Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis

Ayodele Odutayo,1 Christopher X Wong,2 Allan J Hsiao,3 Sally Hopewell,1 Douglas G Altman,1 Connor A Emdin4

ABSTRACT

OBJECTIVE
To quantify the association between atrial fibrillation and cardiovascular disease, renal disease, and death.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
Medline and Embase.

ELIGIBILITY CRITERIA
Cohort studies examining the association between atrial fibrillation and cardiovascular disease, renal disease, and death. Two reviewers independently extracted study characteristics and the relative risk of outcomes associated with atrial fibrillation: specifically, all cause mortality, cardiovascular mortality, major cardiovascular events, any stroke, ischaemic stroke, haemorrhagic stroke, ischaemic heart disease, sudden cardiac death, congestive heart failure, chronic kidney disease, and peripheral arterial disease. Estimates were pooled with inverse variance weighted random effects meta-analysis.

RESULTS
104 eligible cohort studies involving 9 686 513 participants (587 867 with atrial fibrillation) were identified. Atrial fibrillation was associated with an increased risk of all cause mortality (relative risk 1.46, 95% confidence interval 1.39 to 1.54), cardiovascular mortality (2.03, 1.79 to 2.30), major cardiovascular events (1.96, 1.53 to 2.51), stroke (2.42, 2.17 to 2.71), ischaemic stroke (2.33, 1.84 to 2.94), ischaemic heart disease (1.61, 1.38 to 1.87), sudden cardiac death (1.88, 1.36 to 2.60), heart failure (4.99, 3.96 to 5.96), chronic kidney disease (1.31, 1.19 to 1.45) but not haemorrhagic stroke (2.00, 0.67 to 5.96). Among the outcomes examined, the highest absolute risk increase was for heart failure. Associations between atrial fibrillation and included outcomes were broadly consistent across subgroups and in sensitivity analyses.

CONCLUSIONS
Atrial fibrillation is associated with an increased risk of death and an increased risk of cardiovascular and renal disease. Interventions aimed at reducing outcomes beyond stroke are warranted in patients with atrial fibrillation.

Introduction
Atrial fibrillation is a leading cause of morbidity and mortality, with an estimated five million incident cases globally.1 It is increasing in prevalence in both developing and developed countries and is associated with an increased risk of all cause mortality and stroke, as well as higher medical costs and a reduced quality of life.2

Although the prevention and management of stroke in atrial fibrillation has been the primary focus of guidelines3 and clinical trials,4 recent studies have suggested that it can also be associated with a range of different cardiovascular diseases, including ischaemic heart disease and chronic kidney disease.7-10 Individual studies, however, have provided conflicting estimates of the strength of the association between atrial fibrillation and a range of cardiovascular diseases and have not agreed on whether there are relevant associations at all, possibly because of the small sample sizes examined.11-14 Pooling all available evidence could allow for the determination of robust estimates of any associations that could inform outcome selection in future randomised controlled trials and guide public health efforts to reduce the incidence of associated cardiovascular disease.

We conducted a systematic review and meta-analysis of the association between atrial fibrillation and cardiovascular disease and death to determine the relative and absolute risks of death and a range of associated cardiovascular outcomes. We also examined whether associations differed by important patient characteristics, including age, the presence of cardiovascular disease, and baseline risk.

Methods
This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines15 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.16

Data sources and searches
We conducted a systematic search of Medline and Embase (inception to June 2016). A qualified research
librarian developed the search strategy (see table A in appendix). This was supplemented by a review of references of included studies and review articles.

**Study selection criteria**
We included cohort studies of adults with and without atrial fibrillation that reported a measure of relative risk for death or cardiovascular disease (described below) and a corresponding measure of variability. To avoid overestimating the association between atrial fibrillation and our outcomes of interest, we required studies to include a minimum of 50 participants with atrial fibrillation and 50 participants without. Studies were also required to have at least six months’ mean/median follow-up because we sought to assess the mid to long term risks associated with atrial fibrillation. No language restrictions were applied, and non-English studies were translated by AJH, who has extensive experience in translating epidemiological studies.

**Data extraction and quality assessment**
Two reviewers (AO and CAE) independently reviewed titles and abstracts to assess studies for their inclusion. Three reviewers (AO, CXW, CAE) independently abstracted data using standardised forms. When available, we abstracted information on general study characteristics (study name or investigator’s name, recruitment period, median duration of follow-up, year of publication of the primary findings), number of participants with and without atrial fibrillation, mean age, number of men, and relative risk of outcomes.

We abstracted relative risk estimates and associated 95% confidence intervals for the association between atrial fibrillation and all-cause mortality, cardiovascular mortality, major cardiovascular events (a composite of cardiovascular death, fatal and non-fatal stroke, ischaemic heart disease, and congestive heart failure), and disease specific events: fatal and non-fatal stroke (all stroke or a stroke subtype if all stroke was not provided), fatal and non-fatal haemorrhagic stroke, fatal and non-fatal ischaemic stroke, ischaemic heart disease events (a composite of ischaemic heart disease death and non-fatal myocardial infarction), incident development of congestive heart failure, chronic kidney disease, and peripheral arterial disease. Maximally adjusted relative risk estimates were abstracted, along with the list of covariates included in the published multivariable regression model. Studies that did not report the variables that were adjusted for were excluded. One study that reported the development of end stage renal disease was included in the meta-analysis of chronic kidney disease.

