Meta-analysis of the Usefulness of Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure With Preserved Ejection Fraction

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Catheter ablation improves clinical outcomes in atrial fibrillation (AF) patients with heart failure (HF) with reduced ejection fraction (HFrEF). However, the role of catheter ablation in HF with a preserved ejection fraction (HFpEF) is less clear. We performed a literature search and systematic review of studies that compared AF recurrence at one year after catheter ablation of AF in patients with HFpEF versus those with HFrEF. Risk ratio (RR; where a RR <1.0 favors the HFpEF group) and mean difference (MD; where MD <0 favors the HFpEF group) 95% confidence intervals (CI) were measured for dichotomous and continuous variables, respectively. Six studies with a total of 1,505 patients were included, of which 764 (51%) had HFpEF and 741 (49%) had HFrEF. Patients with HFpEF experienced similar recurrence of AF 1 year after ablation on or off antiarrhythmic drugs compared with those with HFrEF (RR 1.01; 95% CI 0.76, 1.35). Fluoroscopy time was significantly shorter in the HFpEF group (MD −5.42; 95% CI −8.51, −2.34), but there was no significant difference in procedure time (MD 1.74; 95% CI −11.89, 15.37) or periprocedural adverse events between groups (RR 0.84; 95% CI 0.54,1.32). There was no significant difference in hospitalizations between groups (MD 1.18; 95% CI 0.90, 1.55), but HFpEF patients experienced significantly less mortality (MD 0.41; 95% CI 0.18, 0.94). In conclusion, based on the results of this meta-analysis, catheter ablation of AF in patients with HFpEF appears as safe and efficacious in maintaining sinus rhythm as in those with HFrEF. **(Am J Cardiol 2021;142:66−73)**

Atrial fibrillation (AF) and heart failure (HF) have become increasingly prevalent and frequently co-occur, resulting in increased morbidity and mortality relative to either disease alone.[1−5] Although there are evidence-based guidelines for diseases,[6,7] it is less clear how to manage patients in whom both AF and HF are present. Although more data has emerged to guide the management of patients with AF and heart failure with reduced ejection fraction (HFrEF), including updated guidelines advocating for ablation of AF in patients with HFrEF, data on patients with heart failure with preserved ejection fraction (HFpEF) were relatively sparse until recently.[7,8] Given that AF has been shown to incur greater morbidity and mortality in patients with HFpEF relative to those with AF and HFrEF and in those with AF and no HF, understanding how to best manage AF in patients with HFpEF is of particular importance.[9−14] The purpose of our current study was to perform a systematic review of the literature and meta-analysis to determine the effect of catheter ablation of AF on rates of recurrent AF, fluoroscopy and procedure times, and rates of periprocedural adverse events, hospitalizations and mortality in patients with HFpEF compared with those with HFrEF, in order to determine any difference in benefits or risks between these groups.

Methods

We searched PubMed, Clinicaltrials.gov, Medline, Google scholar and the Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 09, 2017). This was assessed up to March 2020. No language restriction was applied. The reference list of all eligible studies was also reviewed. Search terms included (*Catheter Ablation)* AND *(Atrial Fibrillation)* AND (*Heart Failure with Preserved Ejection Fraction* OR *Diastolic Dysfunction)*.

Studies were selected by two independent reviewers. The PRISMA statement for reporting systemic reviews and meta-analyses was applied to the methods for this study.[15] The studies had to fulfill the following criteria to be considered in the analysis: (1) Studies were required to evaluate outcomes in patients with HFpEF and HFrEF (HF with a moderately reduced ejection fraction (EF 40% to 49%) was included as part of the HFrEF group); (2) Studies were required to report the rates of recurrent AF; (3) Studies were required to have a minimum follow up of 12 months; (4) Studies were required to have been published in a peer-reviewed scientific journal.

