The long-term outcomes of catheter ablation for atrial fibrillation in heart failure with preserved ejection fraction

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Abstract

Background We aimed to compare the long-term outcomes of catheter ablation and medical treatment in patients with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). **Methods** We retrospectively screened consecutive patients with AF and HFpEF who received catheter ablation or medical treatment from December 2017 to June 2021 in our institution. The primary endpoint was defined as a composite of all-cause death, thromboembolic events and heart failure (HF) hospitalization. Multivariate analysis, 1:1 propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were employed to adjust for potential confounders. **Results** A total of 131 patients were included, among whom 71 patients (54.2%) underwent 1.15 + 0.36 catheter ablation procedures. During a median follow-up of 31.8 months, the incidence of the primary endpoint was significantly lower in catheter ablation group (9.9% vs 25.0%, log rank p = 0.018) compared with medical treatment group. In the multivariate model, catheter ablation was independently associated with a lower incidence of the primary endpoint (hazard ratio 0.281, 95% confidence interval 0.110 – 0.721, p = 0.008), which was consistent both in PSM and IPTW cohorts. The New York Heart Association class [2 (1, 2) vs 2 (2, 2), paired p < 0.001], N-terminal pro-B type natriuretic peptide level [334.3 (187.1, 821.8) vs 859.2 (308.4, 1903.0), paired p < 0.001] and left atrial diameter (39.4 + 6.4 vs 41.1 + 6.2, paired p = 0.001) were significantly improved at the end of follow-up in catheter ablation group. **Conclusion** Catheter ablation was significantly associated with a lower incidence of the composite endpoint, improved HF symptoms and reverse atrial remodeling in AF and concomitant HFpEF.

Introduction

Atrial fibrillation (AF) and heart failure (HF) often coexist and facilitate the occurrence and aggravate the prognosis of each other since they share common predisposing factors and pathophysiological processes[1-3]. However, the management of patients with AF and concomitant HF is often challenging[1].

Catheter ablation has been a well-established curative therapy for AF[1, 4]. In patients with AF and concomitant HF, catheter ablation has been shown to improve symptoms, exercise capacity, quality of life, and LVEF[5]. Recently, studies showed that catheter ablation were associated with a reduction in all-cause mortality and HF hospitalization compared with medical treatment in patients with AF and HFrEF[6-8].

As shown in various studies, AF is a more potent and independent prognostic factor, increasing the mortality and HF hospitalization in patients with HFpEF compared with HFrEF[9, 10]. However, the optimal therapy in patients with AF and HFpEF remains unclear. Specifically, the impact of catheter ablation for AF and HFpEF has not been well established. The present study was conducted to compare the long-term outcomes of catheter ablation and medical treatment in patients with AF and concomitant HFpEF. The impact of catheter ablation was also evaluated with multivariable adjustment, propensity score matching (PSM), and inverse probability of treatment weighting (IPTW).

Methods

Study population

This retrospective observational cohort study initially screened 4640 consecutive AF patients with available follow-up data from December 2017 to June 2021 in our institution. Then, 210 patients with concomitant HF were identified. HF was defined as either a history of HF hospitalization or symptoms and signs of HF with elevated N-terminal pro-B type natriuretic peptide (NT-ProBNP) (> 125 pg/ml with sinus rhythm or > 365 pg/ml with AF)[11, 12]. Patients with New York Heart Association (NYHA) class I or IV, acute decompensated HF or cardiogenic shock were not eligible. After exclusion of 79 patients with LVEF < 50%, severe valvular disease, congenital heart disease, 131 patients were finally included in the study (Figure 1). Severe valvular disease was defined as a history of aortic or mitral replacement or repair, evidence of severe aortic or mitral regurgitation, severe aortic stenosis, or moderate to severe mitral stenosis. The informed consent on receiving catheter ablation was obtained from all patients. This study complies with the Declaration of Helsinki and was approved by the local ethics committee. The data were acquired from routine patient care and all data used for this study were acquired for clinical purposes and handled anonymously.

