



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

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## 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, 3.04 to 8.22), chronic kidney disease (1.64, 1.41 to 1.91), and peripheral arterial 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.<sup>1</sup> 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.<sup>2,3</sup>

Although the prevention and management of stroke in atrial fibrillation has been the primary focus of guidelines<sup>4</sup> and clinical trials,<sup>5,6</sup> 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.<sup>7-10</sup> 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.<sup>11-14</sup> 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) guidelines<sup>15</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>16</sup>

### Data sources and searches

We conducted a systematic search of Medline and Embase (inception to June 2016). A qualified research

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Atrial fibrillation is associated with an increased risk of all cause mortality and stroke, as well as higher medical costs and a reduced quality of life

The association between atrial fibrillation and cardiovascular outcomes other than stroke is less clear

## WHAT THIS STUDY ADDS

Atrial fibrillation is associated with a wide range of cardiovascular 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 cardiovascular outcomes in adults with atrial fibrillation

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.<sup>10</sup>

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,<sup>17</sup> 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  $I^2$  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,  $ARI = (RR - 1) \times (ACR)$  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.<sup>18</sup> We used Centers for Disease Control and Prevention estimates of the incidence of all cause mortality<sup>19</sup> and chronic kidney disease.<sup>20</sup> 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.<sup>21</sup> We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until  $I^2$  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.<sup>22</sup> Funnel plot asymmetry was further confirmed with Egger's test.<sup>23</sup> If asymmetry was present, we used the trim-and-fill method to adjust for publication bias.<sup>24</sup>

### 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 9 686 513 patients in our meta-analysis. Of these individuals, 587 867 (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<sup>21 11 12 14 25-86</sup> involving 1 009 501 patients examined all cause mortality as an outcome. There were 149 746 (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 ( $I^2=93%$ ,  $P<0.001$ ). 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 ( $P\geq 0.2$  for trend, fig 4).

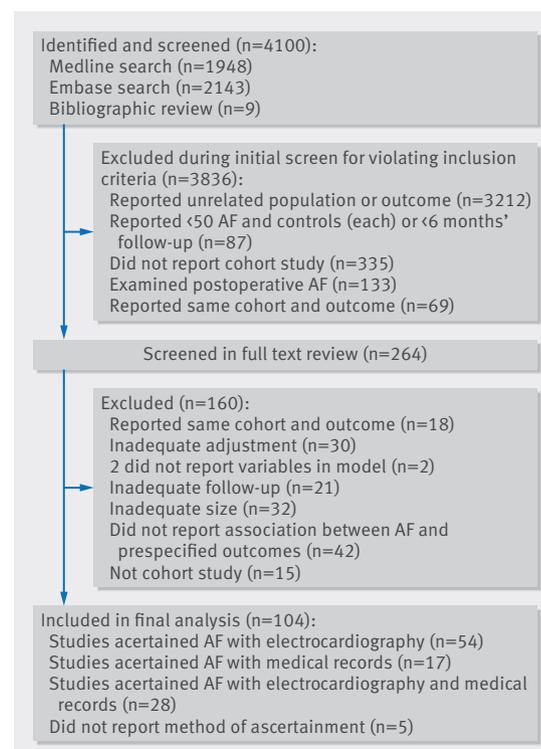


Fig 1 | Identification of studies included in review of atrial fibrillation (AF) and risks of cardiovascular disease, renal disease, and death

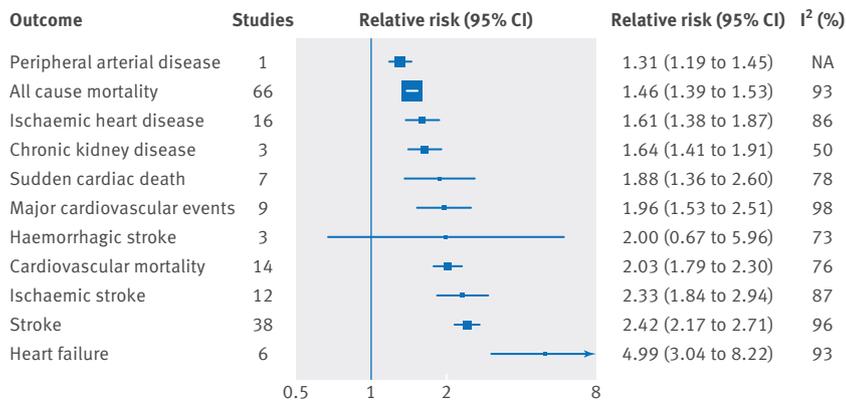


Fig 2 | Association between atrial fibrillation and all cause mortality and cardiovascular and renal disease, showing summary relative risks for each outcome examined. NA=not available

### Cardiovascular mortality and major cardiovascular events

Fourteen studies<sup>2 11 32 61 66 68 70 75 77 78 81 82 87 88</sup> involving 342 453 patients examined cardiovascular mortality as an outcome. There were 17 167 (5.0%) adults with atrial fibrillation, and the prevalence ranged from 0.2% to 56.3%. The median follow-up was 4.9 years (interquartile range 2.8-11.4). The pooled relative risk was 2.03 (95% confidence interval 1.79 to 2.30; fig 2 and fig A in appendix). The absolute risk increase in cardiovascular mortality associated with atrial fibrillation was 2.6 events/1000 participant years (2.0 to 3.3). Nine studies<sup>2 31 41 52 68 71 88-90</sup> involving 2 467 017 patients examined major cardiovascular events as an outcome. There were 21 707 (0.9%) adults with atrial fibrillation, and the prevalence ranged from 0.5% to 29.7%. The median follow-up was 4.4 years (4.0 to 10.1). Overall, atrial fibrillation was associated a 96% higher risk of major cardiovascular events (relative risk 1.96, 1.53 to 2.51; fig 2 and fig B in appendix).

