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ORIGINAL ARTICLE

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Catheter ablation for treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis

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Abstract

Background: Atrial fibrillation (AF) among patients with heart failure with reduced ejection fraction (HFrEF) is associated with adverse clinical outcomes. Our primary aim was to evaluate patient-centered outcomes and surrogate outcomes following catheter ablation (CA) of AF among patients with HFrEF compared to standard medical therapy with or without device therapy (atrioventricular node ablation and cardiac resynchronization therapy).

Methods: A systematic literature review was performed limiting our searches to randomized control trials reporting outcomes of CA compared to standard medical therapy with or without device therapy were included. Patient-centered outcomes were relative reduction in all-cause mortality, heart failure readmissions, and recurrence of AF. Surrogate outcomes of interest were change in ejection fraction, change in peak oxygen consumption, reduction in brain natriuretic peptide levels, change in 6-minute walk distance, and change in Minnesota living with heart failure score.

Results: Seven randomized control trials (Patient n = 721) met our inclusion criteria. All trials used radiofrequency energy for CA of AF. CA for AF was associated with significantly lower all-cause mortality (Risk ratio [RR] = 0.52, 95% confidence interval [CI] = 0.35-0.76, $P = 0.001$, $I^2 = 0\%$), lower rate of heart failure readmission (RR = 0.58, 95% CI = 0.46-0.74, $P < 0.001$, $I^2 = 0\%$) and lower rate of AF recurrence (RR = 0.33, 95% CI = 0.22-0.50, $P < 0.001$, $I^2 = 68\%$) as compared to standard medical therapy. Surrogate outcomes showed a similar benefit favoring CA.

Conclusion and Relevance: Catheter ablation for AF in HFrEF is associated with improvement in patient-centered outcomes and surrogate outcomes when compared to standard medical therapy with or without device therapy.

KEYWORDS
atrial fibrillation, catheter ablation, hospital readmission, mortality, systolic heart failure

Agasthi and Lee equally contributed to the manuscript.

1 | INTRODUCTION

Atrial fibrillation (AF) is increasingly seen in patients with heart failure with reduced ejection fraction (HFrEF).[1,2] Coexistence of AF and HFrEF increases the risk of death, heart failure readmission, and stroke.[3–6] Neurohormonal activation and adverse myocardial remodeling in patients with HFrEF are associated with increased venous pressures, atrial fibrosis, and electrolyte abnormalities which in turn contribute to the development of AF. AF in the setting of increased sympathetic tone seen in HFrEF is associated with rapid ventricular rates that often leads to worsening heart failure, tachycardia-induced cardiomyopathy, and worsening of HFrEF, thereby setting up a vicious cycle.[7–9] Limited efficacy and high risk of adverse events with antiarrhythmic drug (AAD) therapy have increased the interest in utilizing catheter ablation (CA), given its efficacy in symptomatic patients who failed AAD therapy.[10,11]

The aim of our study is to examine whether CA of AF in patients with HFrEF is associated with improvement in patient-centered and surrogate outcomes. We reviewed randomized controlled clinical trials (RCTs) that assessed the efficacy of CA against standard medical therapy or device therapy (atrioventricular node [AVN] ablation with cardiac resynchronization therapy [CRT]) in patients with AF and HFrEF.

2 | METHODS

2.1 | Protocol and registration

The protocol was developed by the Division of Cardiac Electrophysiology services (PA, JZL, and SKM) and institutional review board review was exempted given the nature of study. Methods of the systematic review and meta-analysis as well as the inclusion and exclusion criteria were prespecified in advance and were documented in the protocol registered on "PROSPERO".[12] The current meta-analysis was performed using the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Table S1 in Supporting Information).[13]

2.2 | Eligibility criteria

We selected all published and unpublished parallel arm randomized controlled clinical trials including any adult population with AF and HFrEF comparing CA for treatment of AF to standard medical therapy with or without device therapy (AVN ablation with CRT). We did not restrict our study selection based on outcomes; however, we were able to identify patient-centered outcomes in this study population (Table S2 in Supporting Information) by involving stakeholders (patient and health care provider) perspective. For the purposes of this study, we limited ourselves to three patient-centered outcomes including all-cause mortality, heart failure readmissions, AF recurrence, and five surrogate outcomes including change in ejection fraction (EF), change in peak oxygen consumption (VO_2 Max), reduction in brain natriuretic peptide (BNP) levels, change in 6-minute walk distance (6MWD), and change in Minnesota Living with Heart Failure (MLWHF) score during the follow-up period. We limited our studies to English language publications published after the year 2000 as CA for the treatment of AF was introduced in the late 1990s and well-designed studies were not available until early 2000.

2.3 | Information sources and Search

We performed a search using OVID versions of Medline (2000-2018), EMBASE (2000-2018), SCOPUS (1999 to current), Web of Science (2000-2018), and Cochrane Database (2001-2018) limiting our searches to RCT using a maximally sensitive strategy (Supporting Information). The search strategy was developed by the authors (SKM and PA) working with clinical information specialist (DA). The last search was run on 9 February 2018. Full details of the search strategies are provided in the Supplement. We screened the reference lists from all retrieved articles and from reviews and clinical practice guidelines to identify additional studies. We contacted experts in the field and clinical trial registries for ongoing additional clinical trials. We contacted authors to provide additional data and details about the key validity issues.

