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CLINICAL INVESTIGATIONS

Meta-analysis of randomized controlled trials on atrial fibrillation ablation in patients with heart failure with reduced ejection fraction

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Background: The role of catheter ablation (CA) is increasingly recognized as a reasonable therapeutic option in patients with atrial fibrillation (AF) and heart failure (HF).

Hypothesis: We aimed to compare CA to medical therapy in AF patients with HF with reduced ejection fraction (HFrEF).

Methods: We searched the literature for randomized clinical trials comparing CA to medical therapy in this population.

Results: Six trials with a total of 775 patients were included. AF was persistent in 95% of patients with a mean duration of 18.5 ± 23 months prior enrollment. The mean age was 62.2 ± 7.8 years, mostly males (83%) with mean left ventricular ejection fraction (LVEF) of 31.2 ± 6.7%. Compared to medical therapy, CA has significantly improved LVEF by 5.9% (Mean difference [MD] 5.93, confidence interval [CI] 3.59-8.27, $P < 0.00001$, $I^2 = 87\%$), quality of life, (MD −9.01, CI −15.56, −2.45, $P = 0.007$, $I^2 = 47\%$), and functional capacity (MD 25.82, CI 5.46-46.18, $P = 0.01$, $I^2 = 90\%$). CA has less HF hospital readmissions (odds ratio [OR] 0.5, CI 0.32-0.78, $P = 0.002$, $I^2 = 0\%$) and death from any cause (OR 0.46, CI 0.29-0.73, $P = 0.0009$, $I^2 = 0\%$). Freedom from AF during follow-up was higher in patients who had CA (OR 24.2, CI 6.94-84.41, $P < 0.00001$, $I^2 = 81\%$.

Conclusion: CA was superior to medical therapy in patients with AF and HFrEF in terms of symptoms, hemodynamic response, and clinical outcomes by reducing AF burden. However, these findings are applicable to the very specific patients enrolled in these trials.

KEYWORDS

ablation, atrial fibrillation, heart failure

1 | INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are common medical conditions that often coexist. Up to 50% of patients with HF have AF while AF can also lead to HF and tachycardia induced cardiomyopathy.[1] The presence of AF and HF is associated with increased morbidity, mortality, and healthcare costs.[2,3] Restoration and maintenance of sinus rhythm in patients with AF and HF are often attempted to improve symptoms.[4] However, this approach is limited by suboptimal efficacy and side effects of antiarrhythmic drugs.[5,6] Catheter ablation (CA) has emerged as an effective therapeutic option over the last two decades for treatment of AF.[7] Several studies have evaluated the role of AF ablation in patients with HF with reduced ejection fraction (HFrEF) and demonstrated that sinus rhythm could be often restored with a significant improvement in left ventricular ejection function (LVEF) and symptoms.[8,9] However, most of these studies were small and observational. Recently, several randomized control trials (RCTs) compared the efficacy and outcomes of CA vs medications in patients

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with AF and HFrEF and reported new findings. Therefore, we performed an updated meta-analysis of RCTs comparing CA to medical therapy in patients with AF and HFrEF, not only to evaluate the directionality of the trends but also to refine measures and confidence intervals of odds ratios. Furthermore, this meta-analysis might help mitigate the selection bias, which is a major limitation of these trials.

2 | METHODS

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two authors (T.M.H., R.G.) separately searched PubMed, Web of Science, CINAHL (Cumulative Index of Nursing and Allied Health Literature), and Cochrane Library databases for studies comparing CA to medical therapy in patients with AF and HF from January 1966 through February 2018 (Figure 1). We used the following keywords in various combinations: atrial fibrillation (AF), ablation, and heart failure. Additional details of search terms and strategy are provided in the Supporting Information, Appendix S1. The bibliography of selected manuscripts and review articles were also manually searched for additional studies which were not identified in the original search. Titles and abstracts were then screened to identify studies for full text review.

