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Atrial fibrillation and the risks of cardiovascular disease, renal disease and death: a meta-analysis

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ABSTRACT

Objectives: The relationship between atrial fibrillation (AF) and the development a wide range of cardiovascular diseases is unclear. We aimed to quantify the associations between AF and cardiovascular diseases and death.

Design: Systematic Review and Meta-analysis

Data Sources: We conducted a systematic search of MEDLINE and EMBASE

Eligibility Criteria: We included prospective cohort studies examining the association of AF with cardiovascular disease, renal disease and death. Two reviewers independently extracted study characteristics and the relative risk (RR) of outcomes associated with AF, specifically all-cause mortality, cardiovascular mortality, major cardiovascular events, any stroke, ischemic stroke, hemorrhagic stroke, ischemic heart disease, sudden cardiac death, congestive heart failure, and chronic kidney disease. Estimates were pooled using inverse-variance weighted random effects meta-analysis.

Results: One hundred eligible cohort studies involving 9,620,130 participants (577,317 with AF) were identified. AF was associated with an increased risk of all-cause mortality (relative risk 1.46; 95% confidence interval 1.39, 1.54), cardiovascular mortality (2.04; 1.78, 2.33), major cardiovascular events (1.96; 1.53, 2.51), stroke (2.49; 2.22, 2.79), ischemic stroke (2.44; 1.83, 3.24), ischemic heart disease (1.61; 1.38, 1.87), sudden cardiac death (1.88; 1.36, 2.60), heart failure (4.99; 3.04, 8.22) and chronic kidney disease (1.64; 1.41, 1.91), but not hemorrhagic stroke (2.00; 0.67, 5.96). Among the outcomes examined, the absolute risk increase for heart failure was the greatest. Associations of AF with included outcomes were broadly consistent across subgroups and in sensitivity analyses.

Conclusions: AF is associated with an increased risk of death and an increased risk of cardiovascular diseases. Interventions aimed at reducing cardiovascular risk beyond stroke are warranted in patients with AF.

Introduction

Atrial fibrillation (AF) is a leading cause of morbidity and mortality, with an estimated 5 million incident cases globally.[1] AF 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 AF has been the primary focus of guidelines [5] and clinical trials,[4] recent studies have suggested that AF may also be associated with a range of different cardiovascular diseases, including ischemic heart disease (IHD) and chronic kidney disease (CKD).[2,5-8] However, individual studies have provided conflicting estimates of the strength of the association between AF and a range of cardiovascular diseases and have conflicted on whether there are significant associations at all, possibly due to the small sample sizes examined.[9-12] Pooling all available evidence may allow for the determination of robust estimates of the associations between AF and a range of cardiovascular diseases that could inform outcome selection in future randomized controlled trials and guide public health efforts to reduce the incidence of cardiovascular disease associated with AF.

Consequently, we conducted a systematic review and meta-analysis of the association of AF with cardiovascular disease and death. We aimed to determine the relative and absolute risk of death and a range of cardiovascular outcomes associated with AF. We also examined whether associations differed by important patient characteristics, including age, the presence of cardiovascular disease and cardiovascular risk.

Methods

This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[13] [17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18].

Data Sources and Searches

We conducted a systematic search of MEDLINE and EMBASE (inception to March 2015). A qualified research librarian developed the search strategy. This was supplemented by a review of references of included studies and review articles. Prospective cohort studies which included adults with AF (either at baseline or incident) and adults without AF, and which reported a measure of relative risk for death or cardiovascular disease (described below), and a corresponding measure of variability, were included. Studies were also required to include a minimum of 50 participants with AF and 50 participants without AF with at least 6 months mean/median follow up. No language restrictions were applied and non-English studies were translated by AJH, who has extensive experience in translating epidemiologic 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 standardized forms. Where available, we abstracted information on general study characteristics (study name or investigator's name, recruitment period,

median follow-up duration, year of publication of the primary findings), number of participants with and without AF, mean age, number of men, and relative risk of outcomes.

