Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies

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ABSTRACT

OBJECTIVE
To determine whether atrial fibrillation is a stronger risk factor for cardiovascular disease and death in women compared with men.

DESIGN
Meta-analysis of cohort studies.

DATA SOURCES
Studies published between January 1966 and March 2015, identified through a systematic search of Medline and Embase and review of references.

ELIGIBILITY FOR SELECTING STUDIES
Cohort studies with a minimum of 50 participants with and 50 without atrial fibrillation that reported sex specific associations between atrial fibrillation and all cause mortality, cardiovascular mortality, stroke, cardiac events (cardiac death and non-fatal myocardial infarction), and heart failure.

DATA EXTRACTION
Two independent reviewers extracted study characteristics and maximally adjusted sex specific relative risks. Inverse variance weighted random effects meta-analysis was used to pool sex specific relative risks and their ratio.

RESULTS
30 studies with 4 371 714 participants were identified. Atrial fibrillation was associated with a higher risk of all cause mortality in women (ratio of relative risks for women compared with men 1.12, 95% confidence interval 1.07 to 1.17) and a significantly stronger risk of stroke (1.99, 1.46 to 2.71), cardiovascular mortality (1.93, 1.44 to 2.60), cardiac events (1.55, 1.15 to 2.08), and heart failure (1.16, 1.07 to 1.27). Results were broadly consistent in sensitivity analyses.

CONCLUSION
Atrial fibrillation is a stronger risk factor for cardiovascular disease and death in women compared with men, though further research would be needed to determine any causality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Atrial fibrillation (AF) is associated with an increased risk of stroke and death in men and women

A growing body of literature suggests that women and men experience risk factors for cardiovascular disease differently, including diabetes, smoking, and body mass index

WHAT THIS PAPER ADDS

AF is associated with a stronger relative risk of all cause mortality, cardiovascular mortality, stroke, ischaemic heart disease, and heart failure in women than in men

Whether the differential association of AF with death and cardiovascular disease in women relative to men is causal is unclear

Introduction

Atrial fibrillation (AF) is a leading cause of cardiovascular disease worldwide,[1] with an estimated 33.5 million people affected in 2010.[2] Recent estimates from the Global Burden of Disease study indicated that AF was associated with an age adjusted mortality rate of 1.7 per 100 000 people (95% uncertainty interval 1.4 to 2.1) in 2010[3] and that the prevalence is increasing in both developed and developing countries.[2]

Although AF is associated with an increased risk of stroke[4] and death[5] in men and women, a growing body of literature suggests that women and men experience risk factors for cardiovascular disease differently. Previous analyses have shown that smoking and diabetes are associated with greater proportional risks of coronary heart disease in women than in men.[6 7] Diabetes is also associated with a greater relative risk of stroke in women.[8] It is currently unclear, however, whether such sex differences exist for AF. While being female is a risk factor for stroke among individuals with AF,[9] this could reflect differences in the multivariable adjusted risk of stroke by sex in the general population rather than differential effects of AF by sex. To explore sex differences in the effect of AF, it is necessary to compare sex specific estimates of the effect of AF on risk of death and cardiovascular disease. While some studies have suggested that AF is more strongly associated with the risk of stroke[10] and death[11] in women than men, others have suggested not.[12-14] Sex differences in the association between AF and death and cardiovascular disease would have substantial implications for the estimation of the global and regional burden, for the targeting of treatment to manage it, and for future research into causes of sex differences.

Accordingly, we conducted a meta-analysis of cohort studies to estimate the association between AF and cardiovascular disease and death in women and men and to compare the sexes.

Methods

Search strategy and selection criteria

We conducted a systematic review of cohort studies that reported associations between AF and death or cardiovascular events in men and women. This was

done in accordance with the MOOSE (meta-analysis of observational studies in epidemiology) guidelines.[15] An experienced research librarian designed and conducted the search strategy. Medline and Embase were searched from 1966 to March 2015 with a combined text and MeSH subheading search with the following terms: "atrial fibrillation", "mortality", "death", "cardiovascular disease", "heart failure", "myocardial infarction", "death, sudden, cardiac", "stroke", "kidney", "renal", "peripheral", and "risk factors". We conducted a review of the references of identified studies.

We included any study that reported sex specific associations between AF and any of the following outcomes: all cause mortality, cardiovascular mortality, stroke (fatal and non-fatal), cardiac events (a composite of cardiac death and non-fatal myocardial infarction, excluding heart failure), heart failure, peripheral arterial disease, and chronic kidney disease. For inclusion in the analysis, studies were required to have a minimum of 50 participants with AF, a minimum of 50 participants without AF, and a median follow-up of at least six months. Importantly, we included only studies that reported associations for both men and women to restrict our analysis to comparisons of men and women within studies and to reduce the risk of heterogeneity between studies influencing our results. Additionally, we required all studies to adjust for, at a minimum, age and the presence of cardiovascular disease at baseline. We excluded studies that examined postoperative atrial fibrillation because the differing epidemiology and duration of postoperative atrial fibrillation relative to chronic atrial fibrillation.[16] There were no language restrictions, and an investigator with extensive experience in epidemiological study translation (AJH) translated non-English studies. We contacted authors of studies that did not report separate associations for women and men to provide any unpublished data on adjusted sex specific associations.

Data extraction

Data were extracted, in duplicate, from studies deemed to meet the eligibility criteria. These included details on general study characteristics (study name, duration of follow-up, year of publication), information about the studied population (number of participants with and without AF, mean age, number of men and women, number of participants with a history of coronary heart disease, stroke, and heart failure), and information on the outcomes in the study (all cause mortality, cardiovascular mortality, stroke, cardiac events, heart failure, peripheral arterial disease, and chronic kidney disease). We extracted sex specific adjusted measures of relative risk (hazard ratios, relative risks, and odds ratio) and 95% confidence intervals. We used the maximally adjusted relative risk that was available and risk estimates corresponding to the longest period of follow-up. For cohorts that had multiple reports of the same outcome, we used the report with the largest number of events. Study quality was assessed with the Newcastle-Ottawa scale for cohort studies.[17]

Statistical analysis

For the primary analysis, we derived a ratio of relative risks with 95% confidence intervals of AF for each outcome in women compared with men, as previously described.[8] This relative risk ratio for each study was then pooled with inverse variance weighted random effects meta-analysis. We also pooled relative risks for men and women separately. For one study, which reported separate hazard ratios for men and women in different age groups, we first used inverse variance weighted fixed effects meta-analysis to generate a summary hazard ratio for men and for women.[18] We used funnel plots to examine if publication bias seemed to be present for outcomes that had at least 10 studies present (all cause mortality and stroke).[19] If publication bias was present, we used the trim and fill method to adjust for publication bias.[20] Heterogeneity was quantified with the I^2 statistic and the Q test. $P<0.05$ was considered significant.