RCTs reporting AF treatment with CA vs medical therapy in patients with HF and fulfilling the predefined inclusion and exclusion criteria were selected for inclusion in the systematic review and quantitative analysis. Studies were included in the meta-analysis if they included the following criteria: (a) history of AF with a diagnosis of HF, (b) it was a RCT to treat AF with CA vs medical therapy (rate or

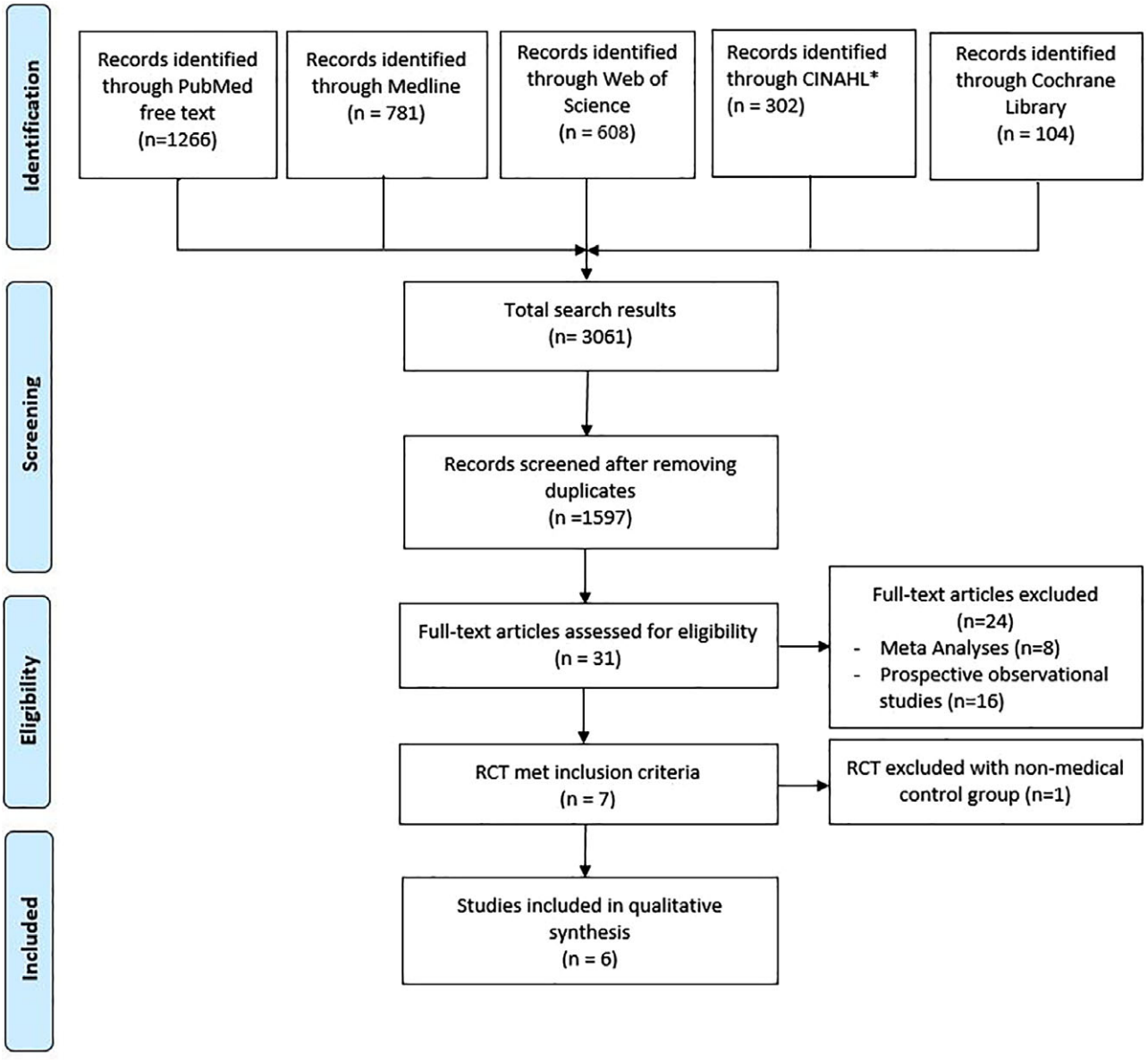

FIGURE 1 Flow diagram of the literature search

rhythm control), (c) reported mean differences and/or number of events for LVEF, HF related hospital admission, 6-minute walk test distance (6MWTD), and overall mortality, and (d) adult subjects (> 18 years of age). Exclusion criteria included (a) published abstract without full text publication, (b) studies assessing the impact of CA on AF without medical treatment group, and (c) studies lacking endpoint measures. We excluded the study by Khan et al[10] because it compared rate control using atrioventricular nodal ablation rather than medical therapy. Echocardiography was the primary imaging method to estimate the LVEF. However, given 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 HF. Two authors independently performed the study selection and data extraction using a standardized data extraction form (T.M.H., R.G.). Differences were resolved by consensus. Quality assessment was performed using the modified Jadad scale (Table S2) and Cochrane Collaboration tool (Table S3) for assessing risk of bias.