Cather ablation procedures

The radiofrequency catheter ablation (RFCA) procedures were performed under conscious sedation. The detail of the procedure has been described previously[13]. After access to the left atrium (LA) via the transseptal puncture needle (Synaptic Medical), two 8.5 - French sheaths (NaviEase, Synaptic Medical) were advanced into LA. Intravenous heparin was administered immediately after the transseptal puncture and to maintain the activated clotting time of 250 - 350 seconds throughout the procedure. A 7-French mapping catheter (PentaRay, Biosense Webster) was used to perform the 3-dimensional electrical anatomical mapping (EAM) under the guidance of the CARTO3 system (Biosense Webster). An 8-French 3.5-mm tip irrigated ablation catheter (SmartTouch, Biosense Webster) with an upper power of 40 W, an upper temperature limit of 43°C, and a flow rate of 17 mL/min was used to perform the catheter ablation. The stepwise ablation strategy was employed: i) circumferential pulmonary vein isolation (CPVI) with bi-directional electric block as the endpoint in every patient; ii) if AF remained after CPVI, the complex fractionated atrial electrogram (CFAE) based ablation was performed; iii) if focal or reentrant atrial tachycardia (AT) was presented during the procedure, a focal or linear ablation based on the EAM and/or entrained mapping was performed; iv) if cavo-tricuspid isthmus (CTI) dependent atrial flutter (AFL) was observed before or during the procedure, linear ablation of the CTI was performed with di-directional conduction block as the endpoint; v) if AF persisted after all these ablation lesions, intravenous ibutilide and/or electric cardioversion was used to restore sinus rhythm. The detailed ablation data in catheter ablation group is shown in Table S1.

Primary and secondary endpoints

The primary endpoint was defined as a composite of all-cause death, thromboembolic (TE) events and HF hospitalization. The secondary endpoint was defined as the NYHA class, NT-ProBNP level, and left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) at the end of follow-up. AF recurrence was defined as symptomatic and/or asymptomatic episodes of AF/AFL/AT lasting > 30 seconds identified on the 12-lead surface electrocardiogram or Holter monitoring after the 3-month of blanking period. All the follow-up data were retrieved from the medical database of our institution. The start of the follow-up period was defined as the day of the last ablation procedure for catheter ablation group, or the day of discharge of the index hospitalization for medical treatment group.

Statistical analysis

Continuous variables with normal distribution were described as the mean+ SD for normally distributed data, and comparisons between groups were performed with Student t test. Nonnormally distributed continuous data were summarized as median (interquartile range) and compared with the Mann-Whitney test. Categorical variables were described as counts and compared by chi-square test. Survival curves were generated with the Kaplan–Meier analysis and compared by log rank test. Cox regression analysis was used to determine the independent predictors for the primary endpoint, with a determination of hazard ratio (HR) and 95% confidence interval (CI) for each variable in the model. Variables selected for testing in the multivariate analysis were those with $P < 0.05$ in the univariate model.

Moreover, 1:1 PSM was performed as sensitivity analysis. PSM was performed between medical treatment group and catheter ablation group. We used a multivariable logistic regression model to estimate propensity scores, with catheter ablation as the dependent variable and the following factors as covariates: age, sex, body mass index, AF type, NYHA class, laboratory findings including NT-ProBNP, estimated glomerular filtration rate, serum ureic acid level, past medical history including hypertension, diabetes mellitus, coronary heart disease, stroke, medication including diuretics, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist/angiotensin receptor neprilysin inhibitor, mineralocorticoid antagonist, anticoagulant, antiplatelet agent, and transthoracic echocardiography (TTE) parameters including LAD, LVEDD, and LVEF. PSM was performed with the nearest neighbor matching algorithm and a 1:1 ratio. Because decreased sample size in PSM might weaken the statistical power and not all covariates were well balanced, we further performed propensity score weighting by IPTW method with the same covariates in PSM.

All tests were 2-tailed, and a statistical significance was established at $P < 0.05$. All analyses were performed using R 4.0.4 and SPSS software (version 22.0; SPSS, Inc., Chicago)

Results

The baseline characteristics of the study population

A totally of 71 patients with AF and HFpEF were included in the present study, among whom 71 underwent the catheter ablation procedure and 60 received medical treatment. The baseline characteristics of the study population is presented in Table 1. Compared with patients receiving medical treatment, the catheter ablation group had a higher prevalence of paroxysmal AF (49.3% vs 18.3%, $p < 0.001$), NYHA class II (87.3% vs 63.3%, $p < 0.001$), beta-blocker (56.3% vs 36.7%, $p = 0.025$) and AADs medication (19.7% vs 3.3%, $p = 0.004$), and had a smaller LAD (41.1 + 6.2 vs 46.1 + 8.2, $p < 0.001$) and a higher LVEF (62.9 + 6.4 vs 60.6 + 6.3, $p = 0.035$). The baseline characteristics of the patients included in PSM and IPTW are listed in Table S2 and S3.

