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ORIGINAL ARTICLE

Catheter ablation of atrial fibrillation in heart failure with impaired systolic function: An updated meta-analysis of randomized controlled trials

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Abstract

Background: The recent Atrial Fibrillation Management in Congestive Heart Failure With Ablation trial did not reveal any benefit of catheter ablation in patients with atrial fibrillation (AF), advanced heart failure (HF), and severely reduced left ventricular ejection fraction (LVEF). We hypothesized that radiofrequency catheter ablation (RFCA) could improve outcomes in HF patients with AF and impaired left ventricular systolic function (LVEF <50%) as compared with only medical therapy.

Methods: We searched the literature for randomized clinical trials (RCTs) that compared RFCA to medical therapy in this population.

Results: Compared with the medical therapy group, the RFCA group had significantly less all-cause mortality, HF hospitalization, and AF recurrence rates. The RFCA group had significantly higher peak oxygen consumption (VO_{2max}), a better quality of life (Minnesota Living with Heart Failure Questionnaire score), and improved LVEF. However, RFCA for AF failed to reduce all-cause mortality in a specific meta-analysis of four RCTs that enrolled patients with LVEF ≤35%.

Conclusion: Compared with medical therapy, RFCA for AF in the setting of HF with impaired systolic function is associated with better clinical (HF hospitalization and all-cause mortality), structural (LVEF improvement), functional (VO_{2max}), and quality of life outcomes. However, RFCA for AF failed to reduce all-cause mortality in RCTs that enrolled patients with LVEF ≤35% and thereby indicated the necessary stratification to identify patients who may benefit more from RFCA.

Keywords: Ablation; Heart failure; Outcomes; Meta-analysis

1. INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) often coexist. Approximately half of HF patients have AF, which can lead to tachycardia-induced cardiomyopathy.[1] The coexistence of AF and HF is associated with increased morbidity, mortality, and healthcare costs,[2,3] and the restoration and maintenance of sinus rhythm in HF patients with AF could alleviate symptoms.[4] In the last two decades, radiofrequency catheter ablation (RFCA) has become a treatment for AF.[5] A meta-analysis of randomized control trials (RCTs) compared the efficacy and outcomes of combination therapy with RFCA and medical therapy in HF patients with AF and showed that, compared to conventional drug therapy, RFCA better improves all-cause mortality, HF hospitalizations, left ventricular systolic function, 6-minute walk test (6-MWT) distance, peak oxygen consumption (VO_{2max}), and quality of life.[6–8] However, the recently published Atrial Fibrillation Management in Congestive Heart Failure With Ablation (AMICA) trial did not reveal any benefit of catheter ablation in advanced HF patients with AF and severely reduced left ventricular ejection fraction (LVEF).[9] Therefore, this systematic review and meta-analysis of RCTs was conducted to compare the safety and efficacy of RFCA with medical therapy for AF in HF patients with mildly reduced ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF).

2. METHODS

2.1. Data sources

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015.[10] Two authors (T.Y.C. and C.Y.L.) independently performed a literature search of PubMed, Medline, and the Cochrane Collaboration Central Register of Controlled Trials from January 2005 to June 2021, and discrepancies, if any, were resolved by a third author (T.F.C.).

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2.2. Selection criteria and data extraction

We included only RCTs that compared the efficacy and safety of RFCA with medical therapy in AF patients with HFmrEF or HFrEF.[11] Two authors (T.Y.C. and C.Y.L.) extracted the data independently and any discrepancies were resolved by a third author (T.F.C.) (Fig 1).

2.3. Outcomes

The outcomes were categorized as follows: clinical (HF hospitalization, all-cause mortality, and serious adverse events), structural (LVEF improvement), functional capacity (6-MWT and VO_{2max}), and quality of life (Minnesota living with heart failure questionnaire (MLHFQ) score). Echocardiography was the primary imaging method that was used to estimate the LVEF. However, owing to the difficulties in measuring the LVEF during AF, some studies used radionuclide ventriculography and cardiac magnetic resonance imaging to measure the LVEF. Adverse events were defined as death, stroke, bleeding, pericardial effusion, cardiac tamponade, pulmonary vein stenosis, and worsening of HF.