Relative risk estimates and associated 95% confidence intervals (CI) for the association between AF and the following study outcomes were abstracted: all-cause mortality, cardiovascular mortality, major cardiovascular events (a composite of cardiovascular death, fatal and non-fatal stroke, IHD, CHF) 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 hemorrhagic stroke, fatal and non-fatal ischemic stroke, IHD events (a composite of ischemic heart disease death and non-fatal myocardial infarction), CHF (incident development of congestive heart failure), peripheral arterial disease (PAD), and CKD. 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 CKD meta-analysis. [8]

Studies were categorized as unadjusted, minimally adjusted or adequately adjusted, as previously performed. Unadjusted studies did not adjust for any confounders. Minimally adjusted studies adjusted for, at minimum, sex, age and the presence of baseline cardiovascular disease. Adequately adjusted studies also adjusted for at least two established cardiovascular risk factors – blood pressure, cholesterol, smoking status and diabetes. Unadjusted studies were excluded. Minimally adjusted studies were excluded in a sensitivity analysis.

Statistical Analysis

For all analyses, overall summary estimates were calculated using inverse-variance weighted random effects meta-analysis. For studies that reported separate relative risk estimates for subgroups (e.g. different age groups, men vs. women), we first used inverse-variance weighted fixed effects meta-analysis to generate an overall study-level relative risks prior to random effects meta-analysis. Individual relative risk estimates and summary estimates were displayed graphically using forest plots. Heterogeneity was quantified using the I^2 statistic and the Q-test.

The absolute risk increase for each vascular outcome associated with AF was calculated by multiplying summary relative risks by the incidence rate of each outcome of interest in the United States general population. American Heart Association estimates of the incidence of cardiovascular mortality, ischemic heart disease, heart failure, sudden cardiac death and stroke were used. [14] Centers for Disease Control and Prevention estimates of the incidence of all-cause mortality[20] and chronic kidney disease were used. [21] Absolute risk increases were expressed in events per 1000 participant-years of follow up. As no estimate for the incidence of major cardiovascular events in the US general population could be obtained, an absolute risk increase associated with AF is not provided for major cardiovascular events.

Stratified Analyses and Sensitivity Analyses

In order to include a sufficient number of studies in each strata, stratified and sensitivity analyses were restricted to outcomes with nine or more studies (all-cause mortality, cardiovascular mortality, major cardiovascular events, ischemic heart disease,

stroke and ischemic stroke). We conducted four stratified analyses to examine whether relative risks of outcomes were influenced by patient characteristics. We divided studies into thirds by the proportion of participants with history of ischemic heart disease at baseline, the proportion of participants with a history of stroke at baseline, by mean age and by absolute risk of death and cardiovascular disease (in events per 1000 patient years of follow up). We tested for trend by these characteristics across studies using meta-regression. We did not examine whether relative risks were influenced by type of AF (chronic vs. paroxysmal) or proportion of patients on anticoagulation, as too few studies examined either characteristic to reliably test by meta-regression (sixteen studies reported on AF type and 27 studies reported on anticoagulation, Supplementary Table 1).

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 e.g. a community-based cohort study [2 2] vs. specific population e.g. a cohort study of individuals with a history of stroke [15]), by year of publication, by duration of follow-up, by region of study conduct (Asia, Europe, United States, International, Other), by method of AF ascertainment (electrocardiogram only, electrocardiogram and medical records, and medical records only) and by level of confounder adjustment (minimally adjusted vs. well adjusted).

We used a sequential exclusion strategy, as described by Patsopoulos et al., to examine whether overall estimates were influenced by the substantial heterogeneity observed. [23] 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. Evidence of publication bias was examined

through funnel plots and confirmed with Egger's test.[16] If present, the trim-and-fill method was used to adjust for publication bias. [17]

Patient Involvement

Patients were not involved in the design or conduct of this study

Ethics Approval and Funding

Ethics approval was not required. This study was unfunded.

RESULTS

In total, 3641 studies were reviewed and 3381 were excluded in the abstract screen. Among 260 full text articles that were reviewed, 160 were further excluded (Supplementary Figure 1). Accordingly, 100 studies involving 9,620,130 patients were included in this meta-analysis. Of these individuals, 577,317 had AF. The general characteristics of included studies are provided in Supplementary Table 1. Adjustments applied in included studies are provided in Supplementary Table 2. No studies reported on peripheral arterial disease.

All-Cause Mortality

Sixty-one studies, involving 948,741 patients (140,740 with AF) examined all-cause mortality as an outcome. The pooled relative risk was 1.46 (95% confidence interval (CI): 1.39, 1.54, Figures 1 and 2). Marked heterogeneity was observed (I^2: 93%, $p<0.001$). The corresponding absolute risk increase in all-cause mortality associated with

AF, based on the US population, was 3.8 events/1000 participant-years (3.2, 4.4). In subgroup analyses, studies were separated into thirds based on the proportion of adults with a history of IHD, the proportion with a history of stroke, mean participant age and baseline absolute risk of all-cause mortality. Relative risks of all-cause mortality were consistent across all subgroups ($p \geq 0.2$ for trend, Figure 3).