Both analyses showed considerable heterogeneity (I<sup>2</sup>=76% and P<0.001 for cardiovascular mortality and I<sup>2</sup>=98% and P<0.001 for major cardiovascular events). In subgroup analyses, the relative risk of cardiovascular mortality was lower with increasing age (P=0.05, fig C in appendix), and the relative risk of major cardiovascular events declined when we stratified studies based on the absolute event rate in their control group (P=0.03, fig D in appendix). Pooled relative risks for both outcomes were consistent for other subgroups examined (figs C and D in appendix).

### Stroke

Thirty eight studies<sup>2 31 33 42 48 52 61 68 70 71 77 78 81 82 87 88 91-112</sup> involving 6 143 925 patients reported results for any stroke. There were 430 600 (7.0%) adults with atrial fibrillation, and the prevalence ranged from 0.2% to 50.7%. The median follow-up was 4.2 years (interquartile range 1.7-8.0). The pooled relative risk was 2.42 (95% confidence interval 2.17 to 2.71; figs 2 and 5). There was considerable heterogeneity (I<sup>2</sup>=96%, P<0.001). The association between atrial fibrillation and stroke was consistent, irrespective of baseline demographics and

clinical characteristics (fig E in appendix). The absolute risk increase of stroke associated with atrial fibrillation was 3.6 events/1000 participant years (3.0 to 4.3).

Twelve studies<sup>36 51 59 68 91 92 100 101 103 107 111 113</sup> specifically reported results for ischaemic stroke. The pooled relative risk estimate was 2.33 (95% confidence interval 1.84 to 2.94), and there was considerable heterogeneity (I<sup>2</sup>=87%, P<0.001; fig 2 and fig F in appendix). The relation between atrial fibrillation and ischaemic stroke was consistent, irrespective of baseline demographics and clinical characteristics (fig G in appendix). The absolute risk increase for ischaemic stroke was 2.9 events/1000 participant years (1.9 to 4.3). Three studies<sup>68 91 107</sup> reported results for haemorrhagic stroke. Atrial fibrillation was not associated with a higher risk of haemorrhagic stroke, although the confidence interval was wide (relative risk 2.00, 0.67 to 5.96; fig 2 and fig H in appendix).

### Ischaemic heart disease and sudden cardiac death

Sixteen studies<sup>2 8 13 14 42 48 52 54 61 66 68 78 82 85 88 101</sup> 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 (I<sup>2</sup>=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 studies<sup>13 45 54 85 114-116</sup> involving 48 694 patients examined sudden cardiac death as an outcome. There were 6061 (12.4%) 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 (I<sup>2</sup>=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 studies<sup>2 42 71 101 117 118</sup> 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 (I<sup>2</sup>=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.