2.4. Statistical analysis

To explore the associations between the ablation and nonablation groups with regard to the outcomes of interest, we calculated the relative risks (RRs) with the 95% confidence intervals (CIs) for the binary outcomes and the mean differences and associated 95% CIs for continuous outcomes. The pooled estimates with 95% CIs were estimated using inverse-variance weighted random-effects models with the DerSimonian and Laird estimators for between-study variances (τ^2). The continuity correction was used both to calculate individual study results and to conduct a meta-analysis based on the inverse variance method. For quantifying heterogeneity, I^2 statistics and τ^2 were assessed. If the I^2 is more than 50% or the *p*-values for τ^2 are less than 0.05, then the studies are considered heterogeneous. The results of the meta-analysis were displayed visually using forest plots. Further sensitivity analysis for the LVEF outcome was performed after excluding the data from the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF), Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device (AATAC), and AMICA trials to assess the heterogeneity of the pooled estimate. All analyses were performed using RStudio, Version 1.2.1335.

3. RESULTS

Table 1 summarizes the characteristics of the enrolled studies. The seven RCTs included 915 patients, of whom 456 and 459 were randomly assigned to the AF ablation and medical therapy groups, respectively. The mean age of patients in the trials ranged from 57 to 65 years. Ischemic cardiomyopathy (ICM) was the predominant cause of HF, except in the Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Heart Failure-An MRI-Guided Multicenter Randomized Controlled Trial (CAMERA-MRI), which excluded patients with ICM. Six trials included patients with persistent AF.[9,12–16] In the CASTLE-AF trial, 52% of the participants had paroxysmal AF.[17] Pulmonary vein isolation with RFCA was the key ablation strategy in all studies; however, in most of the patients, additional ablation techniques including the creation of linear lesions, ablation of complex fractionated atrial electrograms (CFAEs), or their combinations were undertaken. In the AATAC, CASTLE-AF, and AMICA trials, patients in the medical therapy groups received antiarrhythmic drugs. Nonetheless, in the remaining four studies, participants