Studies were categorised as unadjusted, adequately adjusted, or well adjusted. Unadjusted studies did not adjust for any confounders and were excluded. Adequately adjusted studies adjusted for, at a minimum, sex, age, and the presence of baseline cardiovascular disease. Well adjusted studies also adjusted for at least two established cardiovascular risk factors—blood pressure, cholesterol, smoking status, and diabetes. We chose these risk factors because they are important contributors to each of the outcomes examined in our study. Studies that did not report the covariates included in their regression model were also excluded because we could not determine whether they properly adjusted for important cofounders and thus whether they fulfilled the prespecified inclusion criteria of this meta-analysis. In our sensitivity analysis we stratified studies based on the level of adjustment.

We assessed risk of bias using the Newcastle-Ottawa scale, which assesses studies on three broad domains: the selection of participants for study groups; the comparability of study groups; and the ascertainment of the outcome. A star rating system is used and the maximum numbers of stars achievable are: selection (four stars), comparability (two), and outcome (cohort studies only; three stars). We applied strict criteria to assess comparability (of individuals with or without atrial fibrillation) based on which variables were included in the multivariable models. To receive one star for comparability, studies were required to meet the aforementioned criteria for adequate adjustment. To receive two stars, studies were required to meet the criteria for being well adjusted. Finally, studies were considered at low risk of bias if they achieved a full rating in at least two categories of selection, comparability, or outcome assessment.

**Statistical analysis**
For all analyses, we calculated overall summary estimates using inverse variance weighted random effects meta-analysis. For studies that reported separate relative risk estimates for subgroups (for example, different age groups, men versus women), we first used inverse variance weighted fixed effects meta-analysis to generate overall study level relative risks before random effects meta-analysis. Individual relative risk estimates and summary estimates were displayed graphically with forest plots. Heterogeneity was quantified with the I² statistic and the Q test.

We calculated the absolute risk increase for each vascular outcome associated with atrial fibrillation by multiplying summary relative risks by the incidence rate of each outcome of interest. Specifically, ARI = (RR−1)×(ACR) where ARI is the absolute risk increase, RR is the relative risk, and ACR is the assumed control risk. As the US contributed the largest share of studies in our analysis, we used American Heart Association estimates of the incidence of cardiovascular mortality, ischaemic heart disease, heart failure, sudden cardiac death, and stroke. We used Centers for Disease Control and Prevention estimates of the incidence of all cause mortality and chronic kidney disease. Absolute risk increases were expressed in events per 1000 participant years of follow-up. As we could not obtain an estimate for the incidence of major cardiovascular events in the US general population, we have not provided an absolute risk increase associated with atrial fibrillation for major cardiovascular events.

**Stratified analyses and sensitivity analyses**
To include a sufficient number of studies in each stratum, we restricted stratified and sensitivity analyses to...
outcomes with nine or more studies (all cause mortality, cardiovascular mortality, major cardiovascular events, ischaemic heart disease, stroke, and ischaemic stroke). We conducted four stratified analyses to examine whether relative risks of outcomes were influenced by patients’ characteristics. We divided studies into thirds by the proportion of participants with a history of ischaemic heart disease at baseline, the proportion of participants with a history of stroke at baseline, mean age, and absolute risk of death and cardiovascular disease (in events per 1000 patient years of follow-up). We tested for trend in these stratified analyses using random effects meta-regression. We did not examine whether relative risks were influenced by type of atrial fibrillation (chronic versus paroxysmal) as there were fewer than nine studies that reported on type for any given outcome of interest (table B in appendix).

We conducted six sensitivity analyses to examine whether heterogeneity between studies was caused by differences in study characteristics. We stratified studies by type of population (general population—for example, a community based cohort study—versus specific population—for example, a cohort study of individuals with a history of stroke), year of publication, duration of follow-up, region of study conduct (Asia, Europe, US, international, other), method of ascertainment of atrial fibrillation (electrocardiography only, electrocardiography and medical records, and medical records only), and level of adjustment for confounders (adequately adjusted v well adjusted).

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed.21 We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until I² was less than 50%. We then examined whether relative risk estimates were consistent. In accordance with Cochrane, evidence of publication bias was examined through funnel plots if there were more than 10 available studies.22 If asymmetry was present, we used the trim-and-fill method to adjust for publication bias.23

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results
We reviewed 4100 studies and excluded 3836 in the abstract screen. After we reviewed 264 full text articles, we excluded a further 160 (fig 1). We therefore included 104 studies involving 9686313 patients in our meta-analysis. Of these individuals, 587867 (6.1%) had atrial fibrillation. Five studies did not specify the method of ascertainment. Although outcome definitions were broadly consistent, the criteria applied in large prospective studies and secondary analyses of randomised trials were often more detailed than the criteria applied in studies that were strictly reliant on administrative datasets. Based on the Newcastle Ottawa scale, 67 studies were judged to be at low risk of bias, and 69 provided estimates from well adjusted regression models. Detailed general characteristics of the included studies as well as the adjustments applied in regression models, outcome definitions, and risk of bias assessment are provided in tables B-E in the appendix.