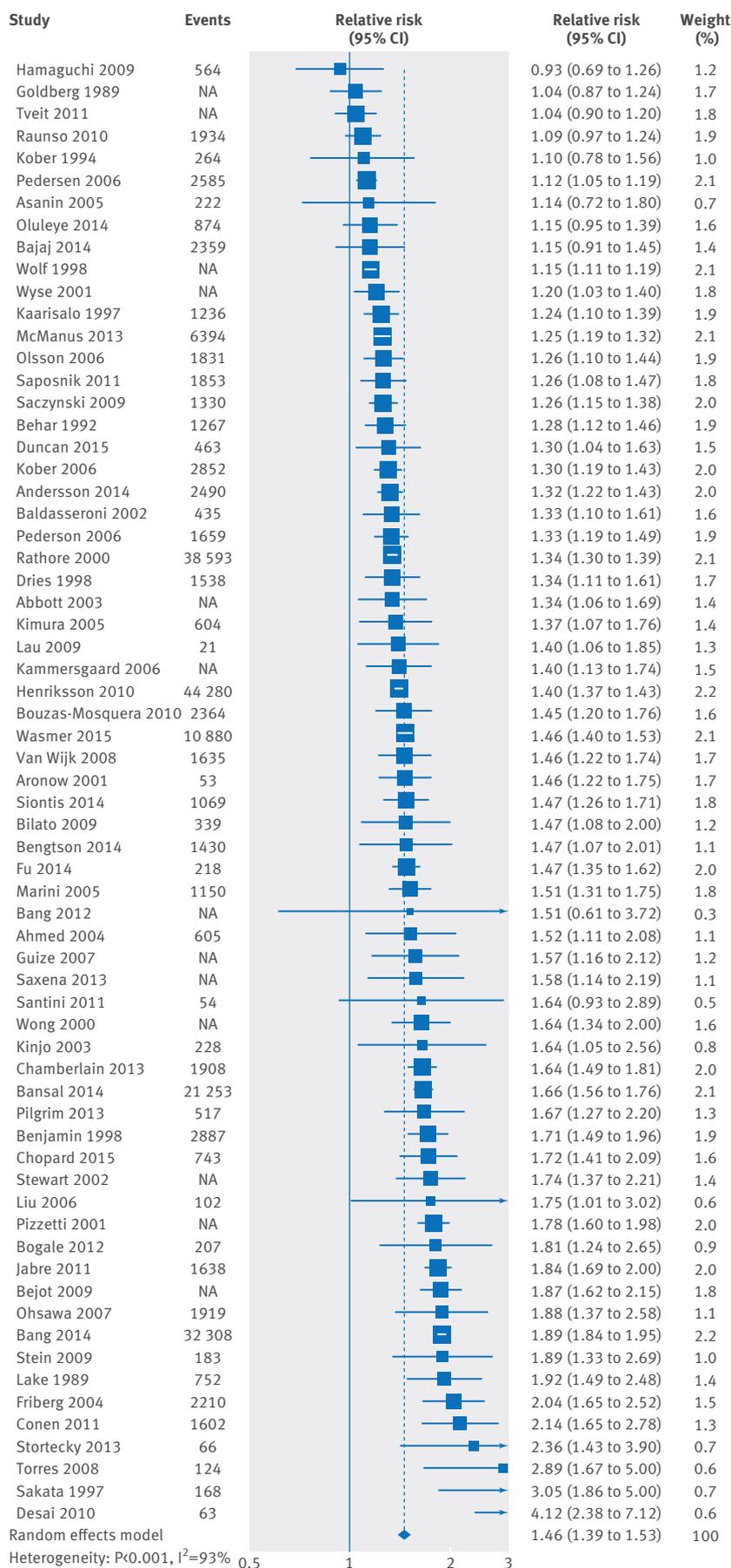


Fig 3 | Association between atrial fibrillation and all cause mortality. NA=not available

### Chronic kidney disease and peripheral arterial disease

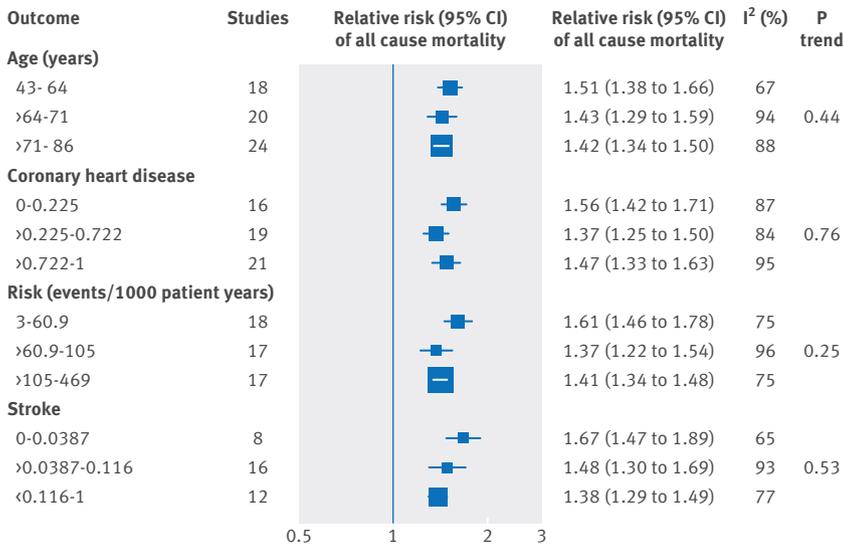
Three studies<sup>10 119 120</sup> involving 467 000 patients examined chronic kidney disease as an outcome. There were 20 312 (4.3%) adults with atrial fibrillation, and the prevalence ranged from 0.7% to 8.6%. The median follow-up was 5.9 years (interquartile range 5.1-6.7). The pooled relative risk of chronic kidney disease was 1.64 (95% confidence interval 1.41 to 1.91; fig L 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<sup>121</sup> 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 ascertainment of 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 ( $I^2 > 75\%$ ) 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) v 1.39 (1.18 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). The relative risk of ischaemic stroke did not vary based on proportion of adults with atrial fibrillation receiving anticoagulation.

When we sequentially excluded studies contributing the largest amount to heterogeneity until  $I^2$  was less than 50%, pooled relative risks for outcomes were similar to the original estimates (table L in appendix). Atrial



**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

fibrillation remained associated with an increased risk of all cause mortality (relative risk 1.41, 95% confidence interval 1.35 to 1.46), cardiovascular mortality (2.02, 1.82 to 2.24), major cardiovascular events (1.72, 1.63 to 1.83), ischaemic heart disease (1.46, 1.34 to 1.59), stroke (2.95, 2.49 to 3.48), and ischaemic stroke (2.64, 2.34 to 2.97).

Funnel plots showed no evidence of publication bias for any outcome (figs M-Q in appendix; Egger’s test  $P > 0.05$ ), except for stroke (fig P in appendix; Egger’s test  $P = 0.006$ ). Use of trim-and-fill method resulted in a relative risk of 1.69 (95% confidence interval 1.51 to 1.89) for stroke.

**Discussion**

In this comprehensive overview of the association between atrial fibrillation and the risk of cardiovascular disease, renal disease, and death, there was an increased risk of a range of different outcomes, including a 46% higher risk of all cause mortality, 61% higher risk of ischaemic heart disease, 64% higher risk of chronic kidney disease, 88% higher risk of sudden cardiac death, and 96% higher risk of a major cardiovascular event. Atrial fibrillation was also associated with a twofold risk of cardiovascular mortality, 2.3-fold risk of stroke, and fivefold risk of incident congestive heart failure. The absolute risk increase for heart failure was the highest among the outcomes examined. Finally, associations between atrial fibrillation and these outcomes were broadly consistent across subgroups and in sensitivity analyses.