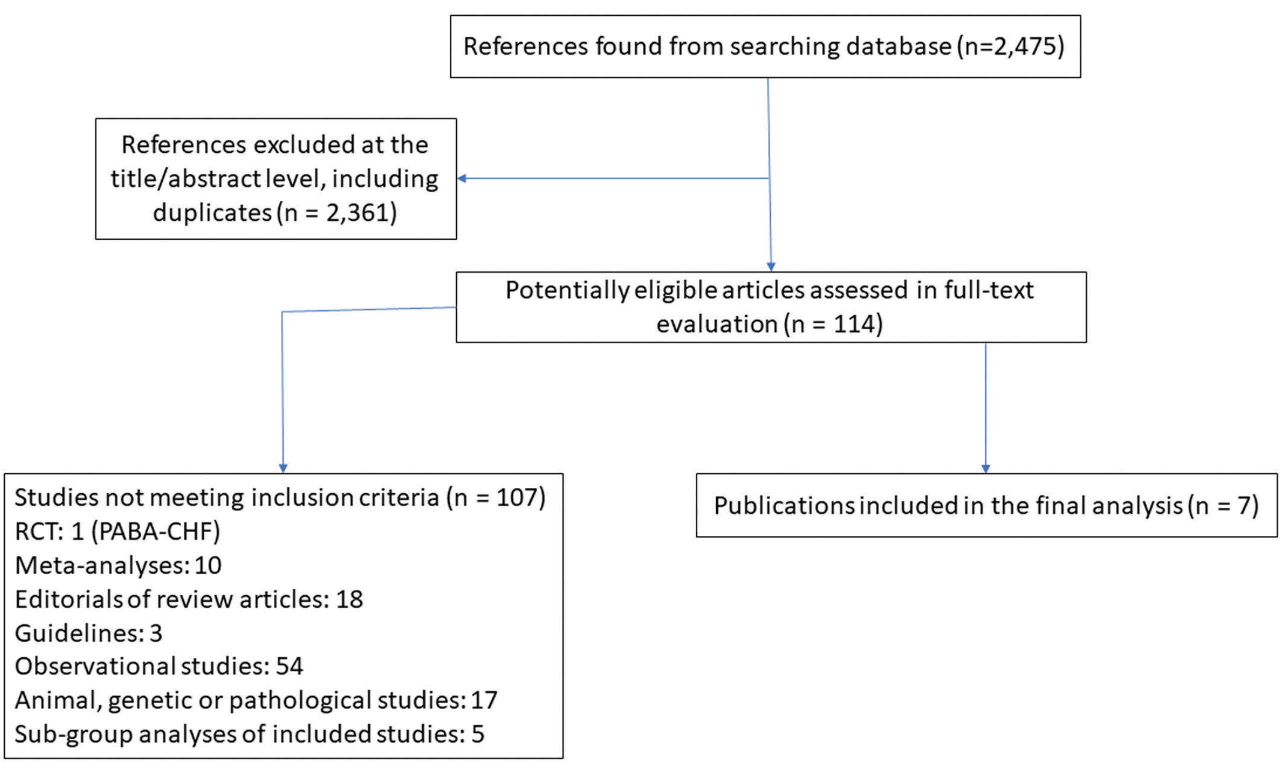


Fig. 1 Evidence searching and selection. PABA-CHF = pulmonary-vein isolation for atrial fibrillation in patients with heart failure; RCT = randomized controlled trial.

Table 1

The characteristics of the enrolled randomized controlled trials

Study, year	MacDonald et al, 2011	ARC-HF, 2013	CAMTAF, 2014	AATAC, 2016	CAMERA-MRI, 2017	CASTLE-AF, 2017	AMICA, 2019
Enrolled patients	41	52	50	203	66	363	140
Age (mean)	63	63	57	61	61	64	65
Characteristics	LVEF≤35%	LVEF≤35%	LVEF≤50%	LVEF<40%	LVEF≤45%	LVEF≤35%	LVEF≤35%
NYHA class	II-III	II-III	II-III	II-III	II-IV	I-IV	II-III
Ischemic CM	49%	33%	26%	62%	0%	46%	50%
Persistent AF	100%	100%	100%	100%	100%	67%	100%
CRT-D	NA	21%	NA	100% (ICD or CRT-D)	NA	28%	44%
Ablation strategy	PVI ± linear ablation	PVI + linear ablation + CFAEs	PVI ± linear ablation ± CFAEs	PVI ± linear ablation ± CFAEs	PVI ± linear ablation	PVI ± linear ablation	PVI ± linear ablation ± CFAEs
Medical strategy	Rate control	Rate control	Rate control	Amiodarone	Rate control	Rhythm and Rate control	Rhythm and Rate control
Monitoring AF recurrence	24-h Holter	24-h Holter	48-h Holter	Cardiac implantable electronic device	implantable loop recorder	Cardiac implantable electronic device	ECG-monitoring card (Vitaphone)
Overall successful rate of RFCA	50%	88%	73%	70%	75%	63%	74%
Significant improvement after RFCA	LVEF	Quality of life	LVEF, peak oxygen consumption, quality of life, serum BNP, NYHA functional class	Mortality, unplanned hospitalization, LVEF, 6MWD, Quality of life	LVEF, Serum BNP, NYHA functional class	Mortality, HF hospitalization, LVEF	NA

6-MWT = 6-minute walk test; AATAC = Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; AF = atrial fibrillation; AMICA = Atrial Fibrillation Management in Congestive Heart Failure With Ablation; BNP = B-natriuretic peptide; CAMERA-MRI = Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Heart Failure-An MRI-Guided Multicenter Randomized Controlled Trial; CFAE = complex fractionated atrial electrogram; CM = cardiomyopathy; CRT-D = cardiac resynchronization therapy-defibrillator; ICD = Implantable cardioverter-defibrillator; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PVI = pulmonary vein isolation; RFCA = radiofrequency catheter ablation.

in the medical therapy groups received only rate-controlling medications.

3.1. Clinical outcomes (HF hospitalization, all-cause mortality, and severe adverse events)

Data on all-cause mortality and HF hospitalization were available from 6 to 5 trials, respectively. Compared with medical therapy, the RFCA of AF was associated with a significant reduction in all-cause mortality (RR, 0.58 [95% CI, 0.40-0.82]) and HF hospitalizations (RR, 0.58 [95% CI, 0.47-0.73]) (Fig. 2A,B). With regard to serious adverse events, there was no significant intergroup difference between the RFCA and the medical therapy groups (RR, 1.07 [95% CI, 0.98-1.17]) (Fig 2C).

