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Systematic review and meta-analysis of stroke and thromboembolism risk in atrial fibrillation with preserved vs. reduced ejection fraction heart failure

Meijuan Zhang[1] and Jie Zhou[1*]

Abstract

Background Stroke and thromboembolism (TE) are significant complications in patients with atrial fibrillation (AF) and heart failure (HF). The impact of ejection fraction status on these risks remains unclear. This study aims to compare the risk of stroke and TE in patients with AF and HF with preserved (HFpEF) or reduced (HFrEF) ejection fraction.

Methods Literature search of PubMed, Embase, and Scopus databases was done for studies in adult (20 years or more) population of AF patients. Included studies had reported on the incidences of stroke and/or TE in patients with AF and associated HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Cohort (prospective and retrospective), case-control studies, and studies that were based on secondary analysis of data from a trial were eligible for inclusion. Methodological quality was assessed using the Newcastle Ottawa Scale (NOS). Pooled hazard ratio (HR) with 95% confidence intervals (CI) were reported. Exploratory analysis was conducted based on the different cut-offs used to define HFrEF and HFpEF.

Results Twenty studies were analyzed. In the overall analysis, HFrEF in AF patients was associated with a significantly reduced risk of stroke and systemic TE (HR 0.88, 95% CI: 0.81, 0.96; $n = 20$, $I2 = 86.6\%$), compared to HFpEF. However, most studies showed comparable risk of stroke among the two groups of patients except for two studies that had documented significantly reduced risk. Upon doing the sensitivity analysis by excluding these two studies, we found similar risk among the two group of subjects and with no heterogeneity (HR 1.01, 95% CI: 0.99, 1.03; $n = 18$, $I2 = 0.0\%$). Exploratory analysis also showed that the risk of stroke and systemic thromboembolism was similar between those with HFpEF and HFrEF.

Conclusion The findings suggest that there is no significantly different risk of stroke and systemic thromboembolism in cases of AF with associated HFpEF or HFrEF. The finding does not support integration of left ventricular ejection fraction into stroke risk assessments.

Keywords Atrial fibrillation, Heart failure, Preserved ejection fraction, Reduced ejection fraction, Stroke, Systemic thromboembolism, Systematic review, Meta-analysis

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Introduction

Atrial fibrillation (AF) is connected to a higher incidence of stroke and systemic thromboembolism (TE) [1, 2]. This risk is particularly significant if accompanied by heart failure (HF) [3, 4], which is recognized as a risk factor for stroke and systemic TE [5, 6]. Echocardiographic parameters allow to stratify HF into two distinct categories based on left ventricular ejection fraction (LVEF): HF with preserved and reduced ejection fraction (HFpEF and HFrEF, respectively) [7, 8]. HFrEF is characterized by impaired pumping capability of the heart, which exacerbates blood stasis, and increases the risk of thrombus formation [9]. HFpEF is defined as HF despite preserved LVEF(≥50%), with elevated natriuretic peptides, and impaired blood flow dynamics [10]. Given the increasing prevalence of AF and HF and their intricate relationship, it becomes imperative to understand nuanced aspects of their association with the risk of stroke and TE [11].

A prior systematic review that was published in 2015 and included seven studies, investigated cardiovascular outcomes among patients with AF and HFrEF, as opposed to HFpEF [12], and revealed that HFrEF correlated with a marked increase in all-cause mortality (Risk ratio, RR 1.24; $N=10$). However, there were no differences in the rates of stroke. During the following half-decade, additional studies have been conducted on this particular aspect, but no recent comprehensive updated meta-analysis attempted to summarize most current data.

This meta-analysis aims to bridge this gap by systematically reviewing and quantitatively synthesizing the available literature to compare the risk of stroke and thromboembolism in AF patients with HFpEF or HFrEF.

Materials and methods

Study protocol

The protocol of the review was preregistered in PROSPERO (https://www.crd.york.ac.uk/prospero/) under the registration number (CRD42024505106). The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Literature search

Electronic searched were done in PubMed, Embase, and Scopus databases to identify relevant studies, published until 31st December 2023 using a combination of key terms: (Atrial fibrillation OR atrial flutter OR tachycardia) AND (heart failure OR cardiac failure OR cardiac disease) AND (preserved ejection fraction OR reduced ejection fraction OR ejection fraction OR cardiac output) AND (complications OR thromboembolism OR stroke OR cerebrovascular accident). Manual search of reference lists and review articles was also conducted.