**Comparison with previous individual studies**

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.<sup>122</sup> 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 37.4% of all deaths, whereas deaths related to stroke and haemorrhage accounted for 9.8% of all deaths.<sup>123</sup> 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.<sup>124</sup> 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

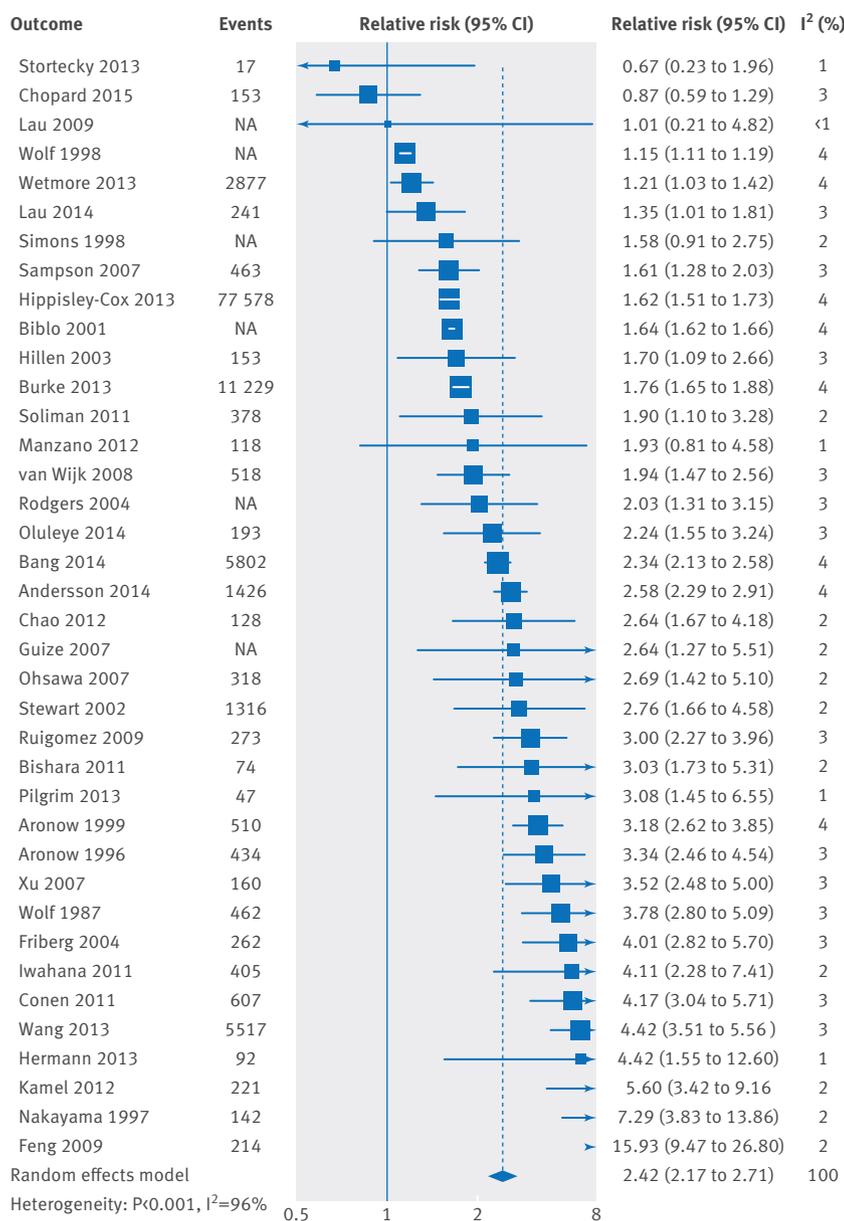


Fig 5 | Association between atrial fibrillation and stroke. NA=not available

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 ( $I^2 > 70\%$ ) 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<sup>8</sup> were comprehensively detailed, whereas the criteria and specific diagnostic codes used in analyses of administrative data were not consistently provided.<sup>51</sup> 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 ( $I^2 < 50\%$ ), 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<sup>2 42 71 101</sup> we 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.<sup>7</sup> It is also possible that the

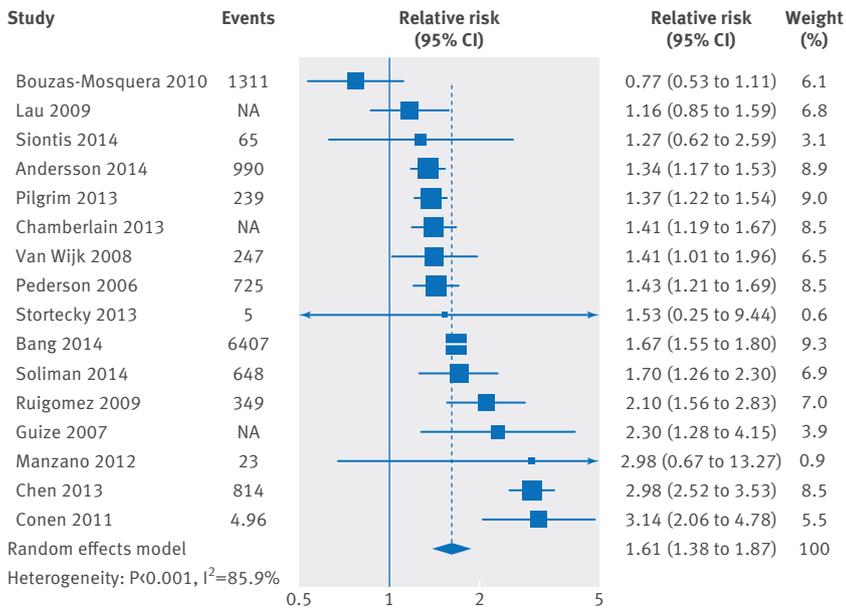


Fig 6 | Association between atrial fibrillation and ischaemic heart disease. NA=not available

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.<sup>125 126</sup>

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.<sup>127-129</sup> 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.<sup>123</sup> Similarly, pharmacological control of atrial fibrillation and the restoration of sinus rhythm has shown no benefit over rate control for sudden cardiac death,<sup>130</sup> worsening heart failure,<sup>131</sup> or mortality.<sup>130</sup> 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.<sup>132</sup> Regular updates should also be provided to patients after lifestyle changes and/or pharmacotherapy have begun as a way to encourage further progress.<sup>132</sup>

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.

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- 1 Chugh SS, Havmoeller R, Narayanan 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, Chae CU, Glynn 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.e1-19. 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.0000000000000040.
- 5 Ruff CT, Giugliano 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.