Cardiovascular Mortality and Major Cardiovascular Events.

Thirteen studies, involving 324,774 patients (17,506 with AF) examined cardiovascular mortality as an outcome. The pooled relative risk was 2.04 (1.78, 2.23; Supplementary Figure 2). The absolute risk increase in cardiovascular mortality associated with AF was 3.3 events/1000 participant-years (2, 3.3). Nine studies, involving 2,452,941 patients (19,646 with AF) examined major cardiovascular events as an outcome. Overall, AF was associated a 96% higher risk of major cardiovascular events (RR 1.96; 1.53, 2.51; Supplementary Figure 3).

Considerable heterogeneity was noted in both analyses (I^2: 78%, $p<0.001$ for cardiovascular mortality and I^2: 98%, $p<0.001$). In subgroup analyses, relative risk of cardiovascular mortality declined with increasing age (p trend=0.039 for trend, Supplementary Figure 4) and relative risk of major cardiovascular events declined with increasing absolute risk of major cardiovascular events (p=0.027, Supplementary Figure 5). Pooled relative risks for both outcomes were consistent for other subgroups examined (Supplementary Figures 4-5).

Stroke

Thirty-seven studies, involving 125,332 patients (19,474 with AF) reported results for any stroke. The pooled relative risk was 2.49 (2.22, 2.79; Figure 4). Considerable heterogeneity was noted (I^2: 96%, p<0.001). The relationship between AF and stroke was consistent, irrespective of baseline demographics and clinical characteristics (Supplementary Figure 6). The absolute risk increase of stroke associated with AF was 3.8 events/1000 participant years (3.1, 4.5).

Ten studies specifically reported results for ischemic stroke and the pooled relative risk estimate was 2.44 (1.83, 3.24) and considerable heterogeneity was also noted (I^2: 88%, p<0.001; Supplementary Figure 7), The relationship between AF and ischemic stroke was consistent, irrespective of baseline demographics and clinical characteristics (Supplementary Figure 8). The absolute risk increase for ischemic stroke was 3.2 events/1000 participant-years (1.8, 4.9). Three studies reported results for haemorrhagic stroke. AF was not associated with a higher risk of hemorhagic stroke, although the confidence interval was wide (RR 2.00; 0.67, 5.96; Supplementary Figure 9).

Ischemic Heart Disease and Sudden Cardiac Death

Sixteen studies, involving 395,957 patients (30,977 with AF) examined IHD as an outcome (Figure 5). The pooled relative risk was 1.61 (1.38, 1.87). Considerable heterogeneity was noted (I^2: 86%, p<0.001). The absolute risk increase in IHD was 1.4 events/1000 participant-years (0.9, 2). The pooled relative risk for IHD was consistent across subgroups of baseline cardiovascular disease, age and baseline risk (p > 0.05 for trend, Supplementary Figure 10).

Seven studies, involving 48,694 patients (6061 with AF) examined SCD as an outcome. The pooled relative risk of sudden cardiac death was 1.88 (1.36, 2.60; Supplementary Figure 11). Considerable heterogeneity was noted (I^2: 78%, p<0.001), although sensitivity analyses were not performed due to the small number of studies. The absolute risk increase in SCD was 0.6 events/1000 participant-years (0.2, 1.1).

Congestive Heart Failure and Chronic Kidney Disease

Six studies, involving 82,476 patients (11,677 with AF) examined incident CHF as an outcome. The pooled relative risk of CHF was 4.99 (3.04, 8.22; Supplementary Figure 12). Considerable heterogeneity was noted (I^2: 93%, p<0.001), although sensitivity analyses were not performed due to the small number of studies. Three studies, involving 467,000 patients (20,312 with AF) examined CKD as an outcome. The pooled relative risk of CKD was 1.64 (1.41, 1.91; Supplementary Figure 13). Heterogeneity was non-significant (I^2: 50%, p=0.137). The absolute risk increases in CHF and CKD associated with AF were 11.1 (5.7, 20) and 6.6 (4.3, 9.4) events/1000 participant-years respectively.