Catheter ablation and AF recurrence

During a median follow-up of 31.8 (18.4, 38.4) months, a total of 66 (50.4%) patients experienced AF recurrence. AF recurrence was compared between patients underwent catheter ablation and medical treatment. In catheter ablation group, 15 patients (21.1%) experienced recurrent AF after 1.15 + 0.36 procedures, while 51 patients (85.0%) in medical treatment group experienced AF recurrence (HR 0.112, 95% CI 0.062 – 0.204, $p < 0.001$). Figure 2A shows the Kaplan-Meier curves for AF recurrence in both groups (log rank $p < 0.001$), which remained significant after a 1:1 PSM (log rank $p < 0.001$) and IPTW analysis (log rank $p < 0.001$), as shown in Figure 2B and 2C.

Catheter ablation and the incidence of the primary endpoint

Totally, the primary endpoint occurred in 22 (16.8%) patients during the follow-up period, among whom 1 (4.5%) died due to cardiogenic shock, 4 (18.1%) had TE events and 19 (86.4%) had HF hospitalization. Figure 3 shows the Kaplan-Meier curves for the cumulative incidence of primary endpoint (log rank $p = 0.018$), all-cause death (log rank $p = 0.250$), TE events (log rank $p = 0.220$), and HF hospitalization (log rank $p = 0.097$). The Kaplan-Meier curves for the primary endpoint with PSM and IPTW are shown in Figure S1 and S2, respectively.

As shown in Table 2, the unadjusted HR for the primary endpoint of catheter ablation group versus medical treatment group derived by Cox regression model was 0.353 (95% CI 0.144 – 0.867, $p = 0.023$). After adjusting for covariates including age, stroke history, eGFR and LVEDD, the HR for catheter ablation was 0.281 (95% CI 0.110 – 0.721, $p = 0.008$). The incidence of the primary endpoint remained lower in catheter ablation group after PSM and IPTW, with the HR of 0.297 (95% CI 0.116 – 0.756, $p = 0.011$) and 0.315 (95% CI 0.110 – 0.906, $p = 0.032$), respectively. Table 3 summarized the HR for the primary endpoint of catheter ablation in various models.

Outcomes of the secondary endpoint

To evaluate the impact of catheter ablation to the patients' functional outcomes, we compared the NYHA class, NT-ProBNP level and TTE parameters between baseline and the end of follow-up. Both groups showed an improved NYHA class [medical treatment group: 2 (2, 3) vs 2 (2, 3), paired $p = 0.001$; catheter ablation group: 2 (1, 2) vs 2 (2, 2), paired $p < 0.001$], and a reduced NT-ProBNP level [medical treatment group: 1002.0 (547.6, 1604.0) vs 1337.0 (719.3, 1860.8), paired $p = 0.002$; catheter ablation group: 334.3 (187.1, 821.8) vs 859.2 (308.4, 1903.0), paired $p < 0.001$]. In TTE examination, only LAD significantly reduced ($39.4 + 6.4$ vs $41.1 + 6.2$, paired $p = 0.001$) in the catheter ablation group, whereas the remaining TTE parameters were comparable between baseline and the end of follow-up in both groups (Figure 4). Sensitive analysis for the secondary endpoint with PSM further confirmed these results, which are shown in Figure S3 - S5.

Discussion

Major findings

This study demonstrated the following key findings. Firstly, catheter ablation was significantly associated with a lower incidence of the composite endpoint of all-cause death, TE events and HF hospitalization in AF and concomitant HFpEF. Secondly, remarkable reduction in AF recurrence was observed with contact force-guided ablation compared with medical treatment. Thirdly, catheter ablation was an independent predictor of improved HF symptoms and reverse atrial remodeling. To the best of our knowledge, this is the first study making a direct comparison of the long-term impact of RFCA to medical treatment on clinical and functional outcomes in patients with HFpEF and AF.

