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A comparison of clinical outcomes following atrial fibrillation ablation for heart failure patients with preserved or reduced left ventricular function: A systematic review and meta-analysis

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ABSTRACT

Background: This review aims to determine if patients who undergo atrial fibrillation (AF) ablation with heart failure with preserved ejection fraction (HFpEF) do better, or worse or the same compared to patients with heart failure with reduced ejection fraction (HFrEF).
Methods: A search of MEDLINE and EMBASE was performed using the search terms: “atrial fibrillation”, “ablation” and terms related to HFpEF and HFrEF in order to identify studies that evaluated one or more of i) AF recurrence, ii) periprocedural complications and iii) adverse outcomes at follow up for patients with HFpEF and HFrEF who underwent AF ablation. Data was extracted from included studies and statistically pooled to evaluate adverse events and AF recurrence.
Results: 5 studies were included in this review and the sample size of the studies ranged from 91 to 521 patients with heart failure. There was no significant difference in the pooled rate for no AF or symptom recurrence after AF ablation comparing patients with HFpEF vs HFrEF (RR 1.07 95%CI 0.86−1.33, $p = 0.15$). The most common complications were access site complications/haematoma/bleeding which occurred in similar proportion in each group; HFpEF (3.1%) and HFrEF (3.1%). In terms of repeat ablations, two studies were pooled to yield a rate of 78/455 (17.1%) for HFpEF vs 24/279 (8.6%) for HFrEF ($p = 0.001$.
Conclusions: Heart failure patients with preserved or reduced ejection fraction have similar risk of AF or symptom recurrence after AF ablation but two studies suggest that patients with HFpEF are more likely to have repeat ablations.
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1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias which affects 1 in 200 patients in the adult population [1]. It is important because it can lead to undesirable symptoms and serious complications such as embolic stroke [2]. Both American and European guidelines endorse either a rate or rhythm control strategy where the former uses negative chronotropic medications and anticoagulation to reduce stroke risk while the latter includes electrical and chemical cardioversion including AF ablation to achieve rhythm control [3,4]. It is not clear that all heart failure patients with AF will benefit from AF ablation. While it is recognized that many patients with heart failure (HF) are comorbid and frail thus increasing their risk of complications from invasive procedures, the CASTLE AF suggested that patients with heart failure with poor left ventricular function have prognostic gain AF ablation [5].

Despite both conditions having similar presentations, the pathophysiology of heart failure with preserved ejection fraction (HFpEF) is very different from heart failure with reduced ejection fraction (HFrEF) which may affect the likelihood of success with AF ablation. In HFrEF there is a failure of left ventricular contraction due to a number of pathologies such as myocardial infarction or cardiomyopathy while in HFpEF the left ventricular contraction is preserved but the stiffness of the ventricle impairs the relaxation

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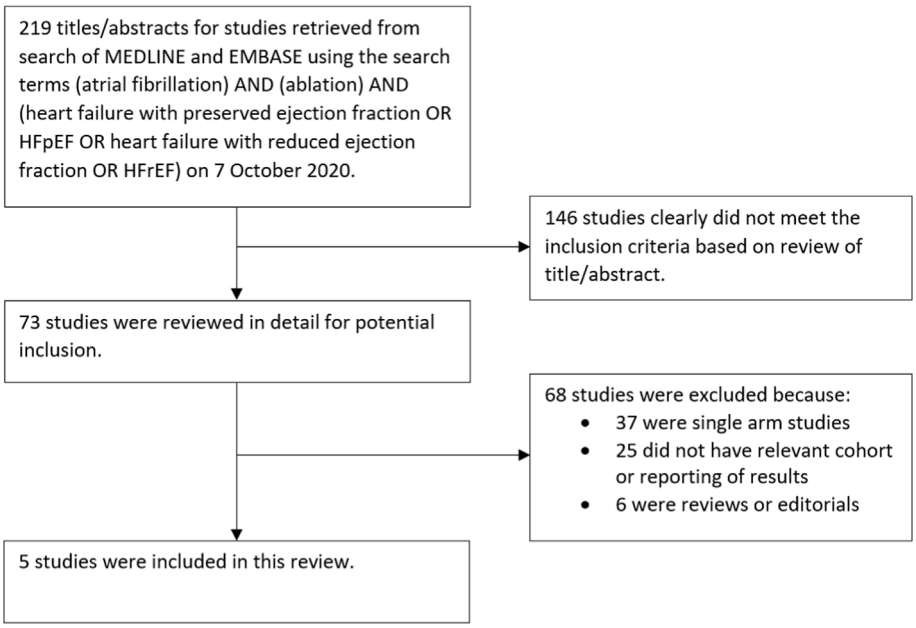

