

Accepted Manuscript

Title: Prognostic Importance of Atrial Fibrillation Timing and Pattern in Adults with Congestive Heart Failure: a Systematic Review and Meta-Analysis

Author: Ayodele Odutayo, Christopher X. Wong, Rashida Williams, Benjamin Hunn, Connor A. Emdin

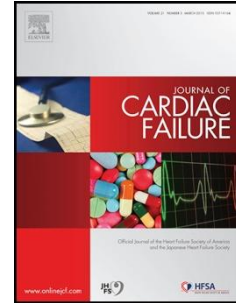
PII: S1071-9164(16)31110-1
DOI: <http://dx.doi.org/doi: 10.1016/j.cardfail.2016.08.005>
Reference: YJCAF 3856

To appear in: *Journal of Cardiac Failure*

Received date: 26-11-2015
Revised date: 3-8-2016
Accepted date: 17-8-2016

Please cite this article as: Ayodele Odutayo, Christopher X. Wong, Rashida Williams, Benjamin Hunn, Connor A. Emdin, Prognostic Importance of Atrial Fibrillation Timing and Pattern in Adults with Congestive Heart Failure: a Systematic Review and Meta-Analysis, *Journal of Cardiac Failure* (2016), <http://dx.doi.org/doi: 10.1016/j.cardfail.2016.08.005>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



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

Odutayo, Atrial Fibrillation in Congestive Heart Failure

Ayodele Odutayo MD MSc^a, Christopher X. Wong PhD^a, Rashida Williams BSc MSc^b, Benjamin Hunn BMedSc(Hons), MBBS^a, Connor A. Emdin HBSc^a

^aUniversity of Oxford, Oxford, United Kingdom.

^bFaculty of Medicine, George Washington University, Washington DC, United States.

Funding: None

Address for Correspondence and Reprints:

Ayodele Odutayo

Brasenose College

Radcliffe Square,

Oxford, Oxfordshire,

United Kingdom.

OX1 4AJ

Telephone: 011-44-74-6211-3024

Email: ayodele.odutayo@bnc.ox.ac.uk

Word Count: 2714; **Abstract Count:** 205

HIGHLIGHTS

- AF was associated with an increased risk of mortality
- The risk of mortality was greater in incident AF compared to prevalent AF
- The risk of mortality did not vary by the pattern of AF.
- AF in CHF was associated with an increased risk of cardiovascular mortality and stroke

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: Forty studies involving 152,215 adults (48,237 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 (RR: 2.21, 95% CI: 1.96-2.49 versus RR: 1.19, 95% CI: 1.03-1.38, respectively, $p < 0.001$ for interaction). The risk of 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.

Keywords: Congestive Heart Failure; Atrial Fibrillation; Mortality; Cardiovascular Disease

INTRODUCTION

Atrial fibrillation (AF) is common among adults with congestive heart failure (CHF). The prevalence of AF in all adults with CHF ranges from 13%-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 prior to 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 versus 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) guidelines (5) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 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), 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 or odds-ratio) for the association between AF and cardiovascular disease and death (see below) 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 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 versus 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 IHD (a composite of coronary heart disease death and non-fatal myocardial infarction).

Relative risk estimates and associated 95% confidence intervals (CI) for the association between AF and the aforementioned study outcomes were abstracted. Only adjusted relative risk estimates were abstracted, along with the list of variables included in the multivariable regression model. We included studies that employed propensity matching but preferentially extracted multivariable adjusted estimates if available (8). If the list of variables that were 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.

In order 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 versus 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 one star for comparability, studies were required to adjust for age and gender. To receive 2 stars, studies were required to adjust for at least one cardiovascular risk factor (hypertension, diabetes, smoking, cholesterol and 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 relative risk estimates for subgroups, we first used inverse-variance weighted fixed effects meta-analysis to generate an overall study-level relative risks prior to random effects meta-analysis. Heterogeneity was quantified using the I² statistic.

We planned to explore heterogeneity by stratifying the studies by risk of bias rating, date of cohort establishment (divided into thirds), age (divided into thirds), and proportion of male subjects (divided into thirds). 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 of less than 0.05 was considered statistically significant.

Funding Source

This study was unfunded.

RESULTS

In total, 3666 studies were reviewed and 3381 were excluded in the abstract screen largely because they were included too few participants or did not follow participants for at least 6 months. Among 285 full text articles that were reviewed, 252 were further excluded (Supplementary Figure 1). Accordingly, 33 studies involving 114,203 adults (43,549 with AF)

were included in this meta-analysis (Supplementary Table 1). All studies except for those by Cioffi et al. and McManus et al. used hazard ratios (see footnote of Supplementary Table 2). Most studies were at low risk of bias (n=21, Supplementary Table 2).

There were three studies included in the most recent meta-analysis on this topic(2) that were excluded from our study. This was because one study had only 1 month of follow up(14), another study included less than 50 participants(15) with AF, the third study combined mortality with heart failure hospitalization as an outcome(16).

Medical Management of Atrial Fibrillation

With respect to the medical management of AF in these studies, anticoagulation use was only reported in 16 of 33 studies and ranged from 30% to 86% (median: 56%). The median proportion of adults with AF receiving anticoagulation was 61% for cohorts recruited between 1980 and 2000 and 56% for cohorts recruited between 2001 and 2008.

All-Cause Mortality – Overall Analysis

Thirty-three studies, involving 113,797 adults (43,475 with AF) examined all-cause mortality as an outcome (Supplementary Table 1). One publication included 2 cohort studies. The median duration of follow up was 3.1 years (inter-quartile interval [IQI]: 1.9-4.9). The pooled relative risk was 1.20 (95% confidence interval (CI): 1.13-1.28, I²: 59%, p<0.001, Figure 1). When stratified by the timing of AF onset, incident AF was associated with a higher risk of

mortality (RR: 2.21, 95% CI: 1.96-2.49; $I^2=0\%$) compared to AF that existed prior to CHF diagnosis (RR: 1.19, 95% CI: 1.03-1.38; $I^2=60\%$; $p<0.001$ for interaction, Figure 2).

Furthermore, the relative risk of mortality associated with paroxysmal and chronic AF was similar (Figure 3).

All-Cause Mortality – Preserved Ejection Fraction

Six studies, involving 39,187 adults with CHF with preserved ejection fraction (15,481 with AF) examined all-cause mortality as an outcome. The median duration of follow up was 3.4 years (IQR 2.6-4.2). The pooled relative risk was 1.24 (95% CI: 1.10-1.41, Figure 4). There was no heterogeneity ($I^2: 0\%$, $p=0.746$). The relative risk of mortality associated with incident AF was 1.86 (95% CI: 1.37-2.53). There were insufficient studies to assess the relative risk of mortality associated with prevalent AF or the risk of mortality stratified by the pattern of AF (paroxysmal versus chronic).

All-Cause Mortality – Reduced Ejection Fraction

Fourteen studies, involving 55,200 adults with CHF with reduced ejection fraction (17,696 with AF) examined all-cause mortality as an outcome. The median duration of follow up was 2.2 years (IQR 1.6-2.7). The pooled relative risk was 1.12 (95% CI: 1.05-1.19, Figure 5). Heterogeneity was limited ($I^2: 20\%$, $p=0.251$). The pooled relative risk of mortality in adults

with CHF with reduced ejection fraction was not significantly different than in adults with preserved ejection fraction ($p=0.14$). The relative risk of mortality associated with incident AF was 1.73 (95% CI: 1.55-1.94). There were insufficient studies to assess the relative risk of mortality associated with prevalent AF or the risk of mortality stratified by the pattern of AF (paroxysmal versus chronic).