We understand that including "atrial flutter" as a keyword was not strictly necessary. We decided to incorporate it to broaden our search and increase the number of potential studies identified. Our goal was to ensure a comprehensive review and reduce the risk of overlooking important studies that could contribute valuable data. Additionally, while not a primary reason, some studies might include results for combined cohorts of atrial fibrillation and atrial flutter patients, and we thought that this keyword may help us identify such studies as well.

Eligibility criteria

This meta-analysis included studies that involved adult populations (aged 20 years or more) diagnosed with AF and concurrent HF where ejection fraction data (preserved or reduced) was documented. We included cohort studies (both prospective and retrospective), case-control studies, and studies that were based on secondary analysis of trial records. The primary outcomes of interest were risk of stroke and systemic thromboembolism in AF patients with associated HF, with a specific focus on the stratification of outcomes by ejection fraction status (HFpEF or HFrEF). Peer-reviewed English-language articles published until 31st December 2023 were considered. We excluded studies involving paediatric patients or patients without a clear diagnosis of AF and/or HR. Review articles, editorials, letters, commentaries, and studies lacking original data, such as case reports, were also excluded. Additionally, non-peer-reviewed sources, such as conference posters, as well as studies with unclear reporting of outcomes or insufficient data were excluded.

Selection of studies for inclusion

Data deduplication was done for the studies identified through the preliminary literature search. Two study authors comprehensively screened titles and abstracts of remaining studies. Full texts of studies that met the initial criteria underwent a detailed evaluation to determine eligibility for inclusion. All discrepancies or disagreements were resolved by discussions.

Quality assessment of the studies

The Newcastle-Ottawa Scale (NOS) was employed for the standardized quality assessment of the selected studies [14]. The assessment is made based on study groups selection, intergroup comparability, and ascertainment of outcomes, with a maximum achievable value of 9. Higher scores indicate better quality [14].

Data extraction

Relevant data were extracted and included study authors, publication year, study location, design, subject characteristics, duration of follow-up, type of AF in the included patients, cut-off for ejection fraction used to

define HFpEF and HFrEF, sample size, and key findings. Any disagreements were resolved by discussions.

Statistical analysis

Pooled effect sizes were reported as hazard ratios (HR) with 95% confidence intervals (CI). For all the statistical comparisons, HFpEF served as the reference. Subgroup analyses were conducted according to study design, type of AF, duration of follow up and sample size. The random-effects model was employed for all analysis to account for differences in participant characteristics and methodological variations among the included studies. The Cochrane $I^2 > 40\%$ indicated significant heterogeneity [15]. Publication bias was assessed by funnel plot and Egger's test [16]. A $P < 0.05$ on Egger's test indicated presence of publication bias and this was supported by visual inspection of funnel plot. All analysis were conducted using STATA software version 15.0. We evaluated the certainty of the evidence using the standard GRADE approach and GRADE Pro software [17].

Results

Literature search across databases identified 1714 studies. After deduplication, 1226 distinct studies remained. After subsequent evaluation of titles and abstracts, full texts of 51 relevant articles were screened, and additional 31 studies were eliminated. Finally, a total of 20 studies were included (Fig. 1) [18–37].

As summarized in Table 1, there were eight studies with a retrospective and seven studies with a prospective cohort design. Remaining five studies were based on secondary analysis of data collected as part of randomized clinical trial. Most studies were conducted in the USA ($n=7$). Three studies were conducted in the Republic of Korea and one study each in Russia, Poland, Japan, Sweden, Canada, and France. Four studies were multicenter. In almost all studies, HFpEF correlated with older age and higher proportion of female gender, compared to HFrEF patients. There were differences in the cut-off values used for defining reduced or preserved ejection fraction (EF) among the included studies. Majority of the studies defined HFrEF as EF < 50% and HFpEF as ≥ 50% ($N=8$) followed by 7 studies that defined HFrEF as EF < 40% and HFpEF as ≥ 50%. This highlights a grey zone for EF between 40 and 50% that should be addressed. Only 11 studies reported on the type of AF. Out of them, eight had predominantly patients with permanent or persistent AF, two had patients with paroxysmal AF and in one study, the equal proportion of patients had either permanent/persistent or paroxysmal AF. We also reported available data from the included studies on CHA2DS2-VASc or CHADS2 score as well as NT-ProBNP or BNP level (Table 1). The data suggests that those with reduced ejection fraction had comparatively lower CHA2DS2-VASc/CHADS2 score and higher NT-ProBNP/ BNP level compared to those with preserved ejection fraction.

