Clinical Investigation

Prognostic Importance of Atrial Fibrillation Timing and Pattern in Adults With Congestive Heart Failure: A Systematic Review and Meta-Analysis

AYODELE ODUTAYO, MD, MSc,[1] CHRISTOPHER X. WONG, PhD,[1] RASHIDA WILLIAMS, BSc, MSc,[2] BENJAMIN HUNN, BMedSc(Hons), MBBS,[1] AND CONNOR A. EMDIN, HBSc[1]

Oxford, United Kingdom; and Washington DC

ABSTRACT

Background: Atrial fibrillation (AF) is common among adults with congestive heart failure (CHF). We conducted a meta-analysis to summarize the risk of mortality and cardiovascular disease associated with AF in CHF and stratified our analyses by AF timing and pattern.

Methods: We searched MEDLINE and EMBASE for observational studies examining the association of AF with cardiovascular disease and death. Eligible studies had a minimum of 50 participants with AF and 50 participants without AF, and a median follow-up of 6 months.

Results: Thirty-three studies involving 114,204 adults (43,549 with AF) were included in this meta-analysis. AF was associated with an increased risk of mortality and this risk varied between incident and prevalent AF (relative risk 2.21, 95% confidence interval 1.96–2.49 vs relative risk 1.19, 95% confidence interval 1.03–1.38, respectively; $P < .001$ for interaction). The risk of mortality associated with incident AF was consistent in adults with CHF with reduced and preserved ejection fraction. The relative risk of mortality did not vary between paroxysmal and chronic AF. Finally, AF was associated with an increased risk of cardiovascular mortality and stroke.

Limitation: Use of anticoagulation was infrequently reported in included studies.

Conclusions: AF was associated with an increased risk of cardiovascular disease and death and, notably, the risk of mortality varied by AF timing. (*J Cardiac Fail 2017;23:56–62*)

Key Words: Congestive heart failure, Atrial fibrillation, Mortality, Cardiovascular disease.

Atrial fibrillation (AF) is common among adults with congestive heart failure (CHF). The prevalence of AF in all adults with CHF ranges from 13% to 27% and may be up to 50% in adults with severe heart failure.[1] Although previous studies have shown that AF is associated with an increased risk of mortality in CHF,[2–4] important gaps exist in current understanding of this risk. First, it is unclear whether the risk of all-cause mortality in incident AF (existing after CHF diagnosis) is greater than that of prevalent AF (existing before CHF diagnosis). Narrative reviews suggest that differences exist but this has not been quantified in meta-analysis.[1] Second, it remains unclear whether the pattern of AF is of prognostic significance and if paroxysmal AF confers the same risk as persistent or permanent AF. Third, the relationship between AF and other cardiovascular outcomes has not been assessed in meta-analysis. Accordingly, we conducted a meta-analysis to assess the association between AF and cardiovascular disease and death. We also stratified our analysis by timing of AF onset (prevalent vs incident AF) and pattern of AF. Where possible, we provided results for adults with reduced and preserved ejection fraction separately.

Methods

This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE)

From the [1]University of Oxford, Oxford, United Kingdom and [2]Faculty of Medicine, George Washington University, Washington DC.

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Reprint requests: Ayodele Odutayo, MD, MSc, Brasenose College, Radcliffe Square, Oxford, Oxfordshire OX1 4AJ, United Kingdom. Tel.: +44 11 44 74 6211 3024. E-mail: ayodele.odutayo@bnc.ox.ac.uk.

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guidelines[5] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6]

Data Sources and Searchers

We conducted a systematic search of MEDLINE and EMBASE (inception to March 2015). A qualified research librarian developed the search strategy and search terms included but were not limited to the following keywords: "Atrial Fibrillation," "Mortality," "Death," "Cardiovascular," "Coronary," "Cerebrovascular," "Myocardial," "Stroke," "Observational Study," "Cohort Study," "Longitudinal Study," and "Heart Failure." The search was supplemented by a review of past meta-analyses[2–4] and review articles[1,7] and a detailed review of references of included studies and citation tracking with Google Scholar.