Data from selected studies were extracted and used to estimate the mean difference (MD) and its 95% confidence interval (CI) for continuous variables and odds ratio (OR) and 95% CI for dichotomous variables. Cochrane Review Manager (RevMan) 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark) was used for meta-analysis. The meta-analysis was conducted with the random effects model using Mantel-Haenszel weighting for dichotomous variables, and random inverse variance method for continuous variables. Heterogeneity was tested using χ^2, Tau-square and *I*-square (I^2) statistics. I^2 index values of 25% to 50%, 51% to 75% and >75% were considered as low, moderate, and high heterogeneity, respectively. Publication bias was analyzed by visually inspecting the funnel plot. Subgroup analyses were performed on the type of medical therapy (rate control only vs rate and/or rhythm control). Sensitivity analysis based on quality score was performed by removing one study at a time and repeating analysis to identify any particularly influential study. Excel 2013 (Microsoft, Redmond, WA) was used to estimate means and SD for continuous variables in pooled groups of CA and medical therapy patients, after which *Z* tests were conducted to compare pooled groups of CA and medical therapy patients for any continuous variables. We calculated the mean and SD for all the variables that were reported as median and interquartile range (IQR) using specific formula.[11] A two sided *P* value of <0.05 was considered statistically significant for all analyses.

3 | RESULTS

A total of 1597 articles were screened, only six trials with a total of 775 patients met the inclusion criteria (CA 388 and medical therapy 387).[12–17] The basic characteristics of the included studies and patients are summarized in Tables 1 and 2. The mean age was 62.2 ± 7.8 years, and 83% were males. The median follow-up is 9 months (IQR 6-24) with an average duration of follow-up ranging from 6 to 37 months. The mean LVEF was 31.2 ± 6.7% and the left atrial diameter was 48.3 ± 6.2 mm. Most patients (96.7%) had New York Heart Association (NYHA) class of II or III. Persistent AF accounted for 95% of the population. The mean duration of AF prior enrollment was 18.5 ± 23 months, with most patients in AF for 1 to 2 years, except for one trial in which AF duration was about 4 years. Postablation blanking period ranged from 1 to 3 months. CA procedural characteristics and complications are reported in Table S1.

Compared to medical therapy, CA significantly improved LVEF by 5.9% (mean difference [MD] 5.93, CI 3.59-8.27, $P < 0.00001$, $I^2 = 87\%$) (Figure S1). CA is associated with significant improvement in quality of life, measured by the Minnesota living with HF (MLWHF) questionnaire (MD −9.01, CI −15.56, −2.45, $P = 0.007$, $I^2 = 47\%$) (Figure 2A). There was also a significant improvement in functional capacity measured by 6MWTD (MD 25.82, CI 5.46-46.18, $P = 0.01$, $I^2 = 90\%$) (Figure 2B), and peak oxygen consumption (VO_2) (MD 3.16, CI 1.04-5.29, $P = 0.004$, $I^2 = 0\%$) (Figure 2C). Patients in the CA group had less HF hospital readmissions (OR 0.5, CI 0.32-0.78, $P = 0.002$, $I^2 = 0\%$) (Figure 3B), and death from any cause (OR 0.46, CI 0.29-0.73, $P = 0.0009$, $I^2 = 0\%$) (Figure 3A). Freedom from AF during follow-up was higher in patients who had CA (OR 24.2, CI 6.94-84.41, $P < 0.00001$, $I^2 = 81\%$) (Figure 3C).

However, there was no difference between both groups in regards to; cardiovascular death (OR 0.62, CI 0.14-2.68, *P* 0.52, $I^2 = 29\%$) (Figure S1, all causes of hospital admissions (OR 0.49, CI 0.19-1.22, $P = 0.12$, $I^2 = 76\%$) (Figure S3), cerebrovascular accidents (OR 0.49, CI 0.18-1.35, $P = 0.17$, $I^2 = 0\%$) (Figure S4), or all adverse events (OR 1.18, CI 0.44-3.15, $P = 0.75$, $I^2 = 29\%$) (Figure S5). Sensitivity analysis showed that removal of the Prabhu et al trial had minor impact on the results of the 6MWTD but not on other endpoints (Figure S6). Removing other trials did not impact the effect measure significantly for the other outcomes. Visual evaluation of the funnel plot shows no evidence of publication bias (Figure S7). There was a statistically significant difference in the LVEF and freedom from AF during follow-up between the subgroup of the rate control only vs rate and/or rhythm control.

