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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.[1] It is increasing in prevalence in both developing and developed countries and is associated with an increased risk of all cause mortality and stroke, as well as higher medical costs and a reduced quality of life.[2 3]

Although the prevention and management of stroke in atrial fibrillation has been the primary focus of guidelines[4] and clinical trials,[5 6] 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.[27-10] Individual studies, however, have provided conflicting estimates of the strength of the association between atrial fibrillation and a range of cardiovascular diseases and have not agreed on whether there are relevant associations at all, possibly because of the small sample sizes examined.[11-14] Pooling all available evidence could allow for the determination of robust estimates of any associations that could inform outcome selection in future randomised controlled trials and guide public health efforts to reduce the incidence of associated cardiovascular disease.

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

Methods

This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16]

Data sources and searches

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

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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.[10]

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,[17] 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)×(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.[18] We used Centers for Disease Control and Prevention estimates of the incidence of all cause mortality[19] and chronic kidney disease.[20] Absolute risk increases were expressed in events per 1000 participant years of follow-up. As we could not obtain an estimate for the incidence of major cardiovascular events in the US general population, we have not provided an absolute risk increase associated with atrial fibrillation for major cardiovascular events.

Stratified analyses and sensitivity analyses

To include a sufficient number of studies in each stratum, we restricted stratified and sensitivity analyses to

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

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

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed.[21] We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until 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.[22] Funnel plot asymmetry was further confirmed with Egger's test.[23] If asymmetry was present, we used the trim-and-fill method to adjust for publication bias.[24]

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[2 11 12 14 25-86] 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≥0.2 for trend, fig 4).

Identified and screened (n=4100):
　Medline search (n=1948)
　Embase search (n=2143)
　Bibliographic review (n=9)

Excluded during initial screen for violating inclusion criteria (n=3836):
　Reported unrelated population or outcome (n=3212)
　Reported <50 AF and controls (each) or <6 months' follow-up (n=87)
　Did not report cohort study (n=335)
　Examined postoperative AF (n=133)
　Reported same cohort and outcome (n=69)

Screened in full text review (n=264)

Excluded (n=160):
　Reported same cohort and outcome (n=18)
　Inadequate adjustment (n=30)
　2 did not report variables in model (n=2)
　Inadequate follow-up (n=21)
　Inadequate size (n=32)
　Did not report association between AF and prespecified outcomes (n=42)
　Not cohort study (n=15)

Included in final analysis (n=104):
　Studies acertained AF with electrocardiography (n=54)
　Studies acertained AF with medical records (n=17)
　Studies acertained AF with electrocardiography and medical records (n=28)
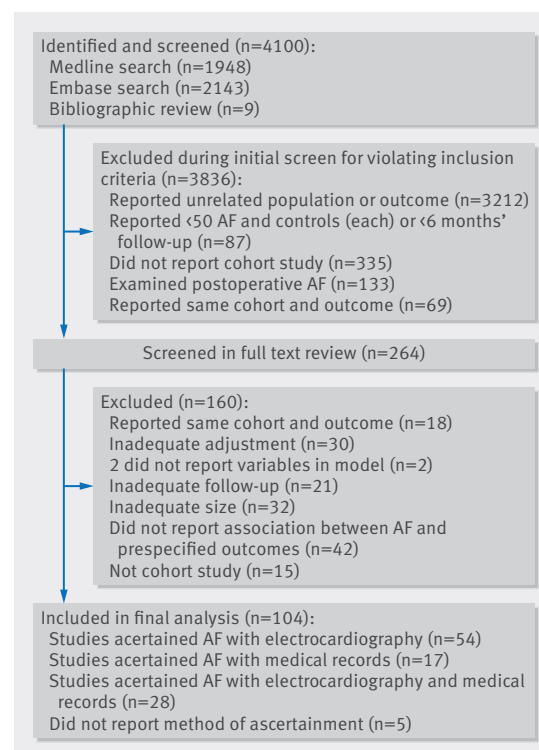　Did not report method of ascertainment (n=5)