3.2. Structural outcome (LVEF improvement)

Compared with medical therapy, RFCA for AF induced a greater improvement of LVEF (mean difference, 5.86% [95% CI, 2.68%-9.03%]; Fig 3A). Although significant heterogeneity (I^2 = 70.4%) was observed, the improvement in LVEF with RFCA of AF was observed in six trials, but not in the AMICA trial.

A sensitivity analysis was performed to investigate the significant heterogeneity observed among trials with regard to changes in LVEF. In the AATAC, CASTLE-AF, and AMICA trials, patients in the medical control groups received antiarrhythmic drugs; however, in the other four studies, participants in the medical control groups received only rate-controlling medications. However, after excluding the AATAC, CASTLE-AF, and AMICA trials, no significant heterogeneity (p for heterogeneity = 0.50; I^2 = 0%) was observed for changes in LVEF, and the increase in mean LVEF with RFCA persisted (mean difference, 8.08% [CI, 5.14%-11.03%]; Fig 3B).

3.3. Functional capacity outcome (6-MWT and VO_2max)

The 6-MWT results, which were available in six trials, showed no improvement in the RFCA group relative to the medical therapy group (mean difference, 8.26 m [CI, −12.13 m to 28.64 m]; Fig 4A). The two trials with VO_{2max} data showed improvement with RFCA as compared with only medical therapy (mean difference, 3.16 [CI, 1.06-5.27] mL/kg/min; Fig 4B).

3.4. Quality of life

All five trials with quality-of-life outcomes showed that RFCA for AF improved the MLHFQ scores, although the findings in the two trials were not significant. In general, the improvement in the MLHFQ scores that was demonstrated in the RFCA group relative to the medical therapy group was statistically significant (mean difference, −6.92 [CI, −12.03 to −1.81] points; Fig 4C).

3.5. AF recurrence and burden

Four trials reported AF-free survival, whereas both CASTLE-AF and CAMERA-MRI reported the percentage of AF burden on follow-up. Figure 4D shows a 68% reduction in AF recurrence with RFCA compared with medical therapy. The CASTLE-AF trial reported a lower AF burden with RFCA, compared with medical therapy (65% at the 60-month follow-up). The CAMERA-MRI reported a mean AF burden of 1.6% ± 5.0% at 6 months in the RFCA group, compared with 100% in the medical therapy group. Similarly, the AMICA trial demonstrated that, during the 1-year follow-up, device-recorded events of high atrial rate were lower in the RFCA group (28%), compared to 56% in the medical therapy group.

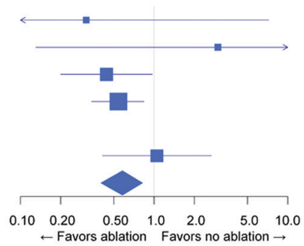
3.6. Specific meta-analysis of four randomized trials enrolling patients with LVEF ≤35%

Fig. 5 showed that, compared with medical therapy, the RFCA of AF was associated with a significant reduction in HF-related hospitalizations (RR, 0.62 [95% CI, 0.46-0.84]) and LVEF improvement (mean difference, 5.16% [CI, 1.68%-8.63%]). In terms of all-cause mortality, there was no difference between the

A

All-cause mortality	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
CAMTAF, 2014	0	26	1	24	0.31 (0.01, 7.21)
ARC-HF, 2013	1	26	0	26	3.00 (0.13, 70.36)
AATAC, 2016	8	102	18	101	0.44 (0.20, 0.97)
CASTLE-AF, 2018	24	179	46	184	0.54 (0.34, 0.84)
CAMERA-MRI, 2017	0	33	0	33	Not estimatable
AMICA, 2019	8	95	8	100	1.05 (0.41, 2.69)
Random effects model		461		468	0.58 (0.40, 0.82)

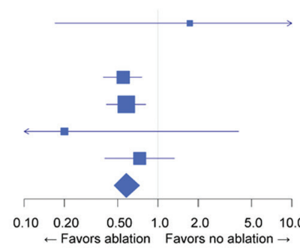
Heterogeneity: $I^2 = 0.0\%$; $\tau^2 = 0.00$; $P = 0.50$