The magnitude of LVEF improvement associated with CA was higher when compared to rate control only strategy (MD 8.40, CI 6.21-10.58, $P = 0.00001$, $I^2 = 0\%$), than the rate and/or rhythm control strategy (MD 3.72, CI 0.29-7.14, $P = 0.03$, $I^2 = 96\%$), Figure S1. CA was also associated with improvement in 6MWTD when compared to rate control only (MD 24.65, CI 11.18-38.12, $P = 0.0003$, $I^2 = 0\%$); however, there was no difference between CA vs rate and/or rhythm control (MD 29.28, CI −3.63 to 62.20, $P = 0.08$, $I^2 = 97\%$), Figure 2B. CA was associated with fewer HF hospital readmissions when compared to rate and/or rhythm control (OR 0.41, CI 0.28-0.59, $P = 0.00001$, $I^2 = 0\%$); however, there was no difference when compared to rate control only (OR 0.92, CI 0.24-3.56, $P = 0.90$, $I^2 = 0\%$), Figure 3B. CA was associated with higher rate of freedom from AF when compared to rate control only vs rate and/or rhythm control (OR 205.15, CI 35.63-1181.18, $P = 0.00001$, $I^2 = 20\%$), (OR 5.30, CI 3.68-7.62, $P = 0.00001$, $I^2 = 0\%$), Figure 3C.

4 | DISCUSSION

This meta-analysis of six RCTs showed that CA in a highly selected population of patients with AF and HFrEF significantly improved

TABLE 1 Trials baseline characteristics

Trials	MacDonald et al 2010[12]		Jones et al 2013[13]		Hunter et al 2014[14]		Di Biase et al 2016[15]		Prabhu et al 2017[16]		Marrouche et al 2018[17]		All trials			
Groups	Ablation	Medical	Ablation	Medical	Ablation	Medical	Ablation	Medical	Ablation	Medical	Ablation	Medical	Ablation	Medical	Total	*P*
Patient numbers	22	19	26	26	26	24	102	101	33	33	179	184	388	387	775	
Mean follow-up mo	6		12		6		24		6		37.6		15			
Male	17 (77%)	15 (79%)	21 (81%)	24 (92%)	25 (96%)	23 (96%)	77 (75%)	74 (73%)	31 (94%)	29 (88%)	156 (87%)	155 (84%)	327 (84%)	320 (83%)	647 (83%)	
Age, y M ± SD	62.3 ± 6.7	64.4 ± 8.3	64 ± 10	62 ± 9	55 ± 12	60 ± 10	62 ± 10	60 ± 11	59 ± 11	62 ± 9.4	64 ± 2.5*	64 ± 2.9*	62.1 ± 7.9	62.4 ± 7.7	62.2 ± 7.8	0.54
LVEF, % M ± SD	36.1 ± 11.9	42.9 ± 9.6	22 ± 8	25 ± 7	32 ± 8	34 ± 12	29 ± 5	30 ± 8	32 ± 9.4	34 ± 7.8	31.5 ± 1.7*	32.5 ± 2.2*	30.5 ± 6.2	32.1 ± 7.1	31.2 ± 6.7	0.0008
LAD, mm M ± SD	NA	NA	50 ± 6	46 ± 7	52 ± 11	50 ± 10	47 ± 4.2	48 ± 4.9	48 ± 5.5	47 ± 8.2	48 ± 1.5	49.5 ± 8.3*	48.1 ± 4.6	48.6 ± 7.6	48.3 ± 6.2	0.28
6MWTD, m M ± SD	278 ± 131	331 ± 117	416 ± 78	411 ± 109	NA	NA	348 ± 111	350 ± 130	491 ± 147	489 ± 132	NA	NA	375 ± 133	382 ± 137	378.5 ± 135	0.62
MLWHF M ± SD	64.3 ± 15	54.9 ± 22.3	42 ± 23	49 ± 21	NA	NA	52 ± 24	50 ± 27	NA	NA	NA	NA	52 ± 23.4	50 ± 25.3	51 ± 24.3	0.48
BNP, pn/mL M ± SD	2550 ± 2150	1846 ± 1687	412 ± 324	283 ± 285	NA	NA	NA	NA	266 ± 210	256 ± 208	NA	NA	933 ± 1501	652 ± 1083	792 ± 1315	0.17
AF duration before enrollment, mo M ± SD	44 ± 36.5	64 ± 47.6	23 ± 22	24 ± 29	24 ± 4*	27 ± 9*	8.6 ± 3.2	8.4 ± 4.1	23 ± 18	21 ± 15	NA	NA	18 ± 21.1	19 ± 24.8	18.5 ± 23	0.45
AF monitoring method during follow-up	ECG and 24 h Holter monitor		ECG, 48 h Holter monitor and existing implanted devices		ECG and 48 h Holter monitor		Remote monitoring using existing implanted devices		ECG and 24 h Holter monitor and existing implanted devices		Remote monitoring using existing implanted devices					
AF freedom during follow-up, %	10 (50%)	0 (0%)	22 (84%)	0 (0%)	19 (73%)	0 (0%)	73 (71%)	37(101%)	33 (100%)	0 (0%)	113 (63%)	41 (22%)	270 (80%)	78 (20%)	348 (45%)	0.0001