To estimate the difference in absolute risks associated with AF between women and men, we multiplied estimated sex specific excess incidence rates for all cause mortality,[21] cardiovascular mortality,[21] coronary heart disease[21] (restricted to coronary heart disease mortality as an incidence rate for the composite of coronary heart disease death and non-fatal myocardial infarction could not be obtained), stroke,[22] and heart failure[23] in the United Kingdom general population by sex specific associations of each outcome with AF. The relative risk associated with each outcome in women was calculated by multiplying the pooled ratio of relative risks by the relative risk in men. We then subtracted the excess risk in men from the excess risk in women to estimate the difference in absolute risks associated with AF between men and women. Confidence intervals were derived through simulation with 10 000 draws from the distribution of the men's relative risk and ratio of relative risks performed.

Sensitivity analyses

We undertook seven sensitivity analyses to determine if the ratio of relative risks in women versus men for mortality and stroke differed by methodological and study characteristics. Firstly, we stratified studies by whether AF was ascertained through electrocardiography at baseline or through medical records. Secondly, we stratified by region (Europe versus non-Europe). For these two stratified analyses (which stratified on categorical variables), we performed tests for interactions between subgroups. Thirdly, we stratified by size of the study (>100 000 versus <100 000 participants) to examine whether the results were consistent we excluded two large studies[24 25] (each with more than 100 000 participants). Fourthly, we stratified by baseline year of enrolment of each cohort (1990 and before versus 1991 or later). Fifthly, we stratified by length of follow-up (≤10 versus >10 years). Sixthly, we stratified by median age (≤65 versus >65 at baseline). Finally, we stratified studies

by the ratio of the event rate in women to men to examine whether our results were influenced by potentially lower absolute risk of outcomes in women than men. For the five analyses that stratified on continuous variables we performed tests for trend using meta-regression. The seven sensitivity analyses were restricted to stroke and all cause mortality because there were too few studies to conduct sensitivity analyses for other outcomes. All statistical analyses were conducted with R version 3.0.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Results

The systematic search identified 3635 studies, of which 268 were examined in the full text review (fig 1) and 238 were excluded. Accordingly, we included 30 cohort studies. None of these studies reported sex specific associations for either peripheral arterial disease or chronic kidney disease. Twenty studies provided published sex specific associations, while 10 studies provided unpublished associations.

Table 1 shows the characteristics of the included studies. Ascertainment of AF status was through electrocardiography or continuous monitoring in 15 studies, medical records in eight studies, and a combination in six studies. One study did not report the method of ascertainment. Quality of included studies, as assessed by the Newcastle-Ottawa Scale, was high (appendix table A).

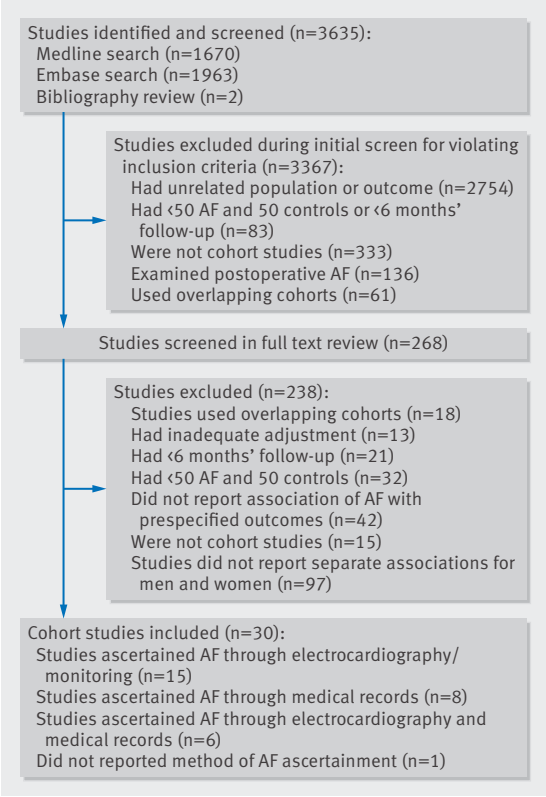

Fig 1 | Identification of cohort studies that reported associations between atrial fibrillation (AF) and death or cardiovascular events in men and women

Studies included a total of 4 371 714 participants, 66 511 with AF (not counting one study[34] with an overlapping cohort as a second study[24]). Twenty six studies reported the number of events. Of these, 14 studies reported on all cause mortality (18 563 events), four studies on cardiovascular mortality (7702 events), 11 studies reported on stroke (83 030 events), six studies on cardiac events (3583 events), and three studies on heart failure (27 468 events). Four additional studies reported relative risks for all cause mortality, cardiovascular mortality, and stroke associated with AF but did not report the number of events. Appendix table B shows pooled incidence rates for studies that reported number of events for men and women separately are provided.

Risk of cardiovascular disease and all cause mortality in women versus men

The pooled relative risk of all cause mortality for individuals with AF compared with those without AF was higher in women than in men (relative risk 1.69 (95% confidence interval 1.50 to 1.90) *v* 1.47 (1.32 to 1.65); fig 2). The pooled ratio of relative risks for women versus men showed a 12% greater risk of all cause mortality associated with AF in women than in men (relative risk ratio 1.12, 95% confidence interval 1.07 to 1.171; fig 3). Although heterogeneity was observed in the relative risk of all cause mortality associated with AF in both women and men (I^2=91% and I^2=89%, respectively, P<0.001; fig 2), no significant heterogeneity was observed in the pooled ratio of relative risks (I^2=2%, P=0.43; fig 3).

