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ORIGINAL ARTICLE

Catheter Ablation Versus Medical Therapy for Atrial Fibrillation in Patients With Heart Failure: A Meta-Analysis of Randomised Controlled Trials

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Background Catheter ablation (CA) is highly efficacious for symptomatic atrial fibrillation (AF) but data predominantly comes from patients with preserved ventricular function. We performed an updated systematic review and meta-analysis of randomised controlled trials (RCT) comparing CA versus medical therapy for AF associated with heart failure (HF).

Methods Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs reporting clinical outcomes of CA versus medical therapy for AF in HF patients with ≥6 months' follow-up (atrioventricular-node ablation/device therapy studies excluded). Primary endpoint was change in left ventricular ejection fraction (LVEF). Secondary endpoints were 6-minute walk test (6MWT) distance, quality of life (QoL; measured by the Minnesota Living with Heart Failure Questionnaire [MLHFQ]), peri-procedural mortality, major peri-procedural complications and mid-term (≥1-year) survival.

Results Six RCTs (n = 772 patients; mean age 62 ± 11 years, LVEF 30 ± 9%) were included. Catheter ablation, compared to medical therapy was associated with: greater improvement in LVEF (mean difference [MD] 5.67%; 95% Confidence Interval [CI], 3–8; I^2 = 87%; p < 0.001), greater increase in 6MWT distance (MD 25.1 metres; 95% CI, 0.6–50; I^2 = 94%; p = 0.04), improved QoL with greater reduction in MLHFQ scores (MD 9.03; 95% CI, 2.5–15.6; I^2 = 47%; p = 0.007), and significantly reduced mid-term mortality (relative risk 0.52; 95% CI, 0.4–0.8; I^2 = 0%; p = 0.001). Freedom from AF after ≥1 procedure was 71%; major complications occurred in 8% of patients.

Conclusion Catheter ablation is superior to medical therapy for AF in patients with heart failure resulting in greater improvement in LVEF, quality of life and functional status, with a survival benefit.

Keywords Atrial fibrillation • Catheter ablation • Medical therapy • Randomised controlled trials • Mortality • Quality of life

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Introduction

Atrial fibrillation (AF) and heart failure (HF) frequently co-exist [1]. AF can be a cause of left ventricular dysfunction or arise as a consequence of the structural and neurohormonal changes seen in HF [2]. In patients with HF, the presence of AF leads to deleterious haemodynamic and symptomatic consequences, and is associated with increased mortality [3].

Catheter ablation (CA) is highly efficacious for the treatment of symptomatic, drug refractory AF. However, the majority of randomised trials of drug therapy versus CA have enrolled patients with preserved ventricular function [4–6]. Recently, randomised controlled trials have shown the benefit of rhythm control with CA over medical therapy for AF associated with HF [7–12]. Prior meta-analyses have also shown significant benefit of rhythm control with CA over medical therapy [13–18]. However, these meta-analyses have included either observational and randomised studies [13–15,18], included studies with duty-cycled phased radiofrequency rather than traditional radiofrequency ablation [17], have not included the recently published Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial [11] or the Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction (CAMERA-MRI) trial [12], or have included studies comparing catheter ablation with atrioventricular nodal ablation and device therapy [16].

Acknowledging the above limitations, we conducted an updated meta-analysis of randomised controlled trials to assess the safety and efficacy of catheter ablation for AF, compared with medical therapy, exclusively in patients with heart failure.

Methods

Search Strategy and Study Selection

Electronic searches were performed using Medline, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from their dates of inception to March 2018. The search terms ''atrial fibrillation'' AND ''catheter ablation OR pulmonary vein isolation'' AND ''heart failure OR left ventricular dysfunction'' were combined as both keywords and MeSH terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

Two reviewers (SAV and SK) independently screened the title and abstract of records identified in the search. Full-text publications were subsequently reviewed separately if either reviewer considered the manuscript as being potentially eligible. Disagreements regarding final study inclusion were resolved by discussion and consensus.

Eligibility Criteria

Eligible studies were randomised controlled trials (RCTs) reporting clinical outcomes of CA versus medical therapy in AF patients with left ventricular dysfunction. Catheter ablation was defined as pulmonary vein isolation with or without additional substrate modification. Medical therapy was defined as either rate and/or rhythm control. Studies comparing CA with atrioventricular-node ablation and device therapy were excluded. To be eligible, studies were required to have a minimum follow-up duration of 6 months. Non-English publications, conference abstracts and review articles were excluded. If institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included.

Data Extraction and Critical Appraisal

All data were independently extracted from text, tables and figures by two investigators (SAV and SK). Discrepancies were resolved by discussion and consensus. For each study, the following information was extracted: study period, institution, inclusion criteria, follow-up duration, baseline clinical characteristics and risk factors, procedural details and outcome measures. Quality assessment was performed for each study using the Cochrane Risk of Bias Tool for RCTs [19]. This included an assessment of randomisation, allocation concealment, blinding, attrition rates, selective reporting and other sources of potential bias.