Abbreviations: 6MTD, 6-minute walk test distance; AF, atrial fibrillation; BNP, Beta natriuretic peptide; ECG, Electrocardiogram; LAD, Left atrial diameter; LVEH, left ventricular ejection fraction; MLWHF, Minnesota living with heart failure.

* indicates that any value with * sign in table 1 is calculated from the main manuscript data.

TABLE 2 Baseline characteristics of the patients

Authors, year	MacDonald et al 2010[12]	Jones et al 2013[13]	Hunter et al 2014[14]	Di Biase et al 2016[15]	Prabhu et al 2017[16]	Marrouche et al 2018[17]
Age Mean ± SD	63.3 ± 7.5	63 ± 9.5	57.4 ± 11	62 ± 10	59 ± 11	64 (median)
Persistent AF, %	100	100	100	100	100	70
BMI	30 ± 5.6	29 ± 4.6	NA	30 ± 8	30 ± 7.5	29.1
Hypertension, %	61	33	NA	45	39	72
Diabetes, %	26	23	NA	22	12	28
Prior TIA/stroke, %	9.8	11.8	NA	NA	6.1	12
COPD, %	22.0	13.7	NA	NA	NA	NA
OSA, %	NA	NA	NA	45	36	NA
NYHA class, %						
NYHA class I	0	0	0	NA	NA	11
NYHA class II	10	52	45	NA	NA	59
NYHA class III	90	48	55	NA	NA	28
NYHA class IV	0	0	0	NA	NA	2
NICM, %	51.4	67.5	74	38	100	60
Amiodarone/antiarrhythmic, %	NA	34	53.8	0	24	28
ACEI/ARB, %	95	98	NA	92	94	94
Beta blocker, %	88	92	NA	76	97	92
Aldosterone antagonist, %	31.6	36.5	NA	45	33	NA
Digoxin, %	51.3	54	NA	NA	NA	20

Abbreviations: ACEI/ARB, Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; NICM, Nonischemic cardiomyopathy; NYHA, New York Heart Association; OSA, Obstructive sleep apnea; TIA, Transient ischemic attack.

LVEF, quality of life and functional capacity, as measured by MLWHF, 6MWTD, and peak VO_2 compared to medical therapy. Furthermore, CA is associated with a significant reduction in HF related admission and total mortality without significant reduction in cardiovascular death or stroke in comparison to medications. There is a strong correlation between LVEF and peak VO_2 level in predicting cardiovascular events.[18,19] Several studies have shown that even modest improvement in peak VO_2 is associated with improved survival in patients with AF and HF.[20,21] These findings are consistent with our results as these improvements in LVEF and peak VO_2 were associated with favorable clinical outcomes (eg, less HF readmissions).

CA is a well-established therapy for patients with AF refractory to antiarrhythmic drugs.[22,23] This meta-analysis addresses the rapidly evolving role of CA in patients with AF and HFrEF.[24] Traditionally, CA in patients with AF and HFrEF has been deemed less desirable due to a potential lower success rate and higher procedural complications. However, the available efficacy and safety data on CA in patients with HFrEF is based mainly on small observational studies.[9,25–27] Previous meta-analysis by Al Halabi et al[28] included four RCTs showed a favorable symptom and hemodynamic response to CA in this population.[10,12–14,28] Since that meta-analysis was published, three additional RCTs (AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device), CAMERA-MRI (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction), and CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation)) comparing CA to medical therapy have reported new findings, such as a mortality benefit with CA and the use of magnetic resonance imaging to define ventricular scar burden to predict a better response to CA.[15–17] These new findings prompted this new meta-analysis. We only retained RCTs in our meta-analysis to minimize selection bias and the impact of unmeasured confounding factors. All available published data from these trials were utilized including some additional data provided in the aforementioned meta-analysis by Al Halabi et al.[28]