Cardiovascular Mortality, Stroke and Ischemic Heart Disease

Five studies, involving 10,587 participants (4,704 with AF) examined cardiovascular mortality as an outcome. The median duration of follow up was 2.4 years (IQI 1.9-3.1). The pooled relative risk was 1.24 (95% CI: 1.09-1.40, I^2 : 13%, $p=0.329$, Supplementary Figure 2). With respect to stroke, 4 studies, involving 60,829 participants (24,600 with AF) were identified. The median duration of follow up was 1.8 years (IQI 1.6-3.1). The pooled relative risk for stroke was 1.98 (95% CI: 1.22-3.21, I^2 : 85%, $p<0.001$, Supplementary Figure 3). One study examined IHD as an outcome, respectively. The relative risk for IHD was 1.44 (95% CI: 0.61-3.43).

Assessment of Bias

Heterogeneity was moderate or statistically significant for the analysis of overall mortality and stroke. With respect to overall mortality, relative risk estimates were consistent with the original estimate and remained statistically significant when studies were stratified based on the risk of bias, date of cohort establishment and age (Table 1). Heterogeneity was

reduced in the subgroup of studies judged to be at low risk of bias ($I^2=10\%$). Due to the small number of studies included, subgroup analyses were not performed for stroke.

Funnel plot asymmetry was not observed for the overall analysis of mortality, nor analyses stratified by ejection fraction, AF timing or AF pattern. There was also no funnel plot asymmetry for cardiovascular mortality.

Sensitivity Analyses

Excluding the 3 studies that reported odds-ratios as opposed to hazard ratios did not change our results.

DISCUSSION

This study summarizes the existing literature on the prognostic importance of AF in adults with CHF. The first major finding was that AF was associated with an increased risk of mortality. Second, the risk of mortality was greater in incident AF compared to prevalent AF and the risk of mortality associated with incident AF was consistent in adults with CHF with reduced and preserved ejection fraction. Third, the risk of mortality did not vary by the pattern of AF. Finally, AF was associated with an increased risk of cardiovascular mortality and stroke.

AF is associated with an increased risk of mortality in adults with CHF (2-4). Multiple studies have also shown that this risk may be lower in adults with reduced ejection fraction compared to adults with preserved ejection fraction(2,4). Although our relative risk estimates for

mortality in adults with CHF with preserved and reduced ejection fraction were consistent with these prior studies, the difference in the risk conferred by AF did not reach statistical significance in our analysis ($p=0.14$). More research is needed to clarify whether the prognostic importance of AF varies based on the type of CHF.

Nonetheless, stratification based solely on ejection fraction provides only limited insight into the risk associated with AF in CHF and previous investigators have shown the relative risk of mortality may also vary based on the timing of AF onset(17) and the pattern of AF (18-20). Our study summarizes these risks in a meta-analysis and we observed that incident AF was associated with a greater relative risk of mortality than prevalent AF (RR: 1.69, 95% CI: 1.39-2.05 versus RR: 1.21, 95% CI: 1.12-1.30) and this risk was elevated in adults with reduced or preserved ejection fraction. The increased risk of mortality associated with incident AF is notable and suggests that a detailed history on atrial fibrillation should form an important aspect of the medical history and counselling of adults with CHF (21), irrespective of whether ejection fraction is reduced or preserved. Notably, we found no difference in the relative risk of mortality associated with paroxysmal and chronic AF.

The mechanism underlying differential risk in prevalent and incident AF is not clear. However, it is conceivable that rapid atrial contraction may predispose to ventricular tachyarrhythmia, demand infarction or thromboembolism, which may be more severe in the context of ventricular dysfunction. New-onset AF may also be a marker of the severity of LV dysfunction or myocardial damage. Finally, we cannot rule out the potential for residual confounding. For instance, it may be that patients need to survive well beyond their first

atrial fibrillation event before they can become a prevalent atrial fibrillation patient. This selects for less sick patients comprising the prevalent heart failure group. Accordingly, differences highlighted in our study should be interpreted with caution.

Lastly, the modestly increased risk of cardiovascular mortality and stroke in our study reinforces the need for timely initiation of antithrombotic therapy in adults with AF and CHF(22). In our study, the use of anticoagulation ranged from 30% to 86% (median 56%) and was not more frequently prescribed in recent cohort studies. By clearly quantifying the risk of stroke in adults with comorbid AF and CHF, our findings may further compel clinical to more regularly consider anticoagulation as a strategy to improve stroke outcomes for this high-risk population.

The strengths of our study is that we assessed the association between AF and cardiovascular mortality and stroke, which has not been done in prior meta-analyses. Furthermore, we conducted a risk of bias assessment and assessed its impact on heterogeneity. However, our study has important limitations. First, despite identifying more studies than recent meta-analyses (2), we may have missed studies, particularly if a regression model was used to adjust for a range of cardiovascular risk factors and this was not mentioned in the abstract. Second, as anticipated, we identified heterogeneity in relative risk estimates for the overall analysis of all-cause mortality. However, we explored this heterogeneity through subgroup analyses based on the risk of bias, the date of cohort establishment and the average age in included studies. When studies were stratified by risk of bias, heterogeneity was reduced for the relative risk estimates of mortality, suggesting that heterogeneity was due to methodological

differences between studies. However, the relative risk remained unchanged. Third, although studies used electrocardiograms to identify AF participants, some cases of paroxysmal AF may not have been identified. However, this misclassification is likely to produce a more conservative relative risk estimate. Fourth, anticoagulation use was only reported for 16 of 33 studies, which may further explain any residual heterogeneity. Finally, although we included studies that generated relative risk estimates from multivariable adjusted risk models, there may still be residual confounding. For instance, participants with prevalent atrial fibrillation may be healthier than adults with incident atrial fibrillation and this confounding may not be fully addressed in multivariable regression models. Accordingly, we can only demonstrate an association between the presence of AF, as well as its timing and pattern, and our outcomes of interest. Whether this association is causal cannot be discerned from our study.

Taken together, AF is associated with an increased risk of all-cause mortality and cardiovascular mortality and morbidity. Notably, the relative risk of mortality varies based on the timing of atrial fibrillation. Further research is required into interventions to improve outcomes for adults with comorbid AF and CHF.

ACKNOWLEDGEMENTS: None

FUNDING: None

DISCLOSURES: None

Accepted Manuscript

REFERENCES

1. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation*. 2009 May 12;119(18):2516–25.
2. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail*. 2014 Dec;16(12):1317–22.
3. Wasywich CA, Pope AJ, Somaratne J, Poppe KK, Whalley GA, Doughty RN. Atrial fibrillation and the risk of death in patients with heart failure: a literature-based meta-analysis. *Intern Med J*. 2010 May;40(5):347–56.
4. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009 Jul;11(7):676–83.
5. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000 Apr 19;283(15):2008–12.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Vol. 151, *Annals of internal medicine*. 2009. pp. 264–9–W64.
7. Khan MA, Ahmed F, Neyses L, Mamas MA. Atrial fibrillation in heart failure: The sword of Damocles revisited. *World J Cardiol*. 2013 Jul 26;5(7):215–27.
8. Winkelmayer WC, Kurth T. Propensity scores: help or hype? *Nephrol Dial Transplant*. 2004 Jul;19(7):1671–3.
9. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail*. 2007 Mar;9(3):258–65.
10. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJV, et al. Atrial fibrillation and risk of

clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol*. 2006 May 16;47(10):1997–2004.

