



Clinical outcomes and structural remodelling after ablation of atrial fibrillation in heart failure with mildly reduced or mid-range ejection fraction

Dan-Ying Lee^{1,2,3} , Ting-Yung Chang^{1,2,3,4*} , Shih-Lin Chang^{1,2,3*}, Yenn-Jiang Lin^{1,2,3}, Li-Wei Lo^{1,2,3}, Yu-Feng Hu^{1,2,3}, Fa-Po Chung^{1,2,3}, Ta-Chuan Tuan^{1,2,3}, Tze-Fan Chao^{1,2,3}, Jo-Nan Liao^{1,2,3}, Chin-Yu Lin^{1,2,3}, Ling Kuo^{1,2,3}, Chih-Min Liu^{1,2,3} and Shih-Ann Chen^{1,2,3,5}

¹Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ²Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan; ³Institute of Clinical Medicine, and Cardiovascular Research Institute, National Yang Ming Chiao Tung University, Taipei, Taiwan; ⁴National Taipei University of Nursing and Health Sciences, Taipei, Taiwan; and ⁵Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan

Abstract

Aims The efficacy of catheter ablation (CA) on clinical outcomes and cardiac structural remodelling in atrial fibrillation (AF) patients with HF with mildly reduced or mid-range ejection fraction (HFmrEF) remains unclear. We aimed to compare the efficacy of CA with medical therapy (MT) in AF patients with HFmrEF.

Methods and results We retrospectively screened a total of 36 879 patients with AF between 2005 and 2020. Patients who were initially diagnosed with echocardiography-proved HFmrEF and had follow-up echocardiography were enrolled. After applying propensity score matching in a 1:1 ratio, 72 patients treated by CA (Group 1) and 72 patients receiving MT (Group 2) were taken into further analysis. The co-morbidities were similar between the two groups, except for hyperlipidaemia. After a mean follow-up duration of 58.9 ± 42.6 months, Group 1 had a lower HF hospitalization and all-cause mortality compared with Group 2 (hazard ratio (HR), 0.089 [95% confidence interval (CI), 0.011–0.747]; *P* = 0.026 and HR, 0.121 [95% CI, 0.016–0.894]; *P* = 0.038, respectively). As for cardiac structural remodelling, the Group 1 had a better improvement in left ventricular ejection fraction (LVEF) and a more decreased left atrium (LA) diameter than Group 2 (+25.0% ± 18.0% vs. +6.2% ± 21.6%, *P* = <0.0001 and −1.6 ± 4.7 mm vs. +1.5 ± 8.2 mm, *P* = 0.008, respectively).

Conclusions In patients with HFmrEF and AF, CA of AF could reduce both HF hospitalization and all-cause mortality as compared with those with MT. A significant improvement in LVEF and decrease in LA diameter were also observed in the CA group. Early rhythm control with CA should be taken into consideration in patients with HFmrEF and AF.

Keywords Ablation; Atrial fibrillation; Heart failure; Mildly reduced ejection fraction; Outcome

Received: 22 June 2022; Revised: 2 September 2022; Accepted: 15 September 2022

*Correspondence to: Ting-Yung Chang and Shih-Ling Chang, Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shipai Road, Beitou District, Taipei 112, Taiwan. Tel: 886-2-2875-7156; +886-2-7735-3832; Fax: 886-2-2873-5656 and +886-2-2872-4082. Email: tingyungchang@gmail.com; slchang4@vghtpe.gov.tw

Introduction

In 2016, the concept of heart failure with mildly reduced or mid-range ejection fraction (HFmrEF) between 40% and 49% was established in the European Society of Cardiology (ESC) guideline,¹ which accounts for 10% to 24% of patients with heart failure (HF).² As one of the phenotypes of HF, HFmrEF not only resembles HF with reduced ejection fraction (HFrEF) regarding age, sex, ischaemic aetiology, and systolic

pressure but also has a similar clinical prognosis and pathophysiological mechanism.^{2,3} So far, there is still no efficient treatment with robust evidence to reduce morbidity and mortality in the patients with HF with preserved ejection fraction (HFpEF) and HFpEF⁴ even though they made up nearly half of HF hospitalization.⁵

Atrial fibrillation (AF) is the most common arrhythmia in patients with HF with an average prevalence of 25%⁶ and associated with higher morbidity and mortality.⁷ AF and HF

often coexist and influence each other, which develops an endless vicious cycle towards further worsening HF symptom and therefore lead to unpleasant clinical outcomes.⁸ The majority of therapy for AF targeted at the population with HF_rEF and the benefit of catheter ablation (CA) to lower mortality in the same population has also been established in several small randomized studies including the seminal CASTLE-AF trial, AATAC trial, and the subgroup analysis of the CANABA trial.^{9–11} Although patients with increasing left ventricular ejection fraction (LVEF \geq 40%) have a higher prevalence of AF than HF_rEF¹² and are associated with similar adverse event rates including death, HF hospitalization, and stroke.¹³ The effective therapeutic strategies for AF focusing on the patients with HF_mrEF as compared with medical therapy (MT) are still lacking. In this study, we aimed to investigate the clinical outcomes and cardiac structural remodelling in patients with HF_mrEF undergoing CA of AF, and compared with those with MT.

Method

Study population

Between 15 June 2005 and 18 February 2020, we retrospectively screened a total of 36 879 patients with AF documented in 12-lead electrocardiogram or 24 h Holter recordings who were admitted to Taipei Veterans General Hospital or follow-up in our clinics. The exclusion criteria were (1) congenital heart disease; (2) severe valvular disease; (3) patients with LVEF $<$ 40% or \geq 50%; and (4) patients lacking follow-up

echocardiography after CA or MT. According to the previous meta-analysis of AF ablation in HF, the HF hospitalization was 16% with CA and 39% with MT.¹⁴ With these anticipated incidences, the minimum number of subjects was 58 for each group for a 1:1 ratio propensity score matching with 5% type I error and 80% power.¹⁵ Propensity score analysis was used to adjust for three confounding factors, including age, gender, and LVEF. They were matched with a 1:1 ratio, which resulted in two balanced groups (72 patients in Group 1 that received CA of AF and 72 patients in Group 2 that received MT). The selection process is depicted in *Figure 1*. AF was defined according to the statement from the 2017 Heart Rhythm Society Expert consensus document.¹⁶