The included studies compared rhythm control with CA to a strategy of using medications either for rate or rhythm control, provided that there was no mortality difference between rate and rhythm control with medications in this population.[29] Four studies used rate control with medications as the control group while two studies used a rhythm control approach, mostly with Amiodarone (all AATAC patients and about 30% of patients in CASTLE-AF).[12–17] Sensitivity analyses excluding these two alternative options used in the control group did not significantly affect the overall results described in this meta-analysis. However, the high degree of heterogeneity noted in LVEF improvement, quality of life measures, functional capacity, and freedom from AF was improved after removal of AATAC and CASTLE-AF. However, there is a low level of statistical heterogeneity for hard clinical end point outcomes, all-cause mortality, and HF readmission (I^2 0%). The overall rate of major complications associated with CA was 5.2% and includes stroke, pericardial effusion, and vascular complications. Based on the present analysis and previous meta-analysis, the rate of CA complications in patients with HFrEF was similar to that reported in general population, Table S1.[28,30,31] This is likely because the procedures were performed by experienced operators in high volume medical centers.

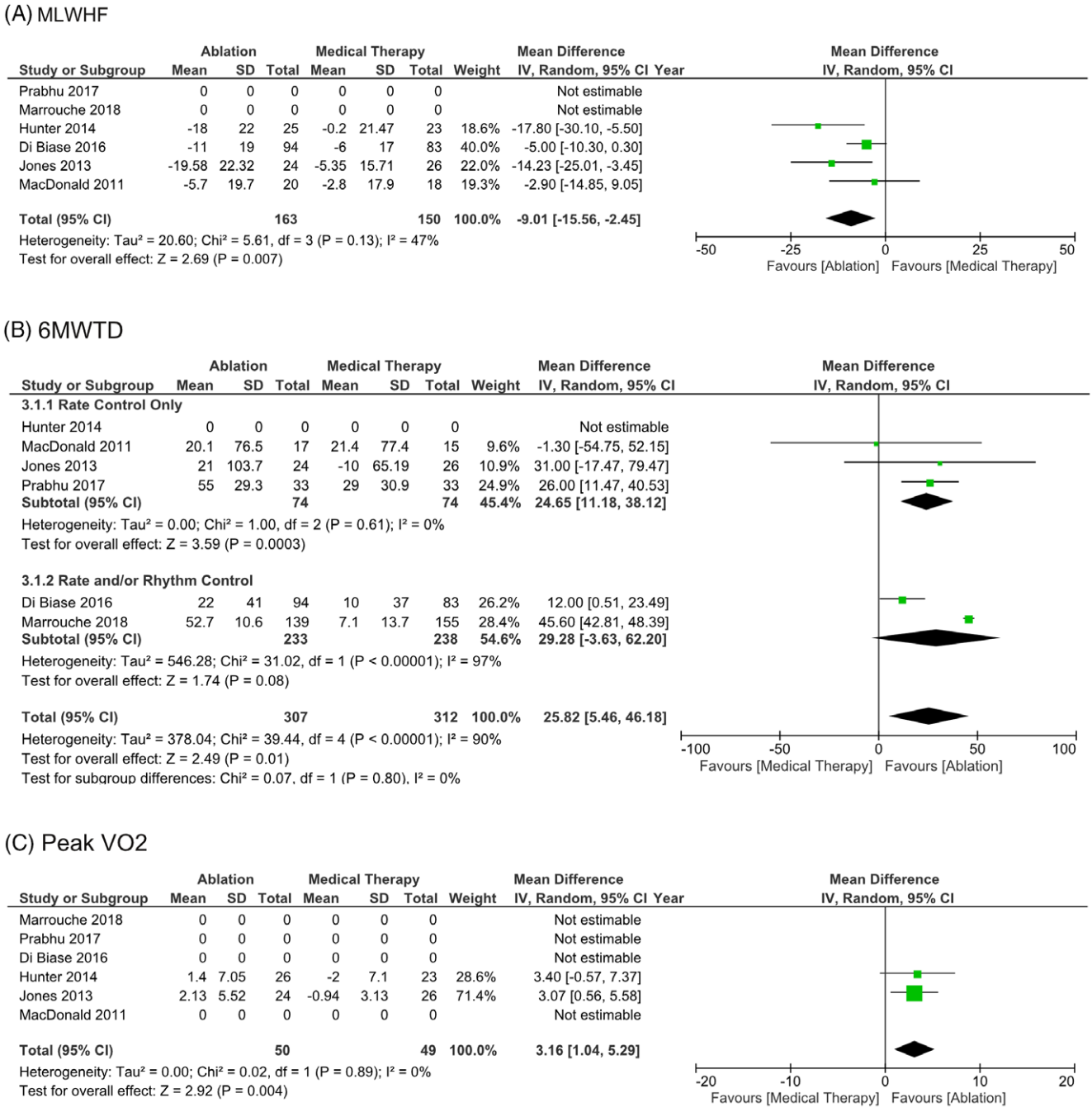

FIGURE 2 A, Health related quality of life measured by Minnesota living with heart failure (MLWHF) in patients with heart failure with reduced ejection fraction and AF randomized to CA vs medical therapy. B, Functional capacity measured by 6-minute walk test distance (6MWTD) in patients with heart failure with reduced ejection fraction and AF randomized to CA vs medical therapy. C, Peak VO_2 in patients with heart failure with reduced ejection fraction and AF randomized to CA vs medical therapy

There was a significant reduction in total mortality from any cause with CA compared to medical therapy, although this has not been demonstrated so far with CA of AF in non-HF patients.[32] The current indication for CA in AF aims to alleviate patients' symptoms and improve their quality of life. This significant finding of mortality benefit, however, needs to be interpreted very cautiously. The decreased total mortality without a difference in cardiovascular mortality, adverse events or stroke is puzzling, as one would expect total mortality to be driven by cardiovascular events. However, we must acknowledge that only two studies with a relatively small number of patients reported cardiovascular deaths, making it unlikely to reach statistical significance for this outcome. Furthermore, the CASTLE-AF study, which is driving the reduction in total mortality in our meta-analysis, has some significant flaws such as a substantial number of patients lost to follow up, which questions the accuracy of mortality outcomes.[17]

There is a complex relationship between AF and HFrEF with HF leading to AF through neurohormonal activation and atrial remodeling. At the same time, AF predisposes to HF via rapid and irregular ventricular rates and loss of atrioventricular synchrony.[1,33,34] An important