2.4 | Studies selection

Eligibility assessment was performed through screening of the search results by two reviewers (PA and JZL) in a systematic manner. The search process was performed in two steps. The initial step involved title and abstract screening, and the second step involved full manuscript evaluation. Disagreements were resolved through consensus. When consensus could not be achieved, a third reviewer (SKM) casted the deciding vote.

2.5 | Data collection process

We developed a data extraction sheet for two steps (screening and full-text data) based on The Cochrane Consumers and Communication Review Group's data extraction template, pilot-tested it on two randomly selected included studies, and refined it accordingly. Both authors independently collected the data and agreement measures were reported using Kappa values. When certain data points were presented only in the form of graphs or plots, we extracted the actual data points using the software Plot Digitizer (version 2.0 Free Software Foundation Inc.). We directly contacted the authors when additional information was missing from the initial studies.

2.6 | Data items

For each included trial, the following information were extracted: (a) characteristics of trial participants (including age, characteristics of AF, and HFrEF and the impact on the structural function) and the trial's inclusion and exclusion criteria; (b) types of intervention

(including lesion set, antiarrhythmic drug therapy use, type of CA) vs standard medical therapy (targets for rate control) or device therapy (AVN ablation with CRT); and (c) type of outcome measures including all-cause mortality, heart failure readmissions, AF recurrence, change in EF, change in VO_2 Max, reduction in BNP levels, change in 6MWD, and change in MLWHF score.

2.7 | Risk of bias in individual studies

To ascertain the validity of eligible randomized trials, pairs of reviewers worked independently and determined the adequacy of randomization and concealment of allocation, blinding of patients, health care providers, data collectors, outcome assessors and extent of loss to follow-up (ie, proportion of patients in whom the investigators were not able to ascertain outcomes). To explore variability in study results (heterogeneity), we specified the hypotheses that effect size may differ according to the methodological quality of the studies before conducting the analysis.

2.8 | Summary measures

Relative reduction in mortality, heart failure readmission and AF recurrence were the patient-centered outcomes. Surrogate outcomes of interest include change in EF, change in VO_2 Max, reduction in BNP levels, change in 6MWD, and change in MLWHF score. The meta-analysis was performed by computing risk ratios (RR) for mortality and the difference in means using random-effects model based on underlying statistical heterogeneity.[14] We included only study results based on the intention-to-treat analyses. The RR and 95% confidence intervals (CIs) for each treatment effect were calculated.

2.9 | Planned method of analysis

The results of individual studies were combined using Review Manager version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical heterogeneity was tested using the I^2 statistic. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance[15] [$I^2 = 100\% \times (Q\text{-}df)/Q$]. I^2 is an intuitive and simple expression of the inconsistency of studies' results. Unlike Q, it does not inherently depend upon the number of studies considered. A CI for I^2 is constructed using either (a) the iterative noncentral chi-squared distribution method of Hedges and Piggott (2001) or (b) the test-based method of Higgins and Thompson.[15] In very few instances, estimates of baseline mean quality of life (QOL) responses were obtained without corresponding estimates of variance (standard deviation [SD] or standard error). In these instances, a SD was imputed from the mean of the known SDs. In a number of cases, the response data available were the mean and variance in a pre-study condition and after therapy. The within-patient variance in these cases could not be calculated directly and was approximated by assuming independence.[16]

2.10 | Risk of bias across individual studies

For each trial, we plotted the effect by the inverse of its standard error. The symmetry of such "funnel plots" was assessed both visually and with the Egger's test to see if the effect decreased with increasing sample size.[17]

2.11 | Additional analysis

Sensitivity analyses were prespecified. The treatment effects were examined according to the degree of improvement in EF. An additional subgroup analysis was performed based on the length of follow-up. Studies with a follow-up to 6 months are termed as short-term follow-up. Summary of evidence table was created to summarize the main results of the systematic review or meta-analysis along with assessment of certainty and quality of the evidence using GRADEPro tool (Guideline Development Tool [Software], McMaster University, 2015 [developed by Evidence Prime, Inc.]). [16]

3 | RESULTS

3.1 | Study selection

A total of seven studies involving seven trials were identified for inclusion in the review.[18–24] The search of Medline, EMBASE, SCOPUS, Web of Science, and Cochrane databases yielded a total of 721 citations (Figure 1). After removing duplicates 518 remained. Of these, 481 studies were excluded based on abstract and title review. The full texts of the remaining 37 citations were examined in detail. Seven studies met the inclusion criteria as described previously and were included in the systematic review. No unpublished relevant studies were found. Kappa for agreement on abstract inclusion and full-text inclusion was 0.721 (95% CI = 0.563-0.878).