All cause mortality
Sixty four studies involving 1009501 patients examined all cause mortality as an outcome. There were 149746 (14.8%) adults with atrial fibrillation, and the prevalence ranged from 0.2% to 56.3%. The median follow-up was 3.1 years (interquartile range 1.5-9). The pooled relative risk was 1.46 (95% confidence interval 1.39 to 1.53; figs 2 and 3). Marked heterogeneity was observed (I²=93%, P<0.001). The corresponding absolute risk increase in all cause mortality associated with atrial fibrillation, based on the US population, was 3.8 events/1000 participant years (3.2 to 4.4). In subgroup analyses, studies were separated into thirds based on the proportion of adults with a history of ischaemic heart disease, the proportion with a history of stroke, mean participant age, and baseline absolute risk of all cause mortality. Relative risks of all cause mortality were consistent across all subgroups (P≥0.2 for trend, fig 4).

---

**Fig 1** | Identification of studies included in review of atrial fibrillation (AF) and risks of cardiovascular disease, renal disease, and death
Ischaemic heart disease and sudden cardiac death

Sixteen studies2 8 13 34 42 68 54 61 68 68 78 82 85 88 101 involving 395,957 patients examined ischaemic heart disease as an outcome (figs 2 and 6). There were 30,977 (7.8%) adults with atrial fibrillation, and the prevalence ranged from 0.2% to 56.3%. The median follow-up was 4.1 years (interquartile range 3.2-8.3). The pooled relative risk was 1.61 (95% confidence interval 1.38 to 1.87).

There was considerable heterogeneity (I²=86%, P<0.001). The absolute risk increase for ischaemic heart disease was 1.4 events/1000 participant years (0.9 to 2). The pooled relative risk for ischaemic heart disease was consistent across subgroups of baseline cardiovascular disease, age, and baseline risk (fig I in appendix).

Seven studies13 45 54 85 114-116 involving 48,694 patients examined sudden cardiac death as an outcome. There were 6061 (12.0%) adults with atrial fibrillation, and the prevalence ranged from 0.6% to 28.9%. The median follow-up was 3.0 years (interquartile range 2.8-4.4). The pooled relative risk of sudden cardiac death was 1.88 (95% confidence interval 1.36 to 2.60; fig J in appendix).

Though there was considerable heterogeneity (I²=78%, P<0.001), we did not perform sensitivity analyses because of the small number of studies. The absolute risk increase in sudden cardiac death was 0.6 events/1000 participant years (0.2 to 1.1).

Congestive heart failure

Six studies2 42 71 101 117 118 involving 82,476 patients examined incident congestive heart failure as an outcome. There were 11,677 (14.2%) adults with atrial fibrillation, and the prevalence ranged from 0.6% to 43.2%. The median follow-up was 5.4 years (interquartile range 3.6-15.4). The pooled relative risk of incident congestive heart failure was 4.99 (95% confidence interval 3.04 to 8.22; fig 2 and fig K in appendix).

Though there was considerable heterogeneity (I²=93%, P<0.001), we did not perform sensitivity analyses because of the small number of studies. The absolute risk increase in incident congestive heart failure associated with atrial fibrillation was 11.1 (5.7 to 20) events/1000 participant years.
Chronic kidney disease and peripheral arterial disease

Three studies involving 467,000 patients examined chronic kidney disease as an outcome. There were 20,312 (4.3%) adults with atrial fibrillation, and the prevalence ranged from 0.7% to 8.6%. The median follow-up was 5.9 years (interquartile range 5.1-6.7). The pooled relative risk of chronic kidney disease was 1.64 (95% confidence interval 1.41 to 1.91; fig I in appendix). Heterogeneity was non-significant ($I^2=50\%$, $P=0.14$). The absolute risk increase in chronic kidney disease associated with atrial fibrillation was 6.6 (4.3 to 9.4) events/1000 participant years.

Only one study\textsuperscript{21} examined the association between atrial fibrillation and peripheral arterial disease. The relative risk was 1.31 (95% confidence interval 1.19 to 1.45) was reported.