Sensitivity Analyses

In sensitivity analyses of study characteristics, stratified by type of population, method of AF ascertainment, level of adjustment, year of publication, median follow up and location, relative risks of outcomes were broadly consistent across strata. No interaction was observed for all-cause mortality and for cardiovascular mortality for any subgroups (p interaction/trend > 0.05, Supplementary Tables 3-4). High levels of

heterogeneity (I^2 > 75%) continued to be observed in most subgroups. A stronger relative risk of major cardiovascular events associated with AF was observed in studies conducted in a general population than a specific population (RR 2.71; 1.82, 4.04 vs. RR 1.39; 1.18, 1.63, respectively; p interaction = 0.002; Supplementary Table 5). Although a test for interaction for major cardiovascular events by location was also observed, this was due to a single study that was conducted in the United States. No other significant interactions for major cardiovascular events were observed (p interaction/trend > 0.05, Supplementary Table 5). No interactions for stroke for any subgroups were observed (Supplementary Table 6). Relative risks of ischemic stroke and ischemic heart disease were stronger in studies conducted in general populations than in studies conducted in specific populations (p interaction < 0.05, Supplementary Tables 7-8). Relative risk of ischemic heart disease was also larger in studies with a longer follow up (p trend = 0.012, Supplementary Table 8).

When studies contributing the largest amount to heterogeneity were sequentially excluded until I^2 was less than 50%, pooled relative risks for outcomes were highly similar (Supplementary Table 9). AF remained associated with an increased risk of all-cause mortality (RR 1.42; 1.36, 1.48), cardiovascular mortality (RR 2.02; 1.80, 2.27), major cardiovascular events (RR 1.72; 1.63, 1.83), ischemic heart disease (RR 1.46; 1.34, 1.59), stroke (RR 2.71; 2.41, 3.05) and ischemic stroke (RR 2.92; 2.61, 3.41).

No evidence of publication bias was observed in funnel plots for any outcome (Supplementary Figures 13-23; Egger's test p > 0.05), except for stroke (Supplementary Figure 18; Egger's test p= 0.003). Use of trim-and-fill method resulted in a RR of 1.68 (1.51, 1.87) for stroke.

DISCUSSION

In this comprehensive overview of AF and the risk of cardiovascular disease and death, AF was associated with an increased risk of a range of different cardiovascular diseases, including a 61% higher risk of ischemic 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. AF was associated with 2.5 times the risk of stroke and five times the risk of incident congestive heart failure, as well as a 46% higher risk of all-cause mortality. The absolute risk increase for heart failure was the highest among the outcomes examined. Finally, associations of AF with other outcomes were broadly consistent across subgroups and in sensitivity analyses.

Comparison with Prior Individual Studies

Our study adds to the growing literature on the association between AF and cardiovascular outcomes beyond stroke. In a retrospective cohort study of Medicare beneficiaries, investigators demonstrated that heart failure was the most common non-fatal cardiovascular event among adults with AF. Furthermore, in an analysis of the RE-LY trial, which was a trial in patients with atrial fibrillation, cardiac deaths – SCD and progressive heart failure – accounted for 37.4% of all deaths, whereas stroke and haemorrhage related deaths accounted for 9.8% of all deaths.[18] In our study, the relative and absolute risk of CHF was the highest among all outcomes studied. Furthermore, we observed that AF was associated with an increased risk of IHD, CKD and SCD, even though some individual studies reported non-significant associations.

Notably, although the relative association of AF with IHD, CKD and SCD were comparable, the absolute risk increase in IHD (1.4 events per 1000 participant-years) and CKD (6.6 events) were several times larger than SCD (0.6 events), due to the lower baseline incidence of SCD 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 prior studies, many of which have limited their analysis to a single patient subgroup, such as those with IHD and CHF.[18] We observed that the association of AF with cardiovascular disease and death was generally consistent, irrespective of baseline history of ischemic heart disease, baseline history of stroke, mean participant age and baseline risk. In two instances, a statistically significant interaction was detected, but the multiplicity of tests being performed, as well as the small number of studies included in these analyses, suggests that these findings should be interpreted with caution. While relative associations of AF with cardiovascular disease and death may have been similar across participant characteristics, absolute increases in risk associated with AF would be expected to be larger among individuals with higher baseline risk of cardiovascular disease. These results therefore suggest that AF is associated with greater absolute increases in risk of cardiovascular disease among individuals at high baseline risk and highlights the importance of risk-stratification of participants with AF.