3.2 | Study characteristics

The characteristics of patients in each study are presented in Table 1. A majority of the patients in the studies had persistent AF with HFrEF and an EF <50%. Most studies involved CA targeting pulmonary vein isolation. Most studies had a control arm in which patients were treated with rate control or rhythm control with AAD therapy. One study had a control arm in which patients received AVN ablation followed by CRT therapy. Outcomes from each study are summarized in Table 1 and majority of the trials had short-term follow-up (6 months). The summary of study reported outcomes is presented in Table S3 in Supporting Information.

3.3 | Risk of bias within studies

The risk of bias of each individual studies using the Cochrane's risk of bias tool is reported in Figures 2 and 3 for our study outcomes. Nearly all trials were open label and details about allocation concealment were not explicitly mentioned for majority of the trials. Random sequence generation was adequate and the outcomes were assessed in a blinded manner.

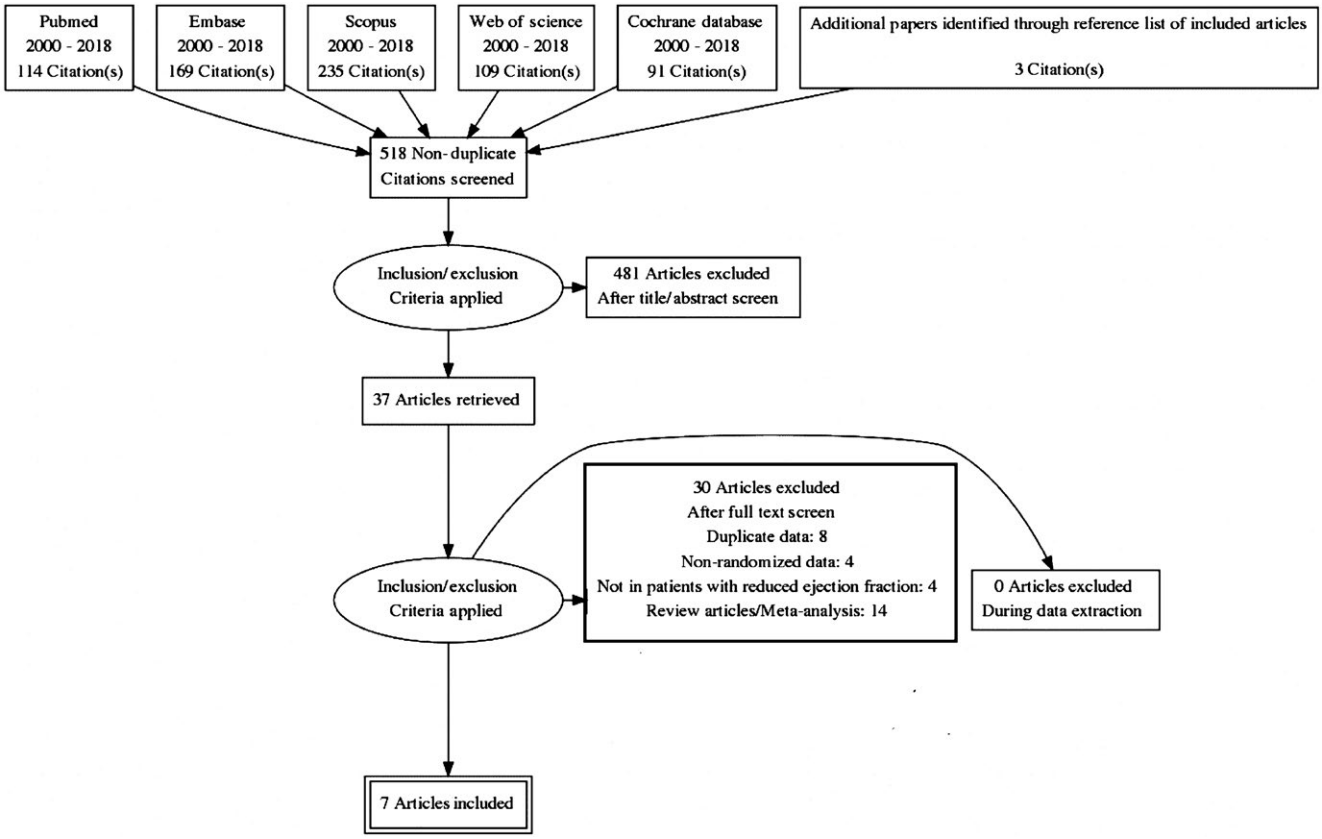

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of included studies

4 | RESULTS OF INDIVIDUAL STUDIES AND SYNTHESIS OF OUTCOMES

4.1 | Patient-centered outcomes

4.1.1 | All-cause mortality

Mortality data were available for four trials, randomizing 668 patients and reporting data for 668 patients. In the pooled analysis, CA for AF was associated with a significantly lower mortality (RR = 0.52, 95% CI = 0.35-0.76, $P = 0.001$). There was no evidence of heterogeneity ($I^2 = 0\%$). The results are summarized in Figure 2A.