Sensitivity analyses

In sensitivity analyses of study characteristics, stratified by type of population, method of ascertaining atrial fibrillation, level of adjustment, year of publication, median follow-up, proportion receiving anticoagulation, and location, the relative risks of outcomes were broadly consistent across strata. The relative risk of all cause mortality was lower in studies with a higher proportion of participants receiving anticoagulation (table F in appendix). No interaction was otherwise observed for all cause mortality and for cardiovascular mortality for any subgroups ($P>0.05$ for interaction/trend; tables F and G in appendix). High levels of heterogeneity ($P>75\%$) continued to be observed in most sensitivity analyses. There was a stronger relative risk of major cardiovascular events associated with atrial fibrillation in studies conducted in a general population than a specific population (relative risk 2.71 [95% confidence interval 1.82 to 4.04] vs 1.39 [1.38 to 1.63], respectively; $P=0.002$ for interaction; table H in appendix). Although a significant test result for interaction for major cardiovascular events by location was also observed, this was because of a single study that was conducted in the US. We found no other significant interactions for major cardiovascular events ($P>0.05$ for interaction/trend, table H in appendix) and no interactions for stroke for any subgroups, including those based on the proportion of adults with atrial fibrillation receiving anticoagulation (table I in appendix). Relative risks of ischaemic stroke and ischaemic heart disease were stronger in studies conducted in general populations than in studies conducted in specific populations ($P<0.05$ for interaction, tables J and K in appendix). Relative risks of ischaemic stroke and ischaemic heart disease were also larger in studies with a longer follow-up ($P=0.04$ and 0.01, respectively, for trend, tables J and K in appendix).

When we sequentially excluded studies contributing the largest amount to heterogeneity until $F$ was less than 50%, pooled relative risks for outcomes were similar to the original estimates (table L in appendix). Atrial fibrillation was associated with a significant increase in the risk of chronic kidney disease and peripheral arterial disease.
Our study adds to the growing literature on the association between atrial fibrillation and cardiovascular outcomes beyond stroke. In a retrospective cohort study of Medicare beneficiaries, investigators showed that heart failure was the most common non-fatal cardiovascular event among adults with atrial fibrillation. Furthermore, in an analysis of the RE-LY trial, which was a trial in patients with atrial fibrillation, cardiac deaths—sudden cardiac death and progressive heart failure—accounted for 37% of all deaths, whereas deaths related to stroke and haemorrhage accounted for 9.8% of all deaths. In our study, the relative and absolute risk of incident congestive heart failure was the highest among all outcomes studied.

Furthermore, we observed that atrial fibrillation was associated with an increased risk of ischaemic heart disease, chronic kidney disease, and sudden cardiac death, even though some individual studies reported non-significant associations. Notably, although the relative associations between atrial fibrillation and these outcomes were comparable, the absolute risk increases for ischaemic heart disease (1.4 events per 1000 participant years) and chronic kidney disease (6.6 events) were several times larger than for sudden cardiac death (0.6 events) because of the lower baseline incidence of sudden cardiac death in the general population.

Our assessment of the consistency of relative risk estimates across demographic and clinical subgroups of participants is an important expansion on previous studies, many of which have limited their analysis to a single patient subgroup, such as those with ischaemic heart disease and congestive heart failure. We observed that the association between atrial fibrillation and cardiovascular disease and death was generally consistent, irrespective of baseline history of ischaemic heart disease, baseline history of stroke, mean participant age, and baseline risk. There were, however, two notable exceptions. Firstly, relative risk estimates for general population studies were typically larger than estimates based on studies in specific settings. This could be related to the selection of the controls and the proportion of patients with atrial fibrillation receiving effective evidence based treatments. Secondly, the relative risk of all cause mortality was lower in studies with a higher proportion of participants receiving anticoagulation, but we did not observe a similar pattern for stroke. The absence of any association between the relative risk of stroke and the use of anticoagulation should be interpreted with caution because of the small number of studies included in this analysis. Furthermore, if warfarin is used, it is difficult to determine the effectiveness of anticoagulation without measurements of INR (international normalised ratio). Differences in the proportion of adults with a low INR would affect our stratified analyses for stroke.

While relative associations between atrial fibrillation and cardiovascular disease and death were generally similar across participant characteristics, absolute increases in risk associated with atrial fibrillation would be expected to be larger among individuals with a higher baseline risk of cardiovascular disease. These results therefore suggest that atrial fibrillation is associated with greater absolute increases in risk of

| Outcome | Studies | Relative risk (95% CI) of all cause mortality | Relative risk (95% CI) of all cause mortality | I² (%) | P trend |
|---------|---------|-----------------------------------------------|-----------------------------------------------|--------|---------|
| Age (years) | | | | | |
| 41-64 | 18 | 1.51 (1.38 to 1.66) | 87 | 77 |
| 65-71 | 20 | 1.43 (1.29 to 1.59) | 84 | 76 |
| >71-86 | 24 | 1.42 (1.34 to 1.50) | 88 | 75 |
| Coronary heart disease | | | | | |
| 0-0.225 | 16 | 1.56 (1.42 to 1.71) | 75 | 65 |
| >0.225-0.722 | 19 | 1.37 (1.25 to 1.50) | 75 | 65 |
| >0.722-1 | 21 | 1.47 (1.33 to 1.63) | 75 | 65 |
| Risk (events/1000 patient years) | | | | | |
| 3-60.9 | 18 | 1.61 (1.46 to 1.78) | 75 | 65 |
| >60.9-105 | 17 | 1.37 (1.22 to 1.54) | 75 | 65 |
| >105-469 | 17 | 1.41 (1.34 to 1.48) | 75 | 65 |
| Stroke | | | | | |
| 0-0.0387 | 8 | 1.67 (1.47 to 1.89) | 75 | 65 |
| >0.0387-0.116 | 16 | 1.48 (1.30 to 1.69) | 75 | 65 |
| >0.116-1 | 12 | 1.38 (1.29 to 1.49) | 75 | 65 |

Fig 4 | Association between atrial fibrillation and mortality, stratified by patient demographics and baseline clinical characteristics. Studies were divided into thirds based on mean age of participants, proportion of participants with history of ischaemic heart disease at baseline, absolute risk of death and cardiovascular disease (in events per 1000 patient years of follow-up), and proportion of participants with history of stroke at baseline. For absolute risk, thirds were 3-60.9 events/1000 patient years, >60.9-105 events/1000 patient years, and >105-469 events/1000 patient years.
cardiovascular disease among individuals at high baseline risk and highlights the importance of risk stratification of participants with atrial fibrillation.