Most studies had a follow up period of more than one year ($n=15$). The follow up period in these studies ranged from 15 months to 5 years. The included studies contributed to a total of 1,73,876 subjects. The mean NOS quality score of the studies was 7.5. There were 10 studies with a score of 8 and 10 studies with a score of 7 (Supplementary Tables 1 and 2). Overall, quality assessment results indicate that the included studies were of acceptable methodological quality.

Risk of stroke and systemic thromboembolism

HFrEF patients had lower risk of stroke and systemic thromboembolism (HR 0.88, 95% CI: 0.81, 0.96; $n=20$, I2 = 86.6%) compared to AF patients with HFpEF (Fig. 2), with no obvious publication bias (Egger's p-value = 0.120) (Supplementary Fig. 1). However, most studies showed comparable risk of stroke among HFrEF and HFpEF patients except for the publication from Uhm et al. and Chung et al. Upon doing the sensitivity analysis by excluding these two studies, we found similar risk among the two group of subjects and with no heterogeneity (HR 1.01, 95% CI: 0.99, 1.03; $n=18$, I2 = 0.0%) (Egger's p-value = 0.341) (Supplementary Fig. 2).

Subgroup analysis showed that the reduced risk of stroke and thromboembolism in HFrEF was only evident in prospective cohort studies (HR 0.74, 95% CI: 0.58, 0.94; $n=7$, I2 = 95.4%), studies with longer follow up (> 1 year) (HR 0.86, 95% CI: 0.77, 0.95; $n=15$, I2 = 90.0%) and studies with larger sample size (≥ 500) (HR 0.85, 95% CI: 0.76, 0.96; $n=17$, I2 = 88.3%) (Table 2, Supplementary Figs. 3–9). No statistically significant association could be found on analysis based on the type of AF i.e., persistent or permanent AF (HR 0.86, 95% CI: 0.69, 1.07; $n=8$, I2 = 86.1%) and paroxysmal AF (HR 0.66, 95% CI: 0.25, 1.77; $n=2$, I2 = 98.3%) (Table 2, Supplementary Figs. 10 and 11).

However, when the two studies i.e., Uhm et al. and Chung et al., were excluded from the subgroup analysis, the risk of stroke and thromboembolism was comparable in the two group of subjects (HFrEF and HFpEF) with low to negligible heterogeneity, irrespective of the study design, duration of follow up and sample size (Supplementary Figs. 12–14). We also conducted an exploratory analysis based on the cut-off used to define reduced and preserved ejection fraction. There were three sets of studies that we identified: first, where EF ≥ 50% indicated HFpEF and EF < 40% indicated HFrEF; second, where EF ≥ 50% indicated HFpEF and EF < 50% indicated HFrEF; and third, where EF ≥ 40% indicated HFpEF and EF < 40% indicated HFrEF. The findings within each of these three strata show that the risk of stroke and systemic thromboembolism is similar between those with