- 6 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67. doi:10.7326/0003-4819-146-12-200706190-00007.
- 7 Soliman EZ, Lopez F, O'Neal WT, et al. Atrial Fibrillation and Risk of ST-Segment-Elevation Versus Non-ST-Segment-Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2015;131:1843-50. doi:10.1161/CIRCULATIONAHA.114.014145.
- 8 Soliman EZ, Safford MM, Muntner P, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014;174:107-14. doi:10.1001/jamainternmed.2013.11912.
- 9 O'Neal WT, Sangal K, Zhang Z-M, Soliman EZ. Atrial fibrillation and incident myocardial infarction in the elderly. *Clin Cardiol* 2014;37:750-5. doi:10.1002/clc.22339.
- 10 Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation* 2013;127:569-74. doi:10.1161/CIRCULATIONAHA.112.123992.
- 11 Hamaguchi S, Yokoshiki H, Kinugawa S, et al. Japanese Cardiac Registry of Heart Failure in Cardiology Investigators. 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;73:2084-90. doi:10.1253/circj.CJ-09-0316.
- 12 Desai H, Aronow WS, Ahn C, et al. Risk factors for appropriate cardioverter-defibrillator shocks, inappropriate cardioverter-defibrillator shocks, and time to mortality in 549 patients with heart failure. *Am J Cardiol* 2010;105:1336-8. doi:10.1016/j.amjcard.2009.12.057.
- 13 Chen LY, Sotoodehnia N, Bůžková P, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA Intern Med* 2013;173:29-35. doi:10.1001/2013.jamainternmed.744.
- 14 Bouzas-Mosquera A, Peteiro J, Broullón FJ, et al. Effect of atrial fibrillation on outcome in patients with known or suspected coronary artery disease referred for exercise stress testing. *Am J Cardiol* 2010;105:1207-11. doi:10.1016/j.amjcard.2009.12.037.
- 15 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12. doi:10.1001/jama.283.15.2008.
- 16 Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, W64. doi:10.7326/0003-4819-151-4-200908180-00135.
- 17 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/nosgen.pdf](http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf).
- 18 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: A Report from the American Heart Association. *Circulation* 2014;131:e29-322. doi:10.1161/CIR.0000000000000152.
- 19 Centers for Disease Control and Prevention (CDC). NVSS - Mortality Data. <http://www.cdc.gov/nchs/nvss/deaths.htm>.
- 20 Centers for Disease Control and Prevention (CDC). Chronic Kidney Disease (CKD) Surveillance Project. <https://nccd.cdc.gov/ckd/>.
- 21 Patsopoulos NA, Evangelou E, Ioannidis JPA. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol* 2008;37:1148-57. doi:10.1093/ije/dyn065.
- 22 Cochrane. Recommendations on testing for funnel plot asymmetry. [http://handbook.cochrane.org/chapter\\_10/10\\_4\\_3\\_1\\_recommendations\\_on\\_testing\\_for\\_funnel\\_plot\\_asymmetry.htm](http://handbook.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm).
- 23 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34. doi:10.1136/bmj.315.7109.629.
- 24 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;56:455-63. doi:10.1111/j.0006-341X.2000.00455.x.
- 25 Goldberg RJ, Seeley D, Becker RC, et al. Impact of atrial fibrillation on the in-hospital and long-term survival of patients with acute myocardial infarction: a community-wide perspective. *Am Heart J* 1990;119:996-1001. doi:10.1016/S0002-8703(05)80227-3.
- 26 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;34:537-42. doi:10.1002/clc.20939.
- 27 Raunso J, Pedersen OD, Dominguez H, et al. EchoCardiography and Heart Outcome Study Investigators. 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;12:692-7. doi:10.1093/eurjhf/hfq052.
- 28 Køber L, Torp-Pedersen C, Gadsbøll N, Hildebrandt P, Højlund-Carlson PF. Is digoxin an independent risk factor for long-term mortality after acute myocardial infarction? *Eur Heart J* 1994;15:382-8.
- 29 Pedersen OD, Søndergaard P, Nielsen T, et al. DIAMOND study group investigators. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. *Eur Heart J* 2006;27:2866-70. doi:10.1093/eurheartj/eh359.