**Strengths and limitations**

The key strength of our study is its sample size. We were able to identify 104 cohort studies, many more than previous analyses of atrial fibrillation restricted to subpopulations. There were, however, some important limitations to consider. Firstly, despite our extensive search strategy, we could have missed relevant studies for inclusion. The large number of studies in our analysis, however, made our results robust to the inclusion of any single study. It also provided us with the power to investigate whether the associations between atrial fibrillation and cardiovascular disease and death differed by important patient and study characteristics as well as to conduct detailed sensitivity analyses.

Secondly, we observed high levels of heterogeneity (I²>70%) for all vascular outcomes except for chronic kidney disease. This was not unexpected and might be caused by differences in study designs, methodological characteristics, type of atrial fibrillation, use of secondary prevention (such as anticoagulation) among included studies, and the definition and ascertainment of endpoints. For instance, the criteria in well established prospective cohorts were comprehensively detailed, whereas the criteria and specific diagnostic codes used in analyses of administrative data were not consistently provided. Differences in the diagnostic codes used in administrative data could have contributed to the high heterogeneity in our study. Nonetheless, when we systematically and sequentially excluded individual studies until heterogeneity was moderate (I²<50%), relative risk estimates for vascular outcomes were consistent and significant, suggesting that the high levels of heterogeneity were not inflating summary relative risk estimates. Thirdly, studies were classified as well adjusted if they adjusted for age, sex, baseline cardiovascular disease, and at least two cardiovascular risk factors. Even though more stringent criteria could be used, such as requiring studies to adjust for drugs and outcome specific risk factors (for example, adjustment for race for the outcome of chronic kidney disease), there will nonetheless be residual confounding in the estimates derived from observational studies. Accordingly, it is likely that there are other variables that contribute to the association between atrial fibrillation and our outcomes of interest, in addition to any possible causal disease specific effects. Fourthly, because of our strict selection criteria, we identified fewer than nine studies for some outcomes and were unable to conduct sensitivity analyses. This is particularly important for congestive heart failure because the relative and absolute risk estimates for incident congestive heart failure were the highest among the outcomes we examined. It is therefore noteworthy that four of the six studies included in our meta-analysis for incident congestive heart failure were conducted in general population cohorts and accounted for 75% of the weight for the summary relative risk. Fifthly, studies that reported significant associations between atrial fibrillation and cardiovascular disease and death might be more likely to be published. We did not, however, observe evidence of publication bias for any outcome other than stroke. Finally, we lacked individual patient data, which would have allowed us to systematically adjust for patient characteristics. We did not, however, observe any interaction when we compared studies based on our risk of bias assessment.

**Implications for clinicians, policy makers, and future research**

The mechanism by which atrial fibrillation is associated with an increased risk of a range of different cardiovascular diseases is unclear. In the case of myocardial infarction, atrial fibrillation could contribute to demand infarction and the subsequent development of type 2 myocardial infarction. It is also possible that the
association between atrial fibrillation and non-stroke cardiovascular disease is not causal. Considering our observation that atrial fibrillation is also associated with an increased risk of heart failure, sudden cardiac death, and chronic kidney disease (in addition to ischaemic heart disease), it seems likely that atrial fibrillation could be acting as a marker for shared underlying risk factors for cardiovascular disease. These include hypertension, which is diagnosed in up to 90% of patients with atrial fibrillation, as well as obesity, diabetes, and obstructive sleep apnoea.125–126

Even though the associations we describe cannot indicate causality for the non-stroke outcomes, there is merit in developing clinical risk prediction models for outcomes such as congestive heart failure; particularly given our relative and absolute risk estimates. To date, three models have been developed with C statistics ranging from 0.7 to 0.84, but none has been externally validated.127–129 Future models might also benefit from inclusion of non-invasive measures of cardiac function and assessments of novel biomarkers.

Finally, our study could have implications for the prioritisation of public health resources and the development of novel interventions for adults with atrial fibrillation. In particular, the development and testing of novel oral anticoagulants has been the principal focus of clinical care in atrial fibrillation, but recent studies have shown that these drugs reduce mortality related to stroke, with little reduction in mortality related to congestive heart failure and sudden cardiac death.130 Similarly, pharmacological control of atrial fibrillation and the restoration of sinus rhythm has shown no benefit over rate control for sudden cardiac death,130 worsening heart failure,131 or mortality.132

It could be that rhythm control treatments might not have been effective at treating atrial fibrillation or that the treatments resulted in additional side effects that outweighed the benefits of restoring sinus rhythm. Alternatively, if atrial fibrillation is not the cause of these non-stroke outcomes, this could explain the absence of treatment benefit even when it is controlled.