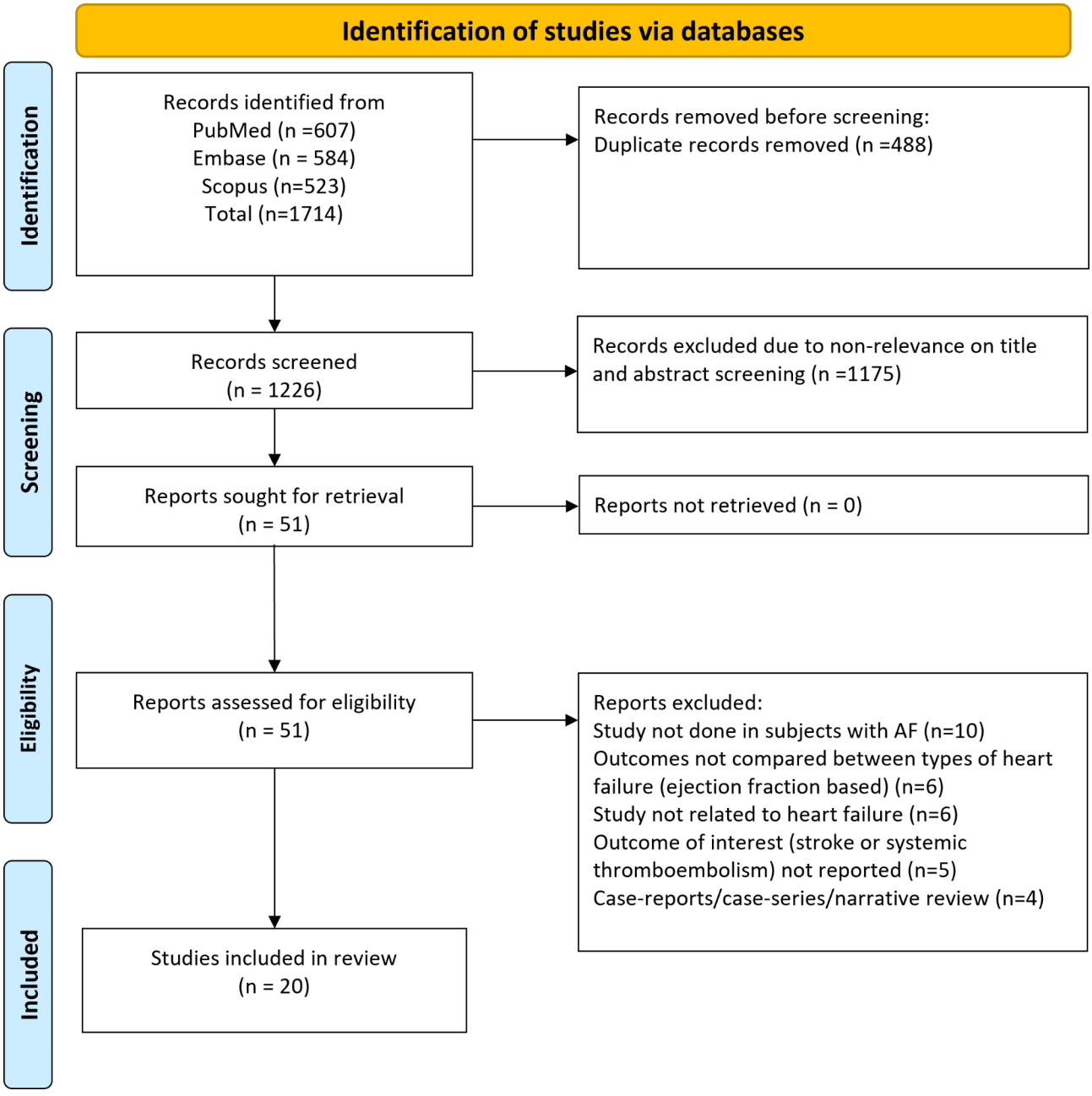

Fig. 1 Process of selecting studies for inclusion

HFpEF and HFrEF (Supplementary Fig. 15). The overall quality of evidence was judged to be "Low" according to the GRADE assessment criteria (Supplementary Fig. 16).

Discussion

Our overall analysis shows that AF patients with HFrEF may have a lower risk of stroke and systemic thromboembolism than AF patients with HFpEF. However, substantial heterogeneity could affect this interpretation. The sensitivity analysis, after excluding the studies by Uhm et al. and Chung et al., clearly showed a similar risk of stroke and systemic thromboembolism between the two groups, with low heterogeneity. Subgroup analyses, after excluding these two studies, showed comparable risks of stroke and thromboembolism in the HFrEF and HFpEF groups, regardless of study design, duration of follow-up, and sample size. Our findings are consistent with and support those of a previous review that included data from seven studies (n=33,773 subjects) and found a comparable risk of stroke in the HFrEF and HFpEF groups [12].

If we examine the overall findings, the significantly reduced risk of stroke and thromboembolism observed

