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Atrial fibrillation and heart failure due to reduced *versus* preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes

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ABSTRACT

Background: Atrial fibrillation (AF) and heart failure frequently coexist, commonly resulting in serious adverse events. With both conditions increasing in prevalence and justified concerns about treatment efficacy, it is vital to understand how the type of heart failure impacts on prognosis.
Methods: We performed a systematic review of studies examining cardiovascular outcomes in AF patients with heart failure and reduced ejection fraction (AF-HFrEF) compared to those with preserved ejection fraction (AF-HFpEF). The primary outcome was all-cause mortality, meta-analyzed using a random-effects model. Prospective registration: PROSPERO-CRD42014007305.
Results: Thirteen studies were included in the systematic review (n = 54,587) with 10 suitable for meta-analysis, including retrospective/prospective cohorts and sub-group analyses of randomized trials. AF-HFrEF was present in 49% and these patients were younger, more often male and with higher NYHA class than AF-HFpEF. Oral anticoagulation use was 55% *versus* 50% respectively ($p < 0.001$). All-cause mortality was significantly higher in AF-HFrEF; risk ratio (RR) 1.24, 95% CI 1.12–1.36, $p < 0.001$ (n = 45,100), with absolute death rates of 24% compared to 18% in AF-HFpEF over 2 years. There were no significant differences in incident stroke (RR 0.85, 95% CI 0.70–1.03, $p = 0.094$; n = 33,773) or heart failure hospitalization (RR 1.21, 95% CI 0.96–1.53, $p = 0.115$; n = 31,583). The risk of bias was generally low, but heterogeneity was substantial.
Conclusions: All-cause mortality is significantly higher in AF patients with HFrEF compared to HFpEF, although stroke risk and heart failure hospitalization are similar. Further studies are needed to address the prevention of adverse outcomes in all AF patients with heart failure, regardless of ejection fraction.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased rates of mortality and serious morbidity, including stroke, worsening of heart failure, sudden death, and reduced quality of life [1]. Both the incidence and prevalence of AF are expected to double in the next 20 years [2]. Patients with AF are twice as likely to be hospitalized as matched controls, with direct medical costs estimated to be 73% higher than non-AF patients [3]. Further, AF is an independent predictor of all-cause mortality, with a two-fold adjusted increase in death [4,5]. While most strokes in AF can be prevented by oral anticoagulation, cardiovascular deaths in AF patients are mostly related to progressive heart failure or sudden death [6–8]. In the context of those diagnosed with a heart failure syndrome, the presence of AF leads to higher rates of death and hospitalization, regardless of other risk variables or which condition comes first [9,10]. Depending on the severity of HF, up to 50% of symptomatic patients will be diagnosed with AF, representing a large and growing unmet clinical need for healthcare improvement [11].

Current risk stratification schemes for AF focus on preventing strokes and systemic embolism by identifying patients at risk that either require or do not require oral anticoagulation [1,12]. Both the $CHADS_2$ and CHA_2DS_2-VASc schemes incorporate a history of heart failure as a risk marker, although based on differing definitions and detection methods. There is conflicting evidence on whether heart failure with reduced ejection fraction (HFrEF) is the major driver for adverse clinical events or if heart failure with preserved ejection fraction (HFpEF) is equally important [13–15]. With regard to prediction of mortality, analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial identified heart failure as an independent predictor of all-cause mortality in AF (adjusted for ejection fraction) and the strongest predictor of cardiac death [6]. We have recently demonstrated that in contrast to patients in sinus rhythm, those with HFrEF and concomitant AF do not benefit from beta-blocker therapy in terms of all-cause mortality, cardiovascular mortality or hospitalization [8]. This highlights

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association; RR, risk ratio.

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the importance of analyzing outcomes specifically in AF, rather than extrapolating from patients with sinus rhythm. With the prevalence of HFpEF now equal to that of HFrEF [16], understanding the relative effects on major adverse events in patients with AF is of major clinical importance and requires further clarification. Our objectives were to systematically assess the available literature on AF patients with heart failure to determine if clinical outcomes in AF-HFpEF were similar to those in AF-HFrEF.

2. Methods

2.1. Eligibility criteria & search strategy

All studies examining comparative outcomes in AF-HFrEF and AF-HFpEF were evaluated, regardless of study design. All cardiovascular outcomes and all populations were considered, including sub-sets of AF patients from larger trials. We excluded studies that did not provide comparative outcomes or were not published as full-text articles. The definitions used by each individual study were accepted, including those of AF, heart failure and whether ejection fraction was preserved or not. A systematic review of MEDLINE (1950 to November 2013 and subsequently extended to August 2014), EMBASE (1980 to December 2013) and the Cochrane Library (until December 2013 and subsequently extended to August 2014) were performed without language restriction (see study selection diagram in Fig. 1). We also manually searched reference lists of relevant studies, investigated registers of ongoing trials and included studies after discussion with content experts. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The project was prospectively registered with the PROSPERO database of systematic reviews (CRD42014007305) [18].