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See page 71 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.11.039

We aimed to compare rates of recurrent AF, fluoroscopy and procedure times, and rates of periprocedural adverse events, hospitalizations and mortality in patients with HFpEF compared with those with HFrEF, from baseline procedure to follow up.

Two authors (O.M.A. and F.L.) independently performed the literature search and extracted data from eligible studies. Outcomes were extracted from original manuscripts and supplementary data. Information was gathered using a standardized protocol and reporting forms. Disagreements were resolved by consensus. Two reviewers (O.M.A. and F. L.) independently assessed the quality items and discrepancies were resolved by consensus or involvement of a third reviewer (J.C.H), if necessary.

Two authors (O.M.A. and F.L.) independently assessed the risk of bias of the included trials using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies were resolved by discussion or adjudication by a third author (J.C.H.).

Data were summarized across treatment arms using the Mantel-Haenszel risk ratio (RR), where a RR <1.0 favored the HFpEF group, and inverse variance mean difference (MD), where a MD <0 favored the HFpEF group. Heterogeneity of effects was evaluated using the Higgins I-squared (I^2) statistic. Random effects models for analyses were used with high heterogeneity (defined as I^2 >25%), otherwise fixed effects models of DerSimonian and Laird were used. Funnel plot analyses were used to address publication bias. The statistical analysis was performed by the *Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.* Descriptive statistics are presented as means and standard deviations (SD) for continuous variables or number of cases (n) and percentages (%) for dichotomous and categorical variables.

Results

An initial search resulted in 325 abstracts, of which 93 were duplicates and 214 were excluded based on titles and abstracts (Figure 1). We included 6 studies in our final analysis; three retrospective[16–18] and 3 prospective[19–21] observational studies. Baseline demographics and characteristics of the 6 studies are summarized in Tables 1 and 2. All of the included studies were observational. The majority of HFpEF and HFrEF patients in all of the included studies had persistent AF and were on antiarrhythmic drugs and β-blockers, with the exception that only 37% of HFrEF patients in the study by Eietl et al. were on antiarrhythmic drugs. We included a total of 1,505 patients. Among these, 764 (51%) patients had HFpEF and 741 (49%) had HFrEF. The risk of bias is summarized in Table 3. Although all the studies accounted for major co-morbidities when making comparisons and had adequate follow-up, the majority of studies did not control for antiarrhythmic drug use. The majority of the studies used a 3-month blanking period.[16–18,21]

There was no difference in the risk of recurrent AF in patients with HFpEF and HFrEF (RR 1.01; 95% confidence interval [CI] 0.76, 1.35) 1 year after ablation (Figure 2). Although fluoroscopy time was significantly shorter in the HFpEF group (MD −5.42; 95% CI −8.51, −2.34), there