The relative risk of stroke was also greater in women than in men (relative risk 4.05 (95% confidence interval 2.52 to 6.50) *v* 1.77 (1.40 to 2.24); fig 4). When we pooled the ratios of relative risks, AF was observed to be associated with twice the relative risk of stroke in women than in men (relative risk ratio 1.99, 95% confidence interval 1.46 to 2.71; fig 5). There was significant heterogeneity between studies (I^2=73%, P<0.001).

AF was associated with a higher relative risk of cardiovascular mortality in women than in men (relative risk ratio 1.93, 95% confidence interval 1.44 to 2.60; fig 6; appendix fig A), with little heterogeneity observed between studies (I^2=8%), and was associated with a 55% higher relative risk of cardiac events (cardiac death or non-fatal myocardial infarction) in women versus men (1.55, 1.15 to 2.08; fig 6 ; appendix fig B). This was consistent when we restricted our analysis to three studies that reported only myocardial infarction, excluding the one study that reported sudden cardiac death[30] (1.64, 1.15 to 2.34). AF was also associated with an increased risk of heart failure in women compared with men (1.16, 1.07 to 1.27; appendix fig C).

When we looked at events per 1000 patient years, corresponding absolute risk increases in outcomes associated with AF in women compared with men were 1.8 (95% confidence interval 1.1 to 2.6) for all cause

Table 1 | Characteristics of included cohort studies that reported associations between atrial fibrillation (AF) and death or cardiovascular events in men and women

Study	Location	Baseline year(s)	AF ascertainment	Total No (with AF)	No of women	Age (years)	Follow-up (years)	No of individuals at baseline with			Maximum adjustment available
								IHD	Stroke	HF	
Andersson 2014[26]	Sweden	1995-2008	Medical records	21 987 (9519)	6816	59	NA	NA	NA	NA	Matched by sex, adjusted for age, comorbidities excluded
Bejot et al, 2009[27]	France	1985-2006	ECG	3064 (572)	1615	75	2.0	620	3064	NA	Age
Benjamin 1998[5]	US	1948	ECG	1863 (621)	975	75	25.6	252	213	201	Age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, vascular disease
Bouzas-Mosquera et al, 2010[28]	Spain	1995-2008	ECG	17 100 (619)	6999	64	6.5	2963	NA	NA	Age, diabetes mellitus, hypertension, hypercholesterolemia, smoking habit, family history of CAD, MI, PCI, CABG, angina, LBBB, medication, chest pain, exercise ECG, METs, peak SBP, heart rate
Chamberlain et al, 2011[29]	US	1983-2006	ECG and medical records	1664 (553)	905	76	4.0	353	NA	1664	Age, BMI, year of heart failure diagnosis, smoking status, derived NYHA class, estimated glomerular filtration rate, anaemia, hypertension, diabetes mellitus, COPD, MI, medication
Chao 2012[10]	Taiwan	2000-09	Medical records	9119 (829)	3520	45	4.8	NA	NA	NA	Age, dyslipidaemia, CKD, asthma, malignancy, liver cirrhosis, autoimmune diseases (stepwise regression)
Chen 2013[30]	US	1989	ECG and medical records	20 918 (2352)	11 713	59	13.1	1786	NA	927	Age, race, field centre, heart rate, smoking status, BMI, hypertension, diabetes mellitus, coronary heart disease
D'Agostino 1994[31]	US	1948	ECG	5734 (140)	3362	66	10	NA	0	NA	Age, systolic blood pressure, antihypertensive therapy, cardiovascular disease, left ventricular hypertrophy, cigarettes, diabetes
Friberg 2004[11]	Denmark	1976-78	ECG	29 310 (276)	16 314	58	4.70	763	0	NA	Age, arterial hypertension, SBP, diabetes, myocardial infarction, left ventricular hypertrophy, smoking, FEV_1
Genovesi et al, 2009[32]	Italy	2003-06	ECG	476 (127)	199	NA	3.0	112	NA	45	Age, ischaemic heart disease, diabetes
Guize 2007[25]	France	1972-1988	ECG	154 070 (298)	55 109	51	15.2	NA	NA	NA	Age, cardiomyopathy, left ventricular hypertrophy, blood pressure, cholesterol, glycaemia, BMI, smoking, alcohol, vital capacity
Hamaguchi 2009[13]	Japan	2004-05	ECG	2659 (937)	1069	71	2.4	851	399	2659	Age, cause of heart failure, medical history, serum creatinine, haemoglobin and BNP levels, LVEF, medication use
Hermann et al, 2013[33]	Germany	2000-03	ECG	4180 (52)	2212	59.2	7.9	0	0	0	Age, systolic blood pressure, LDL and HDL cholesterol, diabetes mellitus, and smoking
Hippisley-Cox et al, 2010[34]	UK	1994-2010	Medical records	2 343 759 (12 031)	1 189 845	48.1	7.0	0	0	0	BMI, SBP, cholesterol, deprivation, ethnic group, family history of coronary heart disease, type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, chronic renal disease (age used as underlying time variable)
Hippisley-Cox 2013[24]	England and Wales	1998-2012	Medical records	3 549 478 (15 371)	1 801 370	45	7	99 561	0	16 294	Age, BMI, BP, cholesterol, deprivation, smoking, ethnicity, vascular disease, other comorbidities
Hippisley-Cox et al, 2015[35]	UK	1998-2014	Medical records	437 806 (13 953)	192 896	60	NA	NA	NA	0	Age, cholesterol/HDL ratio, deprivation, duration of diabetes, smoking status, ethnicity, type 1 diabetes, cardiovascular disease, chronic renal disease

(*Continued*)

Table 1 | Characteristics of included cohort studies that reported associations between atrial fibrillation (AF) and death or cardiovascular events in men and women