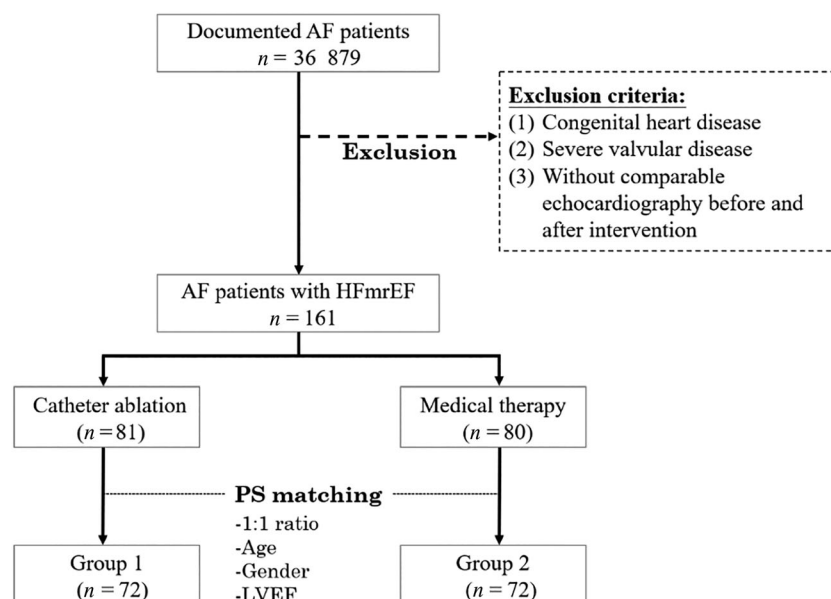
Study design

This retrospective study was conducted at the Taipei Veterans General Hospital in Taipei after approval by the institutional review board of the Taipei Veterans General Hospital (IRB: 2021-11-015BC). The investigation conforms with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii: 177). Both baseline data and echocardiography parameters were collected from the medical records of each patient.

Transthoracic echocardiogram

The baseline echocardiography was performed within 1 year before CA, and the follow-up echocardiography was

Figure 1 Patient allocation and analysis.



performed after CA at least 3 months later in Group 1. Two-dimensional images were got by using an EPIQ CVx (Phillips Healthcare, Andover, USA) or Vivid™ E95 (GE Healthcare, Horten, Norway) with a 2.5–5 MHz Doppler transducer. According to the American Society of Echocardiography recommendations,¹⁷ left ventricle wall thickness and cardiac chamber dimensions including inter-ventricular septal thickness in diastole (IVSd), left ventricular posterior wall thickness in diastole (LVPWd), left ventricular internal diameter in diastole (LVIDD), and left atrium (LA) diameter were measured during M-mode in the parasternal long-axis view. Modified Simpson's rule was used for LVEF calculation, and the septal ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e') was collected to represent LV diastolic function. The RV systolic pressure (RVSP) was measured by adding the TR pressure gradient, which comes from the TR jet and right atrial pressure. The right atrium pressure was measured considering the diameter of the inferior vena cava diameter and determined collapsibility.

The procedure of catheter ablation

Electrophysiological study

An electrophysiological study and CA in the fasting state were performed on each patient after obtaining informed consent. All antiarrhythmic drugs (AADs), except for amiodarone, were discontinued for at least five half-lives before initiation of the procedure. Amiodarone was held 2 weeks before the procedure.

Catheter ablation of paroxysmal and persistent AF

The stepwise procedure of catheter ablation of paroxysmal and persistent AF was achieved, as described in our previous studies.¹⁸ For paroxysmal AF, we performed radiofrequency ablation [wide antral pulmonary vein (PV) isolation] or cryoballoon ablation [wide antral pulmonary vein (PV) isolation]. If the AF persisted after PV isolation, sinus rhythm was restored using electric cardioversion.

For non-paroxysmal AF, wide antral PV isolation was performed. If AF is still sustained after PV isolation, additional linear ablation, CFAE ablation, or posterior box isolation was performed based on the operator's decision. The details had been described in our previous studies.¹⁹ If AF terminated during the linear ablation across the CFAE sites, complete linear ablation to an anatomic obstacle or the nearest line was performed to prevent subsequent arrhythmia. If AF still did not stop after the above procedures, SR was restored by external cardioversion. We then tried to identify the non-pulmonary vein (NPV) focus after the restoration to SR during any step of the ablation procedure or after cardioversion. The endpoint of the non-PV trigger ablation was the disconnection between the superior vena cava and RA as well as

between the coronary sinus and RA, and the elimination of other non-PV ectopic beats with the negative provocation of AF.¹⁹

A right atrial CTI ablation was routinely performed at the end of the paroxysmal or non-paroxysmal AF procedure. Bidirectional conduction block of linear ablation was demonstrated during sinus rhythm.

AADs uses after catheter ablation

After ablation, the AADs were kept during the blanking period and discontinued them after the blanking period if no AF recurrence. AADs may be continued after blanking period based on the operator's concerns about AF recurrence or patient's symptom even no documented AF recurrence.

Outcome assessment

The primary endpoint is HF hospitalization. Other secondary endpoints are all-cause mortality, new stroke, sinus rhythm maintenance, and changes of echocardiography parameters including LVEF and LA diameter. The data on clinical outcomes were obtained from the records of each patient carefully. The beginning of the follow-up period was defined as the point when the final treatment strategy for AF was determined. In Group 1, all patients were followed-up at 2 weeks after CA and every 1–3 months thereafter. The post-ablation follow-up included resting surface 12-lead electrocardiogram, 24 h Holter recordings, and/or cardiac event recording with a recording duration of 1 week performed regularly every 3 months for 1 year and an additional check-up when patients reported clinical symptoms. This was done to evaluate recurrence as suggested by the Heart Rhythm Society Task Force Consensus.²⁰ Transthoracic echocardiography was scheduled after 6 and 12 months of AF ablation. One year after procedures, patients received regular follow-up visits over half a year. As for Group 2, patients treated with MT had regular clinic follow-up with resting surface 12-lead electrocardiogram every 3 months. Transthoracic echocardiography was scheduled after 6 and 12 months of medical treatment, and 24 h Holter monitoring was scheduled to avoid bradycardia.²¹ An additional checkup would be arranged if there has been a deterioration in clinical status.