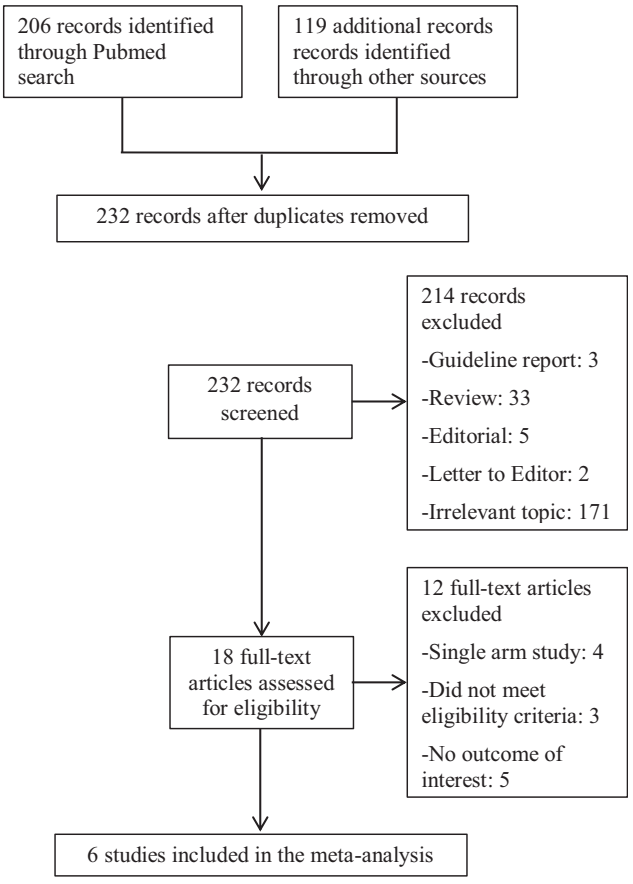

Figure 1. Selection of studies

was no significant difference in procedure times (MD 1.74; 95% CI −11.89, 15.37) or periprocedural adverse events between groups (RR 0.84; 95% CI 0.54, 1.32; Figure 3). Additionally, while there was no significant difference in hospitalizations between groups (MD 1.18; 95% CI 0.90, 1.55), HFpEF patients experienced significantly less mortality (MD 0.41; 95% CI 0.18, 0.94; Figure 4). Funnel plot analysis of the included studies showed no evidence of publication bias on any of the reported outcomes (Figures 2–4). Furthermore, in a sensitivity analysis where only prospective studies were included, the results were similar.

Discussion

This is the first systematic review and meta-analysis of studies comparing outcomes during and after catheter ablation of AF in patients with HFpEF versus those with HFrEF. The results of this meta-analysis show that there are no significant differences in rates of recurrence of AF one year after catheter ablation between patients with HFpEF and HFrEF. Fluoroscopy time was significantly shorter in the HFpEF group, but there were no significant differences in procedure time or periprocedural adverse events between groups. Although there was no significant difference in hospitalizations, HFpEF patients had significantly less mortality over follow-up. These findings should encourage larger, randomized control trials to be done

Table 1
Patient demographics and characteristics

Study (ref)	Cha et al[19]	Black-Maier et al[16]		Ichijo et al[17]		Vecchio et al[21]		Eitel et al[20]		Aldaas et al[18]	
	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF & HFrEF	HFpEF	HFrEF	HFpEF	HFrEF
Patients	157	111	133	97	55	51	35 & 47	333	395	51	40
Age (years)	62 ± 12	55 ± 9	67 ± 10	66 ± 11	64 ± 10	60 ± 11	62 ± 10	65 ± 10	66 ± 10	66 ± 12	65 ± 11
Men	107 (68%)	105 (95%)	77 (58%)	81 (84%)	44 (80%)	41 (80%)	59 (72%)	220 (66%)	284 (72%)	31 (61%)	32 (80%)
Persistent atrial fibrillation	79 (50%)	80 (72%)	76 (63%)	57 (62%)	32 (58%)	39 (76%)	45 (55%)	180 (54%)	252 (64%)	26 (51%)	24 (62%)
Left ventricular ejection fraction (%)	62 ± 4	35 ± 8	55 ± 0	37 ± 11	57 ± 8	38 ± 6	49 ± 13	NR	NR	59 ± 8	39 ± 7
CHA_2DS_2-VASc	NR	NR	5.0 ± 1.5	4.6 ± 2.3	NR	NR	2.0 ± NR	2.5 ± 1.2	3.0 ± 1.7	3.1 ± 1.8	2.7 ± 1.8
Hypertension	75 (48%)	42 (38%)	113 (85%)	78 (80%)	33 (60%)	23 (45%)	55 (67%)	255 (77%)	282 (71%)	38 (75%)	27 (69%)
Diabetes mellitus	15 (10%)	7 (6%)	38 (29%)	19 (20%)	13 (24%)	8 (16%)	7 (9%)	36 (11%)	81 (21%)	8 (16%)	3 (8%)
Coronary artery disease	27 (17%)	14 (13%)	NR	NR	10 (18%)	8 (44%)	17 (21%)	151 (45%)	192 (49%)	19 (37%)	15 (39%)
Sleep apnea	32 (20%)	21 (19%)	54 (41%)	39 (40%)	NR	NR	NR	NR	NR	11 (22%)	2 (5%)
Cerebrovascular accident/transient ischemic attack	8 (5%)	7 (6%)	20 (15%)	13 (13%)	5 (9%)	2 (4%)	4 (5%)	24 (7%)	10 (3%)	5 (10%)	4 (10%)
Medications											
Antiarrhythmic drug	85 (54%)	74 (67%)	83 (62%)	64 (66%)	24 (44%)	24 (47%)	65 (79%)	177 (53%)	145 (37%)	38 (75%)	23 (58%)
Beta blocker	102 (65%)	89 (80%)	97 (73%)	83 (86%)	33 (60%)	28 (55%)	45 (55%)	240 (72%)	315 (80%)	33 (65%)	22 (55%)
Calcium channel blocker	31 (20%)	25 (23%)	NR	NR	15 (27%)	10 (20%)	NR	NR	NR	8 (16%)	13 (33%)
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	NR	NR	77 (58%)	69 (71%)	17 (31%)	20 (39%)	NR	207 (62%)	288 (73%)	32 (63%)	19 (48%)
Aldosterone antagonist	NR	NR	16 (12%)	16 (17%)	NR	NR	NR	NR	NR	3 (6%)	0 (0%)
Digoxin	NR	NR	20 (15%)	13 (13%)	NR	NR	NR	NR	NR	8 (16%)	6 (15%)