4.1.2 | Heart failure readmissions

The heart failure readmissions data were available for five trials, randomizing 740 patients and reporting data for 705 patients. In the pooled analysis, CA for AF was associated with a significantly lower rate of readmission (RR = 0.58, 95% CI = 0.46-0.74, $P < 0.001$). There was no evidence of heterogeneity ($I^2 = 0\%$). The results are summarized in Figure 2B.

4.1.3 | Atrial fibrillation recurrence

The data on AF recurrence were available for six trials, randomizing 493 patients and reporting data for 493 patients. In the pooled analysis, CA for AF was associated with a significantly lower rate of AF recurrence (RR = 0.33, 95% CI = 0.22-0.50, $P < 0.00001$). There was moderate degree of heterogeneity noted ($I^2 = 68\%$). The results are summarized in Figure 2C. The success of CA in maintaining sinus rhythm with one procedure was 67% (95% CI = 61%-73%). More than one ablation improved the maintenance of sinus rhythm to 79% (95% CI = 74%-84%).

4.2 | Surrogate outcomes

4.2.1 | Improvement in ejection fraction

The mean EF change data were available for seven trials, randomizing 856 patients and reporting data for 856 patients. In the pooled analysis, CA for AF was associated with a significant improvement in EF (Mean EF difference = 5.98%, 95% CI = 3.68-8.27, $P < 0.001$, $I^2 = 87\%$). There was significant evidence of heterogeneity ($I^2 = 60.5\%$) in the subgroups based on the duration of follow-up. The results are summarized in Figure 3A.

4.2.2 | Change in peak oxygen consumption

The VO_2 Max data were available for two trials, randomizing 102 patients and reporting data for 102 patients. In the pooled analysis, CA for AF was associated with a significantly higher change in VO_2 Max (mean difference = 3.01 mL/kg/min, 95% CI = 2.05-3.97, $P < 0.001$). There was

TABLE 1 Characteristics of studies included in the systematic review

Author	Population	Intervention	Comparator	Primary outcome	Secondary outcome	Time	Adverse events
Khan[21]	Persistent AF EF ≤40% NYHA II-III N = 82	CA Isolation of PV CFAE and linear lesions as per operator	AVN ablation + BiV pacing	Composite of • EF • 6MWD • MLWHF score	• AF recurrence • LA diameter • QOL by MLWHF • 6MWD • HF readmission • Change in EF	12 months	3 groin bleeds 1 pericardial effusion 1 pulmonary edema 2 pulmonary vein stenosis Control group 1 LV lead dislodgement 2 pocket hematoma 1 pneumothorax
MacDonald[22]	Persistent AF NYHA II-IV EF ≤35% N = 41	CA Isolation of PV CFAE Linear lines CTI—case-by-case	Rate control	EF change by CMR	• NT BNP • 6MWD • QOL by MLWHF • KCCQ • AF recurrence • HF readmission • Change in EF	6 months	1 patient stroke 2 tamponade 3 worsening HF
Jones[20]	Persistent AF NYHA II-IV EF ≤35% N = 52	CA Isolation of PV Linear lines CFAE	Rate control	12 month change in VO_2 consumption	• QOL by MLWHF • All-cause mortality • BNP • 6MWD • EF • AF recurrence • HF readmission • VO_2 Max	12 months	I pericardial effusion requiring sternotomy 2 temporary worsening heart failure 1 Groin bleed 1 Pneumonia
Hunter[19]	Persistent AF NYHA II-IV EF <50% Adequate rate control. N = 50	CA Isolation PV CFAE Linear lines CTI line	Medical rate control	EF change	• LVESV change • All-cause mortality • VO_2 Max • BNP • NYHA Class • QOL by MLWHF • SF-36 • AF recurrence • Change in EF	12 months	1 stroke 1 tamponade
Di biase[18]	Persistent AF NYHA II-III EF <40% N = 203	CA Isolation of PV Posterior wall SVC	Amiodarone + standard medical therapy (ACE/ARB, beta blockers, diuretics, digoxin)	AF recurrence	• HF readmission • All-cause mortality • Change in EF • 6MWD • QOL by MLWHF • AF recurrence	24 months	2 groin hematoma 1 pericardial effusion

(Continues)

TABLE 1 (Continued)

Author	Population	Intervention	Comparator	Primary outcome	Secondary outcome	Time	Adverse events
Prabhu[24]	Persistent AF Non ischemic NYHA II-IV EF ≤45% N = 36	CA Isolation of PV Posterior wall	Medical rate control	Change in EF at 6 months	• Chamber dimensions • NYHA class • BNP • 6MWD • SF 36 scores • AF recurrence • Change in EF	6 months	4 unplanned admissions in the medical therapy arm. 1 groin bleed 1 ILR bleed requiring transfusion.
Marrouche[23]	Paroxysmal or persistent AF NYHA II-IV EF ≤35% N = 363	CA	Rate control	Composite • Mortality • HF admissions	• CVA • All-cause mortality • QOL • 6 MWD • ICD therapies • EF • AF burden • AF free interval • Time to ICD therapies • HF readmission	60 months	3 pericardial effusion 1 PV stenosis 3 acute bleeds 19 strokes (7 intervention and 12 control) 4 pneumonia (3 intervention, 1 control) 1 groin infection 1 worsening CHF