B

HF hospitalization	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
MacDonald et al, 2011	2	22	1	19	1.73 (0.17, 17.59)
ARC-HF, 2013	0	26	0	26	Not estimatable
AATAC, 2016	32	102	58	101	0.55 (0.39, 0.76)
CASTLE-AF, 2018	37	179	66	184	0.58 (0.41, 0.81)
CAMERA-MRI, 2017	0	33	2	33	0.20 (0.01, 4.01)
AMICA, 2019	15	98	21	100	0.73 (0.40, 1.33)
Random effects model		460		463	0.58 (0.47, 0.73)

Heterogeneity: $I^2 = 0.0\%$; $\tau^2 = 0.00$; $P = 0.73$



C

SAEs	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
CAMTAF, 2014	2	26	1	24	1.85 (0.18, 19.08)
MacDonald et al, 2011	4	22	0	19	7.80 (0.45, 135.94)
ARC-HF, 2013	2	26	0	26	5.00 (0.25, 99.25)
AATAC, 2016	2	102	0	101	4.95 (0.24, 101.86)
CASTLE-AF, 2018	151	179	148	184	1.05 (0.95, 1.15)
CAMERA-MRI, 2017	2	33	2	33	1.00 (0.15, 6.68)
AMICA, 2019	64	98	56	100	1.17 (0.93, 1.46)
Random effects model		486		487	1.07 (0.98, 1.17)

Heterogeneity: $I^2 = 0.0\%$; $\tau^2 = 0.00$; $P = 0.57$

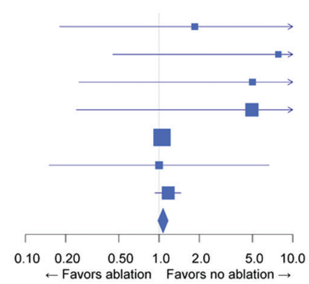


Fig. 2 Forest plot of the improvement in (A) all-cause mortality, (B) HF hospitalization, and (C) severe adverse event with catheter ablation versus medical treatment. AATAC = Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD; AMICA = Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial; ARC-HF = A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; CAMERA-MRI = Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CAMTAF = A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF = Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; HF = heart failure.

RFCA group and the medical therapy group. (RR, 0.69 [95% CI, 0.39-1.23]).

4. DISCUSSION

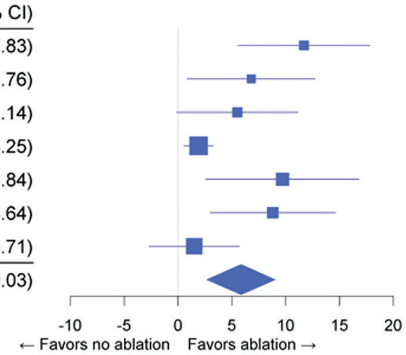
The main findings in this updated meta-analysis are that RFCA of AF in patients with impaired systolic function, including HFmrEF and HfrEF, was associated with better clinical (i.e., HF hospitalization and all-cause mortality), structural (i.e., LVEF improvement), functional capacity (i.e., VO_2max), and quality of life (i.e., the MLHFQ score) outcomes. However, RFCA of AF failed to reduce all-cause mortality in a specific meta-analysis of four RCTs that enrolled patients with LVEF ≤35%.

A search of articles published between 2016 and 2021 identified six other systematic reviews and meta-analyses that indicated a decrease in all-cause mortality and HF hospitalizations with RFCA of AF compared to that with only medical therapy.[6–8,18–20] The favorable outcomes reported with RFCA could be attributed to a reduction in the AF burden and an improvement in LVEF. Our pooled analysis of four RCTs demonstrated greater AF-free survival with RFCA, whereas our analysis of three other RCTs showed substantial reductions in the AF burden with