Values are presented as ± SD or as n (%).

Table 2
Study characteristics

Study (ref)	Study design	Study population	Lesion set	Mean follow-up (months)	Monitoring
Cha et al[19]	Prospective, observational	Symptomatic, drug-resistant AF.	(RF) PVI, left atrial roof, mitral isthmus, superior vena cava, vein of Marshall, coronary sinus, and cavotricuspid isthmus	14.5 ± 15.2	Physical exam, ECG, 24-hour Holter at 3 months, 1 year clinic follow-up and event monitor as needed
Black-Maier et al[16]	Retrospective, observational	AF ablation procedure with clinical diagnosis of HF. Excluded non-radiofrequency ablation.	(RF) PVI, left atrial roof, mitral isthmus, coronary sinus and complex fractioned atrial electrograms	9.9 ± 3.7	Phone calls at 1 week, 3, 6, and 12 months. Chart review of ambulatory monitoring (Holter and/or loop recorder)
Ichijo et[17]	Retrospective, observational	Patients with HF who underwent de novo catheter ablation for AF. HFpEF defined as LVEF >45%.	(RF) PVI, superior vena cava, complex fractionated atrial electrograms, and cavotricuspid isthmus	32.4 ± 18.6	ECG and/or 24-hour Holter every 3 months in first year, then every 6-12 months. 30-day event recorder if symptomatic and 14-day loop recorder if not
Vecchio et al[21]	Prospective, observational	AF and signs and symptoms HF or LVEF <45% who underwent catheter ablation.	(RF) PVI, superior vena cava, coronary sinus, complex fractionated atrial electrograms, and cavotricuspid isthmus	12	ECG and 24-hour Holter at 1, 3, 6, 9 and 12 months
Eitel et al.[20]	Prospective, multicenter, observational	Structural heart disease and HF NYHA class ≥II prior to catheter ablation for symptomatic AF.	(RF/CB) PVI or AVN ablation, linear lesions, complex fractionated atrial electrograms	12	1 year telephone interview and ECG
Aldaas et al[18]	Retrospective, observational	Patients with HF who underwent de novo catheter ablation for AF.	(RF) PVI, left atrial roof, coronary sinus, mitral isthmus, complex fractionated atrial electrograms, and cavotricuspid isthmus	37.4 ± 24.7	ECG at each visit as well as ambulatory monitoring at 6 and 12 months (more if symptomatic).