Endpoints

The pre-determined primary endpoint was change in left ventricular ejection fraction (LVEF). When studies measured LVEF using multiple modalities, the measurement that was specified as the primary endpoint by trial authors was used for quantitative analysis. Secondary endpoints included 6-minute walk test (6MWT) distance, change in maximal oxygen consumption at peak exercise (VO_2 max), change in brain natriuretic peptide (BNP) levels, quality of life (QoL) as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [20], peri-procedural mortality, major adverse events (including major peri-procedural complications of catheter ablation and effects of drugs), and mid-term ($\geq$1-year) survival. Peri-procedural complications were defined as those occurring within 30 days following ablation or during the same hospitalisation.

Statistical Analysis

The mean difference (MD) or relative risk (RR) were used as summary statistics, and reported with 95% confidence intervals (CI). Meta-analyses were performed using random-effects models to take into account the anticipated clinical and methodological diversity between studies. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance, with values exceeding 50% indicative of considerable heterogeneity. For meta-analysis of continuous data, values presented as median and interquartile range were converted to mean and standard deviation using methods described previously [21].

Publication bias was assessed using funnel plots comparing log odds ratios with their standard error. Egger's linear

regression method was used to detect funnel plot asymmetry [22]. Statistical analysis was conducted with Review Manager Version 5.3.5 (Cochrane Collaboration, Oxford, UK) and publication bias assessed using Comprehensive Meta-Analysis v3.0 (Biostat Inc, Englewood, NJ, US). A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 1,147 unique records were identified through the database and bibliographic searches. Of these, 1,086 were excluded on the basis of title and abstract content. After screening the full text of the remaining 61 articles, six RCTs including a total of 772 participants were included (Figure 1) [7–12].

A summary of study characteristics and baseline participant data is provided in Tables 1 and 2. Three studies were multicentred [7,11,12]. Five of the included RCTs exclusively enrolled patients with persistent AF [7–10,12]; in the remaining study, 32.5% of patients had paroxysmal AF [11]. Medical therapy consisted of rate control alone in four RCTs [8–10,12], and both rate and rhythm control in the two other RCTs [7,11].

Across all RCTs, study participants had a weighted mean age of 62.4 ± 11.3 years, LVEF of 30 ± 8.8%, LA diameter 48.7 ± 6.8 mm, AF duration of 22.6 ± 31.9 months and HF duration of 47.8 ± 47.1 months. Overall, 83% were male, 38.9% had NYHA III/IV symptoms at baseline, and 38.1% had heart failure of ischaemic aetiology. Concurrent hypertension, diabetes and cerebrovascular disease were present in 58.8%, 26.2% and 10.2% of patients, respectively. Concurrent angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, ß-blockers and aldosterone antagonists were administered in 92.7%, 89.9% and 67.9% of patients, respectively. Median study follow-up duration was 6 months in three RCTs [8,10,12], 12 months in one RCT [9], 24 months in one RCT [7] and 37.8 months in one RCT [11].

Ablation strategy varied widely within and between studies (Table 3). All studies included pulmonary vein isolation with the majority reporting additional linear ablation (e.g. ablation of the left atrial roof, mitral isthmus and/or cavotricuspid isthmus) and ablation of complex fractionated atrial electrograms. Monitoring in follow-up varied between studies with three reporting intermittent rhythm monitoring with ambulatory Holter and three reporting continuous device monitoring (Table 1).

Quality Assessment and Critical Appraisal

A complete summary of the risk of bias in included trials is displayed in Table 4. The risk of selection bias was universally low as all included trials employed appropriate random sequence generation. Allocation was appropriately concealed in all trials, except one open-label study [9]. No studies