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

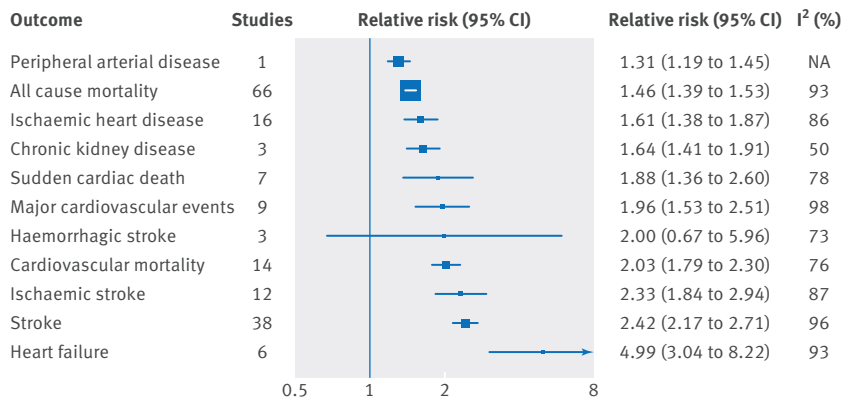| Outcome	Studies	Relative risk (95% CI)	Relative risk (95% CI)	I² (%)
Peripheral arterial disease	1		1.31 (1.19 to 1.45)	NA
All cause mortality	66		1.46 (1.39 to 1.53)	93
Ischaemic heart disease	16		1.61 (1.38 to 1.87)	86
Chronic kidney disease	3		1.64 (1.41 to 1.91)	50
Sudden cardiac death	7		1.88 (1.36 to 2.60)	78
Major cardiovascular events	9		1.96 (1.53 to 2.51)	98
Haemorrhagic stroke	3		2.00 (0.67 to 5.96)	73
Cardiovascular mortality	14		2.03 (1.79 to 2.30)	76
Ischaemic stroke	12		2.33 (1.84 to 2.94)	87
Stroke	38		2.42 (2.17 to 2.71)	96
Heart failure	6		4.99 (3.04 to 8.22)	93

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[2 11 32 61 66 68 70 75 77 78 81 82 87 88] 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[2 31 41 52 68 71 88-90] 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 (I²=76% and P<0.001 for cardiovascular mortality and I²=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[2 31 33 42 48 52 61 66 70 71 77 78 81 82 87 88 91-112] 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 (I²=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[36 51 59 68 91 92 100 101 103 107 111 113] 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 (I²=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[68 91 107] 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[2 8 13 14 42 48 52 54 61 66 68 78 82 85 88 101] involving 395 957 patients examined ischaemic heart disease as an outcome (figs 2 and 6). There were 30 977 (7.8%) adults with atrial fibrillation, and the prevalence ranged from 0.2% to 56.3%. The median follow-up was 4.1 years (interquartile range 3.2-8.3). The pooled relative risk was 1.61 (95% confidence interval 1.38 to 1.87). There was considerable heterogeneity (I²=86%, P<0.001). The absolute risk increase for ischaemic heart disease was 1.4 events/1000 participant years (0.9 to 2). The pooled relative risk for ischaemic heart disease was consistent across subgroups of baseline cardiovascular disease, age, and baseline risk (fig I in appendix).

Seven studies[13 45 54 85 114-116] 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 (I²=78%, P<0.001), we did not perform sensitivity analyses because of the small number of studies. The absolute risk increase in sudden cardiac death was 0.6 events/1000 participant years (0.2 to 1.1).