ACE, angiotensinogen-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AVN, atrioventricular node; BiV, biventricular; BNP, brain natriuretic peptide; CA, catheter ablation; CFAE, complex fractionated atrial electrograms; CMR, cardiac magnetic resonance; CTI, cavotricuspid isthmus; CV, cardiovascular; CVA, cerebrovascular accident; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas city cardiomyopathy questionnaire; LVESV, left ventricular end systolic volume; MLWHF, Minnesota Living with Heart failure; NYHA, New York Heart Association; PV, pulmonary veins; QOL, quality of life; SF-36, short form 36; SVC, superior vena cava; 6MWD, 6-minute walk distance.

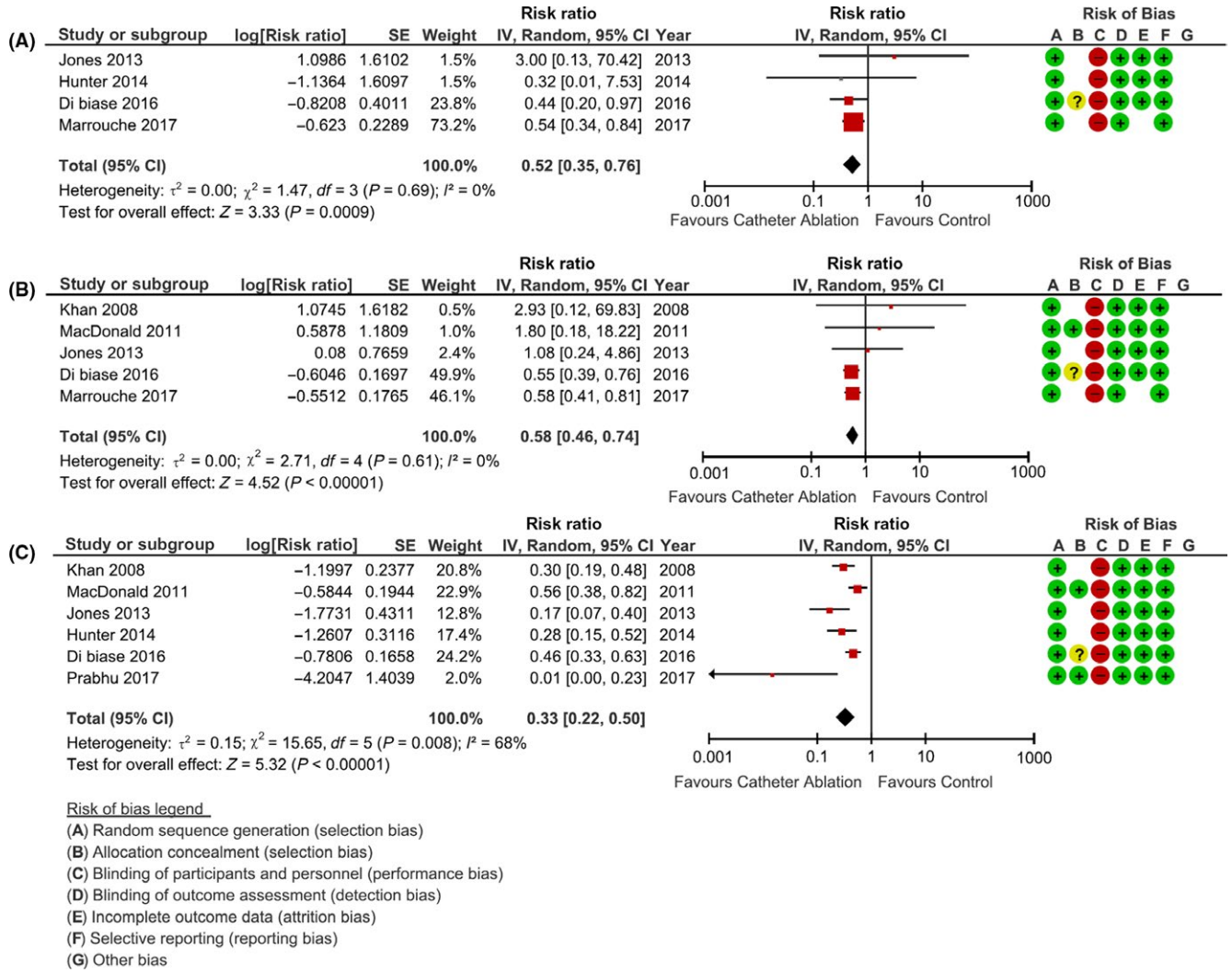

FIGURE 2 Patient-centered outcomes for (A) all-cause mortality, (B) heart failure readmissions, and (C) atrial fibrillation recurrence

no evidence of heterogeneity (I^2 = 0%). The results are summarized in Figure 3B.

