablation and medication at final follow up

The mean number of ablation procedures per patient was similar among the three groups (1.27 ± 0.53, 1.27 ± 0.52, and 1.29 ± 0.57 in patients with HFrEF, HFmrEF, and HFpEF, respectively, $P=0.95$). Oral anticoagulant therapy was continued in many patients (75.5%, 67.3%, and 64.5% of patients with HFrEF, HFmrEF, and HFpEF, respectively, $P=0.111$). Patients with HFrEF received AADs more frequently than patients with HFpEF (39.8% vs. 22.8%, respectively, $P<0.05$) at final follow up.

Primary and secondary endpoints

During the median follow-up period of 1059 days (first-to-third quartile: 858–1228 days), all patients were successfully followed up until a primary endpoint occurred or until the end of the study. The 3-year cumulative risk for the primary endpoint was higher in patients with HFrEF compared with those with HFmrEF or HFpEF (32.7%, 11.7% vs. 11.6%, $P<0.001$, *Figure 2A)*.

The rate of recurrent atrial tachyarrhythmias was similar among the groups (48.2%, 42.8%, and 47.3%, respectively, $P=0.75$) at 3 years (*Figure 2B*). Furthermore, there were no differences in cardiac rhythm, including sinus rhythm, paroxysmal and fixed atrial tachyarrhythmias among the three groups during final follow-up (*Supplementary Table S1)*. Regarding AF subtypes, the 3-year cumulative incidence of recurrent atrial tachyarrhythmias

was significantly higher in patients with long-lasting persistent AF compared with paroxysmal and persistent AF (65.1% vs. 40.2% and 44.3%, $P<0.0001$, *Supplementary Figure S1*).

The 3-year cumulative incidence of all-cause mortality (HFrEF, HFmrEF vs. HFpEF, 9.5%, 3.2% vs. 3.9%, log-rank $P=0.009$), cardiovascular death (4.4%, 1.2% vs. 1.4%, log-rank $P=0.038$), and hospitalisation for HF (27.3%, 6.6% vs. 7.1%, log-rank $P<0.001$) were higher in patients with HFrEF (*Figure 3A, B and C*). The rate of stroke or systemic embolism was similar among all groups (1.1%, 1.9%, and 2.0%, respectively, $P=0.81$) at 3 years (*Figure 3D*). The endpoint analysis is shown in *Table 3*. CV death occurred significantly more frequently in patients with HFrEF compared with patients with HFmrEF and HFpEF, as shown by the log-rank test ($P=0.038$); however, this difference was not confirmed by Pearson's χ^2 test ($P=0.051$).

Cox proportional hazards regression analysis for the primary and secondary endpoints

Hazard ratios (HR) for the association between HFrEF and the primary composite endpoint are shown in *Table 4*. Multivariate Cox proportional hazards regression analysis identified the following significant risk factors for the primary composite endpoint: age ≥65 years, male sex, paroxysmal AF, CCr <50 mL/min, IHD, cardiomyopathies, VHD, CHA_2DS_2-VASc score ≥4, recurrent atrial tachyarrhythmias, and HFrEF. The highest HRs were observed for HFrEF (HR, 2.83; 95% confidence interval 1.74–4.61, $P<0.001$). Furthermore, a sensitivity analysis excluding patients with NYHA III and IV, performed because the distribution of NYHA differed between patients with HFrEF versus HFpEF showed that the primary composite endpoint and hospitalisation for HF occurred more frequently in patients with HFrEF compared with patients with HFmrEF and HFpEF (composite endpoint: $P<0.001$; hospitalisation: $P<0.001$ by log-rank test) (*Figure 4*).

The composite endpoint in the subgroups of interest is shown in Supplementary Figure S2. HRs and *P*-values for interactions were based on Cox logistic-regression analyses. There

was no significant interaction between subgroups, including paroxysmal, persistent, and long-lasting persistent AF.

Multivariate Cox proportional hazards regression analysis revealed that non-ERC and LA diameter ≥45 mm were independently associated with recurrence of atrial tachyarrhythmias (*Supplementary Table S2*).

DISCUSSION

To the best of our knowledge, this is the first study to compare the long-term prognosis of patients undergoing radiofrequency CA for AF according to HF subtype. The main findings are as follows: (1) the primary composite endpoint of all-cause death, hospitalisation for HF, and stroke or systemic embolism occurred more commonly in patients with HFrEF compared with HFmrEF and HFpEF, whereas the secondary endpoint of recurrent atrial tachyarrhythmias was similar among the three groups; (2) the most significant risk factor for the primary composite endpoint was HFrEF; (3) CV death occurred significantly more frequently in patients with HFrEF compared with patients with HFmrEF and HFpEF, as

shown by the Kaplan–Meier curve and log-rank test; however, this difference was not confirmed by Pearson's χ^2 test; (4) successful PV isolation was achieved in almost all patients with HF, and the mean number of ablation procedures per patient was similar between the three groups; and (5) after ablation, in-hospital HF and protracted low blood pressure occurred more frequently in patients with HFrEF compared with patients with HFmrEF or HFpEF.