A

LVEF	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
CAMTAF, 2014	25	8.1	12.2	23	-3.6	9.4	11.70 (5.57, 17.83)
MacDonald et al, 2011	20	8.2	12	17	1.4	5.9	6.80 (0.84, 12.76)
ARC-HF, 2013	24	10.9	11.5	26	5.4	8.5	5.50 (-0.14, 11.14)
AATAC, 2016	94	8.1	4	83	6.2	5	1.90 (0.55, 3.25)
CASTLE-AF, 2018	51	8.7	13.6	37	-1	18.9	9.70 (2.56, 16.84)
CAMERA-MRI, 2017	33	17.7	12.1	33	8.9	12.1	8.80 (2.96, 14.64)
AMICA, 2019	68	8.8	12.6	72	7.3	12.8	1.50 (-2.71, 5.71)
Random effects model	315			291			5.86 (2.68, 9.03)

Heterogeneity: $I^2 = 70.4\%$; $\tau^2 = 11.45$; $P < 0.01$



B

LVEF	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
CAMTAF, 2014	25	8.1	12.2	23	-3.6	9.4	11.70 (5.57, 17.83)
MacDonald et al, 2011	20	8.2	12	17	1.4	5.9	6.80 (0.84, 12.76)
ARC-HF, 2013	24	10.9	11.5	26	5.4	8.5	5.50 (-0.14, 11.14)
CAMERA-MRI, 2017	33	17.7	12.1	33	8.9	12.1	8.80 (2.96, 14.64)
Random effects model	102			99			8.08 (5.14, 11.03)

Heterogeneity: $I^2 = 0.0\%$; $\tau^2 = 0.00$; $P = 0.50$

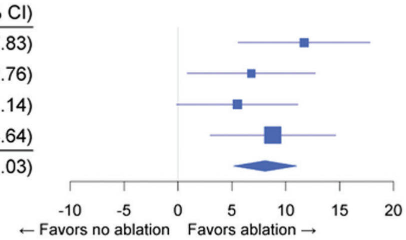


Fig. 3 A, Forest plot of the improvement in LVEF with catheter ablation versus medical treatment. B, A sensitivity analysis was performed to investigate the significant heterogeneity observed among trials with regard to changes in LVEF. LVEF = left ventricular ejection fraction. Other abbreviations as Fig. 2.

RFCA. These results might implicate AF as an important cause of LV systolic dysfunction, independent of tachycardia because most patients in the medical therapy group had good rate control during the follow-up.

In our review, LVEF improvement could be observed with RFCA in six trials, but not in the AMICA trial. A possible explanation of the results of the AMICA trial, which did not demonstrate an LVEF improvement, particularly in cases with a higher prevalence of sinus rhythm in the RFCA group than in the medical therapy group, could be the severity and complexity of HF in patients enrolled in AMICA trial. As shown at the baseline, the RFCA group in AMICA had a lower LVEF (27.6% in AMICA vs. 32.5% in CASTLE-AF), included more patients with New York Heart Association (NYHA) functional classes III or IV (59% in AMICA vs. 30% in CASTLE-AF), and comprised more patients with an implanted cardiac resynchronization therapy defibrillator (44% vs. 28%).[21] Moreover, in the CAMERA-MRI study, we found that patients with left ventricular fibrosis who underwent ablation had less LVEF improvement than those without left ventricular fibrosis.

Furthermore, previous meta-analyses showed that RFCA could improve the 6-MWT distance and VO_{2max}, both of which are independent predictors of survival in HF patients.[22,23] However, the inclusion of the AMICA trial data in the analysis led to no difference in the 6-MWT distance. The AMICA trial was terminated early because of futility, and only 140 patients were enrolled for analysis. Therefore, we performed a specific meta-analysis of four RCTs that enrolled patients with LVEF ≤35% and found no difference in all-cause mortality between the RFCA and medical therapy groups. This result implied that not all patients with AF and HF would benefit from the RFCA of AF despite the restoration of sinus rhythm (SR). Patients with less severe HF and a better LVEF might have a greater tendency to benefit from SR restoration than those with more severe HF.[21]

In addition, the subgroup analysis of the CASTLE-AF trial could support the abovementioned inference. Sohns et al[24] found that, in the RFCA group, patients with moderate/severe (≥20% and <35%) baseline LVEF experienced the primary endpoint less often than patients with severe (<20%) baseline LVEF. Moreover, patients with NYHA functional class I/II at the time of treatment had better clinical outcomes. Consequently, although catheter ablation should be performed early to break the vicious cycle of AF and HF,[25] based on the CASTLE-AF, AMICA, and CAMERA-MRI trials, patients with more severe HF may benefit less from catheter ablation of AF than patients with milder disease. In summary, this updated meta-analysis provides evidence of the benefits for AF ablation in HF, and the specific meta-analysis of RCTs enrolling patients with LVEF ≤35% indicated the stratification that is required to identify potential patient groups that may benefit more from RCFA.