4.2.3 | Reduction in brain natriuretic peptide levels

The data on reduction in BNP levels were available for three trials, randomizing 168 patients and reporting data for 166 patients. In the pooled analysis, CA for AF was associated with a significantly greater reduction in BNP levels (Mean difference = −107.34 pg/mL, 95% CI = −136.07 to −78.61, P < 0.001). There was no evidence of heterogeneity (I^2 = 0%). The results are summarized in Figure 3C.

4.2.4 | Change in 6-minute walk distance

The data for change in 6MWD were available in six trials, randomizing 806 patients and reporting data for 728 patients. In the pooled analysis, CA for AF was associated with a significant increase in 6MWD (Mean difference = 32.23 m, 95% CI = 13.55-50.91, P < 0.001). A high degree of heterogeneity was noted (I^2 = 88%). The results are summarized in Figure 3D.

4.2.5 | Change in Minnesota Living with Heart Failure score

The data for change in MLWHF score were available in five trials, randomizing 427 patients and reporting data for 424 patients. In the pooled analysis, CA for AF was associated with a significantly higher change in MLWHF score (Mean difference = 12.14, 95% CI = 2.71-21.56, P < 0.001). A high degree of heterogeneity was noted (I^2 = 78%). The results are summarized in Figure 3E.

4.2.6 | Risk of bias across studies

Heterogeneity was evaluated for studies reporting patient-centered and surrogate outcomes. Minimal heterogeneity was noted among studies that reported all-cause mortality, VO_2 Max, heart failure readmission, and reduction in BNP levels. A significant heterogeneity was seen among studies that reported AF recurrence, change in 6MWD, change in MLWHF score, and change in EF as an outcome. Funnel plots of all outcomes are