- 30 Asanin M, Perunicic J, Mrdovic I, et al. Prognostic significance of new atrial fibrillation and its relation to heart failure following acute myocardial infarction. *Eur J Heart Fail* 2005;7:671-6. doi:10.1016/j.ejheart.2004.07.018.
- 31 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;7:960-6. doi:10.1161/CIRCHEARTFAILURE.114.001523.
- 32 Bajaj NS, Bhatia V, Sanam K, et al. Impact of atrial fibrillation and heart failure, independent of each other and in combination, on mortality in community-dwelling older adults. *Am J Cardiol* 2014;114:909-13. doi:10.1016/j.amjcard.2014.05.045.
- 33 Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998;158:229-34. doi:10.1001/archinte.158.3.229.
- 34 Wyse DG, Love JC, Yao Q, et al. Atrial fibrillation: a risk factor for increased mortality--an AVID registry analysis. *J Interv Card Electrophysiol* 2001;5:267-73. doi:10.1023/A:1011460631369.
- 35 Kaarisalo MM, Immonen-Räihä P, Marttila RJ, et al. Atrial fibrillation in older stroke patients: association with recurrence and mortality after first ischemic stroke. *J Am Geriatr Soc* 1997;45:1297-301. doi:10.1111/j.1532-5415.1997.tb02927.x.
- 36 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;111:1460-5. doi:10.1016/j.amjcard.2013.01.298.
- 37 Saposnik G, Kapral MK, Liu Y, et al. Investigators of the Registry of the Canadian Stroke Network Stroke Outcomes Research Canada (SORCan) Working Group. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation* 2011;123:739-49. doi:10.1161/CIRCULATIONAHA.110.983353.
- 38 Saczynski JS, McManus D, Zhou Z, et al. Trends in atrial fibrillation complicating acute myocardial infarction. *Am J Cardiol* 2009;104:169-74. doi:10.1016/j.amjcard.2009.03.011.
- 39 Behar S, Zahavi Z, Goldbourt U, Reicher-Reiss H. SPRINT Study Group. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction. *Eur Heart J* 1992;13:45-50.
- 40 Duncan A, Ludman P, Banya W, et al. Long-term outcomes after transcatheter aortic valve replacement in high-risk patients with severe aortic stenosis: the U.K. Transcatheter Aortic Valve Implantation Registry. *JACC Cardiovasc Interv* 2015;8:645-53. doi:10.1016/j.jcin.2015.01.009.
- 41 Køber L, Swedberg K, McMurray JJV, et al. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. *Eur J Heart Fail* 2006;8:591-8. doi:10.1016/j.ejheart.2005.11.007.
- 42 Andersson T, Magnuson A, Bryngelsson I-L, et al. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: a nationwide cohort study of 9519 patients. *Int J Cardiol* 2014;177:91-9. doi:10.1016/j.ijcard.2014.09.092.
- 43 Baldasseroni S, De Biase L, Fresco C, et al. Italian Network on Congestive Heart Failure. 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;23:1692-8. doi:10.1053/euhj.2001.3157.
- 44 Rathore SS, Berger AK, Weinfurt KP, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. *Circulation* 2000;101:969-74. doi:10.1161/01.CIR.101.9.969.
- 45 Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998;32:695-703. doi:10.1016/S0735-1097(98)00297-6.
- 46 Abbott KC, Reynolds JC, Taylor AJ, Agodola LY. Hospitalized atrial fibrillation after renal transplantation in the United States. *Am J Transplant* 2003;3:471-6. doi:10.1034/j.1600-6143.2003.00071.x.
- 47 Kimura K, Minematsu K, Kazui S, Yamaguchi T. Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Mortality and cause of death after hospital discharge in 10,981 patients with ischemic stroke and transient ischemic attack. *Cerebrovasc Dis* 2005;19:171-8. doi:10.1159/000083252.
- 48 Lau DH, Huynh LT, Chew DP, Astley CM, Soman A, Sanders P. Prognostic impact of types of atrial fibrillation in acute coronary syndromes. *Am J Cardiol* 2009;104:1317-23. doi:10.1016/j.amjcard.2009.06.055.
- 49 Kammersgaard LP, Olsen TSOJ. Cardiovascular risk factors and 5-year mortality in the Copenhagen Stroke Study. *Cerebrovasc Dis* 2006;21:187-93. doi:10.1159/000090531.