Unless otherwise stated, a preserved ejection fraction was defined as ≥ 50%.
AF = atrial fibrillation; CB = cryoballoon catheter ablation; ECG = electrocardiogram; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RF = radiofrequency catheter ablation.

Table 3
Newcastle-Ottawa scale

Quality assessment criteria	Acceptable (*)	Cha et al[19]	Black-Maier et al[16]	Ichijo et al[17]	Vecchio et al[21]	Eitel et al[20]	Aldaas et al[18]
Selection							
Representativeness of the exposed cohort?	Truly or somewhat representative of the average patient referred for ablation	*	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from the same community as the exposed cohort	*	*	*	*	*	*
Ascertainment of exposure?	Secure record	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?	Yes	*	*	*	*	*	*
Comparability							
Study controls for antiarrhythmic drug use?	Yes	*	-	-	-	-	*
Study controls for at least 3 additional factors?	Age, sex, HTN, HLD, DM, CAD, CVA/TIA	*	*	*	*	*	*
Outcome							
Assessment of outcome?	Independent blind assessment or record linkage	-	-	-	-	-	-
Was follow-up long enough for outcomes to occur?	Yes	*	*	*	*	*	*
Adequacy of follow up of cohorts?	Complete follow up or subjects lost to follow up unlikely to introduce bias	*	*	*	*	*	*
Overall Quality Score (Maximum = 9)	8	7	7	7	7	8	

AF = atrial fibrillation; CAD = coronary artery disease; CVA = cerebral vascular accident; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; TIA = transient ischemic attack.

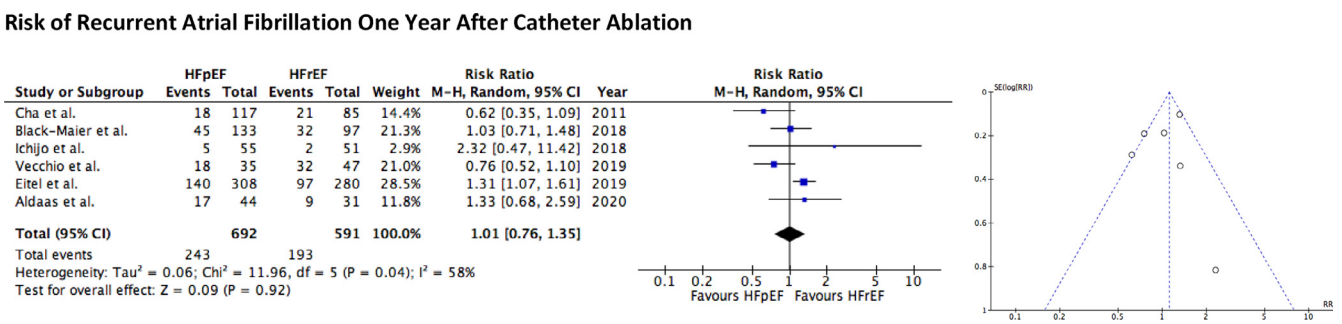

Figure 2. Forrest plots and funnel plots for the comparative analysis of risk of recurrent atrial fibrillation in patients with heart failure with preserved ejection fraction compared to those who have heart failure with reduced ejection fraction at one year after catheter ablation.