Long-term AF recurrence after catheter ablation in AF and HFpEF

Catheter ablation has been shown to be safe and feasible in patients with AF and HFpEF. However, the long-term successful rate is controversial among studies, varying from 45% to 94.8%[14-17], which mainly depends on different characteristics of the study population, different definitions of HFpEF, different ablation strategies, and different follow-up durations. Machino-Ohtsuka et al[14] revealed that multiple-procedure drug-free success rate at 3 years was only 45%. In the present study, 56 (78.9%) patients in catheter ablation group maintained sinus rhythm after multiple procedures during 31.8-month follow-up. We believe that this discrepancy is attributed to following factors: i) almost 70% of patients were persistent or long-standing persistent AF in Machino-Ohtsuka's study, while the proportion was 50% in our study; ii) the ablation technique employed in the present study was contact force-guided, which could improve the durability of ablation lesions.

Catheter ablation and prognosis of AF and HFpEF

Catheter ablation has been shown to be a favorable treatment to improve the long-term prognosis in patients with AF and HFrEF[6, 7]. However, the data on the prognostic value of catheter ablation in patients with AF and HFpEF is limited. Fukui et al[18]retrospectively included 85 patients with AF and HFpEF (defined as LVEF> 50% and a history of HF hospitalization) and revealed that RFCA was associated with a reduced HF hospitalization in HFpEF patients compared with pharmocotherapy. Rattka et al[19] demonstrated that PVI with cryoballoon ablation (CBA) was able to improve the long-term prognosis of patients with HFpEF using PSM analysis. In the present study, we retrospectively enrolled 131 consecutive patients with AF and concomitant HFpEF according to current guidelines and found that catheter ablation was an independent predictor for a reduction in composite endpoint of all-cause death, TE events and HF hospitalization, which was further confirmed by sensitive analysis with PSM and IPTW. We believe that these results will support the catheter ablation in the treatment of AF and HFpEF, although prospective randomized controlled studies are warranted.

Catheter ablation and functional outcomes in AF and HFpEF

Catheter ablation has been shown to improve HF symptoms as well as NT-ProBNP levels in AF and HFpEF[14-16, 19]. A recent study by Rattka et al[16] showed that the average NYHA class improved from 2.6 + 0.7 to 1.7 + 0.9 and the mean NT-ProBNP level improved from 1840 + 2115 pg/ml to 824 +1095 pg/ml 12 months after the ablation procedure. Moreover, the favorable TTE parameters for reverse remodeling associated with catheter ablation have been demonstrated by several studies[14, 19]. Machino-Ohtsuka et al[14] showed that sinus rhythm maintenance with RFCA could significantly improve both the left ventricular systolic and diastolic indices in AF with HFpEF. Also, Rattka et al[19] observed such TTE changes in CBA group rather than medical treatment group. In accordance with these findings, our present study revealed that the NYHA class, NT-ProBNP levels, and LAD significantly improved at the end of follow-up compared with baseline in patients with AF and concomitant HFpEF.

Limitations

This study has several limitations. Firstly, the present study is a retrospective observational study with limited sample size. Consequently, the generalization of these conclusions needs to be further tested in prospective controlled studies with larger cohort. Secondly, all patients of the medical treatment group in our study received rate control therapy. The head-to-head comparison of catheter ablation over rhythm control medical treatment is warranted. Thirdly, all patients in catheter ablation group undergo 24-hours Holter monitoring, rather than implanted loop recorder during follow-up, which may underestimate the recurrence rate. Fourthly, given the retrospective nature, the detailed TTE parameters on diastolic function at the end of follow-up were not available, which limits the further analysis of the diastolic function changes. Fifthly, the reduction of NT-ProBNP level may be explained by the reduction of AF burden in catheter ablation group, aside from the alleviation of HF per se.

Conclusions

In conclusion, catheter ablation was significantly associated with a lower incidence of the composite endpoint of all-cause death, TE events and HF hospitalization. Furthermore, catheter ablation was an independent predictor for improved HF symptoms and reverse atrial remodeling in patients with AF and concomitant HFpEF.

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Declaration of interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1 Flow chart showing the study design. LVEF, left ventricular ejection fraction; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

Figure 2 The Kaplan-Meier curves for atrial fibrillation recurrence in patients receiving catheter ablation and medical treatment. A, the original cohort; B, after 1:1 propensity score matching; C, after inverse probability of treatment weighting. PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

Figure 3 The Kaplan-Meier curves showing the cumulative incidence of primary endpoint (A), death (B), thromboembolic events (C) and heart failure hospitalization (D). TE, thromboembolism; HF, heart failure.