Statistical analysis

Patient characteristics are expressed as mean \pm standard deviation for continuous variables, and as frequency (percentage) for categorical variables. Continuous and categorical variables were compared using the Student's *t*-test and the χ^2 test with Yates' correction, respectively. Proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. One-way analysis of variance was used to compare data

among two groups. To reduce the treatment-selection bias and potential confounding, we adjusted for age, sex, and LVEF with propensity-score (PS) matching.²² The propensity score was obtained using logistic regression. The HF hospitalization-free and all-cause mortality survival curves were examined using the Kaplan–Meier method with the log-rank test. Cox proportional hazards regression was also used to compare the risk among the two groups, with results expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS 20 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics and demographics

The baseline characteristics and demographics of the two groups (Group 1 vs. Group 2) are shown in *Table 1*. The age (59.49 ± 7.5 vs. 61.53 ± 6.8 years; $P = 0.089$), female sex

Table 1 Baseline demographic and clinical factors between the two groups with AF and HFmrEF

Variable (mean \pm SD or %, $N = 144$)	Group 1 (CA) ($N = 72$)	Group 2 (MT) ($N = 72$)	P
Age (year)	59.49 ± 7.5	61.53 ± 6.8	0.089
Female (%)	15 (20.8)	24 (33.3)	0.091
BMI (kg/m^2)	25.16 ± 3.9	24.37 ± 4.2	0.730
Underlying disease			
HTN (%)	44 (61.1)	35 (48.6)	0.132
DM (%)	8 (11.1)	11 (15.3)	0.460
CAD (%)	11 (15.3)	15 (20.8)	0.386
Hyperlipidaemia (%)	20 (27.8)	7 (9.7)	0.006*
CVA (%)	8 (11.6)	8 (11.6)	0.928
COPD (%)	2 (5.6)	3 (4.2)	0.758
Thyroid disease (%)	11 (15.3)	9 (12.5)	0.630
Persistent AF (%)	42 (58.3)	46 (63.9)	0.494
CHA2DS2_VASc	2.52 ± 1.4	2.96 ± 1.5	0.056
HF and AAD medication			
ACE-I/ARB/ARNI	44 (61.1%)	36 (50.0%)	0.180
Ivabradine	1 (1.4%)	0 (0.0%)	0.316
Beta-blocker	27 (37.5%)	34 (47.2%)	0.238
Amiodarone/dronedronone	31 (43.1%)	33 (45.8%)	0.737
Nondihydropyridine CCB	10 (13.9%)	18 (25.0%)	0.092
Adjunctive ablation strategies beyond PVI			
Linear ablation	19 (26.4%)	N/A	-
Trigger ablation	11 (15.3%)	N/A	-
CFAE ablation	13 (18.1%)	N/A	-

Abbreviations: AD, antiarrhythmic drug; ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CA, catheter ablation; CAD, coronary artery disease; CCB, calcium channel blockers; CFAE, complex fractionated atrial electrograms; COPD; chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetic mellitus; HTN, hypertension; MT, medical therapy; PVI, pulmonary vein isolation.

* P -value < 0.05 .

(20.8% vs. 33.3%; $P = 0.091$), BMI (25.16 ± 3.9 vs. 24.37 ± 4.2 kg/m^2 ; $P = 0.730$), CHA2DS2-VASc score (2.52 ± 1.4 vs. 2.96 ± 1.5 points; $P = 0.056$), AF type (persistent AF 58.3% vs. 63.9%; $P = 0.494$), and the use of HF medications/ADDs were similar between the two groups. Only hyperlipidaemia was more common in the Group 1 (27.8% vs. 9.7%; $P = 0.006$). In Group 1, three patients received cryoballoon ablation and the rest received CA (68 with traditional low-power long-duration ablation and 2 with high-power short-duration). In addition to successful PV isolation, additional ablation strategies including linear, trigger, and CFAE ablation were performed in 26.4%, 15.3%, and 18.1% of patients in Group 1, respectively.

Baseline echocardiography parameters

The echocardiography parameters of the two groups are shown in *Table 2*. After similar echocardiography follow-up duration (18.95 ± 8.8 vs. 17.67 ± 14.1 months; $P = 0.517$), baseline LV thickness, LV size, mean left ventricular ejection fraction ($45.51\% \pm 2.7\%$ vs. $45.07\% \pm 2.7\% \pm 9\%$; $P = 0.329$), E/e' ratio (13.64 ± 7.3 vs. 14.40 ± 6.6 ; $P = 0.521$), and RVSP (28.71 ± 7.9 vs. 32.68 ± 12.9 ; $P = 0.058$) were similar between the two groups except for baseline LA diameter, which was larger in the Group 2 (42.88 ± 6.19 vs. 46.30 ± 9.84 mm; $P = 0.014$).

Primary endpoint

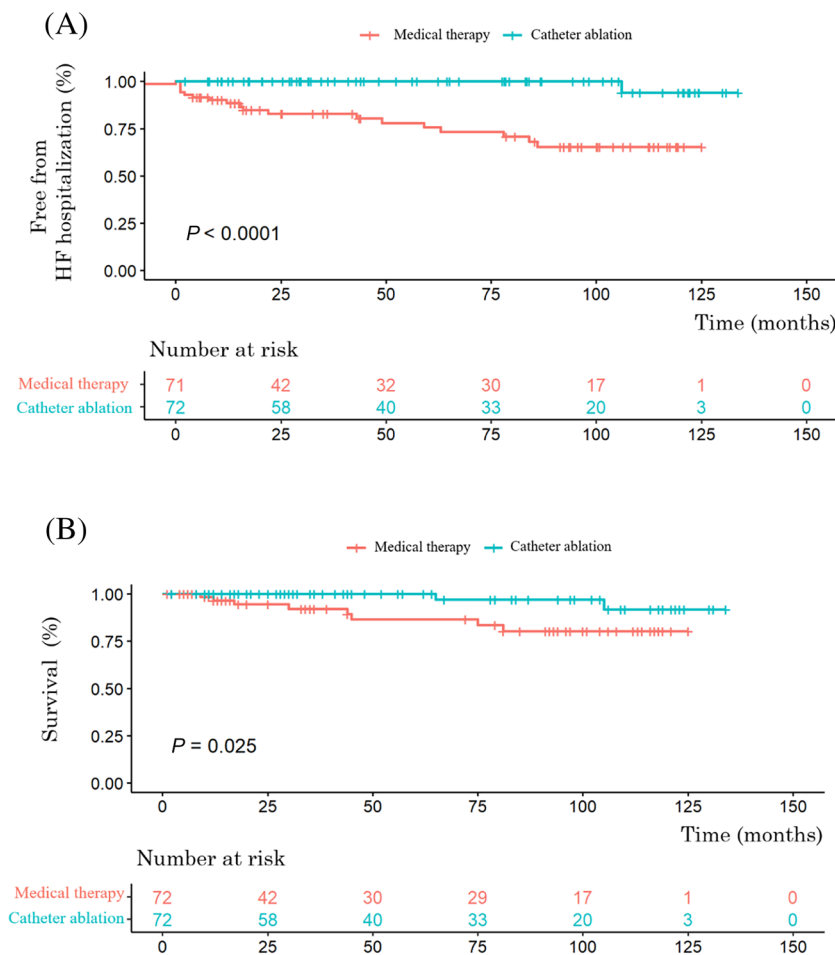
After a mean follow-up duration of 58.9 ± 42.6 months, 19 patients (13.2%) had hospitalizations for HF. Kaplan–Meier curve analysis revealed that more patients in Group 1 were free from HF hospitalizations than in Group 2 significantly (log-rank $P < 0.0001$) (*Figure 2A*). In the multivariable cox