Study	Location	Baseline year(s)	AF ascertainment	Total No (with AF)	No of women	Age (years)	Follow-up (years)	No of individuals at baseline with			Maximum adjustment available
								IHD	Stroke	HF	
Iwahana 2011[36]	Japan	1992-95	ECG	10 929 (54)	6782	56	10.7	NA	0	NA	Area, age, smoking, drinking status, obesity, hypertension, dyslipidaemia, diabetes mellitus
Kaarisalo 1997[37]	Finland	1983-92	ECG and medical records	2635 (767)	1880	82	1	457	2635	NA	Age, recent MI, previous MI, hypertension
Nakayama 1997[38]	Japan	1977	ECG	2302 (NA)	1341	NA	15.5	NA	0	NA	Age, BP, cholesterol, haematocrit, BMI, ECG abnormality, albumin, glucose, optic fundus, cigarettes, alcohol, physical activity, IHD
Ohsawa 2007[39]	Japan	1980	ECG	9483 (60)	5329	51	19	NA	0	NA	Age, BMI, SBP, glucose, cholesterol, history of valvular heart disease, left ventricular hypertrophy, alcohol, smoking
Ruigomez et al. 2002[40]	UK	1996	Medical records	6035 (1035)	NA	NA	2	NA	NA	NA	Age, smoking, diabetes, heart failure, ischaemic heart disease, hypertension, cerebrovascular disease
Saposnik et al, 2011[41]	Canada	2002-04	Medical records	8223 (1405)	3901	72	1	1936	8223	734	Age, sex, severe stroke, nonlacunar stroke subtype, glucose, coronary artery disease, congestive heart failure, cancer, dementia, dialysis, dependency before stroke
Siontis et al, 2014[42]	US	1975-2012	ECG and medical records	3673 (650)	1661	55	4.1	NA	NA	NA	Age, sex, FHx SCD, NYHA class III/IV, obstructive phenotype, aspirin/ warfarin
Soliman et al, 2014[43]	US	2003-07	ECG and self-reported history	23 928 (1631)	13 937	64	4.5	0	NA	NA	Age, race, region, education, income, cholesterol, smoking, SBP, BMI, diabetes, medication, and history of noncardiac vascular disease, eGFR, CRP, albumin
Soliman et al, 2015[44]	US	1987-89	ECG and medical records	14 462 (1545)	8172	54	21.6	0	249	71	Age, race, study field centre, education, income, cholesterol, smoking status, SBP, BMI, diabetes, eGFR, cardiovascular disease, medication use
Stewart et al, 2002[12]	Scotland	1972-76	ECG	15 406 (100)	8354	54	20	NA	197	NA	Age, stroke, chest pain, cholesterol, DBP, cardiothoracic ratio, glucose, FEV_1, bronchitis, Q waves, ST segment, LBBB
Stortecky et al, 2013[14]	Switzerland	2007-11	Continuous monitor	389 (131)	224	83	1	238	30	364	Age, BMI, hypertension, diabetes, medical history, symptoms, cardiovascular risk (stepwise regression)
van Wijk et al, 2007[45]	Netherlands	1986-93	ECG	2659 (186)	946	66	10.1	277	2659	NA	Age, hypertension, smoking, diabetes, Rankin scale, any infarct, white matter lesion on CT scan
Wolf et al, 1998[18]	US	1989	Medical records	26 753 (13 558)	14 416	NA	3	NA	NA	NA	Matched for age and sex, adjusted for AMI, unstable angina, stable angina, heart failure, hypertension, diabetes, valvular disease, stroke, COPD
Wolfe et al, 2006[46]	UK and Barbados	1995-2003	NA	848 (64)	464	69.6	1.7	94	848	NA	Age, Barbados resident, living alone, Bathel score, smoking, alcohol, IHD untreated and treated, hypertension untreated and treated, diabetes, TIA untreated and treated, incontinence, swallow test, hospital admission

NA=not available, ECG=electrocardiogram, CKD=chronic kidney disease, BP=blood pressure, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, CRP=C reactive protein, LBBB=left bundle branch block, AMI=acute myocardial infarction, COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume, LVEF=left ventricular ejection fraction, BNP=B type natriuretic peptide, NYHA=New York Heart Association, IHD=ischaemic heart disease.