Figure 4 The left atrial diameter (A), left ventricular end-diastolic diameter (B), and left ventricular ejection fraction (C) of patients at baseline and the end of follow-up receiving medical treatment and catheter ablation. LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Table 1 The baseline characteristics of the study population

	Catheter ablation (n = 71)	Medical treatment (n = 60)	P value
Age, years	65.8 + 10.2	64.5 + 11.1	0.476
Male sex, n (%)	34 (47.9)	29 (48.3)	0.959
BMI, kg/m^2	24.6 + 3.1	23.7 + 3.2	0.085
Paroxysmal AF, n (%)	35 (49.3)	11 (18.3)	< 0.001
NYHA class	NYHA class	NYHA class	NYHA class
Class II, n (%)	62 (87.3)	38 (63.3)	0.001
Class III, n (%)	22 (12.7)	9 (36.7)	0.001
Past medical history	Past medical history	Past medical history	Past medical history
Hypertension, n (%)	42 (59.2)	32 (53.3)	0.503
Diabetes, n (%)	14 (19.7)	12 (20.0)	0.968
CHD, n (%)	22 (31.0)	13 (21.7)	1.000
Stroke, n (%)	11 (15.5)	11 (18.3)	0.665
Laboratory finds	Laboratory finds	Laboratory finds	Laboratory finds
NT-ProBNP, pg/ml	859.2 (308.4, 1903.0)	1337.0 (719.3, 1860.8)	0.055
eGFR, ml/min/1.73m^2	67.1 + 21.2	65.3 + 22.4	0.851
SUA, umol/L	412.3 + 98.0	409.0 + 103.1	0.622
Medications	Medications	Medications	Medications
Diuretics, n (%)	1 (2.6)	1 (2.6)	1.000
beta-blocker, n (%)	40 (56.3)	22 (36.7)	0.025
ACEI/ARB/ARNI, n (%)	16 (22.5)	11 (18.3)	0.554
MRA, n (%)	9 (12.7)	5 (8.3)	0.423
Anticoagulant, n (%)	9 (12.7)	2 (3.3)	0.055
Anti-platelet agent, n (%)	13 (18.3)	7 (11.7)	0.292
AADs, n (%)	14 (19.7)	2 (3.3)	0.004
TTE	TTE	TTE	TTE
LAD, mm	41.1 + 6.2	46.1 + 8.2	< 0.001
LVEDD, mm	45.8 + 4.1	46.1 + 6.6	0.759

	Catheter ablation (n = 71)	Medical treatment (n = 60)	P value
LVEF, %	62.9 + 6.4	60.6 + 6.3	0.035

BMI, body mass index; AF, atrial fibrillation; NYHA, New York Heart Association; CHD, coronary heart disease; NT-ProBNP, N-terminal pro-B type natriuretic peptide; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; AADs, anti-arrhythmic drugs; TTE, transthoracic echocardiography; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Table 2 Univariate and multivariate analyses for risk factors of the primary endpoint