Fig. 1. Flow diagram of study selection.

process following contraction [6,7]. Predictors of AF ablation failure have been reported to be valvular AF and larger left atrial diameter (>5 cm) [8]. It has been suggested that the HFrEF is associated with increased left atrial diameter [9]. However, patients with HFpEF undergo atrial remodelling which results in increases left atrial pressure and left atrial volume [10]. The increase in left atrial volume is a strong predictor of the recurrence after ablation because of its link to fibrosis and a reduction in atrial wall compliance [11]. It is currently unknown whether the patients who undergo AF ablation with HF and preserved ejection fraction do better, or worse or the same compared to patients with HF reduced ejection fraction.

We, therefore, conducted a systematic review and meta-analysis of studies which compared outcomes in patients with HFpEF and HFrEF who undergo AF ablation. The primary outcome of interest was in AF recurrence but we were also interested in the potential differences in baseline characteristics, periprocedural complications and long-term adverse events.

2. Methods

The reporting of this systematic review is in according to the recommendations of the MOOSE checklist [12] (Supplementary Table 1).

2.1. Eligibility criteria

We selected parallel-group studies that evaluated one or more of i) AF recurrence, ii) periprocedural complications and iii) adverse outcomes at follow up for patients with HFpEF and HFrEF who underwent AF ablation. We included all studies irrespective of design (retrospective or prospective), mode of presentation (i.e., conference abstract) or language of publication. We excluded studies without original data including reviews, editorials and commentaries.

2.2. Search strategy

We searched the OVID platform to identify studies in Embase and MEDLINE was between 1974 to 2020 and 1946 to 2020, respectively. The search terms used were: ("atrial fibrillation") AND ("ablation") AND ("heart failure with preserved ejection fraction" OR "HFpEF" OR "heart failure with reduced ejection fraction" OR "HFrEF"). We also checked the bibliographies of included studies and relevant reviews for additional studies.

2.3. Study selection and data extraction

Two reviewers (GP and CSK) independently and in duplicate assessed the titles and abstracts of the search results and excluded studies that were not relevant. Full-text of potentially relevant studies were retrieved and a detailed review was performed against the eligibility criteria. Any uncertainties about inclusion were resolved by consensus through discussion with other co-authors after a full review of the manuscript. The primary outcome was to assess recurrence of AF or recurrence of symptoms. The secondary outcomes included periprocedural complications, adverse cardiovascular events, hospitalization, repeat ablations and mortality.

2.4. Study characteristics and quality assessment

Two reviewers (GP and CSK) independently extracted data on study characteristics. We recorded data on study design, country, years of study, total number of participants, mean age, % of male participants, participant inclusion criteria, patient demographic variables, comorbidities, medications, definition of heart failure, type of AF, method of AF ablation, follow up and outcome according to HFpEF or HFrEF. Both crude event rates and most adjusted results were extracted.

Study quality was evaluated by considering risk of bias using the Newcastle-Ottawa Scale for cohort studies [13]. Funnel plots were used to evaluated publication bias if the analysis had more than 10 included studies and no evidence of statistical heterogeneity [14].

2.5. Data synthesis

Data was collected and presented in tables. Results for periprocedural complication and long term adverse events were pooled

using methods as previously reported by Kwok et al. [15]. For the primary outcome of a good outcome after AF ablation (no recurrence of AF, no symptoms or clinical success), we used RevMan 5.3 (The Nordic Cochrane Centre) to conduct random-effects meta-analysis for the pooled relative risks (RR), with 95% confidence intervals based on the inverse variance method. Statistical heterogeneity was assessed using the I^2 statistic where 30–60% represent a moderate level of heterogeneity [16].

3. Results

3.1. Study selection

A total of 5 studies were included in this review after screening and reviewing potentially relevant studies in detail (Fig. 1) [17–24].