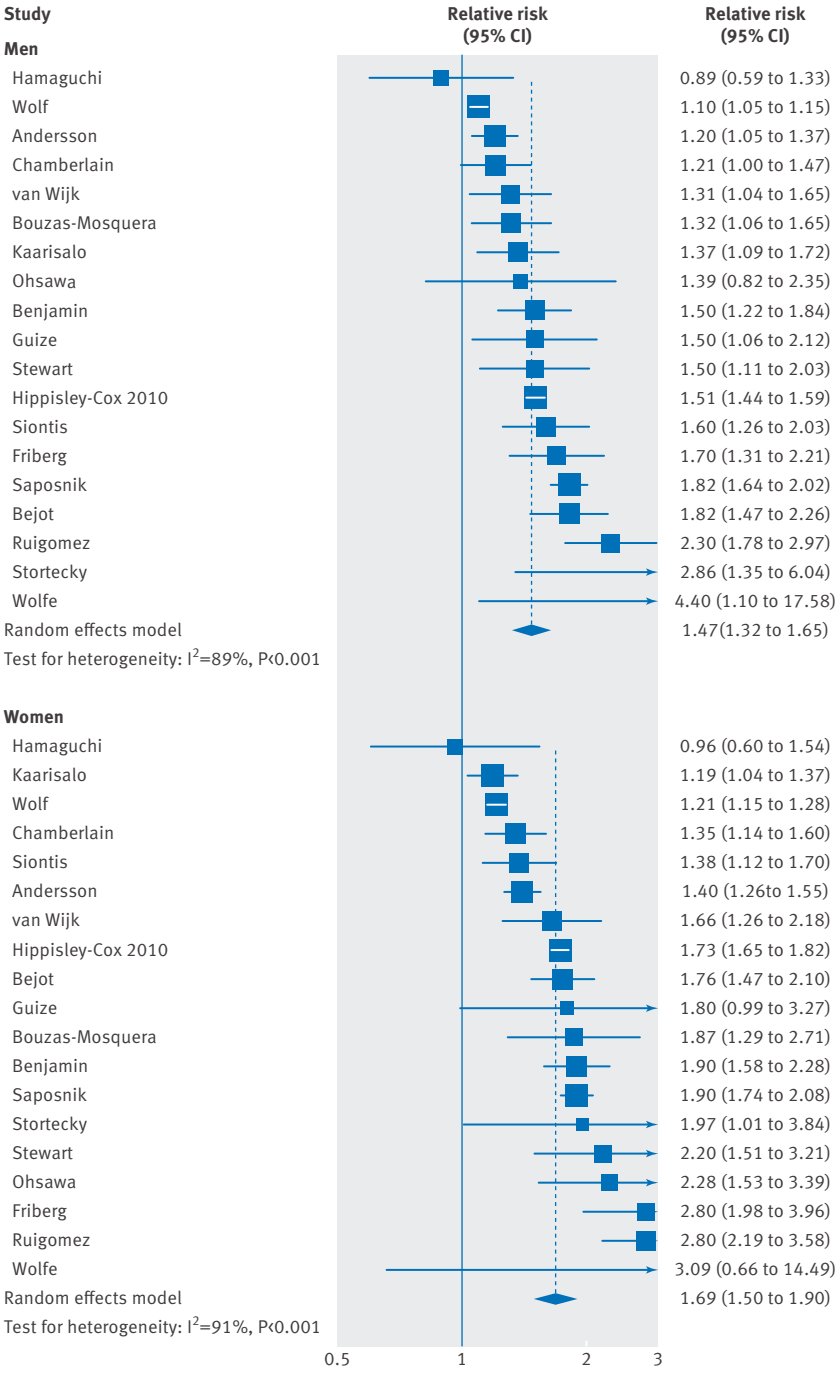

Fig 2 | Maximally adjusted relative risk for all cause mortality for individuals with and without AF by sex. Area of each square is proportional to inverse variance of estimate. Horizontal lines indicate 95% confidence intervals

mortality, 4.3 (1.9 to 7.5) for cardiovascular mortality, 3.1 (1.1 to 6.1) for stroke, 0.6 (0.03 to 1.3) for cardiac events, and 6.1 (2.1 to 12.7) for heart failure.

Sensitivity analyses

Ratios of relative risk for all cause mortality were broadly consistent in seven sensitivity analyses (appendix fig D). Results of tests of interaction were non-significant when we stratified studies by ascertainment of AF through electrocardiography versus use of medical records/self reported history and region (Europe, non-Europe; all P>0.05 for interaction). Results of tests for trend by number of participants, baseline year, and ratio of mortality rate in women to men were also non-significant. Ratios of relative risk, however, declined with increasing length of follow-up and increasing age (appendix fig D).

For ratios of relative risks for stroke, results of tests of interaction by ascertainment method and region were non-significant (appendix fig E). Results of tests for trend by number of participants, baseline year, length of follow-up, and median age were also non-significant. Relative risks were significantly higher in studies with a lower ratio of absolute rate of stroke in women compared with men (P=0.027 for trend for ratio of stroke rate in women to men). When we restricted the meta-analysis to three studies with a ratio of stroke rate in women to men greater than 1 (that is, a greater absolute rate of stroke in women than men), however, atrial fibrillation continued to be associated with a higher relative risk of stroke in women than men (1.47, 95% confidence interval 1.18 to 1.83).

We found no evidence of publication bias for all cause mortality (appendix fig F), though we observed significant publication bias for stroke (appendix fig G; P=0.002). When we used the trim and fill method to control for publication bias, AF was associated with a non-significantly higher risk of stroke in women than in men (relative risk ratio 1.28, 95% confidence interval 0.94 to 1.73).

Discussion

In this systematic review and meta-analysis of 30 studies with 4 371 714 participants, we observed atrial fibrillation (AF) to be a significantly greater risk factor for death and cardiovascular disease in women than in men. AF was associated with a higher relative risk of all cause mortality, stroke, cardiovascular mortality, cardiac events, and heart failure in women compared with men.

Comparison with previous individual studies

Previous studies have presented conflicting evidence on the effect of AF on the risk of death and cardiovascular disease in women. Of the 19 studies on the association of AF with the risk of all cause mortality (fig 2) we included in our analysis, the ratio of relative risks was greater than one but not significant for 11 studies. When we pooled these studies using random effects meta-analysis, the estimate for all cause mortality was significant, indicating that individual studies were underpowered to detect a differential effect of AF on risk of all cause mortality in women compared with men. Similarly, six of the 13 studies that reported a sex specific association of AF with stroke did not detect a significant interaction between women and men (fig 3). When we pooled these studies, however, we observed a significant ratio of relative risks, again indicating a lack of power of some previous individual studies to detect an interaction by sex.

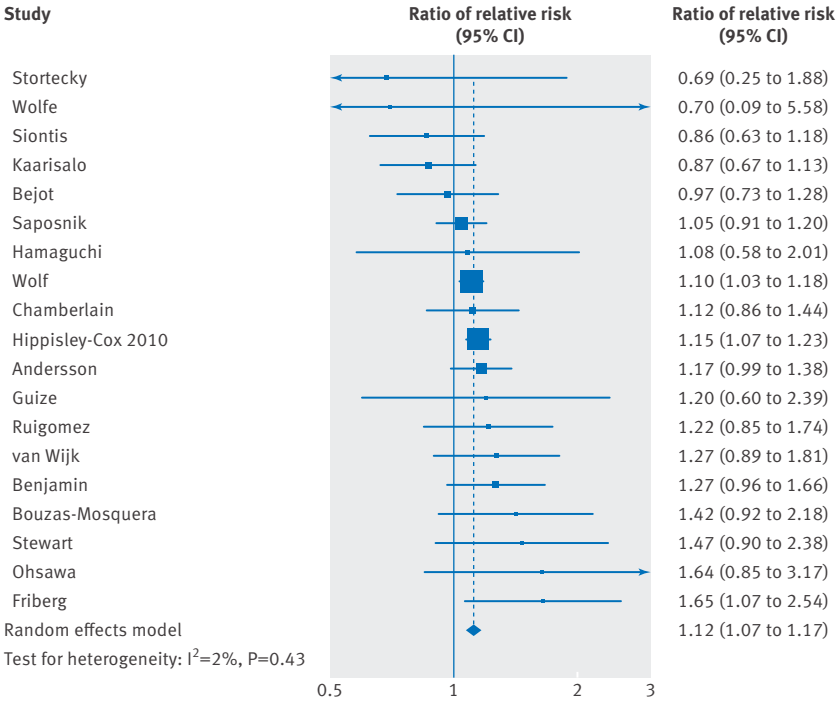

Fig 3 | Maximally adjusted women-to-men ratio of relative risks for any all cause mortality for individuals with and without AF. Area of each square is proportional to inverse variance of estimate. Horizontal lines indicate 95% confidence intervals