11. Wells GA, Shea B, OConnell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses

[Internet]. [cited 2015 Apr 13]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997 Sep 13;315(7109):629–34.
13. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000 Jun;56(2):455–63.
14. Eapen ZJ, Greiner MA, Fonarow GC, Yuan Z, Mills RM, Hernandez AF, et al. Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction. *Am Heart J*. 2014 Mar;167(3):369–375.e2.
15. Testa G, Cacciatore F, Della-Morte D, Galizia G, Mazzella F, Gargiulo G, et al. Role of permanent atrial fibrillation (AF) on long-term mortality in community-dwelling elderly people with and without chronic heart failure (CHF). *Arch Gerontol Geriatr*. 2012 Jul;55(1):91–5.
16. Linssen GCM, Rienstra M, Jaarsma T, Voors AA, Van Gelder IC, Hillege HL, et al. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail*. 2011 Oct;13(10):1111–20.
17. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003 Jun 17;107(23):2920–5.
18. Koitabashi T, Inomata T, Niwano S, Nishii M, Takeuchi I, Nakano H, et al. Paroxysmal atrial fibrillation coincident with

cardiac decompensation is a predictor of poor prognosis in chronic heart failure. *Circ J*. 2005 Jul;69(7):823–30.

19. Raunsø J, Pedersen OD, Dominguez H, Hansen ML, Møller JE, Kjaergaard J, et al. Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease. *Eur J Heart Fail*. 2010 Jul;12(7):692–7.
20. Shotan A, Garty M, Blondhein DS, Meisel SR, Lewis BS, Shochat M, et al. Atrial fibrillation and long-term prognosis in patients hospitalized for heart failure: results from heart failure survey in Israel (HFSIS). *Eur Heart J*. 2010 Feb;31(3):309–17.
21. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. Vol. 16, *Journal of cardiac failure*. 2010. pp. e1–194.
22. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Vol. 33, *European heart journal*. 2012. pp. 1787–847.

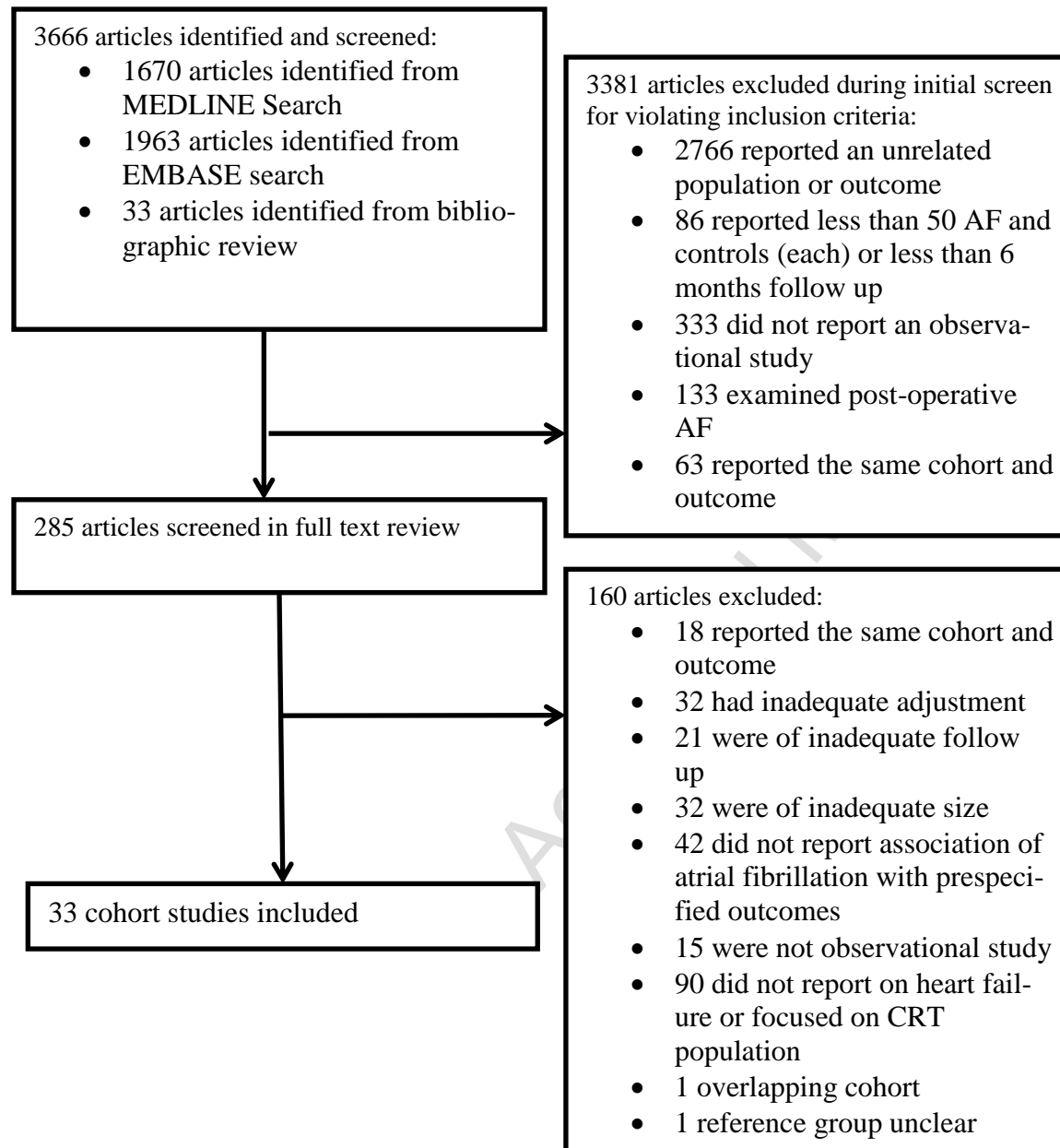
SUPPLEMENTARY MATERIALS

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

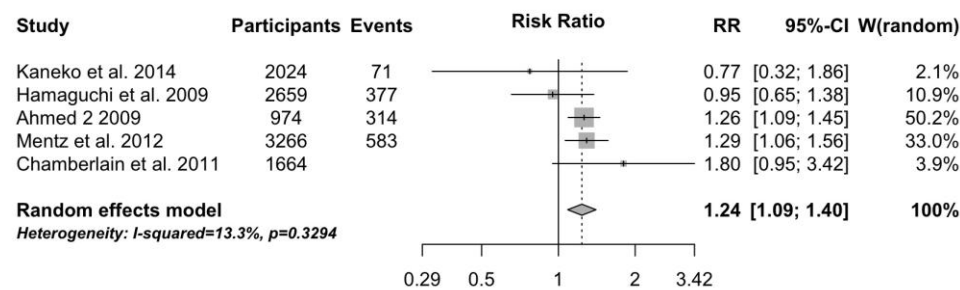
Odutayo et al.