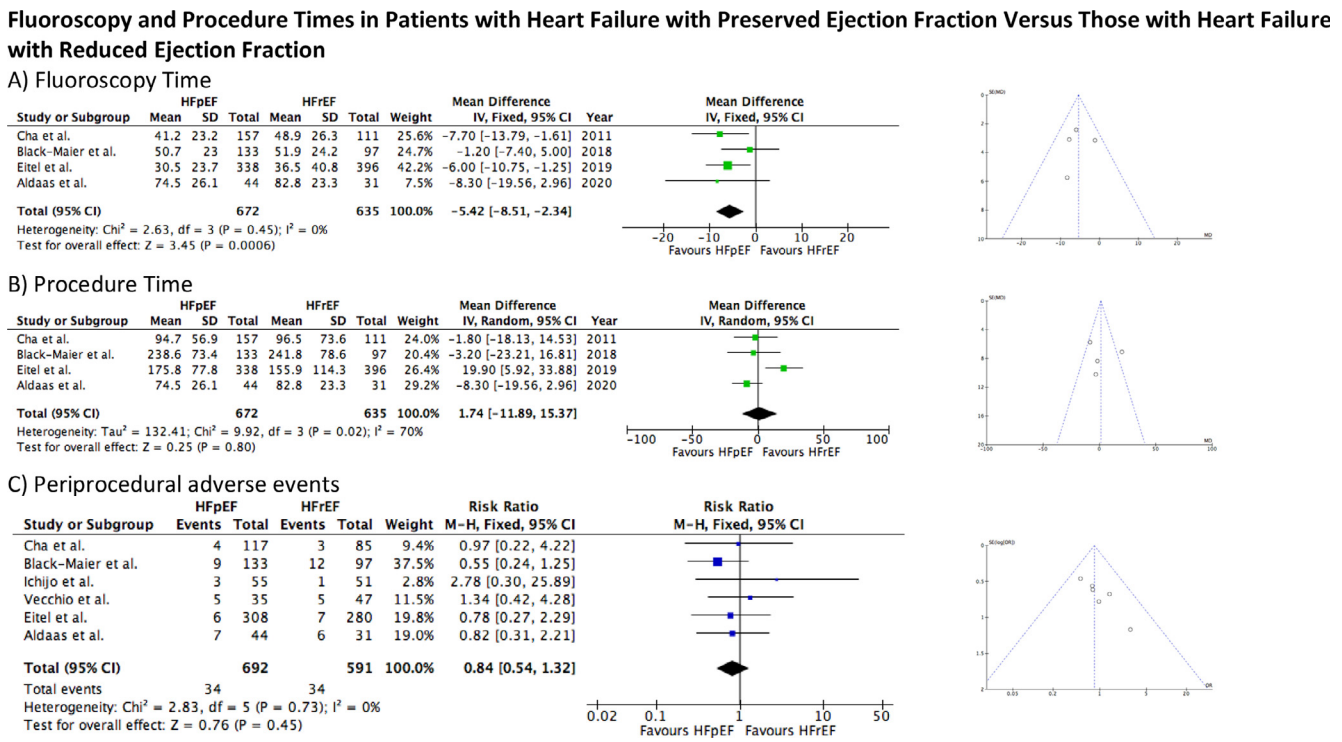

Figure 3. Forrest plots and funnel plots for the comparative analysis of *(A)* fluoroscopy time, *(B)* procedure time, and *(C)* periprocedural adverse events in patients with heart failure with preserved ejection fraction compared to those with heart failure with reduced ejection fraction. Periprocedural adverse events varied by study, including access site/vascular complications, cardiac perforation/tamponade, stroke/transient ischemic attack, pericarditis, acute heart failure, pulmonary vein stenosis, phrenic nerve injury, esophageal atrial fistula, air embolism, and prolonged hospitalization.

specifically in patients with HFpEF, to establish a benefit of catheter ablation in this population of patients.