Accordingly, reduction of the burden of non-stroke events in adults with atrial fibrillation would benefit from a focus on primary prevention and management of cardiovascular risk factors. Evidence based strategies in this regard include discussion of the concept of predicted cardiovascular risk with patients and calculation of their cardiovascular age.132 Regular updates should also be provided to patients after lifestyle changes and/or pharmacotherapy have begun as a way to encourage further progress.132

In conclusion, atrial fibrillation is associated with cardiovascular and renal events, including cardiovascular mortality, major cardiovascular events, heart failure, ischaemic heart disease, chronic kidney disease, and sudden cardiac death, as well as stroke and all cause mortality. The relative and absolute risk increase associated with many of these events is greater than that of stroke. Interventions are needed to reduce the risk of non-stroke outcomes in adults with atrial fibrillation.

Contributors: AO and CAE conceived and designed the study, carried out the statistical analysis, had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and are guarantors. All authors acquired data, analysed and interpreted data, drafted the manuscript, and critically revised the manuscript for important intellectual content.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. AO, CW, AH, and CAE are supported by the Rhodes Trust.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Data and code are available from the lead author on request.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important intellectual content has been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/.

1. Chugh SS, Havmøller R, Narayan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837-47. doi:10.1161/CIRCULATIONAHA.113.005119.
2. Conen D, Choe CI, Ghiyi RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 2011;305:2080-7. doi:10.1001/jama.2011.659.
3. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med 2006;119:448-61. doi:10.1016/j.amjmed.2005.10.057.
4. January CT, Wann LS, Alpert JS, et al. ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:2071-104. doi:10.1161/CIR.0000000000000400.
5. Ruff CT, Guglielmo RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62. doi:10.1016/S0140-6736(13)62343-0.
Cardiovasc Thorac Surg. 2015;8:1346-55. doi:10.1016/j.jcin.2015.06.010.

Baseline Characteristics and Prognostic Implications of Pre-Existing Benj 2014;3:e001303. doi:10.1161/JAHA.114.001303.

Bognt LGS, Chey LY, Chamberlain AM, et al. Temporal trends in the occurrence and outcomes of atrial fibrillation in patients with acute myocardial infarction (from the Atherosclerosis Risk in Communities Surveillance Study). Am J Cardiol 2014;114:692-7. doi:10.1016/j.amjcard.2014.05.059.

Bux CN, Greve AM, Boman K, et al. Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis (the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Am Heart J 2012;163:690-6. doi:10.1016/j.ahj.2012.01.026.

Ahmed A, Thornton P, Perry GJ, Almain RM, DeLong JF. Impact of atrial fibrillation on mortality and readmission in older adults hospitalized with heart failure. Eur J Heart Fail 2004;6:421-6. doi:10.1016/j.ejhf.2003.11.011.

Guize L, Thomas F, Bean K, Benetos A, Pannier B. [Atrial fibrillation: prevalence, risk factors and mortality in a large French population with 15 years of follow-up]. Bull Acad Natl Med 2009;193:791-803, discussion 803-5.

Saxena A, Dinh D, Dimitriu J, et al. Preoperative atrial fibrillation is an independent risk factor for mid-term mortality after concomitant aortic valve replacement and coronary artery bypass graft surgery. J Thorac Cardiovasc Surg 2013;146:488-94. doi:10.1016/j.jtcvs.2013.05.038.

Sanlini M, Gasparini M, Landolina M, et al. Cardiological centers participating in ClinicalService Project. Device-detected atrial tachyarrhythmias predict adverse outcome in real-world patients with implantable biventricular defibrillators. Am J Cardiol 2011;107:167-72. doi:10.1016/j.amjcard.2010.08.624.

Wong CK, White HD, Wilcox RG, et al. New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO-III experience. Am Heart J 2000;140:878-85. doi:10.1016/S0002-9149(00)00030-1.

Kim K, Sato H, Sato H, et al. Osaka Acute Coronary Insufficiency Study (DACIS) Group. Prognostic significance of atrial fibrillation/atrial flutter in patients with acute myocardial infarction treated with percutaneous coronary intervention. Am J Cardiol 2003;92:1150-4. doi:10.1016/j.amjcard.2003.07.021.

Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. Circ Heart Fail 2011;4:746-7. doi:10.1161/CIRCHEARTFAILURE.111.962688.

Bansal N, Fan D, Hsu CY, Ordonez JD, Go AS. Incidental atrial fibrillation and risk of death in adults with chronic kidney disease. Am Heart J 2014;167:1003-10. doi:10.1016/j.amhe.2014.01.003.

Pilgrim T, Kalesan B, Zanchin T, et al. Impact of atrial fibrillation on clinical outcomes among patients with coronary artery disease undergoing revascularisation with drug-eluting stents. EuroIntervention 2013;8:1061-71. doi:10.4244/EIJV9A163.