SUPPLEMENTARY FIGURES

Supplementary Figure 1: Identification of Included Studies – Titles and abstracts were independently reviewed in duplicate to assess studies for their inclusion. Among studies identified for full-text reviews, data was independently abstracted in duplicate using standardized forms.



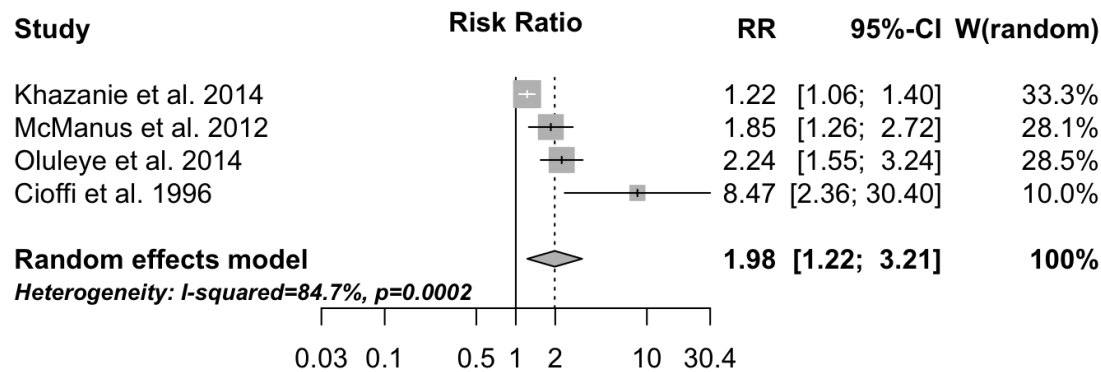
Supplementary Figure 2: Association Between Atrial Fibrillation and Cardiovascular Mortality in Adults with Congestive Heart Failure - AF was associated with an increased risk of cardiovascular mortality in adults with CHF. There was no heterogeneity.



Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Supplementary Figure 3: Association Between Atrial Fibrillation and Stroke in Adults with Congestive Heart Failure – AF

was associated with an increased risk of stroke in adults with CHF. Heterogeneity was considerable.



Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Supplementary Table 1: Baseline Characteristics of Participants In Included Studies

Study Author, Year	Outcome Reported	AF Timing	Heart Failure Type	Participants (AF)	Follow-Up (years)	Mean Age	Male (%)	IHD (%)	Stroke (%)	Anti-coagulation (%)
Ahmed, 2005 (1)	Mortality	Incident and Prevalent	Mixed	944 (345)	4	79	364 (39)	245 (26)	N/A	N/A
Ahmed, 2009 (2)	Mortality, CVD Mortality	Mixed	Reduced EF	974 (487)	1.9	63	836 (86)	634 (65)	N/A	347 (71)
Baldasseroni, 2002 (3)	Mortality	Mixed	Mixed	4311 (933)	1	N/A	3390 (79)	2105 (49)	N/A	N/A
Carson, 1993 (4) †	Mortality	Mixed	Reduced EF	642 (99)	2.5	58	632 (98)	279 (43)	N/A	30 (30)
Carson, 1993 (4) †	Mortality	Mixed	Reduced EF	804 (107)	2.5	60	795 (99)	423 (53)	N/A	44 (41)
Chamberlain, 2011 (5)	Mortality, CVD Mortality, IHD	Incident and Prevalent	Mixed	1664 (937)	4	76	759 (46)	353 (21)	N/A	N/A
Cioffi, 1996 (6)	Stroke	Mixed	Mixed	406 (64)	1.3	54	360 (89)	173 (43)	N/A	47 (73)

Corell, 2007 (7)	Mortality, Stroke	Incident Only	Reduced EF	1019 (269)	1.8	71	718 (71)	513 (50)	114 (11)	149 (55)
Crijns, 2000 (8)	Mortality	Mixed	Reduced EF	409 (84)	1	68	314 (77)	314 (77)	N/A	67 (80)
Gotsman, 2008 (9)	Mortality	Mixed	Mixed	289 (97)	1	73	154 (53)	199 (69)	N/A	N/A
Hamaguchi, 2009 (10)	Mortality, CVD Mortality, Stroke	Mixed	Reduced and Preserved EF	2659 (937)	2.4	71	1590 (60)	851 (32)	399 (15)	657 (70)
Kaneko, 2014 (11)	Mortality	Mixed	Mixed	2024 (310)	3.1	65	1456 (72)	1389 (69)	N/A	217 (70)
Khazanie, 2014 (12)	Mortality, Stroke	Incident and Prevalent	Mixed	27829 (11535)	N/A	80	12654 (46)	17052 (61)	4267 (15)	N/A
Koitabashi, 2005 (13)	Mortality	Mixed	Mixed	427 (188)	6	66	274 (64)	189 (44)	N/A	94 (50)
Makubi, 2014 (14)	Mortality, Stroke	Mixed	Mixed	427 (67)	0.6	55	210 (49)	N/A	16 (4)	N/A
McManus, 2012 (15)	Mortality, Stroke	Incident and Prevalent	Reduced and Preserved EF	23644 (11429)	1.8	74	12361 (52)	3080 (13)	4990 (21)	4804 (42)
McManus, 2013 (16)	Mortality, Stroke	Incident and	Mixed	9748 (4317)	2	76	4279	5456	1298 (13)	2223 (51)

		Prevalent					(47)	(56)		
Mentz, 2012 (17)	Mortality, CVD Mortality, Stroke	Mixed	Reduced EF	3266 (1195)	0.8	64	2387 (73)	2262 (69)	361 (11)	N/A
Olsson, 2006 (18)	Mortality, Stroke	Incident only	Reduced and Preserved EF	7599 (1148)	3.1	66	5199 (68)	3904 (51)	663 (9)	863 (75)
Oluleye, 2014 (19)	Mortality, CVD Mortality, Stroke	Mixed	Preserved EF	4128 (1227)	4.4	72	1637 (40)	2096 (51)	399 (10)	662 (54)
Pedersen, 2005 (20)	Mortality	Mixed	Mixed	N/A (1031)	5	72	N/A	N/A	N/A	N/A
Pedersen, 2006 (21)	Mortality	Mixed	Reduced EF	3479 (818)	8	73	2080 (60)	1974 (57)	N/A	N/A
Raunso, 2010 (22)	Mortality, Stroke	Mixed	Mixed	2881 (1175)	7	75	1749 (61)	1322 (46)	336 (12)	658 (56)
Rusinaru, 2008* (23)	Mortality, Stroke	Mixed	Preserved EF	218 (109)	5	78	94 (43)	18 (8)	11 (5)	N/A
Shotan, 2010 (24)	Mortality, Stroke	Mixed	Mixed	4102 (1360)	4	73	2338 (57)	3371 (82)	511 (13)	613 (45)
Sosin, 2004 (25)	Mortality	Mixed	Mixed	233 (65)	8	N/A	109 (47)	115 (49)	N/A	N/A

Stevenson, 1995 (26)	Mortality	Mixed	Reduced EF	737 (68)	1	51	587 (80)	N/A	N/A	N/A
Swedberg, 2005 (27)	Mortality, Stroke	Incident and Prevalent	Reduced EF	3029 (600)	4.8	62	2417 (80)	1784 (59)	215 (7)	447 (75)
Tribouilloy, 2010 (28)	Mortality, Stroke	Mixed	Mixed	735 (180)	7	75	379 (52)	93 (13)	40 (5)	N/A
Tveit, 2011 (29)	Mortality	Mixed	Mixed	4048 (1391)	2.3	70	2839 (70)	2249 (56)	N/A	1198 (86)
Wang, 2003 (30)	Mortality, Stroke	Incident and Prevalent	Mixed	787 (79)	5.6	73	N/A	339 (43)	93 (12)	N/A
Zafrir, 2011 (31)	Mortality	Mixed	Mixed	481 (197)	2.1	66	340 (71)	280 (58)		N/A
Zakeri, 2013* (32)	Mortality, Stroke	Incident and Prevalent	Preserved EF	939 (631)	3.7	76	573 (61)	151 (16)	194 (21)	N/A

AF is atrial fibrillation, IHD is ischemic heart disease, EF is ejection fraction, CVD is cardiovascular disease, N/A is not available.