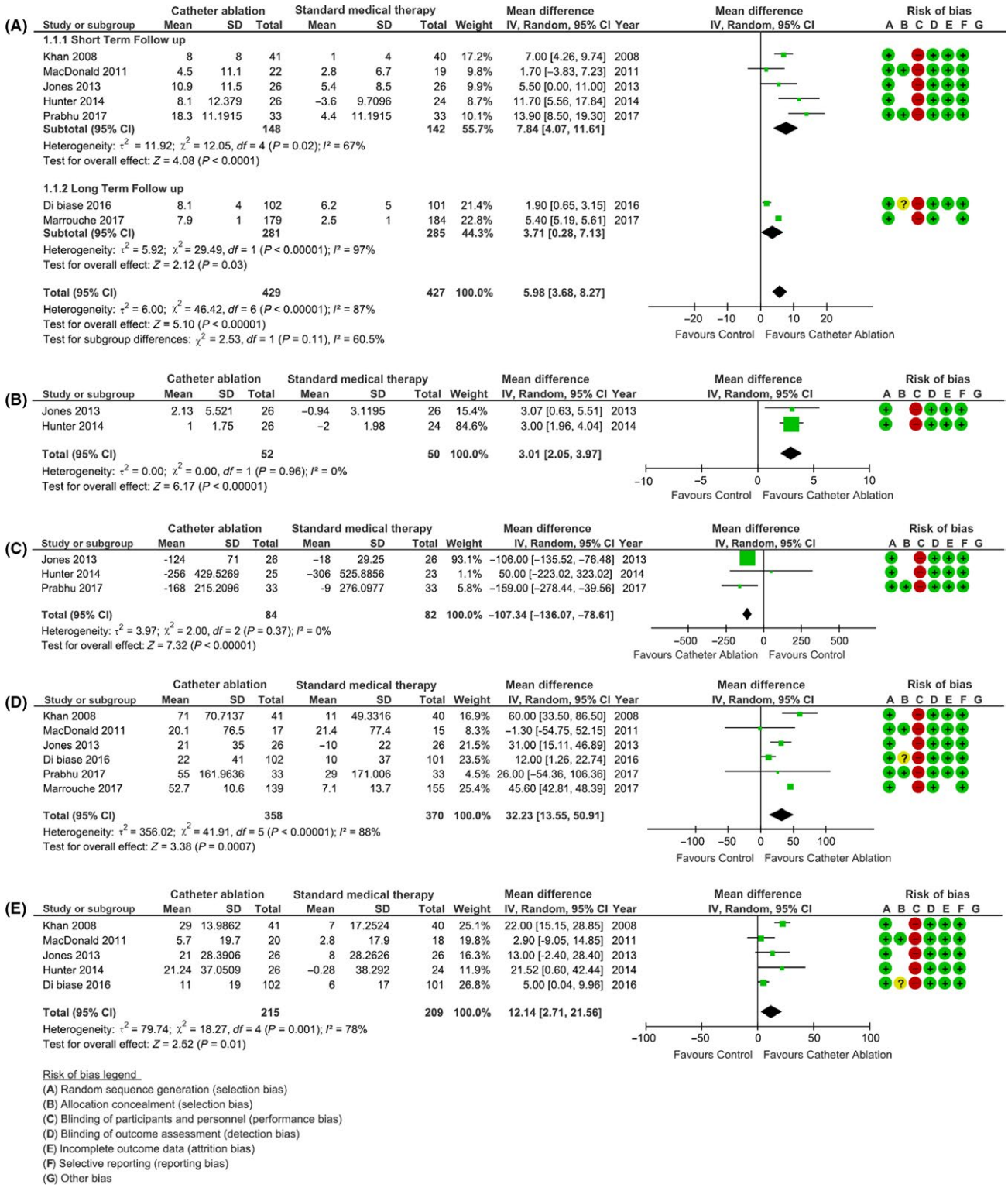

FIGURE 3 Surrogate outcomes for (A) change in left ventricular ejection fraction, (B) change in peak oxygen consumption (VO_2), (C) reduction in brain natriuretic peptide levels, (D) change in 6-minute walk test distance, and (E) change in Minnesota Living with Heart Failure Score (MLWHF)

presented in Supporting Information (Figures S1-S8). Funnel plot for the outcome "change in EF" suggested asymmetry and possible potential publication bias. Several of the smaller studies reported large positive effect sizes compared to studies with longer study duration. This was formally tested in our subgroup analysis ($\chi^2 = 2.53$, $df = 1$, $P = 0.0001$, $I^2 = 60.5\%$) which suggested that a majority of the heterogeneity could be explained by study duration.

TABLE 2 Summary of evidence

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)[a]	Relative effect (95% CI)	Anticipated absolute effects[b]	
				Risk with Medical therapy/AV nodal ablation	Risk difference with catheter ablation
Clinical outcomes					
All-cause mortality	668 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.52** (0.35 to 0.76)	191 per 1000	**92 fewer per 1000** (124 fewer to 46 fewer)
Heart failure readmission	705 (5 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.58** (0.46 to 0.74)	347 per 1000	**146 fewer per 1000** (187 fewer to 90 fewer)
Atrial fibrillation recurrence	493 (6 RCTs)	⊕⊕⊕◯ MODERATE[c]	**RR 0.33** (0.22 to 0.50)	860 per 1000	**576 fewer per 1000** (671 fewer 430 fewer)
Surrogate outcomes					
Change in ejection fraction	856 (7 RCTs)	⊕⊕◯◯ LOW[d,e,f]	—		MD **5.98 higher** (3.68 higher to 8.27 higher)
Change in peak oxygen consumption (VO_2 Max)	102 (2 RCTs)	⊕⊕⊕⊕ HIGH	—		MD **3.01 higher** (2.05 higher to 3.97 higher)
Reduction in brain natriuretic peptide	166 (3 RCTs)	⊕⊕⊕⊕ HIGH	—		MD **107.34 lower** (136.07 lower to 78.61 lower)
Change in 6-minute walk distance	728 (6 RCTs)	⊕⊕⊕◯ MODERATE[f]	—		MD **32.23 higher** (13.55 higher to 50.91 higher)
Change in Minnesota living with heart failure score	424 (5 RCTs)	⊕⊕⊕◯ MODERATE[f]	—		MD **12.14 higher** (2.71 higher to 21.56 higher)

CI, confidence interval; MD, mean difference; RR, risk ratio.
[a]GRADE Working Group grade of evidence: (a) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; (b) Moderate certainty: We are moderately confidence in the effect estimate: The true is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (c) Low certainty: Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect; (d) Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[b]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[c]Moderate degree of heterogeneity among study results.
[d]Inadequate allocation concealment.
[e]Suspicion for publication bias.
[f]High degree of heterogeneity among study results.

4.2.7 | Additional analysis

Sensitivity analysis (best or worst case) was performed by combining studies reporting the outcome "EF change" without the studies that reported the largest and smallest difference separately. There was still significant improvement in EF in the CA for AF arm even when those studies that reported the largest and smallest differences were removed from the pool (Figures S9A and B in Supporting Information).

5 | DISCUSSION

Our meta-analysis of high-quality RCTs shows statistically significant reduction in all-cause mortality, heart failure readmission, AF recurrence, and serum BNP levels, as well as improvement in EF, VO_2 Max, 6MWD, and MLWHF score in patients undergoing CA. By only including RCTs, we were able to limit the influence of unmeasured confounders and selection bias that is inherent in observational studies. We were able to show significant reduction in heart failure readmissions, serum BNP levels, and all-cause mortality in comparison to prior meta-analysis.[25]

We demonstrated statistically significant all-cause mortality benefit with CA in patients with AF and HFrEF in our study. The grade of evidence based on our analysis is high, suggesting that the true effect is in close proximity to the estimated effect. This is predominantly driven by minimal heterogeneity of the studies and low risk of bias (Table 2). A recent meta-analysis revealed a higher risk of all-cause mortality and major adverse cardiac events in patients with AF. The risk was particularly high in patients with heart failure.[26] Uncertainty continues to persist regarding the reason for higher mortality in AF patients with heart failure. Rate control with beta-blockers was to shown to have an incremental mortality benefit in patients with HFrEF in sinus rhythm, which was not seen in

patients in AF. This may suggest the benefit of rhythm control in patients with heart failure.[27] The mortality benefit seen in CA group could also be attributed to the fact that more patients in this group remained in sinus rhythm compared to control group. Moreover, in the last 5 years, the technology and modality of CA have dramatically changed. New advanced irrigated catheter tip and new modules such as contact force monitoring systems may have resulted in the relatively high success rate of CA for AF in HFrEF, which likely contributed to improvements in patient-centered outcomes.