Recent meta-analyses have shown that type 2 diabetes is a greater risk factor for coronary heart disease[7 47] (ratio of relative risk 1.44, 95% confidence interval 1.27 to 1.63) and for stroke[8] (1.27, 1.10 to 1.46) in women than in men and that type 1 diabetes is also a greater risk factor for death and cardiovascular disease in women.[48] Evidence of an increased risk of coronary heart disease associated with type 2 diabetes in women has been cited in European Society of Cardiology guidelines for the treatment of cardiovascular disease in patients with type 2 diabetes.[49] Similarly, evidence of an increased risk of stroke associated with type 2 diabetes in women has been included in American Heart Association/American Stroke Association guidelines for stroke prevention in women.[50] Our results show that AF is also a greater risk factor for death and cardiovascular disease in women than in men and extend these previous works showing that women experience the effects of some key risk factors for cardiovascular disease differently to men.

It is unclear what could cause the observed differences in risk of mortality and cardiovascular disease associated with AF between women and men. One possibility is that women with AF are undertreated relative to men. The results of a cohort study of Canadian patients with AF enrolled in 1990-94 support this hypothesis. Canadian women were half as likely as Canadian men to receive warfarin.[51] Analyses of more contemporary cohorts, including a global registry of 17 814 patients with AF[52] and an analysis of 83 513 patients with AF in Quebec,[53] however, showed no differences in use of anticoagulants between men and women with AF.[53] It is therefore unlikely that broad differences in treatment between the sexes are responsible for the increased relative risks we observed in women. Physiological or psychosocial differences between women and men could result in differential effects of AF on cardiovascular risk. For example, women are at a higher risk of torsade de pointes, an often lethal adverse event of antiarrhythmic drugs prescribed for AF.[54] Response to oral anticoagulants could also differ between the sexes, with a higher risk of bleeding observed among women.[55] Future research is needed to distinguish if one or many of these potential mechanisms underlie the differential effects of AF observed in our analysis.

Strengths and limitations

This analysis has several strengths. Firstly, as a systematic review and meta-analysis of all available studies of AF and risk of death and cardiovascular disease in women compared with men, it has greater power than any of the included individual studies to detect differences. This is evident in the meta-analysis of all cause mortality, in which 16 of the included 19 studies did not detect a difference. Secondly, we included only studies that reported the effect of AF on risk of cardiovascular disease and death separately in men and women. This ensured that our primary analysis (the ratio of relative risks) was a within study comparison, minimising the effect of heterogeneity between studies. Thirdly, we included only cohort studies that were adequately adjusted (prespecified requirement to adjust by at least age and history of cardiovascular disease) and that had a minimum of 100 participants with six months' follow-up to reduce the risk of confounding and small study effects. Fourthly, pooled ratios of relative risk for all cause mortality or stroke were broadly consistent in several different sensitivity analyses.

This analysis also has several limitations. Firstly, while we attempted to contact and acquire unpublished data from eligible cohorts, our results might be influenced by publication bias because studies that detect an interaction between AF and risk of death and cardiovascular disease by sex might be more likely to be published. While there was evidence of publication bias for stroke, however, we found no evidence of this for all cause mortality. Furthermore, use of trim and fill procedures resulted in a non-significantly increased effect of AF on risk of stroke in women compared with in men similar in magnitude to other outcomes. Secondly, as a meta-analysis of observational studies, sex differences in the association of AF with risk of death and cardiovascular disease might be caused by unobserved confounding between sexes. For example, women might have had a greater number of comorbidities at the time of diagnosis of AF, which could not be fully adjusted for. However, we required included studies to adjust for, at minimum, age and presence of cardiovascular comorbidities, and we used the maximally adjusted model available. Thirdly, many of the studies had differences in design, duration of follow-up, outcome ascertainment, and populations. Indeed, we observed a greater absolute increase in cardiovascular death than all