*These studies were only included in the meta-analysis for preserved ejection fraction because their cohorts of these studies overlapped with other studies already included in the meta-analysis. † The study by Carson et al. reported two cohorts, therefore bringing the total number of studies to thirty three.

Supplementary Table 2: Variables Included in Regression Models and Risk of Bias Assessment

Study	Adjustment Variables In Regression model	Selection	Comparability*	Outcome	Overall
Ahmed, 2005 (1)	Age, sex, race, history of heart failure, admission pulse ≥ 100 bpm, admission systolic bp ≥ 140 mmHg, left ventricular systolic dysfunction, discharge use of ACE inhibitors and digoxin, three or more comorbidities (diabetes, hypertension, CAD and COPD), care by cardiologist and hospital	★★★★★	★★	★★★	Low Risk
Ahmed, 2009 (2)	Propensity score	★★★★★	★★	★★★	Low Risk
Baldasseroni, 2002 (3)	Age, IHD, previous hospitalization for congestive heart failure, NYHA class III–IV, reduced systolic blood pressure, third heart sound, ventricular tachycardia, and renal failure	★★★★★	★	★★★	Not Low Risk
Carson, 1993 (4)	N/A	★★★★★		★★★	Not Low Risk

Carson, 1993 (4)	N/A	★★★★		★★★	Not Low Risk
Chamberlain, 2011 (5)	Age, sex, BMI, year of heart failure diagnosis, smoking status, derived NYHA class, estimated glomerular filtration rate, anemia, hypertension, diabetes mellitus, COPD, MI, and β -blockers, ACE inhibitors, and diuretics at the index visit.	★★★★	★★	★★★	Low Risk
Cioffi, 1996 (6) [†]	N/A	★★★		★★	Not Low Risk
Correll, 2007 (7)	Age, sex, LVEF, NYHA functional class, diabetes, previous AMI, p-creatinine, heart rhythm (AF/SR)	★★★★	★★	★★★	Low Risk
Crijns, 2000 (8)	Age, LVEF, NYHA class, rel function, and BP	★★★★	★	★★★	Not Low Risk
Gotsman, 2008 (9)	Age, gender, IHD, hypertension, diabetes, chronic renal failure, AF, residence in a nursing home, discharge sodium <135 mEq/L, and LVF	★★★★	★★	★★★	Low Risk

Hamaguchi, 2009 (10)	Age, cause of heart failure (ischemic, hypertensive or valvular heart disease), medical history (diabetes, hyperlipidemia, hyperuricemia, prior stroke), serum creatinine, hemoglobin and BNP levels, LVEF, and medication use (diuretics, nitrates, aspirin, antiplatelet, warfarin, statin)	★★★★	★★	★★★	Low Risk
Kaneko, 2014 (11)	Age, sex, obesity, hypertension, dyslipidemia, DM, hyperuricacidemia, cigarette smoking, CKD, anemia, IHD, valvular heart disease, DCM, B-type triuretic peptide (BNP), NYHA class, LVEF, and the use of beta-blockers, renin-angiotensin-system inhibitors (RAS-Is), statins, diuretics, digitalis, antiarrhythmic drugs (AADs), antiplatelet drugs, or warfarin	★★★★	★★	★★★	Low Risk
Khazanie, 2014 (12)	Age, gender, race, anemia, COPD, Stroke, Depression, DM, Hypertension, Hyperlipidemia, Ischemic Heart Failure Etiology, Pacemaker, PVD, renal insufficiency, Current Smoker, Chronic liver disease, Dementia, Disability, Malnutrition, Psychiatric Disorder, Systolic Blood Pressure, Respiratory Rate	★★★★	★★	★★★	Low Risk
Koitabashi,	N/A	★★★★		★★	Not Low

2005 (13)					Risk
Makubi, 2014 (14)	Age, gender, education, inpatient status, NYHA class, diabetes, previous cardiovascular admission, pulmonary hypertension, BMI, mean arterial pressure, anemia, creatinine clearance, serum cholesterol	★★★★	★★	★★	Not Low Risk
McManus, 2012 (15)†	Age, sex, left ventricular ejection fraction (in overall models only), prevalent heart failure, acute MI, unstable angina, CABG surgery, PCI, ischemic stroke, other thromboembolic event, ventricular fibrillation or ventricular tachycardia, peripheral arterial disease, cardiac resynchronization therapy, ICD, pacemaker, dyslipidemia, hypertension, diabetes mellitus, hospitalized bleeds, diagnosed dementia, diagnosed depression, chronic lung disease, chronic liver disease, mechanical fall, systemic cancer, estimated GFR, hemoglobin, systolic blood pressure, HDL cholesterol, LDL cholesterol, race, and site.	★★★★	★★	★★★	Low Risk
McManus, 2013 (16)†	Age, gender, race, length of stay, history of COPD, stroke, anemia, diabetes, CAD, CABG, and admission systolic and diastolic BP, HR, creatinine, and serum	★★★★	★★	★★★	Low Risk

	glucose				
Mentz, 2012 (17)	Randomization group and clinically relevant demographic (age, sex, region), clinical (admission systolic blood pressure, EF, QRS duration, ACE inhibitor/ ARB use, β -blocker use, aldosterone blocker use, digoxin use, intravenous inotrope use, diabetes, hypertension, and renal insufficiency), and laboratory values (BNP/NT-proBNP, sodium and BUN)	★★★★	★★	★★★	Low Risk
Olsson, 2006 (18)	Age, sex, ethnicity, EF, HR, BP, BMI, HF, prior cardiovascular disease, medical treatment	★★★★	★★	★★★	Low Risk
Oluleye, 2014 (19)	Age at baseline, sex, race, history of IHD, COPD, hypertension, hyperlipidemia, stroke, rel artery disease, diabetes mellitus, hospitalization for HF in previous 6 months, heart block, and other arrhythmias, CKD, anemia, systolic bp, left ventricular hypertrophy on ECG, albumin, platelet count, and treatment with irbesartan, antiarrhythmic, antiplatelet agent, antithrombotic agent, calcium	★★★★	★★	★★★	Low Risk

	channel blocker, beta-blocker, angiotensin converting enzyme inhibitor, digoxin, diuretic, spironolactone, nitrate, lipid lowering drugs, and an ICD/pacemaker				
Pedersen, 2005 (20)	Age, gender, diabetes, hypertension, prior MI	★★★★	★★	★★	Not Low Risk
Pedersen, 2006 (21)	Age, gender, wall motion index, diabetes, and ischemic heart disease	★★★★	★★	★★★	Low Risk
Raunso, 2010 (22)	Age, gender, LVEF, history of IHD, diabetes, smoking status, body mass index, history of chronic obstructive pulmonary disease, NYHA class at discharge, and serum creatinine levels at baseline	★★★★	★★	★★★	Low Risk
Rusinaru, 2008 (23)	Age, sex, ischaemic aetiology, history of hypertension, diabetes mellitus, history of MI, cancer, stroke, estimated GFR, anaemia and treatment at discharge (ACE-inhibitors, beta-blockers, digoxin, amiodarone, nitrates, antiplatelet agents, and oral anticoagulants).	★★★★	★★	★★★	Low Risk
Shotan, 2010	AF subtypes, age, gender, hypertension, diabetes mellitus, CAD, ACS, valvular	★★★★	★★	★★★	Low