Congestive heart failure

Six studies[2 42 71 101 117 118] involving 82 476 patients examined incident congestive heart failure as an outcome. There were 11 677 (14.2%) adults with atrial fibrillation, and the prevalence ranged from 0.6% to 43.2%. The median follow-up was 5.4 years (interquartile range 3.6-15.4). The pooled relative risk of incident congestive heart failure was 4.99 (95% confidence interval 3.04 to 8.22; fig 2 and fig K in appendix). Though there was considerable heterogeneity (I²=93%, P<0.001), we did not perform sensitivity analyses because of the small number of studies. The absolute risk increase in incident congestive heart failure associated with atrial fibrillation was 11.1 (5.7 to 20) events/1000 participant years.
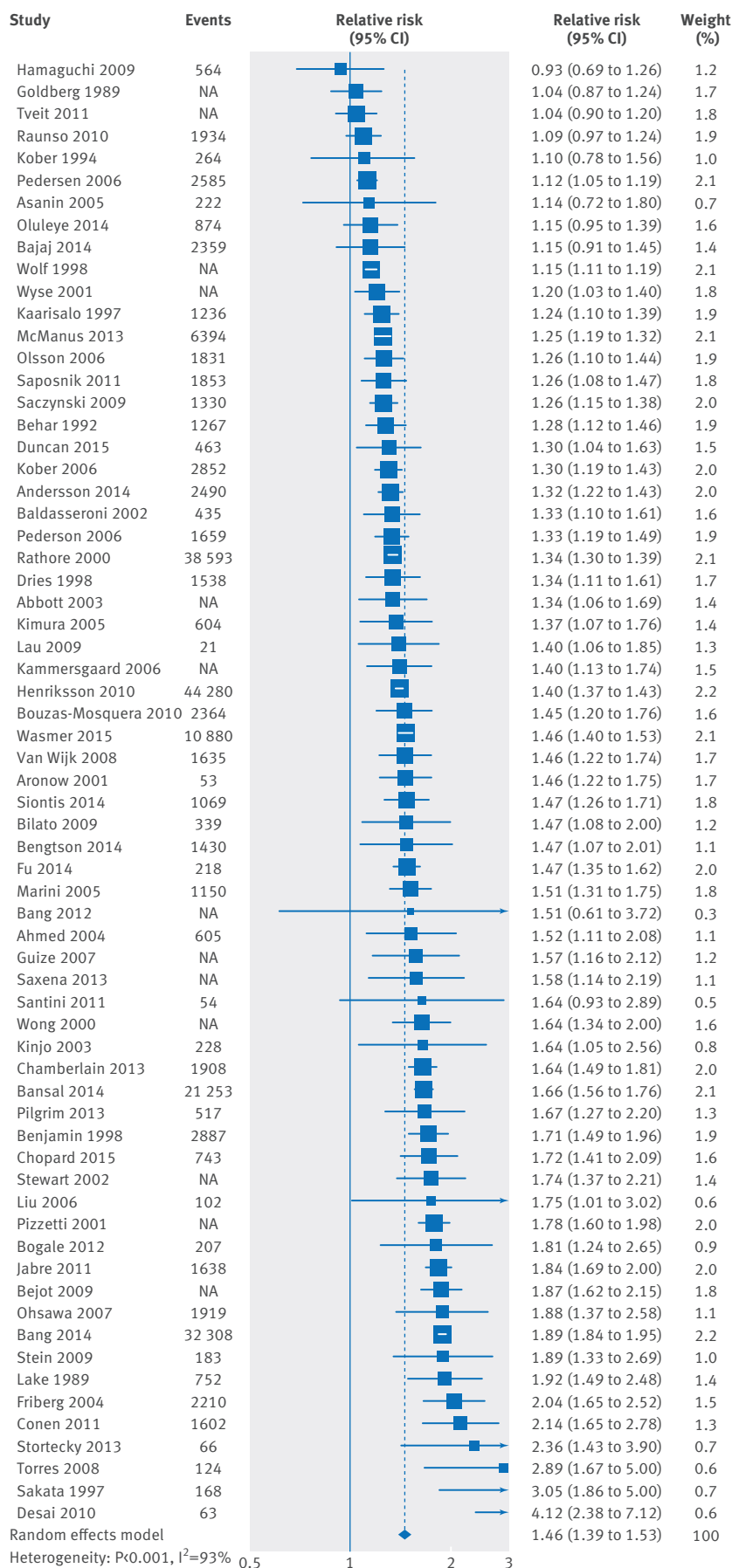
Study	Events		Relative risk (95% CI)	Weight (%)
Hamaguchi 2009	564		0.93 (0.69 to 1.26)	1.2
Goldberg 1989	NA		1.04 (0.87 to 1.24)	1.7
Tveit 2011	NA		1.04 (0.90 to 1.20)	1.8
Raunso 2010	1934		1.09 (0.97 to 1.24)	1.9
Kober 1994	264		1.10 (0.78 to 1.56)	1.0
Pedersen 2006	2585		1.12 (1.05 to 1.19)	2.1
Asanin 2005	222		1.14 (0.72 to 1.80)	0.7
Oluleye 2014	874		1.15 (0.95 to 1.39)	1.6
Bajaj 2014	2359		1.15 (0.91 to 1.45)	1.4
Wolf 1998	NA		1.15 (1.11 to 1.19)	2.1
Wyse 2001	NA		1.20 (1.03 to 1.40)	1.8
Kaarisalo 1997	1236		1.24 (1.10 to 1.39)	1.9
McManus 2013	6394		1.25 (1.19 to 1.32)	2.1
Olsson 2006	1831		1.26 (1.10 to 1.44)	1.9
Saposnik 2011	1853		1.26 (1.08 to 1.47)	1.8
Saczynski 2009	1330		1.26 (1.15 to 1.38)	2.0
Behar 1992	1267		1.28 (1.12 to 1.46)	1.9
Duncan 2015	463		1.30 (1.04 to 1.63)	1.5
Kober 2006	2852		1.30 (1.19 to 1.43)	2.0
Andersson 2014	2490		1.32 (1.22 to 1.43)	2.0
Baldasseroni 2002	435		1.33 (1.10 to 1.61)	1.6
Pederson 2006	1659		1.33 (1.19 to 1.49)	1.9
Rathore 2000	38 593		1.34 (1.30 to 1.39)	2.1