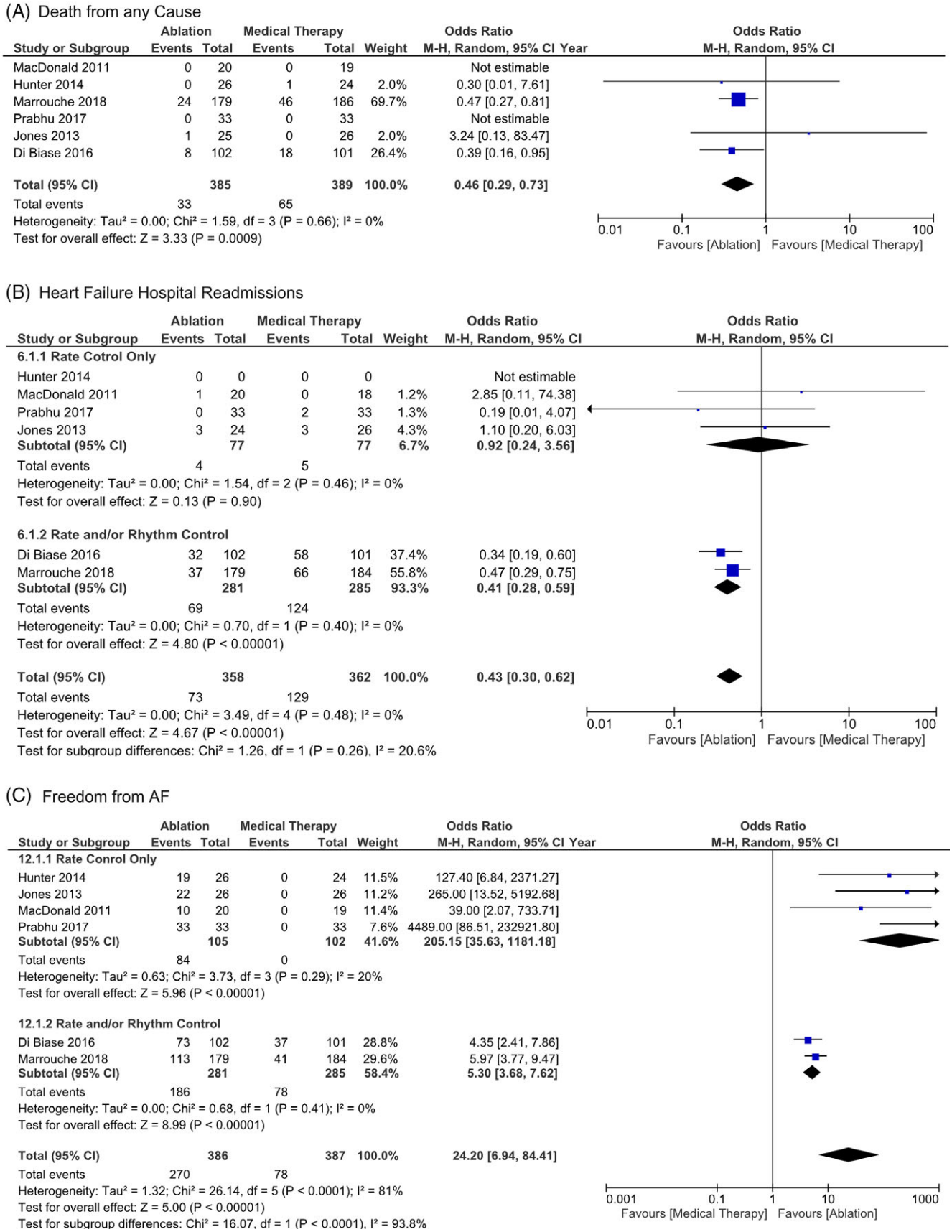

FIGURE 3 A, Death from any cause in patients with heart failure with reduced ejection fraction and AF randomized to CA vs medical therapy. B, Heart failure hospital readmissions in patients with heart failure with reduced ejection fraction and AF randomized to CA vs medical therapy. C, Freedom from AF in patients with heart failure with reduced ejection fraction and atrial fibrillation (AF) randomized to catheter ablation (CA) vs medical therapy

observation from our analysis is that in all the included studies, the use of CA was consistently associated with improvement in LVEF during follow-up. This finding highlights the important role of sinus rhythm in preserving normal hemodynamic function of the left ventricle. The potential mechanisms for an improved LVEF after CA include better rate control and rhythm regularity achieved with sinus rhythm, restoration of atrial emptying, and improved diastolic filling, all of which can lead to an augmented cardiac output. It is notable that CA did not completely eliminate AF in all patients. However, there was a substantial reduction in AF burden, Table S1. This decrease in AF burden was enough to show clinical benefits.

This study has some limitations. In addition to a relatively small number of patients and shorter follow-up duration in the majority of the included studies, there is an obvious selection bias due to the type of patients offered to participate in these RCTs. Patients with advanced HF such as those with NYHA class IV, mostly excluded from these studies, might not have had such favorable outcomes. For instance, MacDonald et al[12] included patients with more advanced HFrEF as evidenced by a lower mean LVEF, higher baseline brain natriuretic peptide level, longer duration of AF in the CA arm (44 months), and more patients with NYHA class III, Table 1.[12] In this trial, only 50% of the patients successfully maintained sinus rhythm with no improvement in the LVEF. There has been significant heterogeneity within and between the studies regarding the use of rate control medication with and without antiarrhythmic agents in the control group. Certain outcomes such as 6MWTD, MLWHF, and cardiovascular mortality were not included in all the studies. The typical patients included in this meta-analysis were younger males with moderately depressed LVEF, shorter duration of persistent AF (mean 18.5 months) and less likely to have coronary artery disease, Table 2. Therefore, the results of our analysis may not be applicable to older patients with severely depressed LVEF and/or longer duration of AF (> 2 years).

We were not able to separate ischemic from nonischemic cardiomyopathy in our analysis. Patients with nonischemic cardiomyopathy may have an under-recognized tachycardia mediated cardiomyopathy, which is associated with considerable improvement in LVEF after restoration of sinus rhythm as demonstrated in the CAMERA-MRI study.[16,35] Another limitation of the included studies is that the ablation strategy was not uniform, Table S1. Although pulmonary vein isolation was the main ablation strategy, variable additional ablation lesions were performed. Finally, although CA procedures were done on oral anticoagulants, no anticoagulant details such as the type of anticoagulant or the dose were available in most studies.

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None.

Conflicts of interest

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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