3.2. Study design and patient characteristics

The description of the study design, patient characteristics and study inclusion criteria is shown in Table 1. There were 4 retrospective cohort studies and 1 prospective cohort study and these studies took place in the USA, Germany, Czech Republic and Japan. The sample size of the study ranged from 91 to 521 patients with heart failure. There were a total 634 patients with HFpEF and 417 patients with HFrEF in the 5 studies which reported proportion of patients with HFpEF and HFrEF. The mean age of the participants ranged from 62.0 to 65.3 years from 3 studies and the percentage of male patients ranged from 68.7% to 80.2%. The average mean age and proportion of male patients (±2SD) across the studies that reported these figures were 63.3 ± 3.5 years and 72.1 ± 10.9%. The average age across the studies was numerically higher among patients in the group with HFpEF compared to HFrEF (64.1 years vs 62.3 years, $p = 0.35$) but the average proportion of male patients was higher in the group with HFrEF (66.2% vs 80.4%, $p = 0.06$). The follow up and procedure related data are summarized in Table 2.

The comparison of patient characteristics for HFpEF and HFrEF is shown in Supplementary Table 2. Among the studies, there was no pattern to suggest that patients with HFrEF were older compared to those with HFpEF but patients with HFrEF appeared to have a greater proportion of patients that were male. The average proportion of patients with hypertension (74.2% vs 66.9%, $p = 0.18$), hyperlipidaemia (51.0% vs 49.0%), diabetes mellitus (19.9% vs 16.2%, $p = 0.24$) and use of β-blockers (67.5% vs 69.3%, $p = 0.42$) and angiotensin converting enzyme inhibitors (42.7% vs 50.8%, $p = 0.26$) were not statistically different for patients with HFpEF and HFrEF. The proportion of male patients was greater among patients with HFrEF compared to HFpEF (80.1% vs 65.0%, $p < 0.001$) (Supplementary Table 3).

3.3. Definitions for heart failure and atrial fibrillation

The definitions of heart failure, AF and description of AF ablation procedure are shown in Supplementary Tables 4 and 5 Different cutoffs for ejection fraction was used to define patients with HFpEF and HFrEF as some studies used 50%, 45% and 40% with others including a heart failure with mid-range ejection fraction. Most studies included a combination of permanent and paroxysmal AF. A variety of methods were used to carry out the ablation along with different anatomical sites for ablation.

3.4. Study quality assessment

The quality assessment of the included studies is shown in Supplementary Table 6. Aside from demonstration that the outcome of interest was not present at the start of the study, all of the studies had reliable criteria for representativeness of cohort, selection of non-exposed cohort, ascertainment of exposure, comparability of the cohorts, assessment of outcome and adequacy and length of follow up for the cohorts.

3.5. Outcomes according to HFpEF and HFrEF

The pooled risk of atrial fibrillation recurrence or no recurrence of symptoms in patients who underwent ablation showed no significant difference for HFpEF vs HFrEF (RR 1.07 95%CI 0.86–1.33, $p = 0.15$, $I^2 = 38\%$) (Fig. 2).

The detailed descriptive data for the included studies are shown in Supplementary Tables 7, 8 and 9. The pooled results for adverse periprocedural events are shown in Table 3. The most common complications were access site complications/haematoma/bleeding, which occurred equally in patients with HFpEF (3.1%) compared to HFrEF (3.1%) ($p = 1.0$). Other complications that appear in less than 1% of patients included stroke/transient ischaemic attack, cardiac perforation/tamponade, death and major adverse cardiovascular events.

The pooled follow up events are shown in Table 4. In terms of repeat ablations, two studies (Black-Meier 2018 and Eitel 2020) were pooled to yield a rate of 78/455 (17.1%) for HFpEF vs 24/279 (8.6%) for HFrEF ($p = 0.001$) and one study (Black-Meier 2018) reported the rate of arrhythmic hospitalization of 19/133 (14.3%) for HFpEF vs 13/97 (13.4%) for HFrEF ($p = 0.85$). In Eitel et al., one-year mortality was significantly greater in patients with HFrEF vs HFpEF

Table 1
Study design, patient characteristics and inclusion criteria.