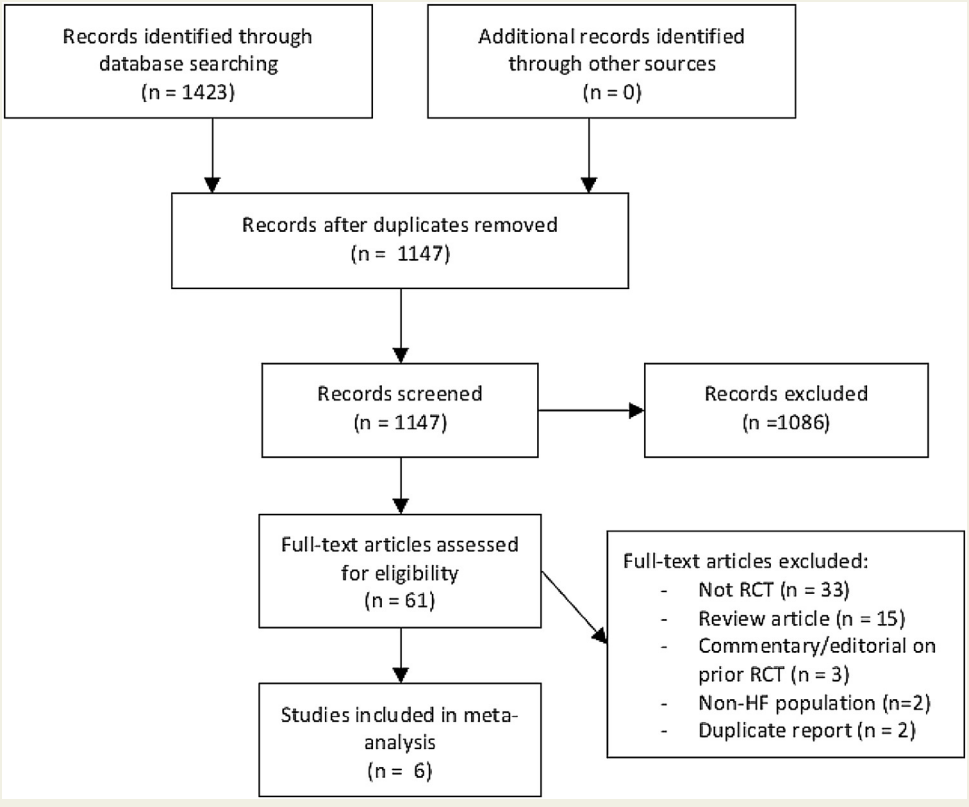

Figure 1 Summary of electronic search and included/excluded studies. Abbreviations: RCT, randomised control trials; HF, heart failure.

Table 1 **Methodological characteristics of included randomised controlled trials comparing catheter ablation and medical therapy in patients with atrial fibrillation and heart failure.**

	McDonald et al. 2011 [10]	Jones et al. 2013 [9]	Hunter et al. 2014 [8]	Di Biase et al. 2016 [7]	Prabhu et al. 2017 [12]	Maroucche et al. 2018 [11]
Comparative groups	CA vs rate control	CA vs rate control	CA vs rate control	CA vs amiodarone	CA vs rate control	CA vs rate or rhythm control
Inclusion	Persistent AF, NYHA II–IV HF despite optimal heart failure treatment for at least 3 months, LVEF <35% no contraindication to CMRi	Persistent AF, symptomatic HF (NYHA II to IV) on optimal HF therapy, LVEF ≤35%.	Persistent AF, symptomatic heart failure (NYHA class II–IV), LVEF <50%	Persistent AF, dual chamber ICD or CRT-D, NYHA II–III, LVEF≤ 40% within the last 6 months	Persistent AF, 18 to 85 years of age, NYHA ≥2, LVEF ≤45% on baseline CMR, no significant CAD or other cause of LV dysfunction	Persistent or paroxysmal AF; absence of response to, unacceptable side effects from, or unwillingness to take AADs; NYHA II–IV HF; LVEF ≤35%
Primary endpoint	Change in LVEF measured using CMRi from randomisation to the last study visit.	Change in peak VO_2 at 12 months	LVEF between the 2 groups at the 6-month time point on an intention to treat basis	Freedom from AF, atrial flutter or atrial tachycardia of >30 seconds' duration off AAD at follow-up	Change in LVEF from baseline at 6 months on CMR	Death from any cause or worsening of heart failure that led to an unplanned overnight hospitalisation
Secondary endpoints	Change in LVEF, RVEF, LVESV, LVEDV, LA diameter, BNP, 6 min walk and quality of life (KCCQ, MLHFQ and SF-36).	Change in LHFQ score, BNP, and 6-min walk distance	Percentage reduction in LVESV, change in VO_2 max, BNP, NYHA class, MLHFQ and SF-36 scores	Complications, all-cause mortality, AF and HF-related unplanned hospitalisations during the post-ablation follow-up, change in LVEF, 6-minute walk distance, and MLHFQ score	Improvement in LVEF; change in CMR chamber dimensions, NYHA class, BNP level, 6MWT distance, physical and mental SF-36 scores; AF recurrence; AF burden; procedural complications.	Death from any cause, unplanned hospitalisation related to heart failure, death from cardiovascular disease, cerebrovascular accident, unplanned hospitalisation for cardiovascular disease, and any hospitalisation. In the ablation group, procedure-related adverse events and AF-free intervals
LV function modality	CMRi and radionucleotide ventriculography	TTE	TTE	TTE	CMR	TTE
Interval of repeat LVEF assessment	6 months	12 months	6 months	24 months	6 months	12 months
Definition of recurrent AF	NR	Any atrial arrhythmia lasting >30 seconds	AF or atrial tachycardia lasting >30 seconds	AF, atrial flutter or atrial tachycardia lasting >30 seconds	AF or atrial tachycardia lasting >30 seconds	Any atrial arrhythmia lasting >30 seconds
Blanking period, months	3	2	3	3	1	3
Frequency of monitoring	Baseline, 6 months	3, 6, and 12 months	1, 3, 6 months	3, 6, 12, 24 months		Continuous rhythm monitoring but also

Table 1. (continued).