Table 1 Key aspects of the included studies

Author	Study design; Location	Participant characteristics;	Follow-up duration	Definition of heart failure with preserved (HFpEF) or reduced ejection fraction (HFrEF)	CHA2DS2-VASc / CHADS2 score; NT-ProBNP/BNP level	Sample size	NOS score
Budnik et al. (2023)	Retrospective cohort; Poland	Older subjects (mean age 72 vs. 67 yrs) and higher proportion of females (66% vs. 26%) in those with pEF Persistent or permanent AF (70%)	Follow up of 12 months	Preserved: EF ≥ 50% Reduced: EF < 40%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 3.8 (1.7) HFpEF: 4.4 (1.5) *NT-ProBNP level (pg/ml)(mean, SD)* HFrEF: 4372 (4541) HFpEF: 2167 (2253)	274 (168 with reduced; 106 with preserved EF)	7
Inciardi et al. (2023)	Secondary analysis of data from RCT; Multicentric	Older subjects (mean age 71 vs. 68 yrs) and higher proportion of females (45% vs. 27%) in those with pEF Persistent or permanent AF (80%)	Median of 2.8 years	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHA2DS2-VASc* score HFrEF: 66.5% with score more than 3 HFpEF: 75.5% with score more than 3	9442 (4574 with reduced; 4868 with preserved EF)	8
Marzouka et al. (2022)	Retrospective cohort; USA	Older subjects (mean age 73 vs. 69 yrs) and similar proportion of males (98% vs. 99%) in those with pEF Type of AF: Paroxysmal	Follow up of 5 years	Preserved: EF ≥ 50% Reduced: EF < 40%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 4.7 (1.5) HFpEF: 5.1 (1.4)	7410 (4745 with reduced; 2665 with preserved EF)	8
Uhm et al. (2021)	Prospective cohort; Republic of Korea	Older subjects (mean age 70 vs. 67 yrs) and higher proportion of females (46% vs. 28%) in those with pEF Paroxysmal AF (~ 50%)	Mean 23 months	Preserved: EF ≥ 50% Reduced: EF < 40%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 3.7 (1.7) HFpEF: 4.0 (1.7) *NT-ProBNP level (pg/ml) (mean, SD)* HFrEF: 4046 (3971) HFpEF: 857 (673)	851 (364 with reduced; 487 with preserved EF)	8
Zhang et al. (2020)	Prospective cohort; USA	Older subjects (mean age 79 vs. 75 yrs) and higher proportion of females (60% vs. 37%) in those with pEF Data on type of AF not provided	Mean of 4.1 years	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 4.6 (1.8) HFpEF: 5.2 (1.6)	859 (412 with reduced; 447 with preserved EF)	8
Son et al. (2020)	Prospective cohort; Republic of Korea	Older subjects (mean age 73 vs. 68 yrs) and higher proportion of females (63% vs. 36%) in those with pEF Type of AF- not provided	Median 4.1 years	Preserved: EF ≥ 50% Reduced: EF < 40%	*NT-ProBNP level (> 5000 pg/ml)* HFrEF: 55.3% HFpEF: 28.4%	1535 (921 with reduced; 614 with preserved EF)	8
Chung et al. (2020)	Prospective cohort; Republic of Korea	Older subjects (mean age 73 vs. 69 yrs) and higher proportion of females (49% vs. 29%) in those with pEF Persistent or permanent AF (60%)	Median 1.3 years	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHA2DS2-VASc score (median, IQR)* HFrEF: 4.0 (2–5) HFpEF: 4.0 (3–5) *NT-ProBNP level (ng/dl; median, IQR)* HFrEF: 1.53 (0.47–4.11) HFpEF: 1.46 (0.49–3.21)	935 (531 with reduced; 404 with preserved EF)	7
Zhirov et al. (2019)	Prospective cohort; Russia	Older subjects (mean age 72 vs. 66 yrs) and higher proportion of females (65% vs. 26%) in those with pEF Non-paroxysmal atrial fibrillation (AF) (73%)	Mean 12 months	Preserved: EF ≥ 50% Reduced: EF < 40%	*CHA2DS2-VASc score (median, IQR)* HFrEF: 4.0 (2–5) HFpEF: 5.0 (3–6) *NT-ProBNP level (pg/ml; median, IQR)* HFrEF: 1484 (289–2866) HFpEF: 562 (425–968)	853 (466 with reduced; 387 with preserved EF)	8

Table 1 (continued)