Study ID	Study design; Country; Year	Total participants	Mean age	% Male	Inclusion criteria
Aldaas 2020	Retrospective cohort study; USA; 2009 to 2015	91: 51 HFpEF, 40 HFrEF	Median HFpEF 67.6, Median HFrEF 68.2	69.2	Patients with AF ablation in the University of California, San Diego AF Ablation Registry.
Black-Meier 2018	Retrospective cohort study; USA; 2007 to 2013	230: 133 HFpEF, 97 HFrEF	Median HFpEF 68.0, Median HFrEF 67.0	68.7	Patients with AF ablation at the Duke Center for Atrial fibrillation.
Eitel 2020	Prospective cohort study; Germany; 2007 to 2010	521: 333 HFpEF, 188 HFrEF	65.3	70.3	Patients aged 18 years or older in the German ablation registry with NYHA class ≥II and symptomatic AF.
Havranek 2020	Retrospective cohort study; Czech Republic; 2010 to 2015	103: 62 HFpEF, 41 HFrEF	62.6	–	Patients with AF ablation and NYHA class ≥II at a single centre in Prague, Czech Republic.
Ichijo 2018	Retrospective cohort study; Japan; 2010 to 2015	106: 55 HFpEF, 51 HFrEF	62.0	80.2	Patients with AF and heart failure who underwent ablation in a centre in Tsuchiura, Japan.

HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, AF = atrial fibrillation, NYHA=New York Heart Association, USA=United States of America, LVEF = left ventricular ejection fraction.

Table 2
Follow up and outcomes for HFpEF vs HFrEF.

Study ID	Duration of follow up	Outcomes for HFpEF vs HFrEF
Aldaas 2020	Median: HFpEF 50.9 months HFrEF 24.2 months	Median procedure time: 277 vs 266 min Median fluoroscopy time: 73 vs 84 min Access site complication: 5/51 vs 6/40 Cardiac perforation/tamponade: 1/51 vs 0/40 Stroke/TIA: 0/51 vs 0/40 Pericarditis: 1/51 vs 0/40 Adjusted hazards of adverse outcomes for HFpEF vs HFrEF: Recurrence of AF/AFL/AT on or off AAD: aHR 1.92 (0.97–3.83) Recurrence of AF/AFL/AT off AAD: aHR 2.52 (0.73–8.77) All-cause hospitalizations: aHR 1.80 (0.97–3.33) All-cause mortality: aHR 0.53 (0.05–6.11)
Black-Meier 2018	Median: HFpEF 10.3 months, HFrEF 10.6 months	Median procedure time: 233 vs 233.5 min Median fluoroscopy time: 58.6 vs 57.1 min Access site bleeding: 4/133 vs 4/97 Stroke/TIA: 0/133 vs 4/97 Acute HF: 5/133 vs 6/97 ECG recurrence: 43/133 vs 31/97 AAD class IC/III use at 12 months: 71/133 vs 46/97 Repeat ablation: 6/133 vs 3/97 All-cause hospitalizations at 12 months: 28/133 vs 31/97 Cardiovascular hospitalization at 12 months: 28/133 vs 22/97 HF hospitalization at 12 months: 8/133 vs 10/97 Arrhythmia hospitalization at 12 months: 19/133 vs 13/97 Adjusted hazards of recurrence by AF type for HFpEF vs HFrEF: Paroxysmal AF: aHR 2.04 (0.41–10.07) Persistent AF: aHR 1.38 (0.53–3.60)
Eitel 2020	12 months follow up was 97% for HFpEF and 97.3% for HFrEF	Fluoroscopy time: 30.5 ± 23.7 vs 26.6 ± 25.8 Procedure duration: 175.8 ± 77.8 vs 122.9 ± 81.1 Death: 0/338 vs 1/188 MACE (death, MI): 0/338 vs 1/188 MACCE (death, MI, stroke): 2/338 vs 1/188 Stroke: 2/338 vs 0/188 Major bleeding: 7/338 vs 0/188 Transient ischaemic attack: 2/338 vs 1/188 Cardiac tamponade: 2/338 vs 2/188 Aneurysm spurium, arteriovenous fistula: 8/338 vs 0/188 Atrio-osophageal fistula: 0/338 vs 0/188 Minor bleeding: 20/338 vs 0/188 Duration of hospital stay: 4 [3,6] vs 4 [2,7] days Follow up data: No symptoms: 61/322 vs 22/182 Rehospitalisation: 150/322 vs 68/182 Re-ablation: 72/322 vs 21/182 1-year mortality: 1.9% (6/322) vs 6.1% (11/182) Non-fatal MI: 0/322 vs 1/182 Non-fatal stroke: 4/322 vs 1/182 Major bleeding: 1/322 vs 3/182 Transient ischaemic attack: 2/322 vs 0/182
Havranek 2020	Mean follow up: 43 months	Radiofrequency time: 53 ± 22 vs 63 ± 26 min Procedural time: 250 ± 75 vs 254 ± 68 min Good rhythm control without AAD: 26/62 vs 10/41 Good rhythm control ± AAD: 47/62 vs 27/41
Ichijo 2018	Mean follow up: HFpEF 32.8 months HFrEF 32.0 months	Procedural complications (cardiac tamponade, air embolism phrenic nerve injury): 3/55 vs 1/51 Free from any recurrent arrhythmias: 47/55 vs 47/51 Arrhythmia-free survival at 4 years: 79.3% (44/55) vs 88.7% (45/51) Heart failure related hospitalization at 4 years: 96.2% (53/55) vs 97.6% (50/51) Freedom from composite endpoint at 4 years: 91.8% (50/55) vs 88.7% (45/51)

HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, TIA = transient ischemic attack, AF = atrial fibrillation, AFL = atrial flutter, AT = atrial tachycardia, AAD = anti-arrhythmic drug, MACE = major adverse cardiac event, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial Infarction, aHR = adjusted hazard ratio.

(6.0% vs 1.9%, $p < 0.001$) but the adjusted analysis be Aldaas found no significant difference after adjustments (aHR 0.53 95%CI 0.05–6.11). There were no significant differences in all-cause hospitalizations ($p = 0.33$), stroke/TIA ($p = 0.59$), heart failure hospitalizations ($p = 0.23$), arrhythmia hospitalizations ($p = 0.85$) non-fatal myocardial infarction ($p = 0.20$) and major bleeding ($p = 0.11$) comparing HFpEF to HFrEF.

4. Discussion

We have conducted this systematic review of 5 studies with total 1051 patients and the main findings of our study are no significant difference in AF recurrence and secondary outcomes of adverse events for patients undergoing AF ablation with regard to the type of heart failure syndrome based on their left ventricular function.

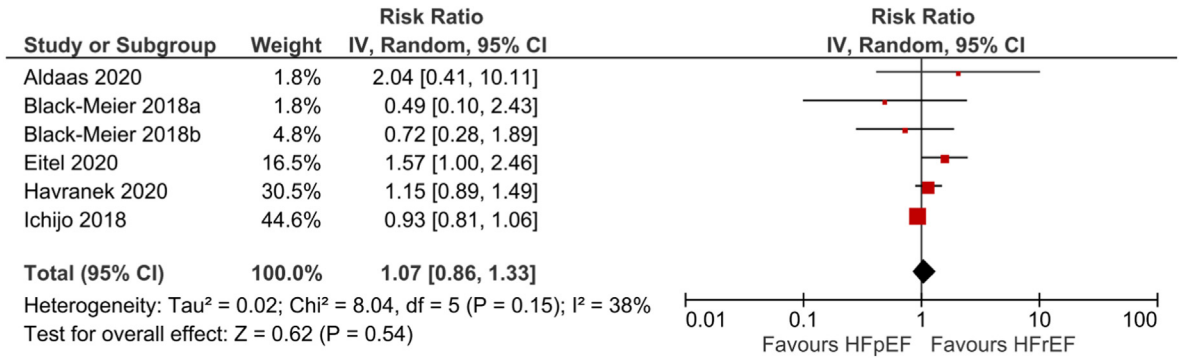

Fig. 2. Meta-analysis of atrial fibrillation recurrence or good outcome for patients with HFpEF vs HFrEF who undergo atrial fibrillation ablation*.

Table 3
Pooled results for periprocedural adverse events.

Outcome	No. studies	HFpEF	HFrEF	p-value
Access site complication/haematoma/bleeding	3	3.1% (16/522)	3.1% (10/325)	1.00
Stroke/TIA	2	0.7% (4/587)	0.2% (1/426)	0.26
Cardiac perforation/tamponade	2	0.8% (3/389)	0.9% (2/228)	0.19
Death	1	0% (0/338)	0.9% (2/228)	0.009
Pericarditis	1	2.0% (1/51)	0% (0/40)	0.53
MACCE (death, MI, stroke)	1	0.6% (2/338)	0.5% (1/188)	0.39

HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, TIA = transient ischaemic attack, MACCE = major adverse cardiac and cerebrovascular event, MI = myocardial infarction.

Table 4
Follow up adverse events.