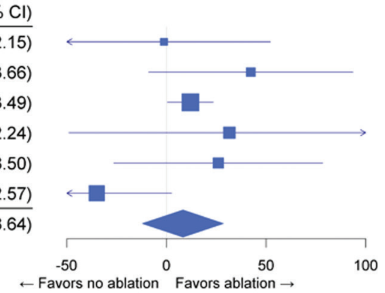
This study has several limitations. First, a meta-analysis may be biased when the literature search fails to identify all relevant trials. To minimize these risks, we performed an extensive search by using multiple literature engines and trial databases and included recent review articles. Second, the success of RFCA for AF relies largely on experienced operators, which should be considered when generalizing the results from clinical trials to real-world clinical practice.

In conclusion, compared with medical therapy, RFCA for AF in the setting of HF with impaired systolic function is associated with better clinical (i.e., HF hospitalization and all-cause mortality), structural (i.e., LVEF improvement), functional capacity (i.e., VO_{2max}), and quality of life (i.e., MLHFQ score) outcomes. However, RFCA for AF failed to reduce all-cause mortality in

A

6-minute walk distance	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
MacDonald et al, 2011	17	20.1	76.5	15	21.4	77.4	-1.30 (-54.75, 52.15)
ARC-HF, 2013	24	19.67	109.8	26	-22.67	69.02	42.34 (-8.98, 93.66)
AATAC, 2016	94	22	41	83	10	37	12.00 (0.51, 23.49)
CASTLE-AF, 2018	50	-6.9	188.8	35	-38.5	185.2	31.60 (-49.04, 112.24)
CAMERA-MRI, 2017	33	55	108.8	33	29	108.8	26.00 (-26.50, 78.50)
AMICA, 2019	72	46	114.2	70	81	114.2	-35.00 (-72.57, 2.57)
Random effects model	290			262			8.26 (-12.13, 28.64)

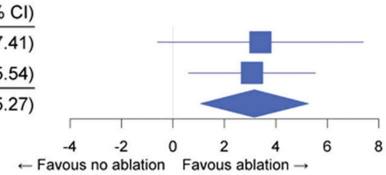
Heterogeneity: $I^2 = 37.2\%$; $\tau^2 = 225.62$; $P = 0.16$



B

Peak oxygen consumption	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
CAMTAF, 2014	25	1.4	7.05	23	-2	7.1	3.40 (-0.61, 7.41)
ARC-HF, 2013	24	2.13	5.4	26	-0.94	3.13	3.07 (0.60, 5.54)
Random effects model	49			49			3.16 (1.06, 5.27)

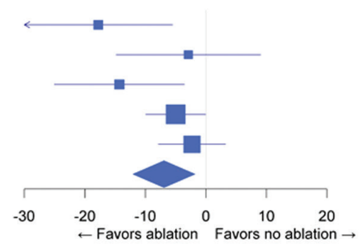
Heterogeneity: $I^2 = 0.0\%$; $\tau^2 = 0.00$; $P = 0.89$



C

Quality of life	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
CAMTAF, 2014	25	-18	22	23	-0.2	21.5	-17.80 (-30.11, -5.49)
MacDonald et al, 2011	20	-5.7	19.7	18	-2.8	17.9	-2.90 (-14.85, 9.05)
ARC-HF, 2013	24	-19.6	22.3	26	-5.3	15.7	-14.30 (-25.07, -3.53)
AATAC, 2016	102	-11	19	101	-6	17	-5.00 (-9.96, -0.04)
AMICA, 2019	79	-11.2	17.8	78	-8.9	17.8	-2.30 (-7.87, 3.27)
Random effects model	250			246			-6.92 (-12.03, -1.81)