Dries 1998	1538		1.34 (1.11 to 1.61)	1.7
Abbott 2003	NA		1.34 (1.06 to 1.69)	1.4
Kimura 2005	604		1.37 (1.07 to 1.76)	1.4
Lau 2009	21		1.40 (1.06 to 1.85)	1.3
Kammersgaard 2006	NA		1.40 (1.13 to 1.74)	1.5
Henriksson 2010	44 280		1.40 (1.37 to 1.43)	2.2
Bouzas-Mosquera 2010	2364		1.45 (1.20 to 1.76)	1.6
Wasmer 2015	10 880		1.46 (1.40 to 1.53)	2.1
Van Wijk 2008	1635		1.46 (1.22 to 1.74)	1.7
Aronow 2001	53		1.46 (1.22 to 1.75)	1.7
Siontis 2014	1069		1.47 (1.26 to 1.71)	1.8
Bilato 2009	339		1.47 (1.08 to 2.00)	1.2
Bengtson 2014	1430		1.47 (1.07 to 2.01)	1.1
Fu 2014	218		1.47 (1.35 to 1.62)	2.0
Marini 2005	1150		1.51 (1.31 to 1.75)	1.8
Bang 2012	NA		1.51 (0.61 to 3.72)	0.3
Ahmed 2004	605		1.52 (1.11 to 2.08)	1.1
Guize 2007	NA		1.57 (1.16 to 2.12)	1.2
Saxena 2013	NA		1.58 (1.14 to 2.19)	1.1
Santini 2011	54		1.64 (0.93 to 2.89)	0.5
Wong 2000	NA		1.64 (1.34 to 2.00)	1.6
Kinjo 2003	228		1.64 (1.05 to 2.56)	0.8
Chamberlain 2013	1908		1.64 (1.49 to 1.81)	2.0
Bansal 2014	21 253		1.66 (1.56 to 1.76)	2.1
Pilgrim 2013	517		1.67 (1.27 to 2.20)	1.3
Benjamin 1998	2887		1.71 (1.49 to 1.96)	1.9
Chopard 2015	743		1.72 (1.41 to 2.09)	1.6
Stewart 2002	NA		1.74 (1.37 to 2.21)	1.4
Liu 2006	102		1.75 (1.01 to 3.02)	0.6
Pizzetti 2001	NA		1.78 (1.60 to 1.98)	2.0
Bogale 2012	207		1.81 (1.24 to 2.65)	0.9
Jabre 2011	1638		1.84 (1.69 to 2.00)	2.0
Bejot 2009	NA		1.87 (1.62 to 2.15)	1.8
Ohsawa 2007	1919		1.88 (1.37 to 2.58)	1.1
Bang 2014	32 308		1.89 (1.84 to 1.95)	2.2
Stein 2009	183		1.89 (1.33 to 2.69)	1.0
Lake 1989	752		1.92 (1.49 to 2.48)	1.4
Friberg 2004	2210		2.04 (1.65 to 2.52)	1.5
Conen 2011	1602		2.14 (1.65 to 2.78)	1.3
Stortecky 2013	66		2.36 (1.43 to 3.90)	0.7
Torres 2008	124		2.89 (1.67 to 5.00)	0.6
Sakata 1997	168		3.05 (1.86 to 5.00)	0.7
Desai 2010	63		4.12 (2.38 to 7.12)	0.6
Random effects model			1.46 (1.39 to 1.53)	100