Author	Study design; Location	Participant characteristics;	Follow-up duration	Definition of heart failure with preserved (HFpEF) or reduced ejection fraction (HFrEF)	CHA2DS2-VASc / CHADS2 score; NT-ProBNP/BNP level	Sample size	NOS score
Mentias et al. (2019)	Retrospective cohort; USA	Similar mean age in the two group (80 years); higher proportion of females (69% vs. 51%) in those with pEF Data on type of AF not provided	Follow up period not provided	Diagnosis of HFpEF or HFrEF based on ICD-9 code	*CHA2DS2-VASc score (mean, SD)* HFrEF: 5.3 (SD not provided) HFpEF: 5.4 (SD not provided) > 95% in both groups with a score of > 3	80,200 (47840 with reduced; 32360 with preserved EF)	7
Sobue et al. (2018)	Prospective cohort; Japan	Older subjects (mean age 78 vs. 74 yrs) and higher proportion of females (57% vs. 34%) in those with pEF Non-paroxysmal AF (86%)	Mean of 26 months	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 4.5 (1.7) HFpEF: 4.9 (1.6) *BNP level (pg/ml; median, IQR)* HFrEF: 265 (164–500) HFpEF: 151 (90–317)	301 (172 with reduced; 129 with preserved EF)	7
Siller-Matula et al. (2018)	Prospective cohort; Multicentric	Older subjects (mean age 76 vs. 72 yrs) and higher proportion of females (40% vs. 24%) in those with pEF Persistent or permanent AF (80%)	Follow up of 12 months	Preserved: EF ≥ 50% Reduced: EF < 40%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 4.1 (SD not provided) HFpEF: 4.7 (SD not provided) 95.1% in HFrEF and 99% in HFpEF group had a score of 2 or more	1074 (458 with reduced; 616 with preserved EF)	7
Sartipy et al. (2017)	Retrospective cohort; Sweden	Older subjects (mean age 79 vs. 74 yrs) and higher proportion of females (54% vs. 27%) in those with pEF Data on type of AF not provided	Median of 2.2 years	Preserved: EF ≥ 50% Reduced: EF ≤ 39%	*CHA2DS2-VASc score (mean, SD)* HFrEF: 4.3 (1.7) HFpEF: 4.9 (1.6) *NT-ProBNP level (ng/l; median, IQR)* HFrEF: 3627 (1732–7550) HFpEF: 2547 (1306–4880)	18,437 (12187 with reduced; 6250 with preserved EF)	8
Sandhu et al. (2015)	Secondary analysis of baseline data from RCT; Canada	Older subjects (mean age 72 vs. 70 yrs) and higher proportion of females (52% vs. 29%) in those with pEF Permanent atrial fibrillation (AF) (75%)	Mean of 3.6 years	Preserved: EF ≥ 50% Reduced: EF < 50%	CHADS2score *(mean, SD)* HFrEF: 2.5 (1.1) HFpEF: 2.8 (1.0)	2072 (1103 with reduced; 969 with preserved EF)	8
Eapen et al. (2014)	Retrospective cohort; USA	Mean age (80 vs. 79 yrs) and proportion of females (63% vs. 61%) almost similar in both groups Data on type of AF not provided	Follow up of 30 days	Preserved: EF ≥ 40% Reduced: EF < 40%	*CHADS2score (mean, SD)* HFrEF: 3.1 (1.2) HFpEF: 3.3 (1.1)	30,557 (13152 with reduced; 17405 with preserved EF)	7
Khazanie et al. (2014)	Retrospective cohort; USA	Median age of subjects 79 yrs; female (56%)	Follow up of 3 years	Preserved: EF ≥ 40% Reduced: EF < 40%	---	9509 (3410 with reduced; 6099 with preserved EF)	7

Table 1 (continued)

Author	Study design; Location	Participant characteristics;	Follow-up duration	Definition of heart failure with preserved (HFpEF) or reduced ejection fraction (HFrEF)	CHA2DS2-VASc / CHADS2 score; NT-ProBNP/BNP level	Sample size	NOS score
McMurray et al. (2013)	Secondary analysis of RCT data; Multicentric	Median age similar in both groups (69 years); higher proportion of females (42% vs. 21%) in those with pEF Persistent or permanent AF (> 85%)	Median 1.5 years	Preserved: EF > 40% Reduced: EF ≤ 40%	*CHADS2score (mean, SD)* HFrEF: 2.22 (1.2) HFpEF: 2.67 (1.08)	5943 (2736 with reduced; 3207 with preserved EF)	8
Banerjee et al. (2012)	Retrospective cohort; France	Older subjects (mean age 75 vs. 71 yrs) and higher proportion of females (50% vs. 22%) in those with pEF Paroxysmal AF (50%); persistent/permanent AF (50%)	Mean 1.3 years	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHA2DS2-VASc score* HFrEF: 90.4% with score of 2 or more HFpEF: 96.2% with score of 2 or more	1276 (691 with reduced; 585 with preserved EF)	8
Badheka et al. (2011)	Secondary analysis of RCT data; USA	Older subjects (mean age 71 vs. 68 yrs) and higher proportion of females (51% vs. 26%) in those with pEF Data on type of AF not provided	Mean 3.4 years	Preserved: EF ≥ 50% Reduced: EF < 50%	*CHADS2score (mean, SD)* HFrEF: 2.46 (1.07) HFpEF: 2.77 (1.05)	722 (402 with reduced; 320 with preserved EF)	7
Olsson et al. (2006)	Secondary analysis of RCT data; Multicentric	Older subjects (mean age 71 vs. 68 yrs) and higher proportion of females (42% vs. 22%) in those with pEF Data on type of AF not provided	Median 3.1 years	Preserved: EF > 40% Reduced: EF ≤ 40%	---	1148 (670 with reduced; 478 with preserved EF)	7
Parkash et al. (2005)	Retrospective cohort; USA	Older subjects (mean age 76 vs. 72 yrs) and higher proportion of females (62% vs. 35%) in those with pEF Data on type of AF not provided	Mean 3.3 years	Preserved: EF > 50% Reduced: EF ≤ 50%	---	478 (260 with reduced; 218 with preserved EF)	7