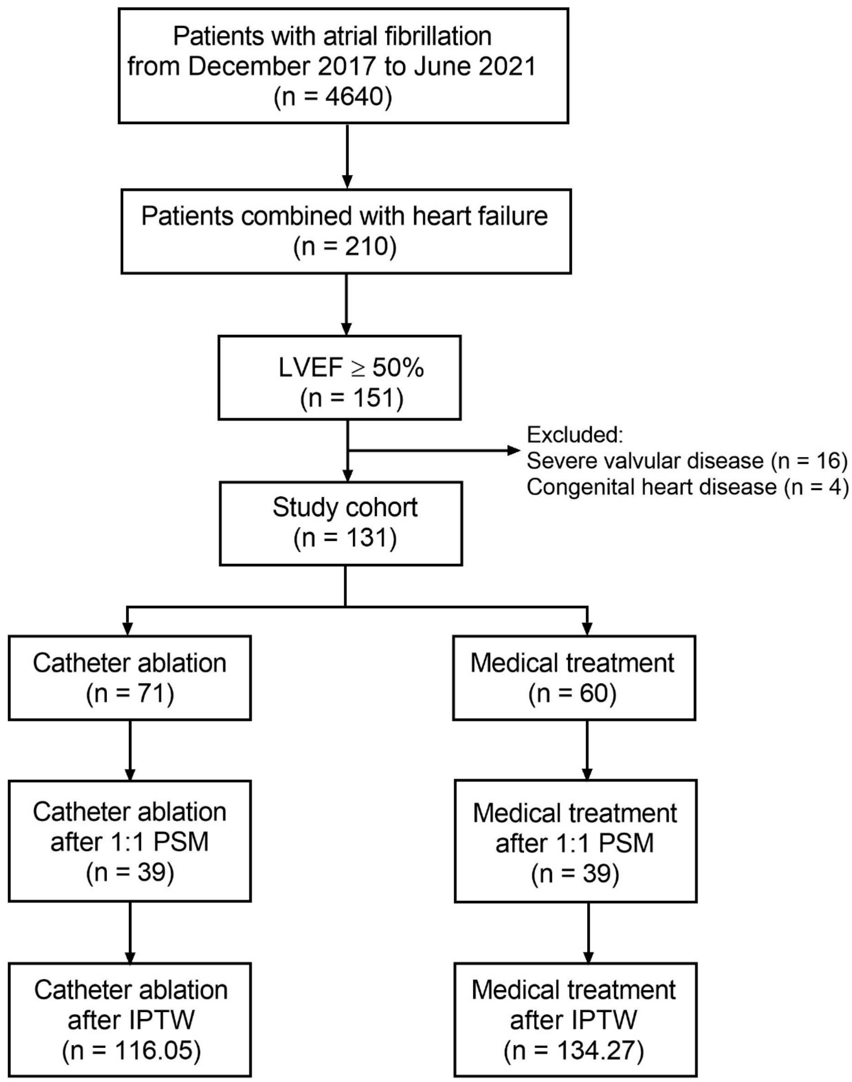
Variables	Univariate analysis	Univariate analysis	Multivariate analysis	Multivariate analysis
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.065 (1.015 – 1.118)	0.010	1.050 (0.992 – 1.111)	0.094
Catheter ablation	0.353 (0.144 – 0.867)	0.023	0.281 (0.110 – 0.721)	0.008
Stroke history	2.605 (1.059 – 6.407)	0.037	3.578 (1.259 – 10.163)	0.017
eGFR	0.979 (0.960 – 0.999)	0.036	0.982 (0.955 – 1.010)	0.216
LVEDD	0.881 (0.808 – 0.962)	0.005	0.895 (0.819 – 0.980)	0.016

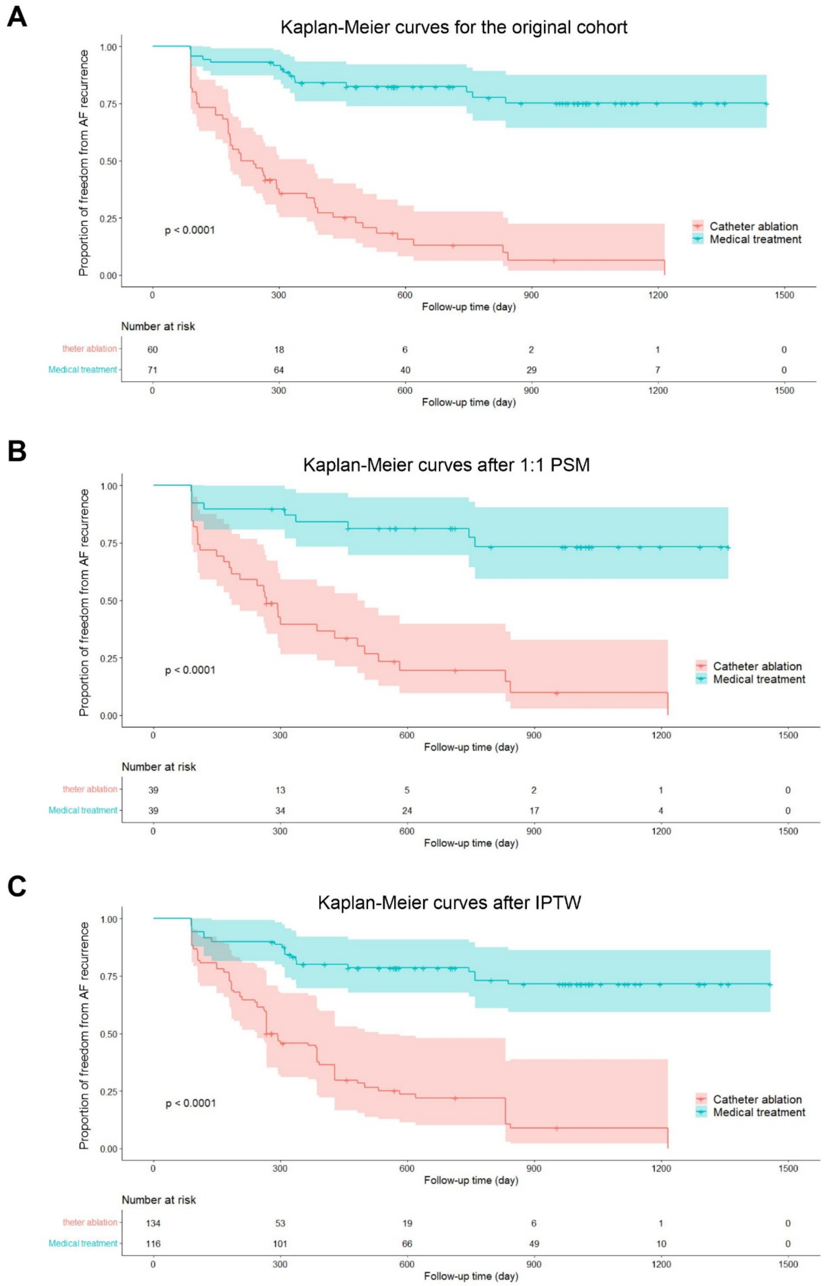
HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter.