	McDonald et al. 2011 [10]	Jones et al. 2013 [9]	Hunter et al. 2014 [8]	Di Biase et al. 2016 [7]	Prabhu et al. 2017 [12]	Maroucche et al. 2018 [11]
heart rhythm, months					Continuous rhythm monitoring but also at 6 weeks, 3 and 6 months	Scheduled visits at 3, 6, 12, 24, 36, 48, and 60 months after baseline
Modality of assessing heart rhythm	Holter	ECG rhythm documentation at 6 to 8 weeks and all follow-ups, 48-h Holter monitoring at 6 and 12 months.	Holter at 1 month, 3 months and 6 months	Device remote monitoring	Implanted loop recorder	Device home monitoring
Ablation strategy	PVI, If AF persisted, then roof line, CFAE ablation	PVI, roof line, MI line, CFAE ablation, map residual AT, cardiovert if residual AF and do CTI line	WACA, CFAEs, if remained in AF linear lesions with MI and roof line, map residual AT if occurred; CTI line if previous typical flutter; cardiovert at end of case if not restored by ablation	PVI, extension of PVI to coronary sinus; posterior wall isolation; SVC isolation; CFAE eliminated; elimination of non-PV triggers	WACA, roof and inferior lines resulting in posterior wall isolation	PVI (rest at discretion of operator: roof line, MI line, CTI line, CFAE)

Abbreviations: AAD, anti-arrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; BNP, brain natriuretic peptide; CA, catheter ablation; CAD, coronary artery disease; CFAE, complex fractionated atrial electrograms; CMR, cardiac magnetic resonance imaging; CRT-D, cardiac resynchronisation therapy defibrillator; CTI, cavotricuspid isthmus; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MI, mitral isthmus; MLHFQ, Minnesota Living with Heart Failure Questionnaires; NYHA, New York Heart Association; PVI, pulmonary vein isolation; RVEF, right ventricular ejection fraction; SF-36, short form 36; TTE, transthoracic echocardiography; VO_2, peak oxygen consumption; WACA, wide antral catheter ablation; 6MWT, 6 minute walk test.

Table 2 Summary of study characteristics and baseline participant data in randomised controlled trials comparing catheter ablation and medical therapy in patients with atrial fibrillation and heart failure.

	McDonald et al. 2011 [10]		Jones et al. 2013 [9]		Hunter et al. 2014 [8]		Di Biase et al. 2016 [7]		Prabhu et al. 2017 [12]		Marroucche et al. 2018 [11]	
	CA	MT (Rate Control)	CA	MT (Rate Control)	CA	MT (Rate Control)	CA	MT (Rhythm Control)	CA	MT (Rate Control)	CA	MT (Rate or Rhythm Control)
Number screened	366		101		390		866		301		3013	
Number eligible	41		75		98		331		77		398	
Multi-centre?	No		No		No		Yes		Yes		Yes	
Total study number	41		52		50		203		66		363	
Group numbers	22	19	26	26	26	24	102	101	33	33	179	184
Mean age (SD), y	62.3 (6.7)	64.4 (8.3)	64 (10)	62 (9)	55 (12)	60 (10)	62 (10)	60 (11)	59 (11)	62 (9)	Median 64 (range 56–71)	Median 64 (range 56–74)
Male, n (%)	17 (77)	15 (79)	21 (81)	24 (92)	25 (96)	23 (96)	77 (75)	74 (73)	31 (94)	29 (88)	156 (87)	155 (84)
Coronary disease, n (%)	11 (50)	9 (47)	11 (42)	13 (50)	6 (23)	7 (29)	63 (62)	66 (65)	0	0	72 (40)	96 (52)
Paroxysmal AF/Persistent AF	0/22	0/19	0/26	0/26	0/26	0/24	0/102	0/101	0/33	0/33	54/125	64/120
Time since HF diagnosis, mean (SD) or median (IQR), months	NR	NR	68 (62)	48 (57)	median 33 (IQR: 20–56)	median 24 (IQR:14–48)	NR	NR	NR	NR	NR	NR
Time since AF diagnosis, mean (SD) or median (IQR), months	44 (36.5)	64 (47.6)	23 (22)	51 (76)	median 23 (IQR:17–33)	median 24 (IQR:12–48)	NR	NR	23 (18)	21 (15)	NR	NR
Hypertension, n (%)	14 (64)	11 (58)	NR	NR	8 (31)	8 (33)	46 (45)	48 (48)	13 (39)	12 (36)	129 (72)	136 (74)
Diabetes, n (%)	7 (32)	4 (21)	NR	NR	NR	NR	22 (22)	24 (24)	4 (12)	5 (15)	43 (24)	67 (36)
Prior TIA/stroke, n (%)	2 (9)	2 (11)	NR	NR	NR	NR	NR	NR	2 (6)	0	21 (12)	21 (11)
Ischaemic cardiomyopathy, n (%)	11 (50)	9 (47)	10 (38)	7 (27)	6 (23)	7(29)	63 (62)	66 (65)	0	0	72 (40)	96 (52)
NYHA class III/IV (%)	20 (91)	17 (89)	12 (46)	13 (50)	15 (58)	12 (50)	NR	NR	NR	NR	53/174 (50)	51/179 (28)
Baseline medical therapy, n (%)												
ACE-I/ARB	21 (95)	18 (95)	25 (96)	26 (100)	26 (100)	24 (100)	94 (92)	89 (88)	31 (94)	31 (94)	166/177 (94)	164/180 (91)
Beta blocker	18 (82)	18 (95)	24 (92)	24 (92)	26 (100)	24 (100)	78 (76)	81 (80)	32 (97)	32 (97)	165/177 (93)	171/180 (95)
Aldosterone antagonist	10 (45)	3 (16)	13 (50)	6 (23)	NR	NR	46 (45)	51 (50)	11 (33)	16 (48)	165/177 (93)	167/180 (93)
Digoxin	12 (55)	9 (47)	16 (62)	12 (46)	NR	NR	NR	NR	NR	NR	NR	NR
Amiodarone	NR	NR	3 (12)	3 (12)	NR	NR	NR	101 (100)	NR	NR	55 (31)	46 (26)
LVEF % at baseline, mean (SD)	16.1 (7.1)	19.6 (5.5)	22 (8)	25 (7)	31.8 (7.7)	33.7 (12.1)	29 (5)	30 (8)	32 (9)	34 (8)	Median 32.5 (IQR 25–38)	Median 31.5 (IQR 27–37)
LA diameter mm at baseline, mean (SD)	NR	NR	50 (6)	46 (7)	52 (11)	50 (10)	47 (4.2)	48 (4.9)	48 (5.5)	47 (8.2)	Median 48 (IQR 45–54)	Median 49.5 (IQR 50–55)