AF: Atrial fibrillation; EF: ejection fraction

in those with HFrEF, might be attributed to distinct aspects of the underlying pathophysiology. We may speculate that left ventricular (LV) diastolic dysfunction, as seen in HFpEF, contributes to a higher risk, compared to LV systolic dysfunction found in HFrEF [38, 39]. Left atrium (LA) to left ventricle (LV) blood flow is delayed in patients with LV diastolic dysfunction, leading to blood stasis in the LA, and subsequent increase in the risk of thromboembolism and stroke [40]. However, this reason may not be sufficient, as HFrEF is also associated with some degree of diastolic dysfunction [41]. Previous study reported higher rates of hypertension and high warfarin usage rate in patients with HFpEF, which might also partly contribute to the risk [42]. Another possible explanation could be the increased age of patients and a higher proportion of female patients with HFpEF in the included studies. The "congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category" (CHA_2DS_2-VASc) score serves as a valuable tool for assessing the risk of stroke associated with AF [43]. It incorporates various clinical risk factors, including age (higher points for older age) and sex (female sex contributing to a higher score). Patients with HFpEF, therefore, may have increased CHA2DS2-VASc score, and, subsequently, higher risk of stroke and thromboembolism. This brings an interesting perspective: there may actually be no significant difference in the risk of stroke and systemic thromboembolism between the two groups. The adjusting covariates differed between the studies included in this meta-analysis. Patients with AF and HFpEF were older and had a higher prevalence of comorbidities, which, if properly adjusted for in the analysis, could have led to a comparable risk. Additionally, there were differences in the definitions of HFrEF and HFpEF among the included studies. Considering these limitations, the reduced risk of stroke in HFrEF patients might not be significant and could be overstated. The sensitivity analysis (after exclusion of Uhm et al. and Chung et al.) also supports the view that there may be no significant risk difference between the two groups. The low quality of evidence, as judged by the GRADE assessment, strongly supports the need for more studies with robust methodology to provide conclusive evidence.