Outcome	No. studies	HFpEF	HFrEF	p-value
1-year mortality (Eitel et al.)	1	1.9% (6/322)	6.0% (11/182)	<0.001
Adjusted HR (Aldaas et al.) aHR 0.53 (0.05–6.11)	1			
All-cause hospitalization (Aldaas et al., Eitel et al.)	2	39.1% (178/455)	35.5% (99/279)	0.33
Adjusted HR (Aldaas et al.) aHR 1.80 (0.97–3.33)	1			
Stroke/TIA (Black-Meier et al., Eitel et al.)	2	1.3% (6/455)	1.8% (5/279)	0.59
Repeat ablation (Black-Meier et al., Eitel et al.)	2	17.1% (78/455)	8.6% (24/279)	0.001
HF hospitalization at 12 months (Black-Meier et al.)	1	6.0% (8/133)	10.3% (10/97)	0.23
Arrhythmia hospitalization at 12 months (Black-Meier et al.)	1	14.3% (19/133)	13.4% (13/97)	0.85
Non-fatal MI (Eitel et al.)	1	0% (0/322)	0.5% (1/182)	0.20
Major bleeding (Eitel et al.)	1	0.3% (1/322)	1.6% (3/182)	0.11

HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, TIA = transient ischaemic attack, HF = heart failure, MI = myocardial infarction.

There are pathophysiological mechanisms that may explain our findings. The substrate responsible for AF is usually due to changes in structure and function of atria [25,26]. These can be secondary to alterations in hemodynamics in heart failure patients or a consequence of the cardiomyopathic process depending on the underlying etiology [27]. In particular, an increase in left atrial volume and pressure which increases left ventricular end-diastolic dimension and pressure and mitral regurgitation can result in fibrosis and remodelling that directly results in the development of AF [28]. The amount of remodelling is directly related to the duration of AF, i.e. Paroxysmal vs persistent; and ongoing hemodynamic strain due to HFpEF or HFrEF. Moreover, the remodelling is influenced by various comorbid conditions like hypertension, diabetes; and previous excessive smoking, excessive alcohol, raised body weight, extremes of exercise [29,30]. However, there is minimal impact by type of heart failure on success or complication rate after AF ablation, hospitalization and MACEs after ablation therapy.

Symptomatic patients suitable for AF ablation represents a small portion of all the patients with AF as most patients with AF are asymptomatic which makes it challenging to determine the true prevalence of AF [31]. It is possible that operators may be selecting patients who are more likely to have successful ablations. Among the factors identified as risk factors for recurrence of AF after ablation, two key factors are left atrial size and stiffness [11]. While both HFpEF and HFrEF may result in both types of left atrial changes the fact that not these changes are not more prevalent in one of the heart failure groups may explain why patients with both HFpEF and HFrEF may stand to equally benefit from ablation as shown in this study. In addition, there may be selection of patients for ablation procedures who are of lower risk such as patients who are young and less comorbid because in the elderly population it may be safer to rate control and anticoagulated patients with medications.

We found that patients with HFpEF have more repeat ablation and arrhythmic hospitalizations compared to HFrEF. One explanation for this difference is due to larger left atrial size and more fibrosis due to raised left ventricular end-diastolic pressure continue to degenerate atrial substrate resulting in higher recurrence in HFpEF. Positive remodelling after the restoration of sinus rhythm in HFrEF can be an explanation of the reduced rate of recurrence after modifiable factor correction.

There are several limitations in this review. First, none of the included studies are randomized trials, so the findings are at risk of

confounding. Also, the sample size of the studies is not large with the largest study included 521 patients. The second group of limitations relate to heterogeneity in the studies, which includes methodological differences in the study such as different definitions for HFrEF, and the patient population including a mixture of paroxysmal and persistent AF. Furthermore, while pulmonary vein isolation is the standard ablation strategy as we had no restriction on the type of ablation and procedural variables due to multiple lines, complex fractionated atrial electrograms, or AV node ablation. In addition, the differences in length of follow-up for AF recurrence, lack of standardized definition of recurrence of arrhythmia, the different cutoffs used for left ventricular ejection fraction for heart failure definition are other limitations to this metanalysis.

In conclusion, our review found that is no difference in AF recurrence comparing HFrEF to HFpEF. However, there is some evidence to suggest that patients with HFpEF are more likely to have repeat ablation compared to HFrEF. While periprocedural complications rates are similarly low for both HFpEF and HFrEF, one-year mortality is greater in patients with HFrEF compared to HFpEF.

Declaration of competing interest

None.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ipej.2021.09.002.

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