Table 2. (continued).

	McDonald et al. 2011 [10]		Jones et al. 2013 [9]		Hunter et al. 2014 [8]		Di Biase et al. 2016 [7]		Prabhu et al. 2017 [12]		Marroucche et al. 2018 [11]	
	CA	MT (Rate Control)	CA	MT (Rate Control)	CA	MT (Rate Control)	CA	MT (Rhythm Control)	CA	MT (Rate Control)	CA	MT (Rate or Rhythm Control)
Number of AF ablation procedures, mean, (SD)	1.23		1.19		1.7 (0.7)		1.4 (0.6)		1		1.3 (0.5)	
RFA procedure duration (mins)	205		333 + 61		NR		168 + 22		200 + 47		NR	
Follow-up, means (SD), months	9.7 (2.7)	6.9 (0.9)	12	12	6 to 12		24		6		37.6 (20.4)	37.4 (17.7)

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AF, atrial fibrillation; CA, catheter ablation; CMR, cardiovascular magnetic resonance; HF, heart failure; IQR, interquartile range; LA, left atrial; LVEF, left ventricular ejection fraction; MT, medical therapy; NYHA, New York Health Association; NR, not reported; RFA, radiofrequency ablation; SD, standard deviation.

employed sham ablation procedures; consequently, patients and investigators were not blinded to treatment group, resulting in high risk of performance bias. The primary endpoint of LVEF was measured by blinded assessors in most studies [7–10,12] but only one trial blinded assessors for other endpoints [9]. Two trials had disproportionately greater losses to follow-up in the ablation arm, predisposing to high risk of attrition bias [7,11]. Other sources of potential bias included significant cross-over rates [11], imbalances between treatment groups at baseline [9,10], and a very small proportion of screened patients undergoing randomisation without reasons provided for exclusions [7,8,11].

Procedural Outcomes

In 384 patients who underwent catheter ablation, the pooled incidence of AF recurrence requiring repeat ablation was 29.2% (95% CI, 16.5–46.3). At last follow-up, pooled rate of freedom from AF after one or more procedures was 71.1% (95% CI, 59.5–80.5). Patients underwent multiple procedures in five trials, with the mean number of ablations ranging from 1.19 to 1.7 [7–11]. Ablation, compared to medical therapy, was associated with a significant reduced risk of recurrent AF at follow-up (RR 0.37, 95% CI, 0.25–0.54; $I^2 = 71\%$; $p < 0.0001$).

Pooled incidence of major peri-procedural complications was 8.2% (95% CI, 3.7–17.2). Major complications included stroke (1.8%; 95% CI, 0.7–4.8), tamponade (2.5%; 95% CI, 0.9–7.3), pericardial effusion (1.6%; 95% CI, 0.7–3.5), acute exacerbation of heart failure (2.3%; 95% CI, 0.6–8.4), pulmonary vein stenosis (1.1%; 95% CI, 0.4–3.1), pneumonia (2.0%; 95% CI, 0.9–4.2), and major bleeding (1.7%; 95% CI, 0.8–3.8). There was no peri-procedural mortality.

Primary Endpoint: Change in LVEF

In 668 patients across six RCTs, catheter ablation demonstrated significantly greater improvement in LVEF (MD 5.67%; 95% CI, 3.01–8.33; $I^2 = 87\%$; $p < 0.0001$; Figure 2). In a sensitivity analysis only including the four RCTs (n = 599) measuring LVEF using transthoracic echocardiography [7,8,11,12], this result was not significantly altered (MD 5.35; 95% CI, 2.43–8.26; $I^2 = 90\%$; $p = 0.0003$).