In addition to the findings reported in this meta-analysis, there are data that suggest ablation of AF in patients with HFpEF portends improvements in quality of life, short-term hospitalizations, and long-term AF recurrence. Although Black-Meier et al[16] found no significant difference in quality of life scores pre- and postablation, both Cha et al and Ichijo et al reported significant improvements in quality of life in patients with HFpEF postablation.[17,19] Elkaryoni et al found that there was no significant difference in the relative reduction in hospitalization rates 120 days before and after index admission for catheter ablation among HFpEF patients (28.5%) and those with HFrEF (25.2%).[22] Fukui et al also showed that catheter ablation significantly reduced HF hospitalizations over a mean follow-up of 720 ± 377 days in patients with HFpEF when compared with conventional pharmacotherapy.[23] Similar to the data presented here, Jayanna et al found, in a subgroup analysis, that there was no difference in AF recurrence 3 months and 1 year postablation between patients with HFpEF and HFrEF, but this data was not included in the analyses as the numbers of patients with HFpEF and HFrEF were not explicitly stated.[24] Much of the AF recurrence data presented at 1 year remained to be true over longer follow-up, with 2 other studies that had extended follow-up out to 5 years showing no difference in recurrence between patients with HFpEF and HFrEF.[18,19] These data suggest that patients with AF and HFpEF do just as well, if not better, than those with AF and HFrEF after catheter ablation, which should encourage larger studies to evaluate this

Rates of Hospitalizations and Mortality in Patients with Heart Failure with Preserved Ejection Fraction Versus Those with a Reduced Ejection Fraction

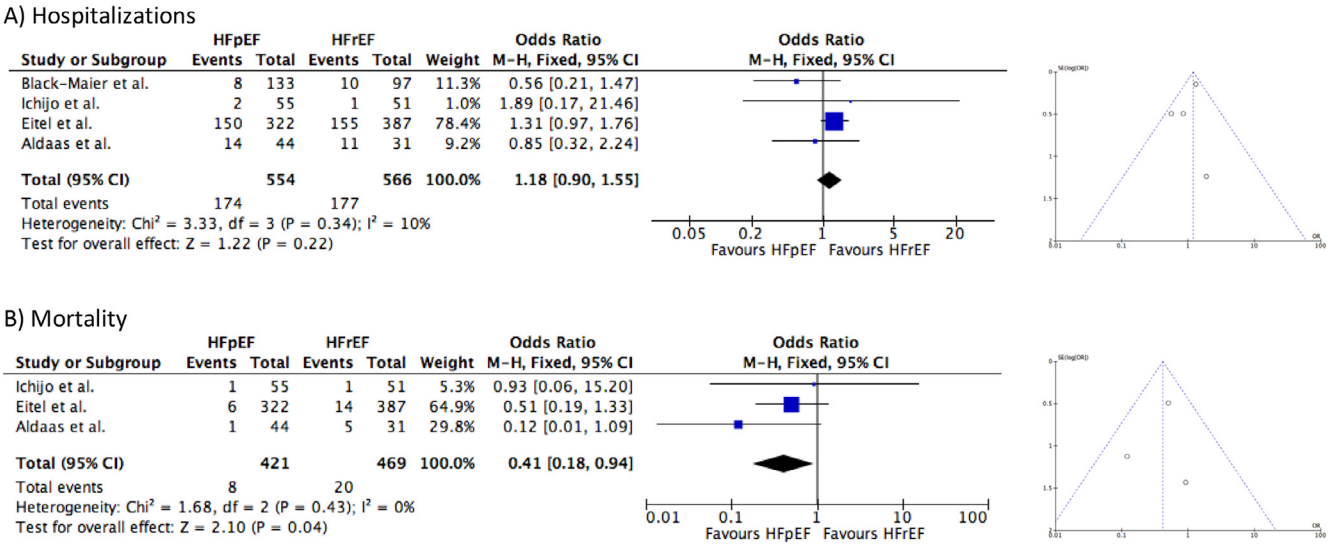

Figure 4. Forrest plots and funnel plots for the comparative analysis of *(A)* hospitalizations and *(B)* mortality in patients with heart failure with preserved ejection fraction compared to those who have heart failure with reduced ejection fraction.

patient population, especially since they are largely lacking from current guidelines.[7]