- 50 Henriksson KM, Farahmand B, Johansson S, Asberg S, Terént A, Edvardsson N. Survival after stroke—the impact of CHADS2 score and atrial fibrillation. *Int J Cardiol* 2010;141:18-23. doi:10.1016/j.ijcard.2008.11.122.
- 51 Wasmer K, Unrath M, Köbe J, et al. Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease. *Int J Cardiol* 2015;199:223-8. doi:10.1016/j.ijcard.2015.06.094.
- 52 van Wijk I, Koudstaal PJ, Kappelle LJ, van Gijn J, Gorter JW, Algra A. LiLAC Study Group. Long-term occurrence of death and cardiovascular events in patients with transient ischaemic attack or minor ischaemic stroke: comparison between arterial and cardiac source of the index event. *J Neurol Neurosurg Psychiatry* 2008;79:895-9. doi:10.1136/jnnp.2007.133132.
- 53 Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older persons with atrial fibrillation versus sinus rhythm. *Am J Cardiol* 2001;87:224-5, A8-9.
- 54 Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;3:e001002. doi:10.1161/JAHA.114.001002.
- 55 Bilato C, Corti MC, Baggio G, et al. Prevalence, functional impact, and mortality of atrial fibrillation in an older Italian population (from the Pro.V.A. study). *Am J Cardiol* 2009;104:1092-7. doi:10.1016/j.amjcard.2009.05.058.
- 56 Bengtson LGS, Chen 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.
- 57 Fu S, Liu T, Luo L, Ye P. Different types of atrial fibrillation, renal function, and mortality in elderly Chinese patients with coronary artery disease. *Clin Interv Aging* 2014;9:301-8. doi:10.2147/CI.A.S55972.
- 58 Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;36:1115-9. doi:10.1161/01.STR.0000166053.83476.4a.
- 59 Bang 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.
- 60 Ahmed A, Thornton P, Perry GJ, Allman 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.ejheart.2003.11.011.
- 61 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* 2007;191:791-803, discussion 803-5.
- 62 Saxena A, Dinh D, Dimitriou 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. *Interact Cardiovasc Thorac Surg* 2013;16:488-94. doi:10.1093/icvts/ivs538.
- 63 Santini 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. *J Am Coll Cardiol* 2011;57:167-72. doi:10.1016/j.jacc.2010.08.624.
- 64 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:10.1067/mhj.2000.111108.
- 65 Kinjo K, Sato H, Sato H, et al. Osaka Acute Coronary Insufficiency Study (OACIS) 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.
- 66 Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. *Circ Heart Fail* 2011;4:740-6. doi:10.1161/CIRCHEARTFAILURE.111.962688.
- 67 Bansal N, Fan D, Hsu C-Y, Ordonez JD, Go AS. Incident atrial fibrillation and risk of death in adults with chronic kidney disease. *J Am Heart Assoc* 2014;3:e001303. doi:10.1161/JAHA.114.001303.
- 68 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/EIJV8I9A163.
- 69 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.98.10.946.
- 70 Chopard R, Teiger 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.
- 71 Stewart S, Hart CL, Hole DJ, McMurray JJ. 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)01236-6.
- 72 Liu X, Xu G, Wu W, Zhang R, 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.
- 73 Pizzetti F, Turazza FM, Franzosi MG, et al. GISSI-3 Investigators. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. *Heart* 2001;86:527-32. doi:10.1136/heart.86.5.527.
- 74 Bogale N, Priori S, Cleland JGF, et al. Scientific Committee, National Coordinators, and Investigators. The European CRT Survey: 1 year (9-15 months) follow-up results. *Eur J Heart Fail* 2012;14:61-73. doi:10.1093/eurjhf/hfr158.
- 75 Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation* 2011;123:2094-100. doi:10.1161/CIRCULATIONAHA.110.990192.
- 76 Bèjot Y, Ben Salem D, Osseby GV, et al. Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006. *Neurology* 2009;72:346-53. doi:10.1212/01.wnl.0000341280.31919.bd.
- 77 Ohsawa M, Okayama A, Okamura 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 DATA80. *Circ J* 2007;71:814-9. doi:10.1253/circj.71.814.
- 78 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: a nationwide study. *J Am Heart Assoc* 2014;3:e000382-2. doi:10.1161/JAHA.113.000382.
- 79 Stein KM, Mittal S, Gilliam FR, et al. Predictors of early mortality in implantable cardioverter-defibrillator recipients. *Europace* 2009;11:734-40. doi:10.1093/europace/eup055.
- 80 Lake FR, Cullen KJ, de Klerk NH, McCall MG, Rosman DL. Atrial fibrillation and mortality in an elderly population. *Aust N Z J Med* 1989;19:321-6. doi:10.1111/j.1445-5994.1989.tb00271.x.
- 81 Friberg J, Scharling H, Gadsbøll N, Truelsen 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.
- 82 Stortecky S, Buellesfeld L, Wenaweser 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.112.000124.
- 83 Torres M, Rocha S, Marques J, et al. Impact of atrial fibrillation in acute coronary syndromes. *Rev Port Cardiol* 2008;27:1407-18.
- 84 Sakata K, Kurihara H, Iwamori K, et al. Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction. *Am J Cardiol* 1997;80:1522-7. doi:10.1016/S0002-9149(97)00746-7.
- 85 Pedersen OD, Abildstrøm SZ, Ottesen MM, et al. TRACE Study Investigators. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. *Eur Heart J* 2006;27:290-5. doi:10.1093/eurheartj/ehi629.
- 86 Olsson LG, Swedberg K, Ducharme A, et al. CHARM Investigators. 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. doi:10.1016/j.jacc.2006.01.060.
- 87 Lau K-K, Wong Y-K, Teo K-C, et al. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. *PLoS One* 2014;9:e88283. doi:10.1371/journal.pone.0088283.
- 88 Manzano JF, De Silva DA, Pascual JLR, Chang HM, Wong MC, Chen CP. Associations of ankle-brachial index (ABI) with cerebral arterial disease and vascular events following ischemic stroke. *Atherosclerosis* 2012;223:219-22. doi:10.1016/j.atherosclerosis.2012.04.009.
- 89 Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 2010;341:c6624. doi:10.1136/bmj.c6624.
- 90 Ruff CT, Bhatt DL, Steg PG, et al. REACH Registry Investigators. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol* 2014;170:413-8. doi:10.1016/j.ijcard.2013.11.030.
- 91 Wetmore JB, Ellerbeck EF, Mahnken JD, et al. Atrial fibrillation and risk of stroke in dialysis patients. *Ann Epidemiol* 2013;23:112-8. doi:10.1016/j.annepidem.2012.12.011.
- 92 Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. *Stroke* 1998;29:1341-6. doi:10.1161/01.STR.29.7.1341.
- 93 Sampson UK, Pfeffer MA, McMurray JJV, Lokhnygina Y, White HD, Solomon SD. VALIANT Trial Investigators. Predictors of stroke in high-risk patients after acute myocardial infarction: insights from the VALIANT Trial. *Eur Heart J* 2007;28:685-91. doi:10.1093/eurheartj/ehl197.