Secondary Endpoints

In five RCTs involving 526 participants [7,9–12], catheter ablation was associated with significantly greater increase in 6MWT distance (MD 25.12 metres; 95% CI, 0.59–49.65; $I^2 = 94\%$; $p = 0.04$; Figure 3). In four RCTs involving 214 participants [7–10], catheter ablation was superior in improving QoL, with greater reduction in MLHFQ score (MD 9.03; 95% CI, 2.48–15.59; $I^2 = 47\%$; $p = 0.007$; Figure 4). Two studies reported change in VO_2 max before vs. after catheter ablation [8,9]. Catheter ablation, compared to medical therapy was associated with significant increase in VO_2 max (MD 3.16; 95% CI, 1.05–5.27; $I^2 = 0\%$; $p = 0.003$). Three studies reported change in BNP before versus after ablation [9,10,12]. Catheter ablation, compared to medical therapy was associated with

Table 3 Summary of ablation strategies employed in the included randomised controlled trials.

Study	PVI	Additional linear ablation[†]	Posterior wall isolation	SVC isolation	CFAE ablation	Elimination of AF triggers
MacDonald 2011	√	√			√	
Jones 2013	√	√			√	
Hunter 2014	√	√			√	
Di Biase 2016	√	√	√	√	√	√
Prabhu 2017	√		√			
Marrouche 2018	√	√	√	√	√	√

Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrograms; PVI, pulmonary vein isolation; SVC, superior vena cava.
[†]Included ablation of the left atrial roof, mitral isthmus and/or cavotricuspid isthmus.

significant reduction in BNP (standardised MD −0.60, 95% CI, −0.92 to −0.27; $I^2 = 0\%$; $p < 0.0001$).

In the three RCTs (n = 618) with minimum 1-year follow-up [7,9,11], catheter ablation demonstrated significantly reduced mid-term mortality (relative risk 0.52; 95% CI, 0.36–0.77; $I^2 = 0\%$; $p = 0.001$; Figure 5).

Publication Bias

There was no evidence of publication bias for the primary endpoint of change in LVEF using Egger's linear regression method ($p = 0.92$). Publication bias could not be assessed for other endpoints due to the insufficient number of trials.

Discussion

In this meta-analysis, catheter ablation for AF in patients with heart failure demonstrated greater improvement in systolic function, functional status (including maximal oxygen consumption at peak exercise and levels), quality of life and mid-term survival, when compared to optimal medical therapy. Although prior meta-analyses have reported similar benefits, these were largely based on observational data [13–15,18], predated large RCTs with longer follow-up duration [16–18], reported on a limited set of endpoints [13,14,16], included ablation modalities other than radiofrequency [17], or included atrioventricular nodal ablation plus device therapy as a comparator [16]. As such, our study represents the most comprehensive and updated analysis of randomised data assessing the safety and efficacy of catheter ablation for AF in patients with HF.

Across the included RCTs, catheter ablation provided 5.67% greater improvement in LVEF than medical therapy (Figure 2). However, there was considerable heterogeneity in the analysis of this endpoint ($I^2 = 87\%$), and this was not ameliorated by sensitivity analysis standardising the method of LVEF measurement. Potential sources of heterogeneity included differences between trial populations with regards to the duration of AF, aetiology and severity of HF, prevalence of co-morbidities known to unfavourably impact on atrial remodelling (e.g. hypertension, obstructive sleep apnoea, obesity), and choice of pharmacological and device therapy (e.g. concurrent cardiac resynchronisation therapy). Notably, the study by MacDonald et al. failed to demonstrate a greater increase in LVEF compared with medical therapy, and this trial population had the lowest baseline LVEF, longest duration of AF and highest proportion of patients with NYHA III/IV symptoms [10]. Interestingly, their study also reported the lowest rate of freedom from AF at follow-up (50%) and subgroup analysis of patients in sinus rhythm post-ablation revealed significant improvement in LVEF. This suggests the improvement in LVEF observed following CA may largely be dependent on successful rhythm restoration, rather than the mode of restoration, which enables regular ventricular filling time and coordinated atrial contraction [23,24].

Catheter ablation was also associated with significantly greater improvement in functional capacity than medical therapy, as evident by longer 6-minute walk distances (Figure 3). This is a key finding as 6MWT distance has been shown to be a strong and independent predictor of mortality, morbidity, hospitalisation and peak oxygen consumption in patients with heart failure [25–27]. Increase in 6MWT distance has also been correlated with enhanced quality of life [27], and this is consistent with our finding of improved MLHFQ scores following catheter ablation (Figure 4).

In our meta-analysis, catheter ablation provided 48% reduction in mid-term mortality risk as compared to medical therapy (Figure 5). In contrast to our findings, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) and Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) trials found no difference in mortality between anti-arrhythmic drug (AAD) therapy and rate control [28,29]. There are several possible explanations for this discrepancy. AADs may not be as efficacious as catheter ablation in providing freedom from AF in patients with heart failure, and there is increasing evidence that the maintenance of sinus rhythm is the key determinant of survival [30]. Alternatively, the mortality benefit of AADs in previous trials may have been offset by their adverse effects, such as the higher rate of torsade de pointes with dofetilide use in the DIAMOND-CHF trial [29].

Table 4 Quality assessment of included randomised controlled trials using Cochrane Risk of Bias Tool.