Table 2 Baseline echocardiographic parameters between the two groups with AF and HFmrEF

Variable (mean \pm SD or %, $N = 144$)	Group 1 (CA) ($N = 72$)	Group 2 (MT) ($N = 72$)	P
Echocardiography			
follow-up duration	18.95 ± 8.8	17.67 ± 14.1	0.517
Pre-LVEF	45.51 ± 2.7	45.07 ± 2.7	0.329
Pre-LA diameter	42.88 ± 6.1	46.30 ± 9.8	0.014*
IVSd	10.14 ± 1.8	10.47 ± 2.3	0.350
LVPWd	10.11 ± 1.9	10.13 ± 1.8	0.935
LVIDd	49.76 ± 6.6	52.16 ± 8.2	0.058
Septal E/e'	13.64 ± 7.3	14.40 ± 6.6	0.521
RVSP	28.71 ± 7.9	32.68 ± 12.9	0.058

Abbreviations: CA, catheter ablation; IVSd, inter-ventricular septal thickness in diastole; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVPWd, left ventricular posterior wall thickness in diastole; MT, medical therapy; RVSP, right ventricle systolic pressure.

* P -value < 0.05 .

Figure 2 Kaplan–Meier curve of all-cause mortality and HF hospitalization (A) HF hospitalization, (B) all-cause mortality.

regression analysis adjusting for age, sex, CHA2DS2-VAS, type of AF, hyperlipidaemia, thyroid disease, and baseline LA diameter, the Group 1 was still associated with a lower HF hospitalization (HR, 0.089 [95% CI, 0.011–0.747]; $P = 0.026$) (Table 3).

Secondary endpoints

During follow-up, there are 10 fatalities. Kaplan–Meier curve analysis also revealed that more patients in Group 1 were free from death significantly (log-rank $P = 0.025$) (Figure 2B). The benefit of CA on all-cause mortality in Group 1 remained significant after adjusting age, sex, baseline LA diameter, baseline septal E/e', CHA2DS2-VAS, type of AF, and DM (HR, 0.121 [95% CI, 0.016–0.894]; $P = 0.038$) (Table 4). As for new-onset stroke, there is no significant difference between the two groups (log-rank $P = 0.273$).

After a mean follow-up duration of 22.1 ± 17.1 months, the patients in Group 1 had a sinus rhythm maintenance

rate of 69.4% and a lower percentage of persistent AF than the patients in Group 2 (12.5% vs. 54.2%, $P < 0.0001$) (Figure 3). Echocardiographic parameters before and after the indexed date of enrolment with a mean interval of 16.3 ± 9.3 months were compared, and we observed a significant improvement in LVEF ($25.0\% \pm 18.0\%$ vs. $6.2\% \pm 21.6\%$, $P < 0.0001$) and a significant decrease in LA diameter (-1.6 ± 4.7 mm vs. 1.5 ± 8.2 mm, $P = 0.008$) in the Group 1 (Figure 4A and 4B) compared with Group 2. The changes in LV thickness, LV size, E/e' ratio, and RVSP have no significant difference between the two groups.

Discussion

The main findings of this study were as follows: (1) In patients with HFmrEF undergoing CA of AF, there was less event rate of HF hospitalization than those with medical therapy. (2)

Table 3 Predictors of heart failure hospitalization

	Univariate analysis			Multivariate analysis			
	Events (N = 19)	Non-events (N = 125)	P-value	Exp(B)	95% CI		P-value
					Lower bond	Upper bond	
Age, years	63.16 ± 5.0	60.10 ± 7.4	0.029*	1.009	0.906	1.125	0.867
Female, %	47.4	24	0.033*	0.948	0.300	2.998	0.928
BMI, kg/m ²	25.13 ± 5.4	24.72 ± 3.9	0.683				
CHA2DS2_VASc	3.37 ± 2.1	2.63 ± 1.30	0.037*	1.514	1.022	2.243	0.039*
Persistent AF	36.8	64.8	0.020*	0.502	0.171	1.478	0.211
HTN, %	47.4	56.0	0.481				
DM, %	21.1	12	0.277				
CAD, %	10.5	19.2	0.360				
Hyperlipidaemia, %	0	21.6	0.025*				
CVA, %	21.1	9.8	0.152				
Thyroid disease, %	7	13	0.002*	10.245	2.187	47.985	0.003*
Pre-LVEF, %	44.68 ± 3.0	45.38 ± 2.6	0.299				
Pre-LA diameter, mm	50.44 ± 12.0	43.73 ± 7.3	0.032*	1.052	0.997	1.112	0.066
Septal E/e'	17.49 ± 9.3	13.49 ± 6.4	0.088				
AF Ablation, %	5.9	58.8	0.000*	0.089	0.011	0.747	0.026*

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetic mellitus; HTN, hypertension; LA, left atrial; LVEF, left ventricular ejection fraction.

*P-value <0.05.

Table 4 Predictors of all-cause mortality

	Univariate analysis			Multivariate analysis			
	Events (N = 10)	Non-events (N = 134)	P-value	Exp(B)	95% CI		P-value
					Lower bond	Upper bond	
Age, years	65.00 ± 6.5	60.17 ± 7.1	0.040*	1.087	0.922	1.280	0.320
Female, %	60	24.6	0.015*	0.710	0.153	3.288	0.661
BMI, kg/m ²	24.08 ± 2.7	24.82 ± 4.1	0.581				
CHA2DS2_VASc	4.20 ± 2.1	2.61 ± 1.3	0.046*	0.916	0.551	1.522	0.734
Persistent AF	30	63.4	0.036*	0.401	0.091	1.767	0.227
HTN, %	50	55.2	0.749				
DM, %	40	11.2	0.009*	1.103	0.142	8.593	0.925
CAD, %	40	16.4	0.061				
Hyperlipidaemia, %	10	19.4	0.462				
CVA, %	30	9.9	0.054				
Thyroid disease, %	20	13.4	0.562				
Pre-LVEF, %	45.70 ± 2.9	45.26 ± 2.7	0.625				
Pre-LA diameter, mm	38.40 ± 5.5	45.03 ± 8.3	0.015*	0.908	0.805	1.024	0.116
Septal E/e'	18.70 ± 5.2	13.67 ± 7.0	0.028*	1.193	1.047	1.360	0.008*
AF Ablation, %	20	52.2	0.049*	0.121	0.016	0.894	0.038*

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetic mellitus; HTN, hypertension; LA, left atrial; LVEF, left ventricular ejection fraction.