Heterogeneity: P<0.001, I²=93%

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

Chronic kidney disease and peripheral arterial disease

Three studies[10 119 120] 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[121] 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 of heterogeneity until I^2 was less than 50%, pooled relative risks for outcomes were similar to the original estimates (table L in appendix). Atrial
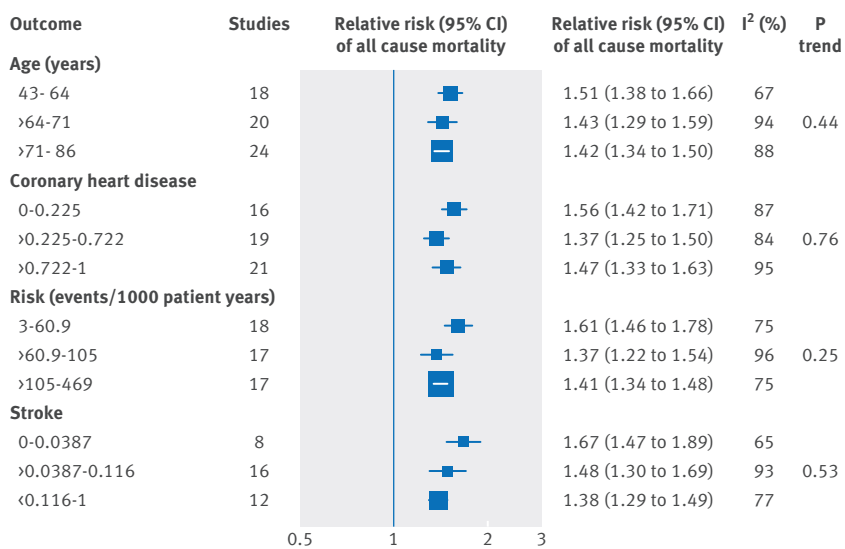
Outcome	Studies	Relative risk (95% CI) of all cause mortality	Relative risk (95% CI) of all cause mortality	I^2 (%)	P trend
Age (years)					
43-64	18		1.51 (1.38 to 1.66)	67	
>64-71	20		1.43 (1.29 to 1.59)	94	0.44
>71-86	24		1.42 (1.34 to 1.50)	88	
Coronary heart disease					
0-0.225	16		1.56 (1.42 to 1.71)	87	
>0.225-0.722	19		1.37 (1.25 to 1.50)	84	0.76
>0.722-1	21		1.47 (1.33 to 1.63)	95	
Risk (events/1000 patient years)					
3-60.9	18		1.61 (1.46 to 1.78)	75	
>60.9-105	17		1.37 (1.22 to 1.54)	96	0.25
>105-469	17		1.41 (1.34 to 1.48)	75	
Stroke					
0-0.0387	8		1.67 (1.47 to 1.89)	65	
>0.0387-0.116	16		1.48 (1.30 to 1.69)	93	0.53
<0.116-1	12		1.38 (1.29 to 1.49)	77	

0.5   1   2   3

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.[122] 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.[123] 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.[124] We observed that the association between atrial fibrillation and cardiovascular disease and death was generally consistent, irrespective of baseline history of ischaemic heart disease, baseline history of stroke, mean participant age, and baseline risk. There were, however, two notable exceptions. Firstly, relative risk estimates for general population studies were typically larger than estimates based on studies in specific settings. This could be related to the selection of the controls and the proportion of patients with atrial fibrillation receiving effective evidence based treatments. Secondly, the relative risk of all cause mortality was lower in studies with a higher proportion of participants receiving anticoagulation, but we did not observe a similar pattern for stroke. The absence of any association between the relative risk of stroke and the use of anticoagulation should be interpreted with caution because of the small number of studies included in this analysis. Furthermore, if warfarin is used, it is difficult to determine the effectiveness of anticoagulation without measurements of INR (international normalised ratio). Differences in the proportion of adults with a low INR would affect our stratified analyses for stroke.