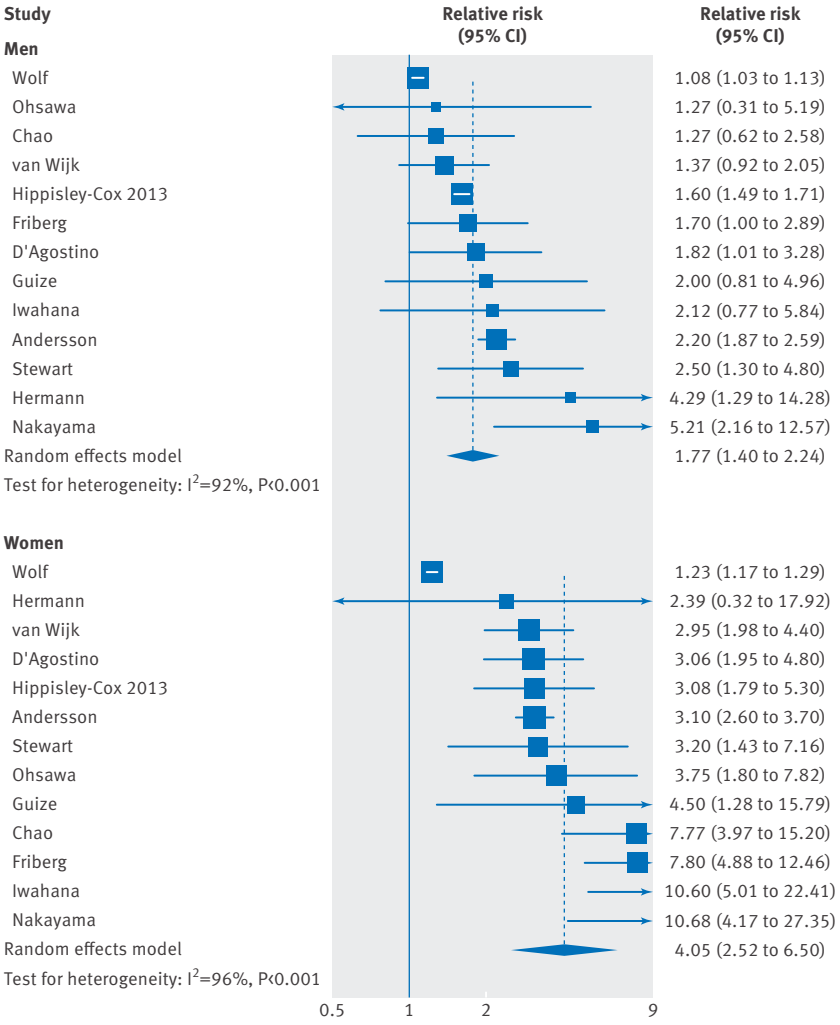

Fig 4 | Maximally adjusted relative risk for stroke for individuals with and without AF by sex. Area of each of each square is proportional to inverse variance of estimate. Horizontal lines indicate 95% confidence intervals

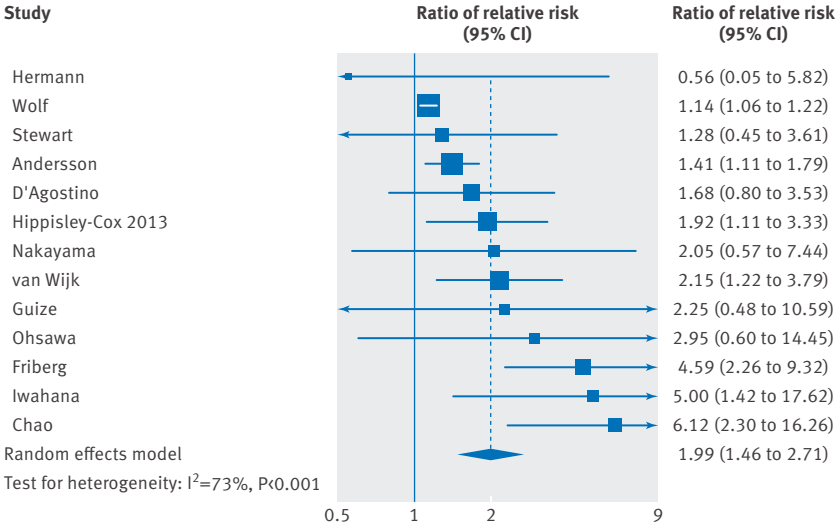

Fig 5 | Maximally adjusted women-to-men ratio of relative risks for stroke for individuals with and without AF. Area of each square is proportional to inverse variance of estimate. Horizontal lines indicate 95% confidence intervals

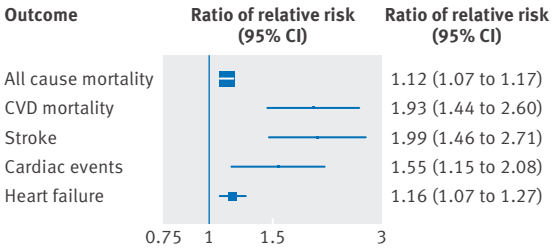

Fig 6 | Maximally adjusted pooled women-to-men ratio of relative risks for all cause mortality, CVD (cardiovascular) mortality, stroke, cardiac events, and heart failure, comparing individuals with and without AF. Area of each square is proportional to inverse variance of estimate. Horizontal lines indicate 95% confidence intervals

cause death because of differing studies contributing to either outcome. Because our primary analysis was focused on comparisons within studies (the ratio of relative risks between women and men), however, heterogeneity was low for outcomes other than stroke. Fourthly, our primary analysis focused on the ratio of relative risks, which might not reflect absolute differences in risk of death and cardiovascular disease associated with AF between sexes. We found no evidence of a difference in ratios of relative risk in studies in which the absolute risk of all cause mortality was higher in men (appendix fig D), and a higher ratio of relative risks continued to be observed in studies in which women had a higher absolute rate of stroke than men (appendix fig E). Finally, we were unable to ascertain the underlying cause of the sex differences in the association of AF with risk of mortality and cardiovascular disease.

Implications for clinicians, policy makers, and future research

This analysis has several implications. With respect to clinical care, our results indicate that AF is associated with worse outcomes in women than in men. Although female sex is incorporated as a risk factor for stroke in the widely used CHA_2DS_2-VASc score,[56] AF seems to affect women and men differently. The American Heart Association recently recommended the development of a specific risk score for stroke in women as some risk factors for stroke are unique to women, others are more prevalent in women, and others differentially increase the risk of stroke in women.[57] These results support the development of such a score. They also, however, show that AF is associated with an increased risk of all cause mortality, cardiovascular mortality, and cardiac events in women relative to men. Therefore, it might be appropriate for clinicians to consider more aggressive treatment of risk factors in women with AF as they seem to be at higher proportional risk of death and cardiovascular disease.

With regard to public health policy, these results indicate that sex differences in the effect of AF on risk of death and cardiovascular disease exist. Consequently, estimation of the global and regional burden of AF should be independent of sex. Allocation of public health resources for prevention and treatment

of AF should also consider the differential effects of AF by sex. Future research should be encouraged to determine the underlying causes of the observed sex differences.