- 94 Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ* 2013;346:f2573. doi:10.1136/bmj.f2573.
- 95 Biblo LA, Yuan Z, Quan KJ, Mackall JA, Rimm AA. Risk of stroke in patients with atrial flutter. *Am J Cardiol* 2001;87:346-9, A9.
- 96 Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD. South London Stroke Register. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke* 2003;34:1457-63. doi:10.1161/01.STR.0000072985.24967.7F.
- 97 Burke JF, Stulc JL, Skolarus LE, Sears ED, Zahuranec DB, Morgenstern LB. Traumatic brain injury may be an independent risk factor for stroke. *Neurology* 2013;81:33-9. doi:10.1212/WNL.0b013e318297eefc.
- 98 Soliman EZ, Howard G, Meschia JF, et al. Self-reported atrial fibrillation and risk of stroke in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke* 2011;42:2950-3. doi:10.1161/STROKEAHA.111.621367.
- 99 Rodgers H, Greenaway J, Davies T, Wood R, Steen N, Thomson R. Risk factors for first-ever stroke in older people in the north East of England: a population-based study. *Stroke* 2004;35:7-11. doi:10.1161/01.STR.0000106914.60740.78.
- 100 Chao T-F, Liu C-J, Chen S-J, et al. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHA2DS2-VASc score of 0 or 1? *Stroke* 2012;43:2551-5. doi:10.1161/STROKEAHA.112.667865.
- 101 Ruigómez A, Johansson S, Wallander M-A, Edvardsson N, García Rodríguez LA. Risk of cardiovascular and cerebrovascular events after atrial fibrillation diagnosis. *Int J Cardiol* 2009;136:186-92. doi:10.1016/j.ijcard.2008.04.050.
- 102 Bishara R, Telman G, Bahouth F, Lessick J, Aronson D. Transient atrial fibrillation and risk of stroke after acute myocardial infarction. *Thromb Haemost* 2011;106:877-84. doi:10.1160/TH11-05-0343.
- 103 Aronow WS, Ahn C, Kronzon I, Gutstein H. Association of left ventricular hypertrophy and chronic atrial fibrillation with the incidence of new thromboembolic stroke in 2,384 older persons. *Am J Cardiol* 1999;84:468-9, A9.
- 104 Aronow WS, Ahn C, Gutstein H. Prevalence of atrial fibrillation and association of atrial fibrillation with prior and new thromboembolic stroke in older patients. *J Am Geriatr Soc* 1996;44:521-3. doi:10.1111/j.1532-5415.1996.tb01436.x.
- 105 Xu G, Liu X, Wu W, Zhang R, Yin Q. Recurrence after ischemic stroke in Chinese patients: impact of uncontrolled modifiable risk factors. *Cerebrovasc Dis* 2007;23:117-20. doi:10.1159/000097047.
- 106 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147:1561-4. doi:10.1001/archinte.1987.00370090041008.
- 107 Iwahana H, Ishikawa S, Ishikawa J, et al. Atrial fibrillation is a major risk factor for stroke, especially in women: the Jichi Medical School cohort study. *J Epidemiol* 2011;21:95-101. doi:10.2188/jea.JE20090149.
- 108 Wang T-J, Keller JJ, Sheu J-J, Lin HC. A 3-year follow-up study on the risk of stroke among patients with conjunctival haemorrhage. *Acta Ophthalmol* 2013;91:226-30. doi:10.1111/j.1755-3768.2011.02359.x.
- 109 Hermann DM, Gronewold J, Lehmann N, et al; Heinz Nixdorf Recall Study Investigative Group. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke* 2013;44:1008-13. doi:10.1161/STROKEAHA.111.678078.
- 110 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.
- 111 Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H. A 15.5-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.
- 112 Feng S-J, 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.
- 113 Ruel 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, discussion 83-4. doi:10.1016/j.athoracsur.2003.12.058.
- 114 Marijon E, Trinquart L, Otmani A, et al. Evaluation Médico-Economique du Défibrillateur Automatique Implantable (EVADEF) Investigators. Competing risk analysis of cause-specific mortality in patients with an implantable cardioverter-defibrillator: The EVADEF cohort study. *Am Heart J* 2009;157:391-397.e1. doi:10.1016/j.ahj.2008.09.023.
- 115 Genovesi S, Valsecchi MG, Rossi 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.
- 116 Okin PM, Bang CN, Wachtell K, et al. Relationship of sudden cardiac death to new-onset atrial fibrillation in hypertensive patients with left ventricular hypertrophy. *Circ Arrhythm Electrophysiol* 2013;6:243-51. doi:10.1161/CIRCEP.112.977777.
- 117 Smit MD, Van Dessel PFHM, Nieuwland W, et al. Right ventricular pacing and the risk of heart failure in implantable cardioverter-defibrillator patients. *Heart Rhythm* 2006;3:1397-403. doi:10.1016/j.hrthm.2006.08.006.
- 118 Ruel M, Kapila V, Price J, Kulik A, Burwash IG, Mesana TG. Natural history and predictors of outcome in patients with concomitant functional mitral regurgitation at the time of aortic valve replacement. *Circulation* 2006;114(Suppl):1541-6. doi:10.1161/CIRCULATIONAHA.105.000976.
- 119 O'Neal WT, Tanner RM, Efrid JT, 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.
- 120 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.
- 121 Chang C-J, Chen Y-T, Liu C-S, 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.0000000000003002.
- 122 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/ehf483.
- 123 Marijon E, Le Heuzey J-Y, 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.112.000491.
- 124 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;16:1317-22. doi:10.1002/ehf.187.
- 125 Manolis AJ, Rosei EA, Coca A, et al. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. *J Hypertens* 2012;30:239-52. doi:10.1097/HJH.0b013e32834f03bf.
- 126 Leong DP, 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/ehf044.
- 127 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.amjcard.2012.04.049.
- 128 Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Lip GY. Predictors and prognostic implications of incident heart failure following the first diagnosis of atrial fibrillation in patients with structurally normal hearts: the Belgrade Atrial Fibrillation Study. *Eur J Heart Fail* 2013;15:415-24. doi:10.1093/eurjhf/hft004.
- 129 Schnabel RB, Rienstra M, Sullivan LM, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. *Eur J Heart Fail* 2013;15:843-9. doi:10.1093/eurjhf/hft041.
- 130 Caldeira D, David C, Sampaio C. Rate versus rhythm control in atrial fibrillation and clinical outcomes: updated systematic review and meta-analysis of randomized controlled trials. *Arch Cardiovasc Dis* 2012;105:226-38. doi:10.1016/j.acvd.2011.11.005.
- 131 Roy D, Talajic M, Nattel S, et al. Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;358:2667-77. doi:10.1056/NEJMoa0708789.
- 132 Grover SA, Lowensteyn I, Joseph L, et al. Cardiovascular Health Evaluation to Improve Compliance and Knowledge Among Uninformed Patients (CHECK-UP) Study Group. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. *Arch Intern Med* 2007;167:2296-303. doi:10.1001/archinte.167.21.2296.

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**Appendix:** Search strategy, supplementary tables A-L, supplementary figures A-Q, web references