Table 3 Summary of hazard ratio for the primary endpoint of catheter ablation

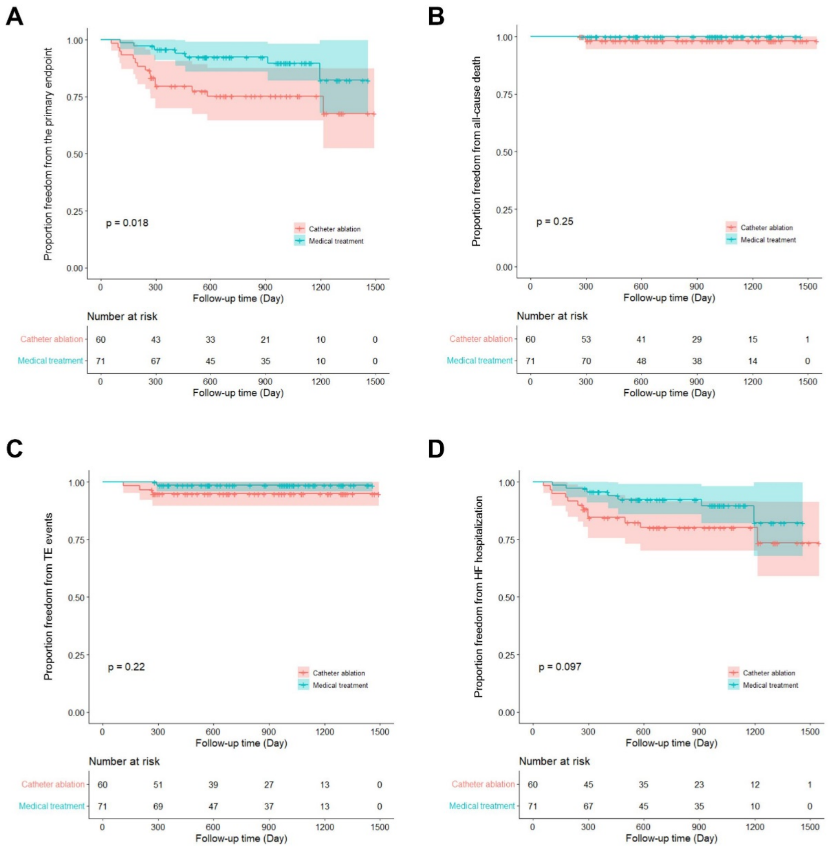
Analysis	Sample size	Sample size	Primary endpoint	Primary endpoint	Primary endpoi
	Catheter ablation	Medical treatment	No. (%)	HR (95% CI)	P value
Unadjusted	71	60	7 (9.9) vs 15 (25.0)	0.353 (0.144 – 0.867)	0.023
Multivariate	71	60	7 (9.9) vs 15 (25.0)	0.281 (0.110 – 0.721)	0.008
PSM	39	39	7 (17.9) vs 12 (30.8)	0.297 (0.116 – 0.756)	0.011
IPTW	116.05	134.27	11.9 (10.3) vs 38.0 (28.3)	0.315 (0.110 – 0.906)	0.032