We demonstrated statistically significant reduction in heart failure readmission in the CA group. In comparison, prior meta-analysis showed no significant change in heart failure readmission with CA.[25] Our statistical significance was predominantly driven by the newer RCT's[18,23] with a larger study size.

Additionally, this is the first study to evaluate change in EF for short- and long-term follow-up.[25] The grade of evidence of was determined to be low and our confidence in the estimate is limited. There is a possibility that of the true effect is substantially different from our estimate (Table 2). This is primarily due to a high degree of heterogeneity within the data, a suspicion for publication bias and inadequate allocation concealment. Despite performing substantial subgroup and sensitivity analyses, the heterogeneity remained high. Atrial fibrillation promotes progression of heart failure predominantly by two mechanisms: (a) rapid irregular conduction of atrial fibrillatory waves to the ventricles leading to left ventricular dysfunction and occasionally development of additional tachycardia-induced cardiomyopathy and (b) loss of left atrial "kick" or systolic ejection fraction impairing left ventricular filling during ventricular diastole, thereby attenuating cardiac output by up to 25%. Restoration of sinus rhythm in patients with AF improves left ventricular filling and prolongs left ventricular systolic ejection duration thereby increasing the cardiac output and EF before subsequent improvement in contractility is noted.[28] In our study, patients in the CA group had a lower rate of AF recurrence which in turn explains the significantly higher improvement in EF noted in the CA group compared to patients in the control group.

The greater reductions in serum BNP levels were also noted in the CA group. The grade of evidence based on our analysis is high driven by minimal heterogeneity of the studies and low risk of bias (Table 2). The significance of this outcome is consistent with decreased heart failure readmissions noted in our study.

Quality of life endpoints including change in VO_2 Max, 6MWD, and MLWHF score were higher in patients who underwent CA. This finding is consistent with prior meta-analysis.[25] However the grade of evidence is moderate given the high degree of heterogeneity (Table 2). The VO_2 Max as well as 6MWD are established prognostic indicators of mortality and heart failure readmissions.[29,30] The improvement in VO_2 Max and 6MWD noted in our study mirrors the reduction in mortality and heart failure readmissions demonstrated previously.

Given the invasive nature of the procedure, CA carries certain procedural risk including stroke, pericardial effusion, atrioesophageal fistula, bleeding, pulmonary stenosis, pneumonia, and rarely death. The periprocedural complication rate in our study was 5.3%.

This was comparable to complication rates noted in prior studies (2.9%-5.2%) in patients with structurally normal heart.[31,32] Extrapolation of our results to patients with paroxysmal AF is limited since majority of the patients in our meta-analysis were in persistent AF.

5.1 | Summary of evidence

Overall, the evidence is sufficiently robust to determine the comparative effectiveness of CA for AF in patients with HFrEF and medical with or without device treatment alone. The outcomes with the highest grade of evidence include all-cause mortality, heart failure readmission, change in VO_2 Max, and reduction in BNP levels, which showed a significant benefit with CA in patients with HFrEF. The outcomes with moderate grade of evidence include AF recurrence, change in 6MWD, and reduction in MLWHF score, also showed a significant benefit with CA in patients with HFrEF. Although the outcome "change in EF" showed a statistically significant benefit of CA in patients with HFrEF, it had a low grade of evidence. Therefore, the external validity of this outcome is uncertain.

5.2 | Limitations

This study has several limitations.

Outcome level: The meta-analysis reported here combines data across studies in order to estimate treatment effects with more precision than is possible in a single study. The main limitation of the evidence generated from our meta-analysis, is that the patient population, inclusion criteria and the techniques for measurement of EF are not the same across studies.

Study level: The quality of the studies varied. Randomization was adequate in all trials; however, four of the studies did not provide details about allocation concealment. All the trials were open label, which could lead to overestimation of treatment effect in these trials. Analyses did not identify an association between components of quality and adverse events, and the effect size in favor of CA for AF remained statistically significant when we excluded trials that were reported as abstracts.

Publication bias might account for some of the effect we observed. Smaller trials are, in general, analyzed with less methodological rigor than larger studies, and an asymmetrical funnel plot suggests that selective reporting may have led to an overestimation of effect sizes in small trials. The study population is predominantly skewed towards male sex, therefore applicability of our results in women with HFrEF and AF is unclear.

6 | CONCLUSION

Catheter ablation for AF in HFrEF is associated with reduction in all-cause mortality, heart failure readmissions, and AF recurrence when compared to standard medical therapy with or without device therapy. CA for AF can be considered for patients with HFrEF for improving EF change during the short-term follow-up and mortality during the long-term follow-up after shared decision making.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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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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