2.2. Data collection and quality assessment

Two investigators (RC and DK) independently extracted and tabulated data in a standardized data-extraction form. Discrepancies and missing data were resolved by group discussion, reference to the original publication and additional independent adjudication. Unadjusted data were extracted for meta-analysis and adjusted data for systematic review. Additional unpublished data were provided from the lead authors of two studies [8,19]. The study by Kotecha et al. (2014) includes pooled individual patient data from 10 randomized controlled trials of beta-blockers in patients with heart failure [20]. In another study, outcome rates were extrapolated from the 88.9% of patients with available follow-up [21]. Study quality was assessed using the Cochrane Collaboration's Risk of Bias tool and the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS), which address key criteria such as selection bias, exposure measurement, blinding, the completeness of outcome data and selectivity of reporting [22,23].

2.3. Primary and secondary outcomes

The predefined primary outcome was all-cause mortality. Secondary outcomes of interest were incident stroke, systemic embolism, myocardial infarction (MI), heart failure hospitalization and major bleeding. Meta-analysis was suitable for three outcomes; all-cause mortality, incident stroke and heart failure hospitalization.

2.4. Statistical analysis

Demographics were averaged using a weighted mean (and standard deviation) with t-tests used for between-group comparisons. Meta-analysis was pre-specified to use a random-effects model as the true effect size was likely to vary in the individual studies owing to the variety in populations assessed and different study designs. Pooled binary event data for AF-HFrEF and AF-HFpEF were compared using a risk ratio (RR) with associated 95% confidence intervals (CI) using the method of DerSimonian and Laird. [24] Sensitivity analyses for the primary outcome were performed according to a pre-defined mean anticoagulation rate of 70% and by study design (post-hoc examination of randomized subjects compared to cohort studies). The latter analysis utilized a fixed-effects model with the method of Mantel and Haenszel [25].

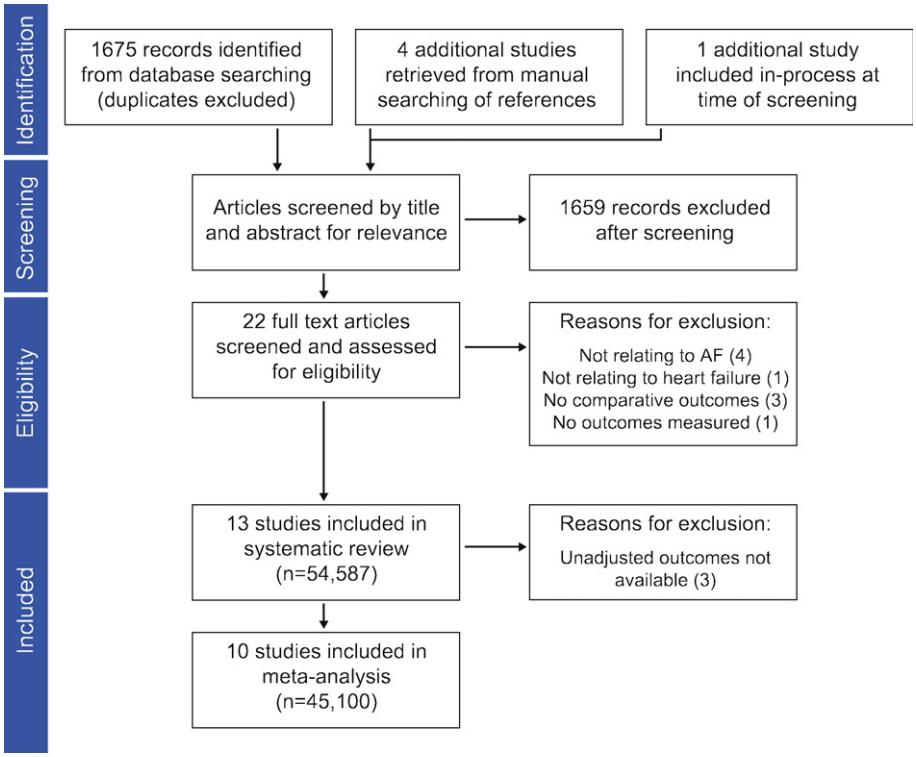

Fig. 1. Study selection diagram. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.