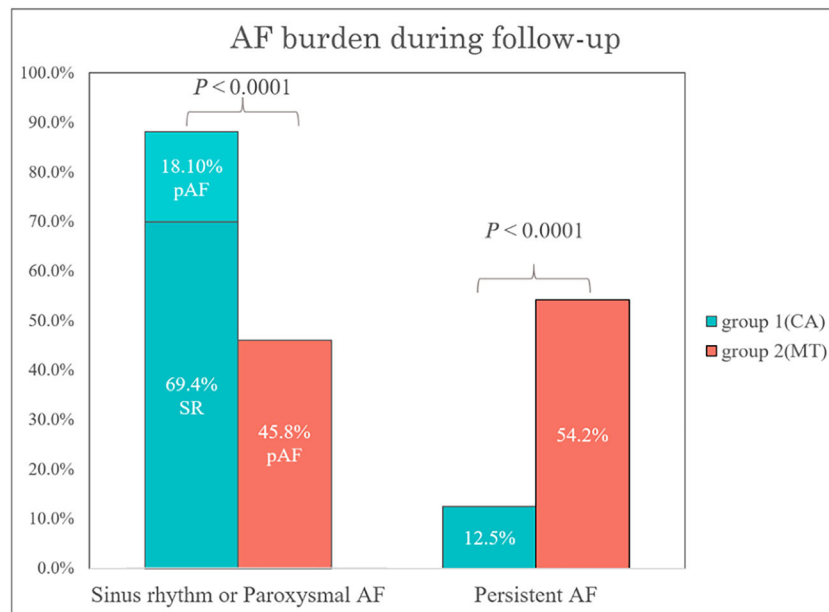
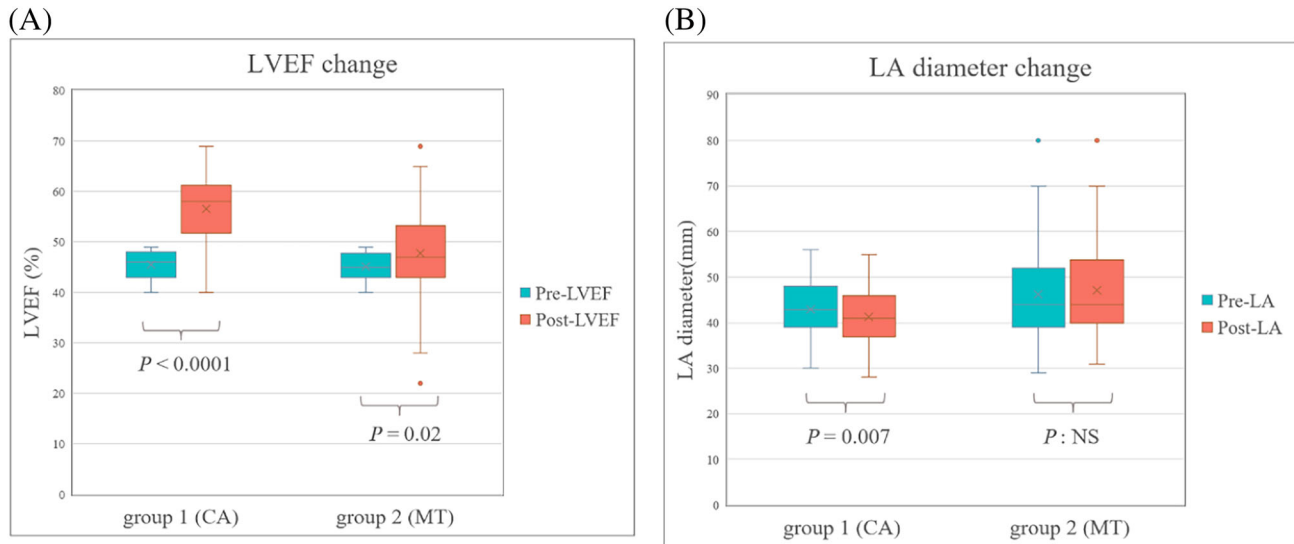
*P-value <0.05.

Patients undergoing CA of AF had lower all-cause mortality than those with medical therapy. (3) After the CA of AF, the LVEF improved and LA diameter decreased significantly as compared with those on medical therapy.

The strategy of rhythm or rate control for patients with AF and HFmrEF

HFmrEF was first introduced in the 2016 ESC guideline as one of the HF phenotypes that shed the light on patients in this

grey area who may benefit from the research targeted at this population with different aetiology, demographics, co-morbidities, and responses to treatment.¹ Like HFpEF, there is no treatment has yet been shown to reduce mortality in patients with HFmrEF. As for the effect of treatment on HF hospitalization in HFmrEF patients with concomitant AF, beta-blockers are ineffective, either angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors is inconclusive, and digoxin has not yet been studied. However, a meta-analysis studying the efficacy of beta-blockers in HFReEF patients has demonstrated the reduction

Figure 3 Comparison of AF types between the two groups during follow-up.**Figure 4** Changes in echocardiography parameters (A) change of LVEF (B) change of LA diameter.

in all-cause mortality presented only in patients with sinus rhythm (HR 0.73, [95% CI, 0.67–0.80]; $P < 0.001$) but not in patients with AF, which highlights the importance of sinus rhythm maintenance to reduce mortality.²³ In the present study, we observed a decreased AF burden after CA with a sinus rhythm maintenance of 69.4% and a lower percentage of persistent AF (12.5% in Group 1 vs. 54.2% in Group 2,

$P < 0.0001$). The advantages of sinus rhythm maintenance have not only been found in the patients with HFREF but have also been seen in the patients with HFpEF.²⁴ In the present study focusing on a population with HFmrEF, rhythm control by the CA was also associated with a lower risk of HF hospitalizations and all-cause mortality than medical therapy significantly (log-rank $P < 0.0001$ and 0.025, respectively).