HF can trigger AF through structural and hemodynamic changes in the LA, such as dilatation, elevated pressure, and fibrosis caused by LV dysfunction.[15] AF can impair LV performance through the loss of LA contraction. Sartipy et al.[8] reported an association between AF and higher risk of all-cause death, hospitalisation for HF, and stroke or transient ischaemic attack in patients with HF, independent of LVEF. Thus, we consider that maintaining sinus rhythm is preferable.

Mortality rates were reported to be similar between patients with HFrEF and HFpEF in earlier studies in which not all patients had undergone CA.[4,5] In our study, CA was performed in all patients with HF and AF and the long-term prognosis after CA was poorest in patients with HFrEF compared with HFmrEF and HFpEF. Particularly, the rate of hospitalisation for HF was higher in patients with HFrEF compared with patients with HFpEF. A simple reason for the discrepancy between earlier studies and ours might be that CA affects the prognosis. Treatment with CA might improve the prognosis more in patients with HFpEF and HFmrEF than those with HFrEF. To the best of our knowledge, only one report has evaluated the effect of CA on all-cause hospitalisation and all-cause mortality in patients with HF, which showed a similar prognosis in patients with EF <50% and those with EF ≥50% after CA.[16] These findings were not consistent with ours. However, an explanation for this is not clear. We should wait for large-scale prospective studies because the present study was a post-hoc hypothesis-generating analysis. The prescription rate of β-blockers and renin-angiotensin-

aldosterone system blockers were lower in the present study than in other clinical trials and registries targeting HFrEF. This might be another reason why the prognosis of HFrEF patients was poorer than those of HFmrEF or HFpEF patients in the present study.

However, this result does not rule out the effectiveness of CA for AF in patients with HFrEF. The CASTLE-AF study was a multicentre, randomised trial of CA and drug therapy for AF in 363 patients with HFrEF of NYHA II–IV and LVEF of <35% transplanted with an ICD. The composite primary endpoint of all-cause death and hospitalisation for HF was significantly lower in the ablation group versus the drug-treated group.[11] Furthermore, CA for AF improved symptom severity and NYHA functional class at 12 months in patients with HFrEF.[17] These findings indicate that CA for AF is effective in patients with HFrEF. From these studies, we would like to emphasise that patients with HFrEF should be followed up more carefully than those with HFmrEF and HFpEF after CA for AF. To improve the prognosis of patients with HFrEF, we must consider other treatments besides CA, such as cardiac resynchronisation therapy and drug regulation.

Regarding predictors of the primary endpoint, paroxysmal AF but not persistent and chronic AF, was a significant predictor in the present study, in contrast to the general perception that persistent or chronic AF are associated with worse prognosis. However, in the present study, all HF patients had undergone CA, so the effect of subtype of AF before CA on prognosis might be different from that in patients without CA. The relatively small sample size of each subtype of AF in the present study suggests sampling bias might have affected our results. Therefore, further studies with a larger sample size are needed to confirm the effect of preceding AF subtype on the prognosis of patients with HF and AF ablation. Recurrent atrial tachyarrhythmias were a significant predictor for the primary endpoint, but the cumulative incidence of recurrence of atrial tachyarrhythmia in all preceding AF categories and each subtype of preceding AF categories was similar among the three HF subtypes. Recently, AF

burden after CA was reported to be an important factor for prognosis.[19] Unfortunately, the present study included only 41 patients (6%) who received device therapy. Therefore, we could not evaluate the effect of AF burden on the prognosis.

To understand the long-term success of CA, we performed multivariate analysis of factors for recurrent atrial tachyarrhythmias after CA (*Supplementary Table S2*). Most significant predictors were hard to be intervened, but ERC was the sole intervention factor. As shown in a recent study[20] and considering our results, early CA should be recommended for HF patients who have had a recent onset of AF. The use of AADs after CA was not regulated by the protocol, so that approximately half of the patients took AADs, some of which are contraindicated for HFrEF. However, treatment with AADs was not associated with the primary endpoint (data not shown) or recurrence of atrial tachyarrhythmia. Therefore, AADs are not recommended for HF patients after CA.