(24)	heart disease, non-ischaemic CMP, renal failure, anemia, PVD, COPD, stroke, NYH class III–IV, Killip class, LVEF—preserved, moderately, and severely decreased, primary HF, secondary HF, acute new onset HF, acute exacerbation of chronic HF, chronic HF, amiodarone, antiarrhythmics, anticoagulants, aspirin, clopidogrel, ACE-I, ARBs, beta-blockers, furosemide, aldosterone blockers, CCBs—dihydropyridines, CCBs— non-dihydropyridines, digoxin, nitrates, and statins				Risk
Sosin, 2004 (25)	Age, echocardiogram performed, creatinine >120, european ethnicity, ACE inhibitor use, beta-blocker use	★★★★★	★	★★★	Not Low Risk
Stevenson, 1995 (26)	Age; LVEF; serum sodium levels; admission and predischage systolic blood, pulmory capillary wedge and pulmory artery systolic pressures; predischage cardiac index and HR; history of syncope, AF or cardiac arrest; CAD; permanent pacemaker; ICD; and entry after year 1990 (step wise)	★★★★★	★★	★★★	Low Risk
Swedberg,	Age, gender, EF,BP, NYHA class, aetiology, previous angi, S-creatinine, S-	★★★★★	★	★★★	Not Low

2005 (27)	sodium, and dose of furosemide.				Risk
Tribouilloy, 2010 (28)	Age, gender, smoker status, history of hypertension, CAD, valvular heart disease, idiopathic dilated cardiomyopathy, DM, stroke, peripheral artery disease, prior MI, chronic AF, COPD, cancer, estimated GFR, traemia, and treatment at discharge ACE inhibitors, beta-blockers, nitrates, oral anticoagulants and statins]	★★★★	★★	★★★	Low Risk
Tveit, 2011 (29)	Age, gender, EF, NYHA, CAD, hypertension, valvular heart disease, heart rate, beta blockers, ACEI/ARB, frusemide, bumetanide, any loop diuretic, thiazide, warfarin, Hb, creatininie, (stepwise regression)	★★★★	★★	★★	Not Low Risk
Wang, 2003 (30)	Age, time period, MI, stroke/transient ischemic attack, diabetes, valvular disease, ECG left ventricular hypertrophy, systolic blood pressure, antihypertensive therapy, and smoking.	★★★★	★★	★★★	Low Risk
Zafrir, 2011	Age, gender, BMI, HF etiology, hypertension, diabetes, ICD, six minute walk test,	★★★★	★★	★★★	Low

(31)	NYHA, beta blockers, ACE inhibitors or ARBs, Spironolactone, Diuretics, CCB				Risk
Zakeri, 2013 (32)	Age, sex, BMI, estimated GFR, hypertension, COPD, ACEI or ARB use, Beta-Blocker use, statin, anti-arhythmic drug use.	★★★★	★	★★★	Not Low Risk

* To receive one star for comparability studies were required to adjust for age and gender. To receive two stars, studies were required to adjust for at least one cardiovascular risk factor (hypertension, diabetes, smoking, cholesterol and chronic kidney disease) and a baseline history of cardiovascular disease. †Used odds ratios as opposed to hazard ratios

REFERENCES

1. Ahmed A, Perry GJ. Incident atrial fibrillation and mortality in older adults with heart failure. *Eur. J. Heart Fail.* 2005;7:1118–1121.
2. Ahmed MI, White M, Ekundayo OJ, et al. A history of atrial fibrillation and outcomes in chronic advanced systolic heart failure: a propensity-matched study. *Eur Heart J* 2009;30:2029–2037.
3. Baldasseroni S, De Biase L, Fresco C, et al. Cumulative effect of complete left bundle-branch block and chronic atrial fibrillation on 1-year mortality and hospitalization in patients with congestive heart failure. A report from the Italian network on congestive heart failure (in-CHF database). *Eur Heart J* 2002;23:1692–1698.
4. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87:VI102–10.
5. Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial Fibrillation and Mortality in Heart Failure: A Community Study. *Circ Heart Fail* 2011;4:740–746.
6. Cioffi G, Pozzoli M, Forni G, et al. Systemic thromboembolism in chronic heart failure. A prospective study in 406 patients. *Eur Heart J* 1996;17:1381–1389.
7. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur. J. Heart Fail.* 2007;9:258–265.
8. Crijns HJ, Tjeerdsma G, de Kam PJ, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J* 2000;21:1238–1245.
9. Gotsman I, Zwas D, Planer D, et al. Clinical outcome of patients with heart failure and preserved left ventricular function. *Am J Med* 2008;121:997–1001.
10. Hamaguchi S, Yokoshiki H, Kinugawa S, et al. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009;73:2084–2090.
11. Kaneko H, Suzuki S, Kano H, et al. Impact of atrial fibrillation on long-term clinical outcomes in outpatients with heart failure. *Journal of Arrhythmia* 2014;30:186–191.
12. Khazanie P, Liang L, Qualls LG, et al. Outcomes of medicare beneficiaries with heart failure and atrial fibrillation. *JACC Heart Fail* 2014;2:41–48.
13. Koitabashi T, Inomata T, Niwano S, et al. Paroxysmal atrial fibrillation coincident with cardiac decompensation is a predictor of poor prognosis in chronic heart failure.

Circ J 2005;69:823–830.

14. Makubi A, Hage C, Lwakatare J, et al. Contemporary aetiology, clinical characteristics and prognosis of adults with heart failure observed in a tertiary hospital in Tanzania: the prospective Tanzania Heart Failure (TaHeF) study. *Heart* 2014;100:1235–1241.

15. McManus DD, Hsu G, Sung SH, et al. Atrial Fibrillation and Outcomes in Heart Failure With Preserved Versus Reduced Left Ventricular Ejection Fraction. *Journal of the American Heart Association* 2012;2:e005694–e005694.

16. McManus DD, Saczynski JS, Lessard D, et al. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). *Am J Cardiol* 2013;111:1460–1465.

17. Mentz RJ, Chung MJ, Gheorghiade M, et al. Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial. *Am Heart J* 2012;164:884–92.e2.

18. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997–2004.

19. Oluleye OW, Rector TS, Win S, et al. History of atrial fibrillation as a risk factor in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2014;7:960–966.

20. Pedersen OD, Bagger H, Køber L, Torp-Pedersen C, TRACE Study Group. Impact of congestive heart failure and left ventricular systolic function on the prognostic significance of atrial fibrillation and atrial flutter following acute myocardial infarction. *Int J Cardiol* 2005;100:65–71.