Comparison between the strategy of CA and MT for patients with AF and HFpEF

Similarly, several studies including the ARC-HF and CAMERA-MRI trials have shown that rhythm control by CA is more effective than rate control in improving quality of life, LVEF, and B-type natriuretic peptide in patients with HFpEF and persistent AF.²⁵ However, the AF-CHF trial did not prove the superiority of pharmacological rhythm control versus rate control to lower CV death.²⁶ The benefits of rhythm control on mortality may be masked by the side effect of the AADs but unveiled by CA. The superiority of rhythm control by CA versus AADs has been demonstrated in the multicenter randomized AATAC trial, in which HFpEF patients with persistent AF receiving CA were significantly more likely to be free from AF recurrence (70% vs. 34%, $P < 0.001$) and have lower mortality rate (8% vs. 18%) than the patient receiving amiodarone.⁹ Even with similar AF burden reduction, patients receiving AADs did not benefit from low AF burdens like patients receiving CA who had a significant reduction of hard clinical outcomes such as death and rehospitalizations.²⁷ Based on the confirmations of CA efficacy on mortality reduction from larger randomized control trials—CASTLE-AF trial and subgroup analysis of the CABANA trial—CA has been given a *Class IIA indication* for AF patients with HFpEF in the 2020 ESC AF and 2021 ESC HF guidelines.⁴

The rationale for CA in patients with AF and HFmrEF

In agreement with previous randomized control trials targeted at HFpEF,^{9,10} we observed substantial improvement in all-cause mortality and HF hospitalization in patients with HFmrEF and paroxysmal or persistent AF after CA. In contrast, the AMICA trial is a negative trial comparing CA and medical therapy in HF patients with persistent AF, and a mean of LVEF of 24.8 to 27.6% indicated that not all patients with AF and HFpEF will profit from a CA despite restoration of sinus rhythm.²⁸ This is also proved by the subgroup of the CASTLE-AF trial, in which the beneficial effect of CA was not observed in the patients with advanced HF symptoms (New York Heart Association functional class III) and very severe reduced LVEF (<25%) (HR, 1.36 [95% CI, 0.69–2.65]; $P = 0.01$).¹⁰ It seems that the benefit of CA is more prominent in patients with relatively better LVEF and less advanced HF stage. This idea was also supported by Fujimoto *et al.* who found that compared with patients with HFpEF, patients with HFmrEF or HFpEF had a lower composite of all-cause death, HF hospitalization, and stroke or systemic embolism (HFpEF, HFmrEF vs. HFpEF, 31.6%, 12.2% vs. 10.4%, log-rank $P < 0.001$).²⁹

Reviewing the trials of HFpEF,⁴ patients with HFmrEF comprise 11.7% of the CABANA trial, which is the first large RCT to describe an important mortality benefit from CA in patients mostly with preserved systolic function (HR, 0.57 [95% CI, 0.33–0.96] for all-cause mortality). However, the benefit of CA on mortality could only be seen in the subgroup with LVEF $\geq 50\%$ in the post hoc analysis (HR, 0.40 [95% CI, 0.18–0.88]).¹¹ In contrast, our study demonstrated that the ablation effect was still associated with lower all-cause mortality (HR, 0.121 [95% CI, 0.016–0.894]; $P = 0.038$). The discrepancy between the CABANA trial and our study may be due to 27% missing data of baseline EF in the CABANA trial. It could lead to underestimation of the benefit from CA in this specific population with HFmrEF by using the statistical method of multiple imputations to fill up missing values and due to an insufficient number of patients with LVEF <50% to reach normal distribution.¹²

Other independent predictors of long-term outcomes

In addition to CA, we also found that higher CHA2DS2-VASc scores were associated with higher HF hospitalization (HR, 1.514 [95% CI, 1.022–2.243]; $P = 0.039$, and higher septal E/e' ratio was associated with higher all-cause mortality in the patients with AF and HFmrEF (HR, 1.193 [95% CI, 1.047–1.360]; $P = 0.008$). The CHA2DS2-VASc score is not only a well-known predictor of stroke caused by AF but also a proven independent predictor of HF in patients with non-valvular AF.³⁰ Interestingly, in the study conducted by Koeda *et al.*, a higher CHA2DS2-VASc score significantly predicts HF event in patients with HFpEF which was defined as LVEF $\geq 45\%$ (HR, 1.46 [95% CI, 1.13–1.87]), whereas no significant differences were shown in patient with EF < 45%.³⁰ Unlike HFpEF, HFmrEF are generally older, more hypertensive, obese, diabetic, and more likely to display AF, and these co-morbidities are also major compositions of CHA2DS2-VASc score.³¹ The difference in pathophysiology of HFpEF and HFmrEF may explain why CHA2DS2-VASc score is only a stronger predictor of HF in the population with HFpEF.

As for septal E/e', a retrospective study included a total of 12 421 eligible HFpEF patients with or without AF has also demonstrated the E/e' ratio is not just fleeting haemodynamic transients with elevated filling pressures but is independently and incrementally linked to long-term mortality (HR, 1.21 [95% CI, 1.07–1.37]; $P = 0.003$ for E/e' > 20 and HR, 1.15 [95% CI, 1.02–1.29]; $P = 0.02$ for E/e' > 14 to 20).³² This finding warrants the regular echocardiographic follow-up for evaluating the diastolic function, which is essential for risk stratification of patients with HF and strategy adjustment to upgrade medical therapy or consider new interventions.

Cardiac structural reverse remodelling after CA of AF in patients with HF

Favourable structural remodelling after CA including improvement in LVEF and decreases in LAD and LVEDD has been demonstrated in a retrospective cohort that included a total of 153 patients with 59% HFmrEF and 41% HFrEF.³³

Left atrial reverse remodelling

Similarly, LA diameter reduction and LVEF improvement were observed in the patients receiving CA in our study. LA diameter is an important index of diastolic dysfunction. Although the mechanism of HFmrEF remains unclear. HFmrEF and HFpEF share things in common about some aspects of the pathophysiology mechanism which is a complex, synergistic interplay between AF, HF, and LA dysfunction.³ Unlike HFrEF, which is more likely to have ischaemic aetiology and left bundle branch block,² HFpEF usually has diastolic dysfunction, which was triggered by abnormalities in excitation-contraction coupling and ventricular stiffness.³⁴ In the spectrum of different LVEF, the HFmrEF group is closer to the HFrEF group concerning age, sex, systolic blood pressure, and ischaemic aetiology,² but HFmrEF was found to associate with higher fibrosis-related biomarkers, including C-terminal propeptide of procollagen type I (PICP) and N-terminal propeptide of procollagen type III (PIIINP) and a higher ratio of PICP/PIIINP, which shifts the equilibrium towards the type I collagen synthesis and results in cardiac fibrosis.³⁵

Interestingly, AF also plays a role in the formation of cardiac fibrosis by the natural evolution of tachycardia-mediated cardiomyopathy³⁶ and the severity of cardiac fibrosis which is proportional to the AF burden.³⁷ The study of Ling et al. included over 50 patients with paroxysmal or persistent AF undergoing cardiac magnetic resonance imaging and revealed that the presence of persistent AF was independently predictive of diffuse LV fibrosis, regardless of ejection fraction.³⁷ It raises concern that the patients with HFmrEF may get benefit from the rhythm control targets to decrease AF burden.