Limitations

The present study was subject to the limitations of a registry analysis. First, this was a post-hoc sub-analysis of the KPAF study, which initially enrolled patients who underwent CA. Therefore, the diagnosis of HF was not strictly defined but made by attending cardiologists based on subjective findings, including clinical symptoms, signs, and laboratory findings. Second, unmeasured factors might have caused residual confounding despite confounding factors being adjusted for where possible. Third, the study population was small, especially in the HFrEF group, which may have widened the confidence interval. Fourth, the NYHA distribution differed between patients with HFrEF, HFmrEF, and HFpEF. Fifth, 114 patients were excluded because of a lack of echocardiographic data at baseline. Sixth, the study protocol did not specify criteria for treatments such as additional AF ablation and AAD administration, these decisions being left to the attending cardiologists. Seventh, the study cohort was almost

completely composed of East Asian individuals, and racial bias may have influenced the study results. Finally, a contact force-sensing catheter was not used. Further investigations are required to overcome these limitations and to clarify our observations.

CONCLUSIONS

The present study suggests a hypothesis whereby patients with HFrEF and AF have approximately 3 times higher risk for a composite of all-cause death, HF hospitalisation, and stroke or systemic embolism after AF ablation compared with patients with HFmrEF or HFpEF.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY

The data underlying this article were accessed from Kyoto University Graduate School of Medicine and the Research Institute for Production Development in Kyoto, Japan. The

derived data generated in this research will be shared on reasonable request to the corresponding author.

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. 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.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, AJS Coats, et al., for the ESC Scientific Document Group. 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.

4. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260–269.

5. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC Heart Fail 2018; 6:678–685.

6. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al., for the Heart Failure Association of the European Society of Cardiology (HFA). EURObservational research programme: regional differences and 1-year follow-up results

of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013; 15: 808–817.

7. 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.

8. 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.

9. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al., for the CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA 2019; 321: 1275–1285.

10. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. Eur Heart J 2016; 37: 2478–2487.

11. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al., for the CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018; 378: 417–427.

12. Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, et al., for the UNDER-ATP Trial Investigators. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine Triphosphate (UNDER-ATP) trial. Eur Heart J 2015; 36: 3276–3287.

13. Kaitani K, Inoue K, Kobori A, Nakazawa Y, Ozawa T, Kurotobi T, et al., for the EAST-AF Trial Investigators. Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation (EAST-AF) trial. Eur Heart J 2016; 37: 610–618.

14. Tanaka N, Inoue K, Kobori A, Kaitani K, Morimoto T, Kurotobi T, et al. Sex differences in atrial fibrillation ablation outcomes: insights from a large-scale multicentre registry. Europace 2020; 22: 1345–1357.

15. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation 1999; 100: 87–95.

16. Aldaas OM, Malladi CL, Mylavarapu PS, Lupercio F, Darden D, Han FT, et al. Comparison of outcomes after ablation of atrial fibrillation in patients with heart failure with preserved versus reduced ejection fraction. Am J Cardiol 2020; 136: 62–70.

17. 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.

18. Koitabashi T, Inomata T, Niwano S, Nishii M, Takeuchi I, Nakano H, et al. Paroxysmal atrial fibrillation coincident with cardiac decompensation is a predictor of poor prognosis in chronic heart failure. Circ J 2005; 69: 823–830.

19. Brachmann J, Sohns C, Andresen D, Siebels J, Sehner S, Boersma L, et al. Atrial fibrillation burden and clinical outcomes in heart failure: The CASTLE-AF Trial. JACC Clin Electrophysiol 2021; S2405–500X(20)31208-1.

20. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al., EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 2020; 383: 1305–1316.

FIGURE LEGENDS

Figure 1. Flowchart of patients.

KPAF = Kansai plus atrial fibrillation registry.

Figure 2. Kaplan–Meier curves stratified by the three ejection fraction groups for the cumulative incidence of (A) the composite endpoint (all-cause death, hospitalisation for heart failure, and stroke or systemic embolism) and (B) the secondary endpoint (recurrent atrial tachyarrhythmias with a 90-day blanking period post-ablation).

Figure 3. Kaplan–Meier curves stratified by the three ejection fraction groups for the cumulative incidence of (A) all-cause death, (B) cardiovascular death, (C) hospitalisation for heart failure, and (D) stroke or systemic embolism.

Figure 4. Kaplan–Meier curves stratified by the three ejection fraction groups for the cumulative incidence of (A) the composite endpoint of all-cause death, hospitalisation for heart failure, and stroke or systemic embolism, and (B) hospitalisation for heart failure, excluding NYHA III and IV.

Supplementary Figure S1. Kaplan–Meier curves stratified by the three ejection fraction groups for the cumulative incidence of the composite endpoint of all-cause death, hospitalisation for heart failure, and stroke or systemic embolism, divided into paroxysmal, persistent, and long-lasting atrial fibrillation.

Supplementary Figure S2. Subgroup analyses of the composite end point.