21. Pedersen OD, Søndergaard P, Nielsen T, et al. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. *Eur Heart J* 2006;27:2866–2870.

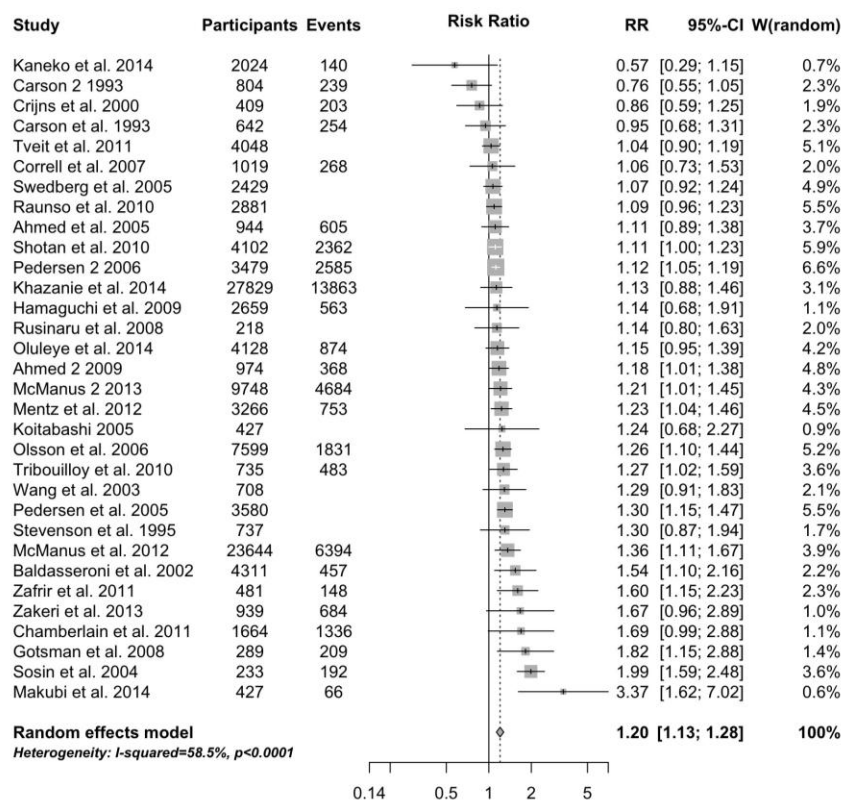
22. Raunsø J, Pedersen OD, Dominguez H, et al. Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease. *Eur. J. Heart Fail.* 2010;12:692–697.

23. Rusinaru D, Leborgne L, Peltier M, Tribouilloy C. Effect of atrial fibrillation on long-term survival in patients hospitalised for heart failure with preserved ejection fraction. *Eur. J. Heart Fail.* 2008;10:566–572.

24. Shotan A, Garty M, Blondhein DS, et al. Atrial fibrillation and long-term prognosis in patients hospitalized for heart failure: results from heart failure survey in Israel (HFSIS). *Eur Heart J* 2010;31:309–317.

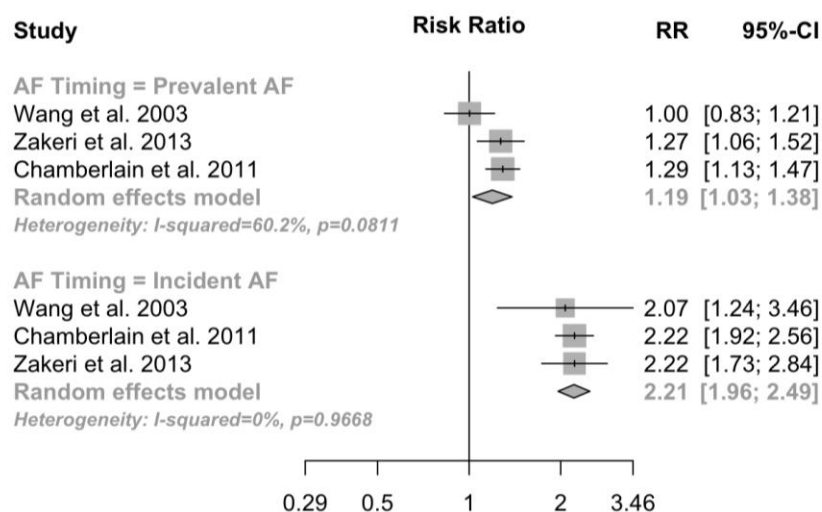
25. Sosin MD, Bhatia GS, Zarifis J, Davis RC, Lip GYH. An 8-year follow-up study of acute admissions with heart failure in a multiethnic population. *Eur. J. Heart Fail.* 2004;6:669–672.
26. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with advanced heart failure: a study of 737 consecutive patients. *JAC* 1995;26:1417–1423.
27. Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005;26:1303–1308.
28. Tribouilloy C, Buiciuc O, Rusinaru D, Malaquin D, Lévy F, Peltier M. Long-term outcome after a first episode of heart failure. A prospective 7-year study. *Int J Cardiol* 2010;140:309–314.
29. Tveit A, Flonaes B, Aaser E, et al. No impact of atrial fibrillation on mortality risk in optimally treated heart failure patients. *Clin Cardiol* 2011;34:537–542.
30. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920–2925.
31. Zafrir B, Paz H, Wolff R, et al. Mortality rates and modes of death in heart failure patients with reduced versus preserved systolic function. *Eur. J. Intern. Med.* 2011;22:53–56.
32. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013;128:1085–1093.

Figure 1: Association Between Atrial Fibrillation and All-Cause Mortality in Adults with Congestive Heart Failure – AF was associated with an increased risk of all-cause mortality. Heterogeneity was moderate.



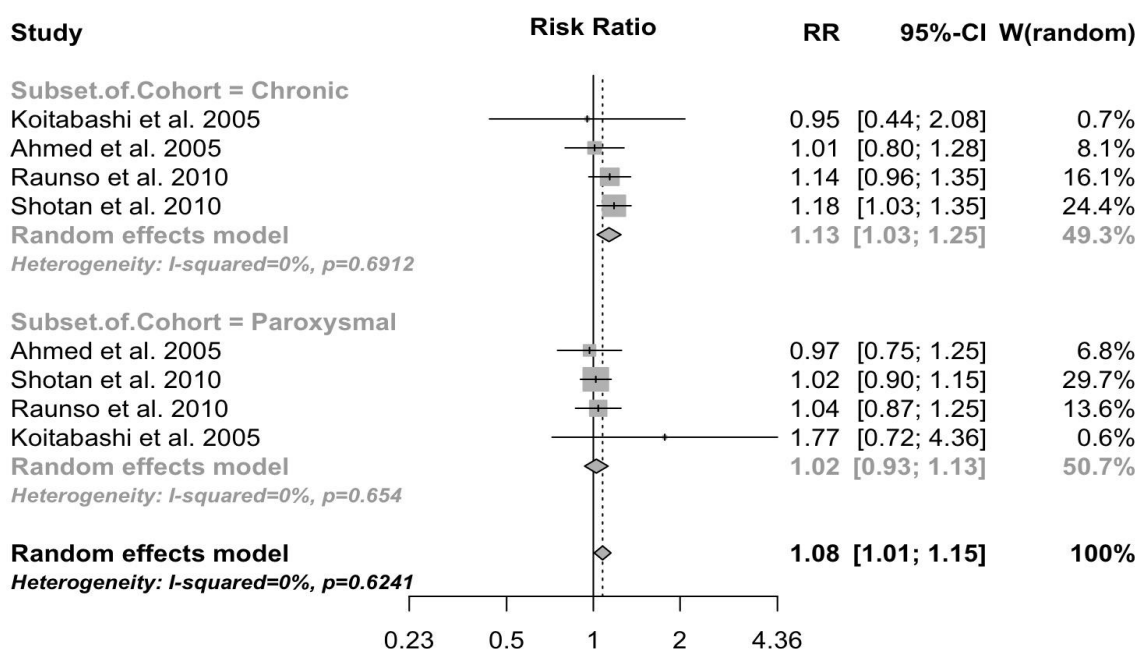
Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Figure 2: Association Between Atrial Fibrillation and All-Cause Mortality in Adults with Congestive Heart Failure, By Timing of Atrial Fibrillation Onset – Results were stratified by timing of AF onset. Incident AF was associated with a higher risk of mortality compared to AF that existed prior to CHF diagnosis (p<0.001 for interaction).