Domain	McDonald et al. 2011	Jones et al. 2013	Hunter et al. 2014	Di Biase et al. 2016	Prabhu et al. 2017	Maroucche et al. 2018
Random sequence generation (selection bias)	**Low risk** (computer generated sequences used to achieve randomisation).	**Low risk** (computer generated sequences used to achieve randomisation).	**Low risk** (random number generator used to achieve randomisation).	**Low risk** (computerised block randomisation performed at central site).	**Low risk** (block randomisation performed centrally by independent third party using software).	**Low risk** (computerised randomisation performed centrally)
Allocation concealment (selection bias)	**Low risk** (sealed enveloped used to conceal allocation).	**High risk** (open label study).	**Low risk** (sealed enveloped used to conceal allocation).	**Low risk** (randomly selected blocks provided to individual sites).	**Low risk** (allocation appropriately concealed)	**Low risk** (allocation appropriately concealed)
Blinding of participants and personnel (performance bias)	**High risk** (patients not blinded and investigators only blinded until baseline assessment).	**High risk** (patients not blinded and only investigators measuring outcomes were blinded).	**High risk** (patients not blinded and investigators only blinded until baseline assessment).	**High risk** (patients not blinded and only investigators measuring LVEF were blinded).	**High risk** (patients not blinded and only investigators measuring LVEF were blinded).	**High risk** (neither patients nor investigators blinded)
Blinding of outcome assessment (detection bias)	**Low risk** for endpoint of LVEF change (blinded assessment) **High risk** for other endpoints (assessors not blinded).	**Low risk** for all endpoints (assessors blinded to treatment group)	**Low risk** for endpoint of LVEF change (blinded assessment) **High risk** for other endpoints (assessors not blinded).	**Low risk** for endpoint of LVEF change (blinded assessment) **High risk** for other endpoints (assessors not blinded).	**Low risk** for endpoint of LVEF change (blinded assessment) **High risk** for other endpoints (assessors not blinded).	**Unclear risk** for all endpoints (blinding of assessors not specified)
Incomplete outcome data (attrition bias)	**Low risk** (low attrition rate, intention to treat analysis performed).	**Low risk** (low attrition rate, intention to treat analysis performed).	**Low risk** (low attrition rate, intention to treat analysis performed).	**High risk** (greater attrition rate in ablation arm for LVEF endpoint).	**Low risk** (low attrition rate, intention to treat analysis performed).	**High risk** (greater attrition rate in ablation arm, intention to treat analysis performed).
Selective reporting (reporting bias)	**Low risk** (all pre-specified endpoints reported).	**Low risk** (all pre-specified endpoints reported).	**Low risk** (all pre-specified endpoints reported).	**Low risk** (all pre-specified endpoints reported).	**Low risk** (all pre-specified endpoints reported).	**Low risk** (all pre-specified endpoints reported).
Other bias	89% of screened patients excluded from randomisation (reasons for exclusion given).	49% of screened patients excluded from randomisation (reasons for exclusion given). Minor imbalances between groups at baseline.	86% of screened patients excluded from randomisation (reasons not given).	77% of screened patients excluded from randomisation (reasons for exclusion not given).	77% of screened patients excluded from randomisation (reasons for exclusion given). Cross over of 9% from medical therapy group to ablation arm.	87% of screened patients excluded from randomisation (reasons for exclusion not given). Cross over of 16% from ablation to medical therapy, and 10% from medical therapy to ablation.

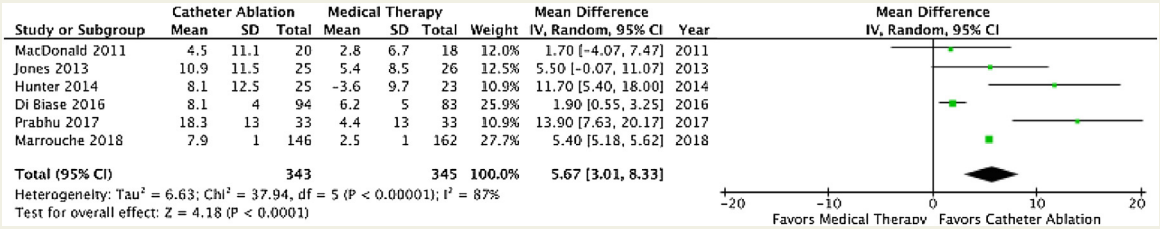

Figure 2 Forest plot displaying mean difference (MD) in left ventricular ejection fraction (LVEF) change in patients with atrial fibrillation and heart failure undergoing catheter ablation (CA) versus medical therapy (MT).