While relative associations between atrial fibrillation and cardiovascular disease and death were generally similar across participant characteristics, absolute increases in risk associated with atrial fibrillation would be expected to be larger among individuals with a higher baseline risk of cardiovascular disease. These results therefore suggest that atrial fibrillation is associated with greater absolute increases in risk of
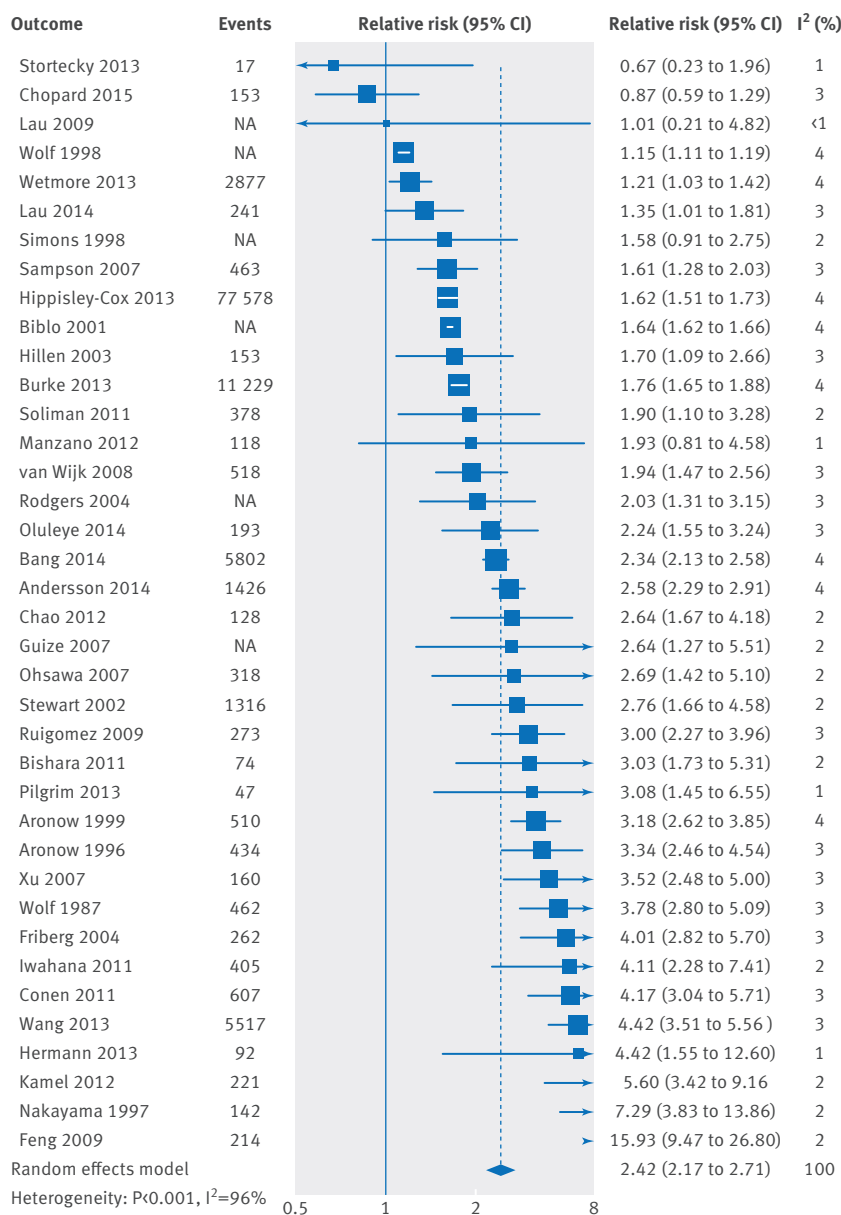
Outcome	Events	Relative risk (95% CI)	Relative risk (95% CI)	I² (%)
Stortecky 2013	17		0.67 (0.23 to 1.96)	1
Chopard 2015	153		0.87 (0.59 to 1.29)	3
Lau 2009	NA		1.01 (0.21 to 4.82)	<1
Wolf 1998	NA		1.15 (1.11 to 1.19)	4
Wetmore 2013	2877		1.21 (1.03 to 1.42)	4
Lau 2014	241		1.35 (1.01 to 1.81)	3
Simons 1998	NA		1.58 (0.91 to 2.75)	2
Sampson 2007	463		1.61 (1.28 to 2.03)	3
Hippisley-Cox 2013	77 578		1.62 (1.51 to 1.73)	4
Biblo 2001	NA		1.64 (1.62 to 1.66)	4
Hillen 2003	153		1.70 (1.09 to 2.66)	3
Burke 2013	11 229		1.76 (1.65 to 1.88)	4
Soliman 2011	378		1.90 (1.10 to 3.28)	2