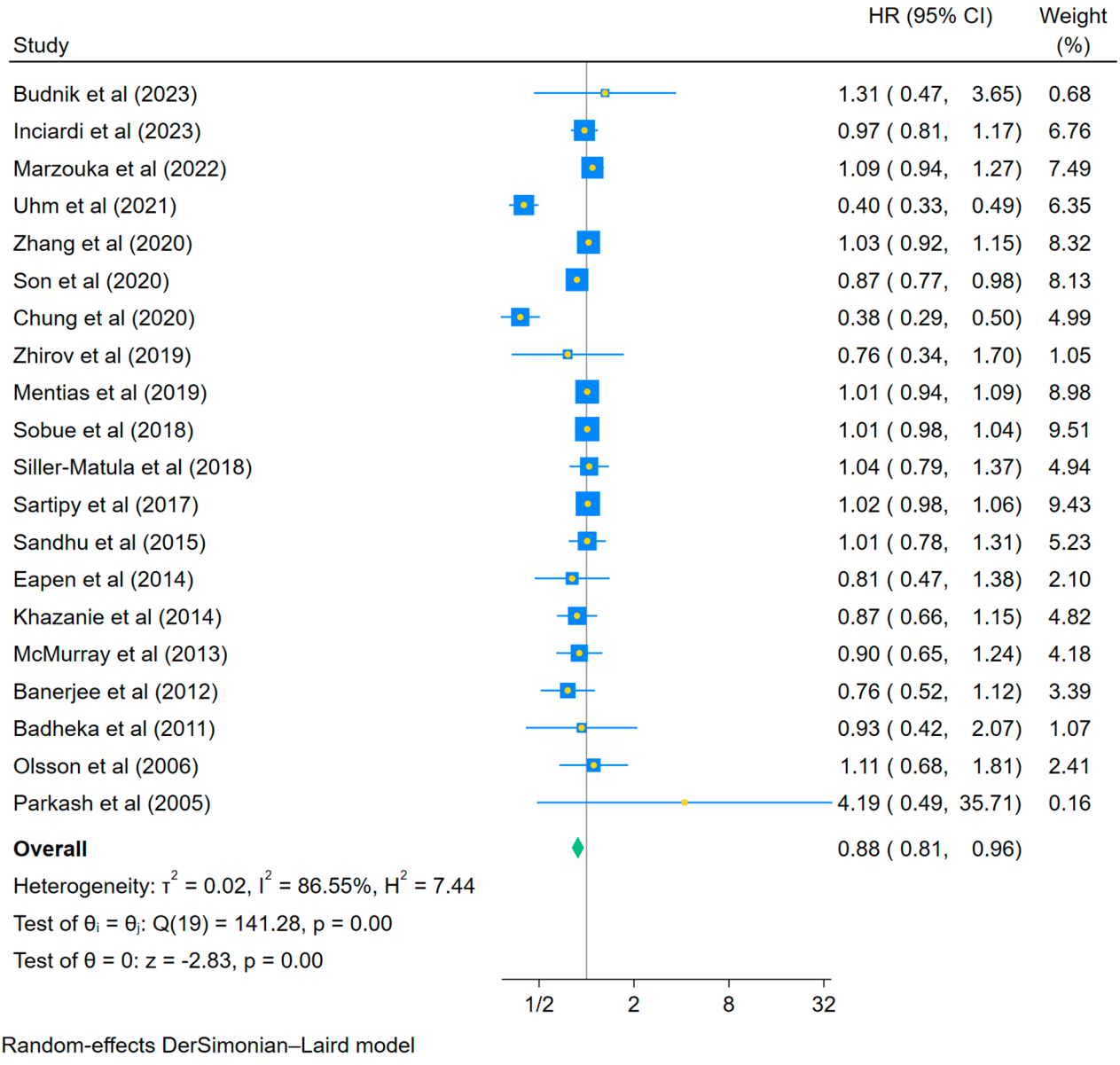

Fig. 2 Risk of stroke and systemic thromboembolism among subjects with atrial fibrillation and associated reduced ejection fraction (HFrEF), compared to patients with preserved ejection fraction (HFpEF)

There were some limitations of our review. We found significant heterogeneity in the reported outcomes which could be due to some differences in the definitions of HFpEF and HFrEF, baseline characteristics of the patients, as well as differences in the methodology (study design and follow up period). The included studies were observational in design and therefore, despite efforts to control for confounding variables, there remains a possibility that some of the important confounders may not have been accounted for. This will ultimately influence the robustness of observed associations. The often-limited longitudinal data in many of the included studies may impact the ability to capture the dynamic nature of HF and AF progression. Additionally, the impact of changing treatment modalities over time on the risk of stroke was not assessed in this review. We were also not able to provide mechanistic insights into the risk of stroke.

Conclusion and implications for clinical practice

In conclusion, the "low" quality evidence from this meta-analysis does not provide convincing evidence that there is significantly different risk of stroke and systemic thromboembolism in cases of AF with associated HFpEF or HFrEF. The finding does not support integration of left ventricular ejection fraction into stroke risk assessments.

Table 2 Findings of the subgroup analysis

Subgroups	Risk of stroke and systemic thromboembolism
	Pooled Hazard ratio (HR) with 95% CI (Number of studies; I^2)
Study design	
Prospective cohort	0.74 (0.58, 0.94) (7; 95.4%) *
Retrospective cohort	1.02 (0.98, 1.05) (8; 0.0%)
Secondary analysis of RCT data	0.98 (0.86, 1.11) (5; 0.0%)
Type of Atrial Fibrillation (AF)	
Persistent or Permanent	0.86 (0.69, 1.07) (8; 86.1%)
Paroxysmal	0.66 (0.25, 1.77) (2; 98.3%)
Follow up duration	
> 1 year	0.86 (0.77, 0.95) (15; 90.0%) *
≤ 1 year	0.98 (0.78, 1.23) (4; 0.0%)
Sample size	
≥ 500	0.85 (0.76, 0.96) (17; 88.3%) *
< 500	1.01 (0.98, 1.04) (3; 0.0%)

*Indicates statistical significance at $p < 0.05$

Nursing staff may potentially play a crucial role in preventing risk of stroke and systemic thromboembolism in patients with HF and AF. They could be instrumental in educating patients about the importance of adherence to anticoagulation therapy and regularly monitoring their health. Nursing professionals could be involved in assessing medication effectiveness, managing potential complications, and collaborating with healthcare teams for necessary treatment adjustments. They can also contribute to risk stratification, developing individualized care plans based on patient characteristics, and ensuring effective communication within multidisciplinary care teams. Considering limitations of our study, further research would need to focus on the underlying mechanisms contributing to the thromboembolic risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04133-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
MZ, JZ: initial concept ideas, protocol planning and drafting, search screening, analyzing, and drafting all manuscript versions. MZ: methods advice, protocol drafting, and approving final draft. MZ, JZ: data extraction, analysis, and drafting final version.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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