Heterogeneity: $I^2 = 49.2\%$; $\tau^2 = 15.52$; $P = 0.10$



D

AF recurrence	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
CAMTAF, 2014	5	26	24	24	0.21 (0.10, 0.44)
MacDonald et al, 2011	10	22	19	19	0.47 (0.30, 0.73)
ARC-HF, 2013	3	26	26	26	0.13 (0.05, 0.35)
AATAC, 2016	31	102	67	101	0.46 (0.33, 0.63)
Random effects model		176		170	0.32 (0.20, 0.52)

Heterogeneity: $I^2 = 66.9\%$; $\tau^2 = 0.15$; $P = 0.03$

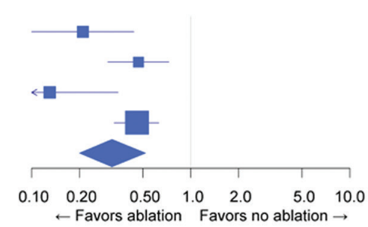


Fig. 4 Forest plot of the improvement in (A) distance on the 6-minute walk test and (B) peak oxygen consumption (C) quality of life and (D) AF recurrence with catheter ablation versus medical treatment. AF = atrial fibrillation. Other abbreviations as Fig. 2.

the specific meta-analysis of four randomized trials that enrolled patients with LVEF ≤35%, and thereby indicated the necessary stratification criteria to identify patients who would potentially benefit more from the intervention.

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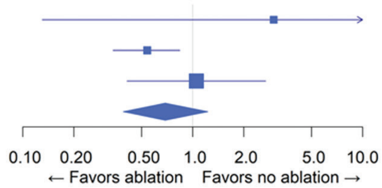
A

All-cause mortality	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
ARC-HF, 2013	1	26	0	26	3.00 (0.13, 70.36)
CASTLE-AF, 2018	24	179	46	184	0.54 (0.34, 0.84)
AMICA, 2019	8	95	8	100	1.05 (0.41, 2.69)
Random effects model		300		310	0.69 (0.39, 1.23)

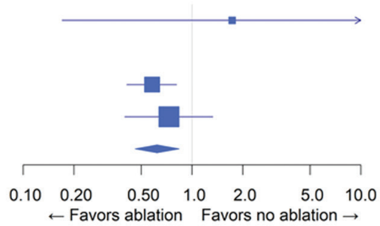
Heterogeneity: I^2 = 22.5%; τ^2 = 0.08; *P* = 0.28



B

HF hospitalization	Ablation, n		No Ablation, n		
Study, Year	Events	Total	Events	Total	RR (95% CI)
MacDonald et al, 2011	2	22	1	19	1.73 (0.17, 17.59)
ARC-HF, 2013	0	26	0	26	Not estimatable
CASTLE-AF, 2018	37	179	66	184	0.58 (0.41, 0.81)
AMICA, 2019	15	98	21	100	0.73 (0.40, 1.33)
Random effects model		325		329	0.62 (0.46, 0.84)

Heterogeneity: I^2 = 0.0%; τ^2 = 0.00; *P* = 0.55



C

LVEF	Ablation			No Ablation			Mean Difference
Study, Year	Total, n	Mean	SD	Total, n	Mean	SD	(95% CI)
MacDonald et al, 2011	20	8.2	12	17	1.4	5.9	6.80 (0.84, 12.76)
ARC-HF, 2013	24	10.9	11.5	26	5.4	8.5	5.50 (-0.14, 11.14)
CASTLE-AF, 2018	51	8.7	13.6	37	-1	18.9	9.70 (2.56, 16.84)
AMICA, 2019	68	8.8	12.6	72	7.3	12.8	1.50 (-2.71, 5.71)
Random effects model	163			152			5.16 (1.68, 8.64)

Heterogeneity: I^2 = 35.6%; τ^2 = 4.49; *P* = 0.20

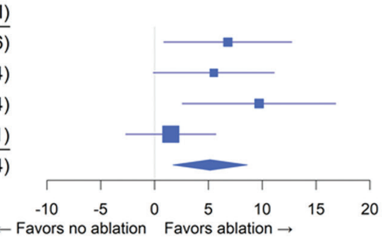


Fig. 5 Forest plot of the improvement in (A) all-cause mortality, (B) HF hospitalization, and (C) LVEF improvement with catheter ablation versus medical treatment. LVEF = left ventricular ejection fraction, HF = heart failure. Other abbreviations as Fig. 2.

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