Atrial remodeling, AF and HFpEF share similar risk factors, which in part explain the increased prevalence of one disease in the presence of the other [25–28] AF can lead to HFpEF predominantly through hemodynamic effects and left ventricular fibrosis. The loss of atrial systole, loss of atrioventricular synchrony and decreased filling time seen in AF decreases cardiac output and results in a series of neurohormonal changes. The excess sympathetic tone and renin activity result in an increase in central venous pressure and the rise in plasma norepinephrine and subsequent arteriolar vasoconstriction increases the afterload.[29,30] Additionally, there are data to suggest that the burden of AF is important in the development of fibrosis.[31] Conversely, HFpEF can also promote AF through several mechanisms including atrial fibrosis,[32,33] left atrial mechanical dysfunction,[9,34] changes in calcium handling,[35,36] and electrical remodeling.[37] The shared risk factors and pathophysiology may account for the increased burden and mortality of AF in the HFpEF population relative to those with HFrEF.[9,38] Due to the pathophysiology of AF in patients with HFpEF, the importance of our meta-analysis findings in aggregate show that catheter ablation of AF in patients with HFpEF is important and may be as effective at improving clinical outcomes as has been shown in patients with HFrEF.

The current systematic review and meta-analysis has several important limitations that should be acknowledged. First, all of the included studies were observational and, with the exception of the study by Eitel et al, were single-center, which significantly restricts the generalizability of the results. Second, there were different study protocols, with both retrospective and prospective studies included and various lesion sets employed. Third, each study had different protocols to monitor for arrhythmia recurrence, but all met the standard of consensus guidelines.[39,40] Fourth, follow-up was only analyzed out to 12 months postablation. However, as mentioned above, reported results were similar in the studies that extended follow-up out for several years. In conclusion, based on the results of this meta-analysis, catheter ablation of AF in patients with HFpEF appears as safe and efficacious in maintaining sinus rhythm as in those with HFrEF.

Author Contributions

Omar M. Aldaas, MD: Conceptualization, methodology, formal analysis, data curation, writing original draft, visualization, project administrationl; **Florentino Lupercio, MD**: Data curation, formal analysis, writing review and editing, visualization; **Douglas Darden, MD:** Data curation, writing review and editing, visualization; **Praneet S. Mylavarapu, MD:** Data curation, writing original draft, visualization; **Chaitanya L. Malladi, MD**: Data curation, writing original draft, visualization; **Frederick T. Han, MD**: Writing review and editing, visualization; **Kurt S. Hoffmayer, MD, PharmD**: Writing review and editing, visualization; **David Krummen, MD:** Writing review and editing, visualization; **Gordon Ho, MD**: Writing review and editing, visualization; **Farshad Raissi, MD**: Writing review and editing, visualization; **Ulrika Birgersdotter-Green, MD**: Writing review and editing, visualization; **Gregory K. Feld, MD:** Writing review and editing, visualization; **Jonathan C. Hsu, MD, MAS:** Conceptualization, methodology, formal analysis, data curation, writing review and editing, visualization, supervision, project administration

Disclosures

Dr. Hsu reports receiving honoraria from Medtronic, Abbott, Boston Scientific, Biotronik, Zoll Medical, Biosense-Webster, Janssen Pharmaceuticals, and Bristol-Myers

Squibb, research grants from Biotronik and Biosense-Webster, and has equity interest in Acutus Medical and Vektor Medical. Dr Krummen reports owning equity in Vektor Medical Inc for unrelated work. Dr. Ho reports receiving a research grant from the American Heart Association (AHA 19CDA34760021), owns equity in Vektor Medical Inc and fellowship support from Medtronic, Abbott, Boston Scientific, and Biotronik. Dr. Feld reports receiving consulting fees from Acutus Medical, Inc., Vektor Medical, Inc., and Altathera Pharmaceuticals, Inc., fellowship stipend support from Medtronic, Inc., Boston Scientific, Inc., Biotronik, Inc., Biosense Webster, Inc., and St. Jude Medical, Inc., is cofounder of Perminova, Inc., and has received stock or stock-options from Acutus Medical, Inc., and Perminova, Inc.

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