Benjamin EJ, Wolf PA, D’Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52. doi:10.1161/01.CIR.98.9.946.

Chopard R, Teger E, Meneveau N, et al. FRANCE-2 Investigators. Baseline Characteristics and Prognostic Implications of Pre-Existing and New-Onset Atrial Fibrillation After Transcatheter Aortic Valve Implantation: Results from the FRANCE-2 Registry. JACC Cardiovasc Interv 2015;8:1346-55. doi:10.1016/j.jcin.2015.06.010.

Stewart S, Hart CL, Hole DJ, McMurray J. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359-64. doi:10.1016/s0002-9343(02)01236-3.

Liu X, Xu G, Wu W, Zhang B, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in Chinese patients. The Nanjing Stroke Registry. Cerebrovasc Dis 2006;22:130-6. doi:10.1159/000093241.

Pizziello F, Turazzi FM, Franzosi MG, et al. GISSI-3 Investigators. Incidence and prognostic significance of atrial fibrillation with acute myocardial infarction: the GISSI-3 data. Heart 2001;86:527-32. doi:10.1136/heart.86.5.527.

Bognt B, Prioli S, Cletand IG, et al. Scientific Committee, National Coordinators, and Investigators. The European CPR Survey in Europe (1996-97): results from 15 countries. Resuscitation 1998;37:321-31. doi:10.1016/S0300-9572(98)00003-8.

Jabre P, Jouvenc X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: implementation of a new-onset atrial fibrillation with acute myocardial infarction: the GISSI-3 data. Heart 2001;86:527-32. doi:10.1136/heart.86.5.527.

w业 T, Ben Salem D, Oussay EF, et al. Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006. Neurology 2009;73:344-53. doi:10.1212/01.wnl.0000341280.31919.3d.

Ohnasa M, Okayama A, Otani T, et al. Mortality risk attributable to atrial fibrillation in middle-aged and elderly people in the Japanese general population: nineteen-year follow-up in NIPPON DATA61. Circ J 2009;73:91-9. doi:10.1253/circj.cj.73.91.

Bang CN, Gislason GH, Greve AM, et al. New-onset atrial fibrillation is associated with cardiovascular events leading to death in a first-time myocardial infarction population of 89,703 patients with long-term follow-up. Eur J Heart Fail 2012;14:619-24. doi:10.1002/ejhf.21.

Stein KM, Mittal S, Gilliam FR, et al. Predictors of early mortality in implantable defibrillator recipients. J Am Coll Cardiol 2004;43:221-6. doi:10.1016/j.amjcard.2003.12.032.

Friedberg I, Schafinger H, Gaddis NL, Truelent T, Jensen GB. Copenhagen City Heart Study. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). Am J Cardiol 2004;94:889-94. doi:10.1016/j.amjcard.2004.06.023.

Stortecky S, Buellesfeld L, Wnenaweser P, et al. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. Circ Cardiovasc Interv 2013;6:77-84. doi:10.1161/CIRCINTERVENTIONS.111.00124.

Torres M, Rocha S, Marques J, et al. Impact of atrial fibrillation in acute coronary syndromes. Rev Port Cardiol 2010;27:1407-18.

Sakata K, Kunihara H, Iwami K, et al. Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction. Am J Cardiol 1997;80:919-22. doi:10.1016/S0002-9149(97)00746-7.

Andersen T, Pedersen O, Rossen J, et al. Atrial fibrillation is a risk marker for one-year survival of patients following ischemic stroke. Eur J Heart Fail 2012;14:619-24. doi:10.1002/ejhf.21.

Liu X, Zhu S, Liu T, Luo L, Ye P. Different types of atrial fibrillation, renal function, and mortality in elderly Chinese patients with coronary artery disease. Circulation 2007;116:1995-2002. doi:10.1161/CIRCULATIONAHA.106.5838. doi:10.1016/j.amjcard.2003.07.021.

Aasland K, Hasun P, Actin K, Royston P, et al. Validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease. BMJ 2016;354:i6482. doi:10.1136/bmj.i4482 on 6 September 2016. Downloaded from http://www.bmj.com.

BMJ: first published as 10.1136/bmj.i4482 on 6 April 2016. Downloaded from http://www.bmj.com on 6 April 2024 by guest. Protected by copyright.
A 15.5-year follow-up study of stroke in a Japanese provincial city. The Nak study.

Recurrence and the risk factors. Nephrol Dial Transplant 2009;29:983-5.

Evaluation to Improve Compliance and Knowledge Among Stroke Patients: The EVALUATION 2009 Trial. Arch Intern Med 2009;169:2267-72. doi:10.1001/archinte.1987.00370090041008.

Rodrigues H, Greenaway, Davies T, Wood R, Steen N, Thomson R. Risk factors for first-ever stroke in older people in the north east of a population-based study. Stroke 2004;35:75-11.

Choi TF, Liu C, Chen SJ, et al. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHADS2-VASc score of 0 or 1? Stroke 2012;43:2551-5. doi:10.1161/STROKEAHA.111.627367.