Manzano 2012	118		1.93 (0.81 to 4.58)	1
van Wijk 2008	518		1.94 (1.47 to 2.56)	3
Rodgers 2004	NA		2.03 (1.31 to 3.15)	3
Oluleye 2014	193		2.24 (1.55 to 3.24)	3
Bang 2014	5802		2.34 (2.13 to 2.58)	4
Andersson 2014	1426		2.58 (2.29 to 2.91)	4
Chao 2012	128		2.64 (1.67 to 4.18)	2
Guize 2007	NA		2.64 (1.27 to 5.51)	2
Ohsawa 2007	318		2.69 (1.42 to 5.10)	2
Stewart 2002	1316		2.76 (1.66 to 4.58)	2
Ruigomez 2009	273		3.00 (2.27 to 3.96)	3
Bishara 2011	74		3.03 (1.73 to 5.31)	2
Pilgrim 2013	47		3.08 (1.45 to 6.55)	1
Aronow 1999	510		3.18 (2.62 to 3.85)	4
Aronow 1996	434		3.34 (2.46 to 4.54)	3
Xu 2007	160		3.52 (2.48 to 5.00)	3
Wolf 1987	462		3.78 (2.80 to 5.09)	3
Friberg 2004	262		4.01 (2.82 to 5.70)	3
Iwahana 2011	405		4.11 (2.28 to 7.41)	2
Conen 2011	607		4.17 (3.04 to 5.71)	3
Wang 2013	5517		4.42 (3.51 to 5.56)	3
Hermann 2013	92		4.42 (1.55 to 12.60)	1
Kamel 2012	221		5.60 (3.42 to 9.16	2
Nakayama 1997	142		7.29 (3.83 to 13.86)	2
Feng 2009	214		15.93 (9.47 to 26.80)	2
Random effects model			2.42 (2.17 to 2.71)	100
Heterogeneity: P<0.001, I²=96%				