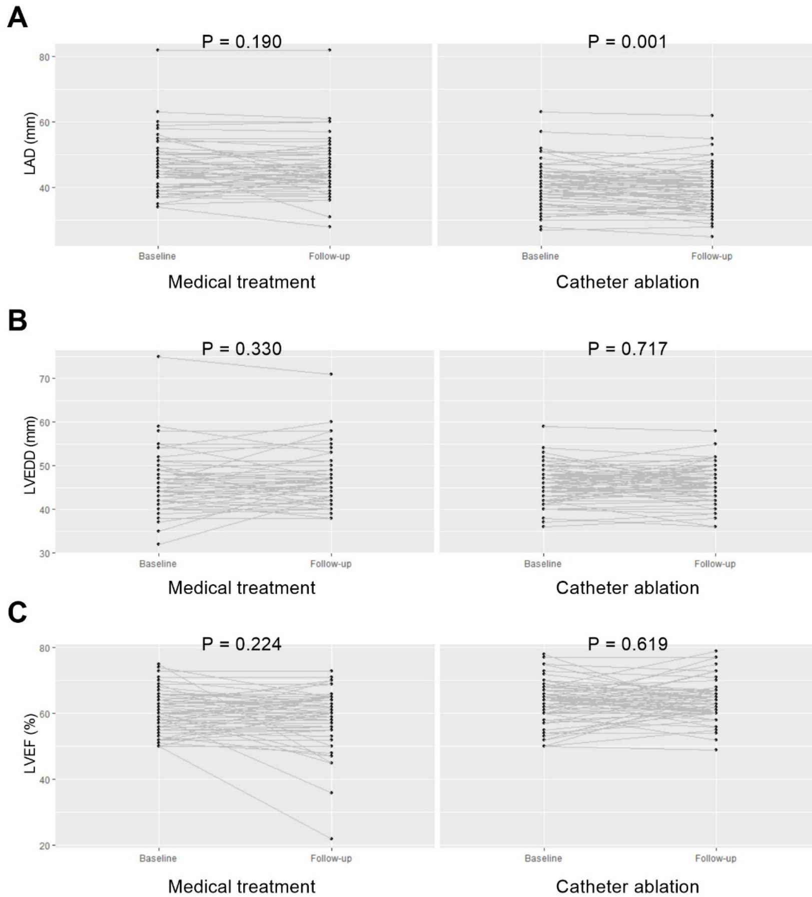
HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; IPTW, inverse probability of treatment weighting


Patients with atrial fibrillation from December 2017 to June 2021 (n = 4640)
Patients combined with heart failure (n = 210)
LVEF ≥ 50% (n = 151)
Excluded:
Severe valvular disease (n = 16)
Congenital heart disease (n = 4)
Study cohort (n = 131)
Catheter ablation (n = 71)
Medical treatment (n = 60)
Catheter ablation after 1:1 PSM (n = 39)
Medical treatment after 1:1 PSM (n = 39)
Catheter ablation after IPTW (n = 116.05)
Medical treatment after IPTW (n = 134.27)


A
Kaplan-Meier curves for the original cohort
Proportion of freedom from AF recurrence
p < 0.0001
Catheter ablation
Medical treatment
Follow-up time (day)
Number at risk
theter ablation 60 18 6 2 1 0
Medical treatment 71 64 40 29 7 0
B
Kaplan-Meier curves after 1:1 PSM
Proportion of freedom from AF recurrence
p < 0.0001
Catheter ablation
Medical treatment
Follow-up time (day)
Number at risk
theter ablation 39 13 5 2 1 0
Medical treatment 39 34 24 17 4 0
C
Kaplan-Meier curves after IPTW
Proportion of freedom from AF recurrence
p < 0.0001
Catheter ablation
Medical treatment
Follow-up time (day)
Number at risk
theter ablation 134 53 19 6 1 0
Medical treatment 116 101 66 49 10 0

Kaplan-Meier curves of the primary endpoint




A
P = 0.190
P = 0.001
LAD (mm)
80
60
40
Baseline
Follow-up
Medical treatment
Catheter ablation
B
P = 0.330
P = 0.717
LVEDD (mm)
70
60
50
40
30
Baseline
Follow-up
Medical treatment
Catheter ablation
C
P = 0.224
P = 0.619
LVEF (%)
80
60
40
20
Baseline
Follow-up
Medical treatment
Catheter ablation