AF is not only one cause of HF but also can drive clinical heart failure symptoms by a significant cardiac output decrement due to loss of efficient atrial systole and impaired LV diastolic function at higher heart rates during AF attack.³⁸ Increased LA volume during HF could start another round of vicious circle by enhancing structural changes within the LA, namely, atrial fibrosis, which may not only increase AF burden but also cause a profound dysfunction in LA mechanics. Ultimately, further worsening of HF could be expected in patients with HFmrEF. In the present study, there is a proportional trend for increased baseline LA diameter and HF hospitalization but did not reach statistically significant after adjustment (HR, 0.40 [95% CI, 0.18–0.88], $P = 0.066$).

Left ventricular reverse remodelling

Finally, LVEF, as an important prognostic factor in patients with HF, our studies observed a significant increment in the CA group. The LVEF increased from $45.5 \pm 2.7\%$ to $56.6 \pm 7.1\%$ ($P < 0.001$) after ablation. Different prognoses were noted in patients with HFmrEF based on the changes of LVEF including improved, stable, and deteriorated levels that have been demonstrated in previous studies.³⁹ In the patients receiving CA for AF, Yazaki et al. revealed that LVEF transition from HFmrEF to HFrEF had more poor outcomes (HF hospitalization or death).⁴⁰ In this study, 14 of 144 patients had LVEF transitions from HFmrEF to HFrEF, and most of them had medication control (MT 85.7% vs. CA 14.3%, $P = 0.005$). Having a unique situation that could be either converted to HFpEF or HFrEF, patients with HFmrEF are worth interfering with a more aggressive therapeutic strategy to reach LVEF improvement for a better prognosis. To the best of our knowledge, this is the first study focusing on patients with HFmrEF and AF to compare clinical outcomes and cardiac structural reverse remodelling between CA and medical therapy.

Limitation

First, the case–control methodology was used to minimize the need for case numbers in this study. Further prospective randomized studies with a larger sample size are required to investigate the exact role of CA in patients with HFmrEF. Second, propensity score matching was applied to balance age, gender, and LVEF between the two groups, because we wanted to reflect target patients' characteristics in the real-world data and minimize the propensity score matching paradox. The baseline LA diameter per se is an independent predictor for major adverse cardiac events, which is higher in the MT group than in the CA group significantly. Thus, results should be interpreted cautiously in light of potential selection bias. Although there was no difference in the AADs between the two groups, this could be due to the small sample size in this study. Third, the CA group was younger and had lower baseline RVSP, LVIDd, and CHA2DS2_VASc but did not reach statistical significance. These potential confounding factors could be masked by the small sample size in this study. Although the schedule used for 12-lead electrocardiogram and echocardiography was similar between the two groups, the follow-up Holter in MT group was not regular. The inconsistent follow-up Holter between the two groups in this retrospective study may also be a potential confounder. Finally, sinus maintenance was determined by reviewing a 12-lead electrocardiogram and/or 24 h Holter recordings around the date the follow-up echocardiography was performed rather than continuous monitoring. And the EKG and/or 24 h Holter recordings were usually arranged for symptomatic patients

during the follow-up period, which may underestimate the sinus rhythm maintenance rate in both groups.

Conclusions

In patients with HFmrEF and AF, CA of AF could reduce both HF hospitalization and all-cause mortality as compared with those with MT. A significant improvement in LVEF and decrease in LA diameter were also observed in the CA group. Early rhythm control with CA should be taken into consideration in patients with HFmrEF and AF.

Acknowledgement

This work is particularly supported by “Yin Yen-Liang Foundation Development and Construction Plan” of the College of Medicine, National Yang Ming Chiao Tung University.

Conflicts of interest

None declared.

Funding

This study was supported, in part, by research grants from the Taipei Veterans General Hospital (V108C-055, V109C-008, V110C-004, and V111C-075), Ministry of Science and Technology of Taiwan (MOST106-2314-B-010-035-MY3, 109-2314-B-010-063, 110-2314-B-A49A-542, and 111-2314-B-A49-007-MY3), Szu-Yuan Research Foundation of Internal Medicine (108010, 109024, 110008, and 111003), and “Yin Yen-Liang Foundation Development and Construction Plan” of the College of Medicine, National Yang Ming Chiao Tung University.

References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, 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 J Heart Fail.* 2016; **18**: 891–975.
- Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC heart failure long-term registry. *Eur J Heart Fail.* 2017; **19**: 1574–1585.
- Li P, Zhao H, Zhang J, Ning Y, Tu Y, Xu D, Zeng Q. Similarities and differences between HFmrEF and HFpEF. *Front Cardiovasc Med.* 2021; **8**: 678614.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021; **42**: 3599–3726.
- 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.
- Lardizabal JA, Deedwania PC. Atrial fibrillation in heart failure. *Med Clin North Am.* 2012; **96**: 987–1000.
- Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation.* 2017; **135**: 1547–1563.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham heart study. *Circulation.* 2003; **107**: 2920–2925.
- Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: Results from the AATAC multicenter randomized trial. *Circulation.* 2016; **133**: 1637–1644.
- Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D, CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018; **378**: 417–427.
- Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, Poole JE, Bahnson TD, Lee KL, Mark DB, CABANA Investigators. Ablation versus drug therapy for atrial fibrillation in heart failure: Results from the CABANA trial. *Circulation.* 2021; **143**: 1377–1390.
- Zafir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, De Mora Martin M, Polonski L, Silva-Cardoso J, Amir O, ESC-HFA HF Long-Term Registry Investigators. 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.
- 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.