Kamel H, Johnson DR, Hegde M, et al. Detection of atrial fibrillation after stroke and the risk of recurrent stroke. Stroke Cerebrovasc Dis 2012;21:726-31. doi:10.1016/j.jstrokecerebrovasdis.2011.03.008.

Nakayama T, Date C, Yokoyama T, Yoshikawa N, Yamaguchi M, Tanaka H. A 3.5 year follow-up study of stroke in a Japanese provincial city. The Shibata Study. Stroke 1997;28:45-52. doi:10.1161/01.STR.28.1.45.

Feng SJ, Liu M, Li W-Z, Li W, Zhang SH. [A prospective study of stroke recurrence and the risk factors]. Nan Fang Yi Ke Da Xue Xue Bao 2009;29:983-5.

Bael M, Masters RG, Rubens FD, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. Ann Thorac Surg 2004;78:26-7. doi:10.1016/j.athoracsur.2003.12.058.

Manjón E, de Heuzey JY, Connolly S, et al. RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013;128:2192-201. doi:10.1161/CIRCULATIONAHA.112.00491.

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 Heart Fail 2014;16:1317-22. doi:10.1002/ejhf.187.

Pinna LS, Polonara MM, Licina MM, Marinovic JM, Lip GW. Predictors and clinical outcomes of paroxysmal atrial fibrillation. Eur Heart J 2013;34:1027-30. doi:10.1093/eurheartj/eht044.

Sakai S, Sakagawa K, Otsuka T, et al. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. Am J Cardiol 2012;110:678-82. doi:10.1016/j.ajcard.2012.04.049.

Potpara TS, Polvovina MV, Licina MM, Marinovic JM, Lip GW. Predictors and clinical outcomes of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2013;6:843-9. doi:10.1161/CIRCEP.112.977777.

Sinnema P, van den Berg S, Straathof AJ, van der Meer R, Liem DW, Grootendorst AD, et al. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Neurology 2009;73:75-82. doi:10.1212/01.wnl.0000318913.92694.60.

O’Neill WT, Tanner RM, Efrid JF, et al. Atrial fibrillation and incident end-stage renal disease: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Int J Cardiol 2015;185:219-23. doi:10.1016/j.ijcard.2015.03.104.

Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2009;158:629-36. doi:10.1016/j.ahj.2009.06.031.

Chang CJ, Chen YT, Liu CS, et al. Atrial Fibrillation Increases the Risk of Peripheral Arterial Disease With Relative Complications and Mortality: A Population-Based Cohort Study. Medicine (Baltimore) 2016;95:e3002. doi:10.1097/MD.00000000000003002.

Piccini JP, Hammill BG, Sinner MF, et al. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. Eur Heart J 2014;35:250-6. doi:10.1093/eurheartj/ehu483.

Marioni E, Le Heuzey JY, Connolly S, et al. RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013;128:2192-201. doi:10.1161/CIRCULATIONAHA.112.00491.

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 Heart Fail 2014;16:1317-22. doi:10.1002/ejhf.187.

Manolis AJ, Roece EA, Coca A, et al. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group ‘Hypertension Arhythmias and Thrombosis’ of the European Society of Hypertension. J Hypertens 2012;30:239-52. doi:10.1097/HJH.0b013e32834f030f.

Leong BP, Eikelboom JW, Healey JS, Connolly SJ. Atrial fibrillation is associated with increased mortality: causation or association? Eur Heart J 2013;34:1027-30. doi:10.1093/eurheartj/eht044.

Suzuki S, Sagara K, Otsuka T, et al. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. Am J Cardiol 2012;110:678-82. doi:10.1016/j.ajcard.2012.04.049.

Kamel H, Johnson DR, Hegde M, et al. Detection of atrial fibrillation after stroke and the risk of recurrent stroke. J Stroke Cerebrovasc Dis 2012;21:726-31. doi:10.1016/j.jstrokecerebrovasdis.2011.03.008.

Nakayama T, Date C, Yokoyama T, Yoshikawa N, Yamaguchi M, Tanaka H. A 3.5 year follow-up study of stroke in a Japanese provincial city. The Shibata Study. Stroke 1997;28:45-52. doi:10.1161/01.STR.28.1.45.

Feng SJ, Liu M, Li W-Z, Li W, Zhang SH. [A prospective study of stroke recurrence and the risk factors]. Nan Fang Yi Ke Da Xue Xue Bao 2009;29:983-5.

Bael M, Masters RG, Rubens FD, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. Ann Thorac Surg 2004;78:77-83. doi:10.1016/j.athoracsur.2003.12.058.

Manjón E, Trinquart L, Ottman A, et al. Evaluation Médico-Económique du Défibrillateur Automatique Implantable (EVADE) Investigators. Competing risk analysis of cause-specific mortality in patients with an implantable cardioverter-defibrillator: The EVADEF cohort study. Am Heart J 2009;157:391-396. doi:10.1016/j.ahj.2008.09.023.

Genovesi S, Vallecchi MG, Rossì E, et al. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. Nephrol Dial Transplant 2009;24:2529-36. doi:10.1093/ndt/gfp104.