Observational studies of adults with CHF that reported a measure of relative risk (hazard ratio, relative risk [RR], or odds ratio) for the association between AF and cardiovascular disease and death (see the following section) were included. We included both retrospective and prospective studies. Studies were also required to include a minimum of 50 participants with and without AF with at least 6 months of mean/median follow-up. No language restrictions were applied.

Data Extraction and Quality Assessment

Titles and abstracts were independently reviewed in duplicate to assess studies for their inclusion. Among studies identified for full-text review, we independently abstracted data using standardized forms. Discrepancies between 2 independent reviewers were resolved by a third reviewer. Where available, we abstracted information on general study characteristics (study name or investigator's name; recruitment date [mid-point of the recruitment period]; mean follow-up duration; year of publication of the primary findings), summary information about the studied population: number of participants with and without AF; timing of AF onset, type of CHF (preserved vs reduced ejection fraction), mean age, number of men; and duration of follow-up. We extracted information on the following outcomes: all-cause mortality, cardiovascular mortality, and disease-specific events: stroke, and ischemic heart disease (IHD; a composite of coronary heart disease death and nonfatal myocardial infarction).

RR estimates and associated 95% confidence intervals (CI) for the association between AF and the aforementioned study outcomes were abstracted. Only adjusted RR estimates were abstracted, along with the list of variables included in the multivariable regression model. We included studies that used propensity matching but preferentially extracted multivariable adjusted estimates if available.[8] If the list of variables included in the regression model was not provided, we included the study for the main analysis and performed a sensitivity analysis with the study excluded as part of a risk of bias assessment. Unadjusted studies were excluded.

To be included in the analysis on AF timing, studies were required to perform comparison between mutually exclusive categories of adults with no AF during the entire follow-up (reference group), adults with prevalent AF (explicitly stated as having developed AF before CHF), and adults with incident AF during the period of follow-up. In 2 instances,[9,10] the reference group was a combination of adults with no AF and adults with incident, and these studies were excluded from the AF timing analysis. This approach was also followed for the subgroup analysis based on AF pattern, and studies were required to report results for both chronic vs paroxysmal AF.

A risk of bias assessment was performed using the Newcastle-Ottawa Scale,[11] which assesses studies on 3 broad categories: the selection of participants for study groups; the comparability of study groups; and the ascertainment of the outcome. A star rating system is used to identify studies that are at low risk of bias and the maximum numbers of stars achievable are: selection (4 stars), comparability (2 stars), and outcome (3 stars). Studies achieving the maximum number of stars in all categories were considered to be at low risk of bias. The assessment of comparability is based on variable adjustment in the multivariable models of included studies. We applied strict criteria when evaluating studies. To receive 1 star for comparability, studies were required to adjust for age and gender. To receive 2 stars, studies were required to adjust for at least 1 cardiovascular risk factor (hypertension, diabetes, smoking, cholesterol, or chronic kidney disease) and a baseline history of cardiovascular disease if applicable.

Data Synthesis and Analysis

For all analyses, overall summary estimates were calculated using inverse-variance weighted random effects meta-analysis. For studies that reported separate RR estimates for subgroups, we first used inverse-variance weighted fixed effects meta-analysis to generate an overall study-level RRs before random effects meta-analysis. Heterogeneity was quantified using the I^2 statistic.

We planned to explore heterogeneity by stratifying the studies by risk of bias rating, date of cohort establishment, and age. Where more than 5 studies were included in an analysis, assessment for publication bias was performed by visual inspection of funnel plots and confirmed with Egger's test.[12] Where necessary, the trim and fill method was used to account for small study effect bias.[13]

Finally, we performed 2 sensitivity analyses. Three studies reported their results as odds ratios as opposed to hazard ratios. We excluded these studies from analyses to determine their effect on our study findings. All analyses were performed using R Statistical Software (version 3.0). A P value less than .05 was considered statistically significant.

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