14. Turagam MK, Garg J, Whang W, Sartori S, Koruth JS, Miller MA, Langan N, Sofi A, Gomes A, Choudry S, Dukkipati SR, Reddy VY. Catheter ablation of atrial fibrillation in patients with heart failure: A meta-analysis of randomized controlled trials. *Ann Intern Med.* 2019; **170**: 41–50.
15. Rosner B. *Fundamentals of Biostatistics*, 7th ed. Boston, MA: Brooks/Cole; 2011.
16. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017; **14**: e275–e444.
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016; **29**: 277–314.
18. Cheng WH, Lo LW, Lin YJ, Chang SL, Hu YF, Hung Y, Chung FP, Liao JN, Tuan TC, Chao TF, Tsai TY, Liu SH, Chen SA. Ten-year ablation outcomes of patients with paroxysmal atrial fibrillation undergoing pulmonary vein isolation. *Heart Rhythm.* 2019; **16**: 1327–1333.
19. Higa S, Tai CT, Chen SA. Catheter ablation of atrial fibrillation originating from extrapulmonary vein areas: Taipei approach. *Heart Rhythm.* 2006; **3**: 1386–1390.
20. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Lesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 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. *Europace.* 2012; **14**: 528–606.
21. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC, Lin YJ, Yin WH, Kuo JY, Lin WS, Tsai CT, Liu YB, Lee KT, Lin LJ, Lin LY, Wang KL, Chen YJ, Chen MC, Cheng CC, Wen MS, Chen WJ, Chen JH, Lai WT, Chiou CW, Lin JL, Yeh SJ, Chen SA. 2016 guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc.* 2016; **115**: 893–952.
22. Lin YJ, Chao TF, Tsao HM, Chang SL, Lo LW, Chiang CE, Hu YF, Hsu PF, Chuang SY, Li CH, Chung FP, Chen YY, Wu TJ, Hsieh MH, Chen SA. Successful catheter ablation reduces the risk of cardiovascular events in atrial fibrillation patients with CHA2DS2-VASc risk score of 1 and higher. *Europace.* 2013; **15**: 676–684.
23. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis. *Lancet.* 2014; **384**: 2235–2243.
24. Machino-Ohtsuka T, Seo Y, Ishizu T, Yamamoto M, Hamada-Harimura Y, Machino T, Yamasaki H, Sekiguchi Y, Nogami A, Aonuma K, Ieda M. Relationships between maintenance of sinus rhythm and clinical outcomes in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Cardiol.* 2019; **74**: 235–244.
25. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: The CAMERA-MRI study. *J Am Coll Cardiol.* 2017; **70**: 1949–1961.
26. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008; **358**: 2667–2677.
27. Brachmann J, Sohns C, Andresen D, Siebels J, Sehner S, Boersma L, Merkely B, Pokushalov E, Sanders P, Schunkert H, Bänsch D, Dagher L, Zhao Y, Mahnkopf C, Wegscheider K, Marrouche NF. Atrial fibrillation burden and clinical outcomes in heart failure: The CASTLE-AF trial. *JACC Clin Electrophysiol.* 2021; **7**: 594–603.
28. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schlüter M, Tilz RR, Piorkowski C, Gellér L, Kleemann T, Hindricks G. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: The randomized AMICA trial. *Circ Arrhythm Electrophysiol.* 2019; **12**: e007731.
29. Fujimoto H, Doi N, Okayama S, Naito M, Kobori A, Kaitani K, Inoue K, Kurotobi T, Morishima I, Yamaji H, Matsui Y, Nakazawa Y, Kusano K, Hirai K, Nakai T, Suzuki M, Yano H, Sakai S, Kimura T, Shizuta S, Saito Y, KPAF investigators. Long-term prognosis of patients undergoing radiofrequency catheter ablation for atrial fibrillation: Comparison between heart failure subtypes based on left ventricular ejection fraction. *Europace.* 2022; **24**: 576–586.
30. Koeda Y, Komatsu T, Matsuura Y, Morioka H, Uchimura Y, Taguchi Y, Tanaka K, Kawakami J, Nakamura M, Takahashi S, Takahashi Y, Naganuma Y, Endo H, Ito T, Morino Y, Nakamura M. CHADS(2) and modified CHA(2)DS(2)-VASc scores for the prediction of congestive heart failure in patients with nonvalvular atrial fibrillation. *J Arrhythm.* 2017; **33**: 488–493.
31. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation.* 2011; **123**: 2006–2013 discussion 2014.
32. Benfari G, Miller WL, Antoine C, Rossi A, Lin G, Oh JK, Roger VL, Thapa P, Enriquez-Sarano M. Diastolic determinants of excess mortality in heart failure with reduced ejection fraction. *JACC Heart Fail.* 2019; **7**: 808–817.
33. Ribeiro JM, Sousa PA, António N, Baptista R, Elvas L, Barra S, Gonçalves L. Impact of catheter ablation for atrial fibrillation in patients with heart failure and left ventricular systolic dysfunction. *Rev Port Cardiol (Engl Ed).* 2021; **40**: 437–444.
34. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschöpe C. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation.* 2008; **117**: 2051–2060.
35. Lebedev DA, Lysanikova EA, Vasilyeva EY, Babenko AY, Shlyakhto EV. Type 2 diabetes mellitus and chronic heart failure with midrange and preserved ejection fraction: A focus on serum biomarkers of fibrosis. *J Diabetes Res.* 2020; **2020**: 6976153.
36. Spinale FG, Zellner JL, Johnson WS, Eble DM, Munyer PD. Cellular and

- extracellular remodeling with the development and recovery from tachycardia-induced cardiomyopathy: Changes in fibrillar collagen, myocyte adhesion capacity and proteoglycans. *J Mol Cell Cardiol.* 1996; **28**: 1591–1608.
37. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol.* 2016; **13**: 131–147.
38. Meisner JS, Keren G, Pajaro OE, Mani A, Strom JA, Frater RW, Laniado S, Yellin EL. Atrial contribution to ventricular filling in mitral stenosis. *Circulation.* 1991; **84**: 1469–1480.
39. Zhang X, Sun Y, Zhang Y, Chen F, Zhang S, He H, Song S, Tse G, Liu Y. Heart failure with midrange ejection fraction: Prior left ventricular ejection fraction and prognosis. *Front Cardiovasc Med.* 2021; **8**: 697221.
40. Yazaki K, Ejima K, Kataoka S, Higuchi S, Kanai M, Yagishita D, Shoda M, Hagiwara N. Prognostic significance of post-procedural left ventricular ejection fraction following atrial fibrillation ablation in patients with systolic dysfunction. *Circ Rep.* 2020; **2**: 707–714.