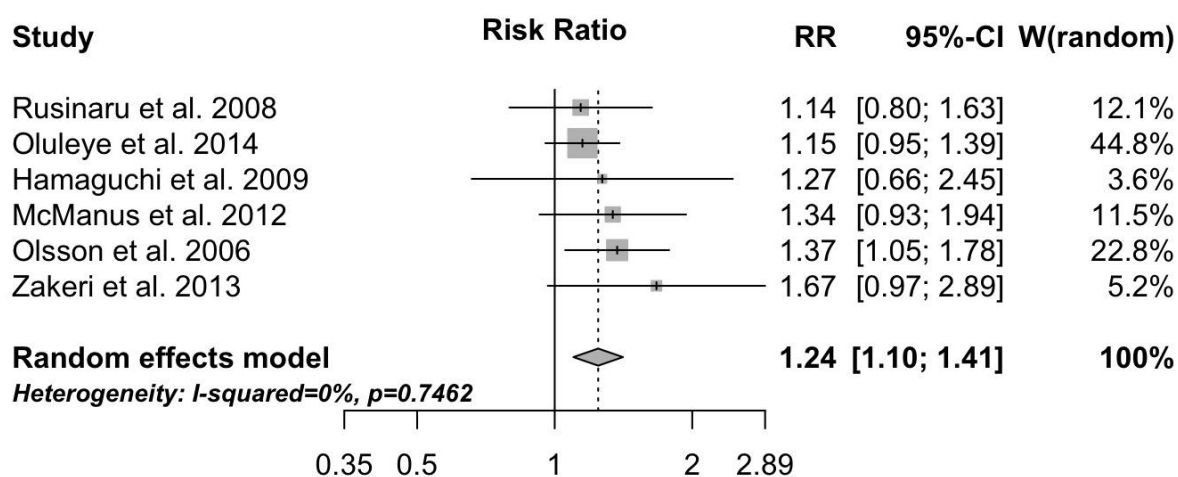
Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Figure 3: Association Between Paroxysmal and Chronic Atrial Fibrillation and All-Cause Mortality in Adults with Congestive Heart Failure – Results were stratified by the pattern of AF. There was no difference in the relative risk of mortality based on the pattern of AF ($p=0.137$).



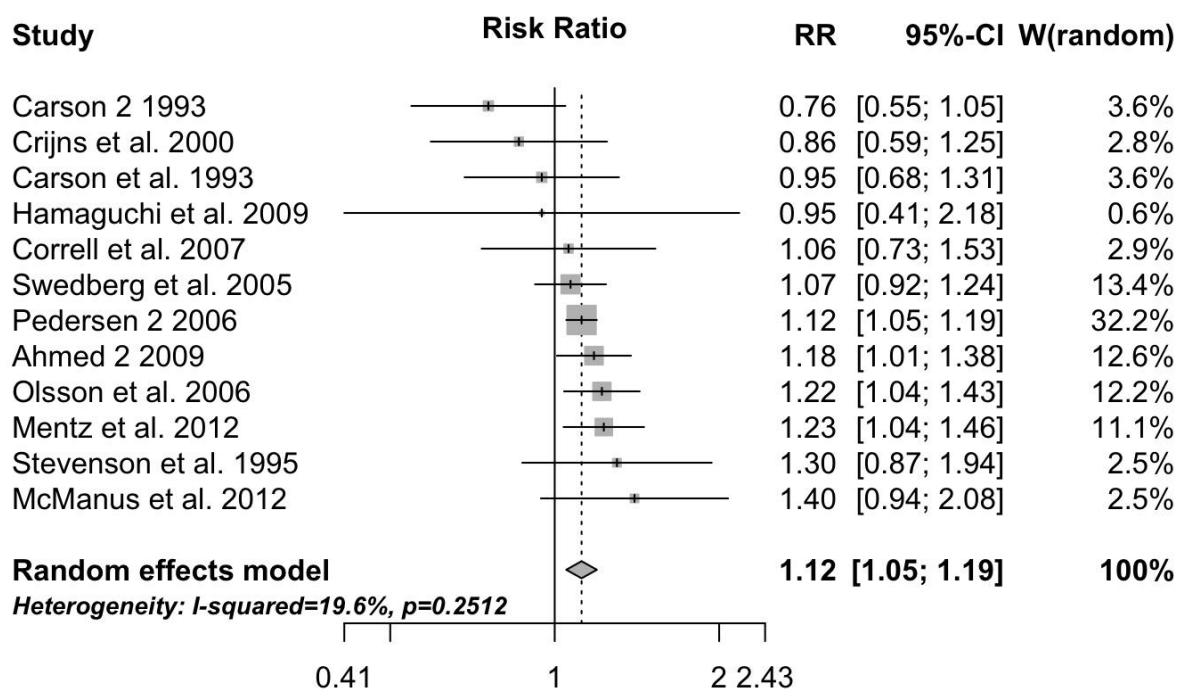
Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Figure 4: Association Between Atrial Fibrillation and All-Cause Mortality in Adults with Congestive Heart Failure and Preserved Ejection Fraction – AF was associated with an increased risk of all-cause mortality in adults with CHF with preserved ejection fraction. There was no heterogeneity.



Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Figure 5: Association Between Atrial Fibrillation and All-Cause Mortality in Adults with Congestive Heart Failure and Reduced Ejection Fraction - AF was associated with an increased risk of all-cause mortality in adults with CHF with reduced ejection fraction. There was no heterogeneity.



Area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals. W(Random) is the weight of each study.

Table 1: Subgroup Analysis to Explore Heterogeneity

Study Group	Variable	Stratification	Number of Studies	Relative Risk	95% CI	I² (%)
All-cause Mortality (Overall)	Risk of Bias	Low Risk	21	1.17	1.12-1.22	10
		Not at Low Risk	11	1.23	1.03-1.46	81
	Date of Cohort	1983-1999	12	1.15	1.06-1.24	51
		2000-2008	9	1.12	1.05-1.19	13
	Age	No date	11	1.44	1.24-1.67	60
		51-71	15	1.12	1.01-1.25	56
		72-80	15	1.18	1.12-1.23	19
		No Age	2	1.80	1.42-2.30	34