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

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Murray CJL, Vos T, Lozano R etal. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380: 2197-223. doi:10.1016/S0140-6736(12)61689-4. 23245608
2 Chugh SS, Havmoeller R, Narayanan K etal. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129: 837-47. doi:10.1161/CIRCULATIONAHA.113.005119. 24345399
3 Lozano R, Naghavi M, Foreman K etal. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380: 2095-128. doi:10.1016/S0140-6736(12)61728-0. 23245604
4 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22: 983-8. doi:10.1161/01.STR.22.8.983 1866765
5 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 9737513
6 Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;378: 1297-305. doi:10.1016/S0140-6736(11)60781-2. 21839503
7 Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014;57: 1542-51. doi:10.1007/s00125-014-3260-6. 24859435
8 Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;383: 1973-80. doi:10.1016/S0140-6736(14)60040-4. 24613026
9 Friberg L, Benson L, Rosenqvist M, Lip GYH. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012;344: e3522. doi:10.1136/bmj.e3522. 22653980
10 Chao T-F, Liu C-J, Chen S-J etal. 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. 22871677
11 Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GBCopenhagen 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. 15464671
12 Stewart S, Hart CL, Hole DJ, McMurray JJV. 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 12401529
13 Hamaguchi S, Yokoshiki H, Kinugawa S etalJapanese 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 19755750
14 Stortecky S, Buellesfeld L, Wenaweser P etal. 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. 23386662
15 Stroup DF, Berlin JA, Morton SC etal. 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 10789670
16 Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med* 2001;135: 1061-73. doi:10.7326/0003-4819-135-12-200112180-00010 11747385
17 Wells GA, Shea B, O'connell D, Peterson J, Welch V. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (accessed 3 Jul2015).
18 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 9472202
19 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 9310563
20 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 10877304
21 Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015;101: 1182-9. doi:10.1136/heartjnl-2015-307516. 26041770
22 Carroll K, Murad S, Eliahoo J, Majeed A. Stroke incidence and risk factors in a population-based prospective cohort study. *Health Stat Q* 2001;12; 18- 26.
23 de Giuli F, Khaw K-T, Cowie MR, Sutton GC, Ferrari R, Poole-Wilson PA. Incidence and outcome of persons with a clinical diagnosis of heart failure in a general practice population of 696,884 in the United Kingdom. *Eur J Heart Fail* 2005;7: 295-302. doi:10.1016/j.ejheart.2004.10.017. 15718168
24 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. 23641033
25 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- 805.
26 Andersson T, Magnuson A, Bryngelsson I-L etal. 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. 25499348

27 Béjot Y, Ben Salem D, Osseby GV etal. 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. 19171832
28 Bouzas-Mosquera A, Peteiro J, Broullón FJ etal. 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. 20403467
29 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. 21920917
30 Chen LY, Sotoodehnia N, Bůžková P etal. 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. 23404043
31 D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994;25: 40-3. doi:10.1161/01.STR.25.1.40. 8266381
32 Genovesi S, Valsecchi MG, Rossi E etal. 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. 19293137
33 Hermann DM, Gronewold J, Lehmann N etalHeinz 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. 23449263
34 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. 21148212
35 Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. *BMJ Open* 2015;5: e008503. doi:10.1136/bmjopen-2015-008503. 26353872
36 Iwahana H, Ishikawa S, Ishikawa J etal. 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 21307613
37 Kaarisalo MM, Immonen-Räihä P, Marttila RJ etal. 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 9361653
38 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 8996487
39 Ohsawa M, Okayama A, Okamura T etal. 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 17526974
40 Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA. Risk of mortality in a cohort of patients newly diagnosed with chronic atrial fibrillation. *BMC Cardiovasc Disord* 2002;2: 5. doi:10.1186/1471-2261-2-5 11897013
41 Saposnik G, Kapral MK, Liu Y etalInvestigators of the Registry of the Canadian Stroke NetworkStroke 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. 21300951
42 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. 24965028
43 Soliman EZ, Safford MM, Muntner P etal. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014;174: 107-14. doi:10.1001/jamainternmed.2013.11912. 24190540
44 Soliman EZ, Lopez F, O'Neal WT etal. 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. 25918127
45 van Wijk I, Koudstaal PJ, Kappelle LJ, van Gijn J, Gorter JW, Algra ALiLAC 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. 18096680
46 Wolfe CDA, Corbin DOC, Smeeton NC etal. Poststroke survival for black-Caribbean populations in Barbados and South London. *Stroke* 2006;37: 1991-6. doi:10.1161/01.STR.0000230647.77889.84. 16794207
47 Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;332: 73-8. doi:10.1136/bmj.38678.389583.7C. 16371403
48 Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;3: 198-206. doi:10.1016/S2213-8587(14)70248-7. 25660575
49 Rydén L, Grant PJ, Anker SD etal. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34: 3035-87. doi:10.1093/eurheartj/eht108. 23996285
50 Bushnell C, McCullough L. Stroke prevention in women: synopsis of the 2014 American Heart Association/American Stroke Association guideline. *Ann Intern Med* 2014;160: 853-7. doi:10.7326/M14-0762. 24935489
51 Humphries KH, Kerr CR, Connolly SJ etal. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. *Circulation* 2001;103: 2365-70. doi:10.1161/01.CIR.103.19.2365 11352885
52 Lip GYH, Rushton-Smith SK, Goldhaber SZ etalGARFIELD-AF Investigators. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes* 2015;8(Suppl 1): S12-20. doi:10.1161/CIRCOUTCOMES.114.001556. 25714828
53 Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012;307: 1952-8. doi:10.1001/jama.2012.3490. 22570463
54 Roden DM, Kannankeril P, Darbar D. On the relationship among QT interval, atrial fibrillation, and torsade de pointes. *Europace* 2007;9(Suppl 4): iv1-3. doi:10.1093/europace/eum165. 17766319
55 Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis. *Thromb Res* 2013;132: 185-9. doi:10.1016/j.thromres.2013.07.017. 23932014
56 Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137: 263-72. doi:10.1378/chest.09-1584. 19762550
57 Bushnell C, McCullough LD, Awad IA etalAmerican Heart Association Stroke CouncilCouncil on Cardiovascular and Stroke NursingCouncil on Clinical CardiologyCouncil on Epidemiology and PreventionCouncil for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45: 1545-88. doi:10.1161/01.str.0000442009.06663.48. 24503673

Appendix: Supplementary tables A and B; figures A-G; extra references