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 (I²>70%) for all vascular outcomes except for chronic kidney disease. This was not unexpected and might be caused by differences in study designs, methodological characteristics, type of atrial fibrillation, use of secondary prevention (such as anticoagulation) among included studies, and the definition and ascertainment of endpoints. For instance, the criteria in well established prospective cohorts[8] were comprehensively detailed, whereas the criteria and specific diagnostic codes used in analyses of administrative data were not consistently provided.[51] Differences in the diagnostic codes used in administrative data could have contributed to the high heterogeneity in our study. Nonetheless, when we systematically and sequentially excluded individual studies until heterogeneity was moderate (I²<50%), relative risk estimates for vascular outcomes were consistent and significant, suggesting that the high levels of heterogeneity were not inflating summary relative risk estimates. Thirdly, studies were classified as well adjusted if they adjusted for age, sex, baseline cardiovascular disease, and at least two cardiovascular risk factors. Even though more stringent criteria could be used, such as requiring studies to adjust for drugs and outcome specific risk factors (for example, adjustment for race for the outcome of chronic kidney disease), there will nonetheless be residual confounding in the estimates derived from observational studies. Accordingly, it is likely that there are other variables that contribute to the association between atrial fibrillation and our outcomes of interest, in addition to any possible causal disease specific effects. Fourthly, because of our strict selection criteria, we identified fewer than nine studies for some outcomes and were unable to conduct sensitivity analyses. This is particularly important for congestive heart failure because the relative and absolute risk estimates for incident congestive heart failure were the highest among the outcomes we examined. It is therefore noteworthy that four of the six studies[24 42 71 101] 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.[7] It is also possible that the
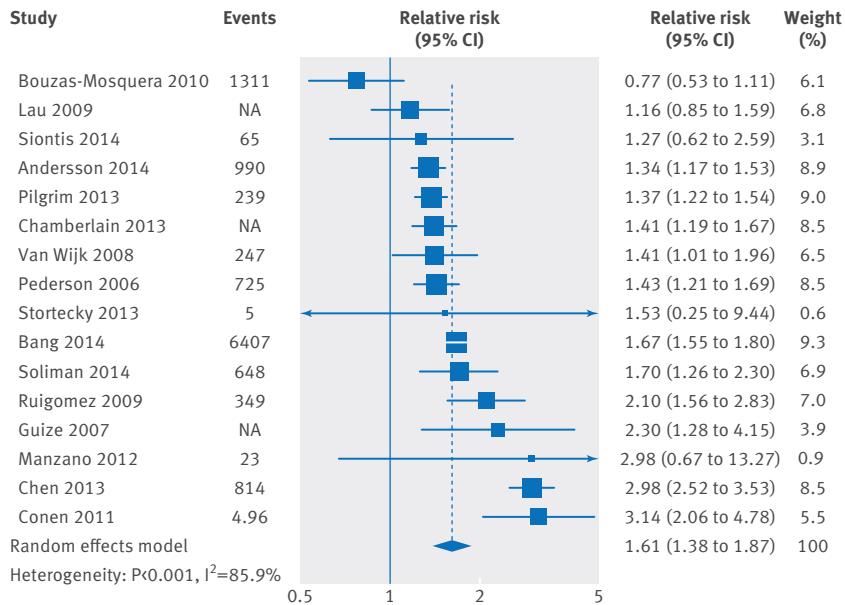
Study	Events	Relative risk (95% CI)	Relative risk (95% CI)	Weight (%)
Bouzas-Mosquera 2010	1311		0.77 (0.53 to 1.11)	6.1
Lau 2009	NA		1.16 (0.85 to 1.59)	6.8
Siontis 2014	65		1.27 (0.62 to 2.59)	3.1
Andersson 2014	990		1.34 (1.17 to 1.53)	8.9
Pilgrim 2013	239		1.37 (1.22 to 1.54)	9.0
Chamberlain 2013	NA		1.41 (1.19 to 1.67)	8.5
Van Wijk 2008	247		1.41 (1.01 to 1.96)	6.5
Pederson 2006	725		1.43 (1.21 to 1.69)	8.5
Stortecky 2013	5		1.53 (0.25 to 9.44)	0.6
Bang 2014	6407		1.67 (1.55 to 1.80)	9.3
Soliman 2014	648		1.70 (1.26 to 2.30)	6.9
Ruigomez 2009	349		2.10 (1.56 to 2.83)	7.0
Guize 2007	NA		2.30 (1.28 to 4.15)	3.9
Manzano 2012	23		2.98 (0.67 to 13.27)	0.9
Chen 2013	814		2.98 (2.52 to 3.53)	8.5
Conen 2011	4.96		3.14 (2.06 to 4.78)	5.5
Random effects model			1.61 (1.38 to 1.87)	100
Heterogeneity: P<0.001, I^2=85.9%				

0.5   1   2   5

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.[125 126]

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

Finally, our study could have implications for the prioritisation of public health resources and the development of novel interventions for adults with atrial fibrillation. In particular, the development and testing of novel oral anticoagulants has been the principal focus of clinical care in atrial fibrillation, but recent studies have shown that these drugs reduce mortality related to stroke, with little reduction in mortality related to congestive heart failure and sudden cardiac death.[123] Similarly, pharmacological control of atrial fibrillation and the restoration of sinus rhythm has shown no benefit over rate control for sudden cardiac death,[130] worsening heart failure,[131] or mortality.[130] It could be that rhythm control treatments might not have been effective at treating atrial fibrillation or that the treatments resulted in additional side effects that outweighed the benefits of restoring sinus rhythm.

Alternatively, if atrial fibrillation is not the cause of these non-stroke outcomes, this could explain the absence of treatment benefit even when it is controlled.

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

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

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