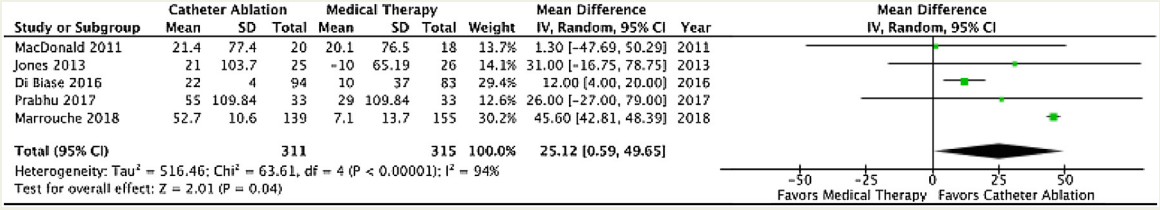

Figure 3 Forest plot displaying mean difference (MD) in 6-minute walk test (6MWT) distance in patients with atrial fibrillation and heart failure undergoing catheter ablation (CA) versus medical therapy (MT).

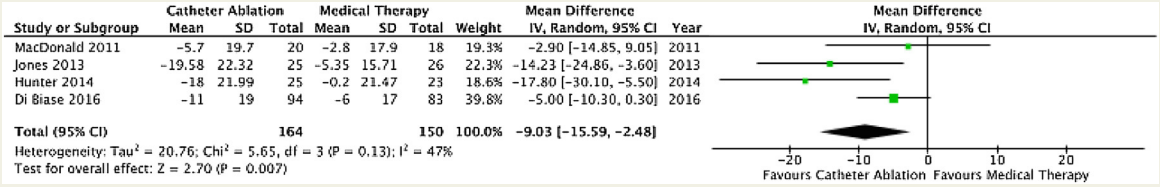

Figure 4 Forest plot displaying mean difference (MD) in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores in patients with atrial fibrillation and heart failure undergoing catheter ablation (CA) versus medical therapy (MT).

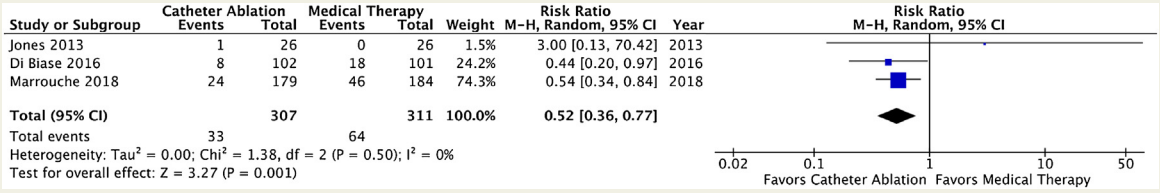

Figure 5 Forest plot displaying relative risk (RR) for mid-term mortality in in patients with atrial fibrillation and heart failure undergoing catheter ablation (CA) versus medical therapy (MT).

The pooled incidence of major peri-procedural complications across included RCTs was 8.2% (95% CI, 3.7–17.2%), which is considerably higher than the pooled complication rates of 2.9% reported in a recent systematic review of contemporary AF ablation studies [31]. In addition to heart failure, study populations of trials included in our meta-analysis had a significant burden of co-morbidities such as renal insufficiency, diabetes mellitus, and chronic obstructive pulmonary disease. Hence, it is unclear whether the presence of HF independently predisposes to an increased risk of adverse peri-procedural complications or whether it is a marker of a more complex pathophysiological milieu. Regardless, in selecting patients with HF for catheter ablation of AF, the increased risk of major peri-procedural events must be carefully weighed against the potential improvement in systolic function, quality of life and functional status.

The pooled freedom from AF was 71.1% (95% CI, 59.5–80.5), which was unexpectedly high given the vast majority of study participants had persistent AF [32]. However, it is important to note that a significant proportion of study participants underwent multiple procedures, with mean number of ablations per patient ranging from 1.19–1.7 (Table 2). Furthermore, included RCTs were exclusively conducted at high-volume centres with experienced operators. It remains unclear whether these results can be translated to

broader clinical settings. There was also significant heterogeneity detected (I^2 = 71%; p = 0.004) for this outcome, which is likely reflective of the variability across included trials with regards to the frequency and modality used to detect recurrent AF.

Limitations

Our meta-analysis has several limitations, which must be considered when interpreting its findings. First, a small number of trials were included, and only two had a median follow-up duration of at least 24 months; whether benefits of CA are sustained in the longer term are unknown. Second, due to the lack of individual patient data, it was not possible to perform meta-regression or subgroup analyses to assess for the impact of potential confounders. Notably, it was not feasible to compare outcomes of patients with primary AF begetting heart failure (e.g. tachycardia-induced cardiomyopathy) from individuals in which AF likely arose as a secondary phenomenon. Third, beyond pulmonary vein isolation, strategies for further left atrial ablation varied *within and between* studies, from posterior left atrial isolation, linear ablation of the left atrial roof and/or mitral isthmus, targeting of complex fractionated atrial electrograms and superior vena cava isolation. Lastly, due to the small number of included trials, publication bias was only assessed for the primary endpoint of LVEF and even this analysis is likely to be severely underpowered.

Conclusions

In conclusion, the present meta-analysis suggests that CA, compared to medical therapy for AF in patients with heart failure results in significant improvement in LVEF, quality of life and functional status, with a survival benefit. Larger RCTs with longer follow-up duration are required to confirm longevity of benefits and to identify specific subgroups of patients with AF and HF that would most benefit from CA.

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