Strengths and Limitations

The key strength of our study is its sample size. We were able to identify one hundred cohort studies, many more than previous analyses of AF restricted to

subpopulations. The large number of included studies made our results robust to the inclusion of any single study and provided us with the power to investigate whether associations of AF with cardiovascular disease and death differed by important patient and study characteristics. However, our study has important limitations. First, we observed high levels of heterogeneity ($I^2 > 70\%$) for all vascular outcomes except for CKD. This was not unexpected and may be due to differences in study designs, differences in methodological characteristics, differences in ascertainment of endpoints, differences in AF type and differences in use of secondary prevention (such as anticoagulation therapy) among included studies. Although we conducted multiple subgroup and sensitivity analyses to explore sources of heterogeneity, high levels of heterogeneity continued to be observed in most analyses. However, when we systematically and sequentially excluded individual studies until heterogeneity was moderate ($I^2 < 50\%$), relative risk estimates for vascular outcomes were consistent and significant, suggesting that the high levels of heterogeneity were not inflating summary relative risk estimates. Second, studies that reported significant associations of AF with cardiovascular disease and death may be more likely to be published. However, we did not observe evidence of publication bias for any outcome other than stroke. Third, we lacked individual patient data for studies, which would have allowed us to systematically adjust for patient characteristics and use of preventative therapies such as anticoagulation. However, we did not observe any interaction when we compared well-adjusted cohort studies to adequately adjusted studies.

Implications for clinicians, policy makers and future research

The mechanism by which AF is associated with an elevated risk of a range of different cardiovascular diseases is unclear. Uncontrolled rapid atrial contraction may predispose to ventricular tachyarrhythmia, and may lead to demand infarction and cardiomyopathy. [5] However, it is also possible that the relationship between atrial fibrillation and non-stroke cardiovascular disease is not causal. Considering our observation that AF is also associated with an increased risk of heart failure, sudden cardiac death and chronic kidney disease (in addition to ischemic heart disease), it appears likely that AF may be acting as a marker for shared underlying risk factors for cardiovascular disease, [23] in addition to any possible causal disease-specific effects. Nonetheless, use of atrial fibrillation as a prognostic marker may allow for improved risk stratification by clinicians and targeting of therapies to high-risk individuals.

Our study may have implications for the prioritisation of public health resources and the development of novel interventions for adults with AF. In particular, the development and testing of novel oral anticoagulants has been the principal focus of clinical care in AF but recent studies have shown that these medications reduce stroke related mortality, with little incremental benefit over warfarin for reducing CHF and SCD related mortality.[24] Reducing the burden of non-stroke events may therefore require a renewed focus on primary prevention and cardiovascular risk factor management in adults with AF. These results also highlight the importance of including non-stroke cardiovascular events, including heart failure, ischemic heart disease and sudden cardiac death, as endpoints in trials conducted in AF populations.

In conclusion, AF is associated with a wide range of cardiovascular events, including cardiovascular mortality, major cardiovascular events, heart failure, ischemic heart disease, chronic kidney disease, 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 AF.

What is Already Known on this Subject?

Atrial fibrillation (AF) 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 AF and cardiovascular outcomes beyond stroke is less clear.

What This Paper Adds

AF is associated with a wide range of cardiovascular events, including cardiovascular mortality, major cardiovascular events, heart failure, ischemic heart disease, chronic kidney disease, 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 AF.

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COMPETING INTEREST

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS:

Ayodele Odutayo and Connor Emdin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Emdin, Odutayo

Acquisition of data: All authors

Analysis and interpretation of data: All authors

Drafting of the manuscript: All authors

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Emdin, Odutayo

CONFLICTS OF INTEREST AND FUNDING

The authors declare no conflicts of interest.

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TRANSPARENCY STATEMENT

AO and CAE 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.

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DATA SHARING

Data and code are available from the lead author upon request.

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Figures

Figure 1. Association of Atrial Fibrillation with All-cause Mortality and Cardiovascular Disease

Figure 2. Association of Atrial Fibrillation with All-Cause Mortality

Figure 3. Association of Atrial Fibrillation with Mortality, Stratified by Patient Demographics and Baseline Clinical Characteristics

Figure 4. Association of Atrial Fibrillation with Stroke

Figure 5. Association of Atrial Fibrillation with Ischemic Heart Disease

Figure 1. Association of Atrial Fibrillation with All-cause Mortality and Cardiovascular Disease

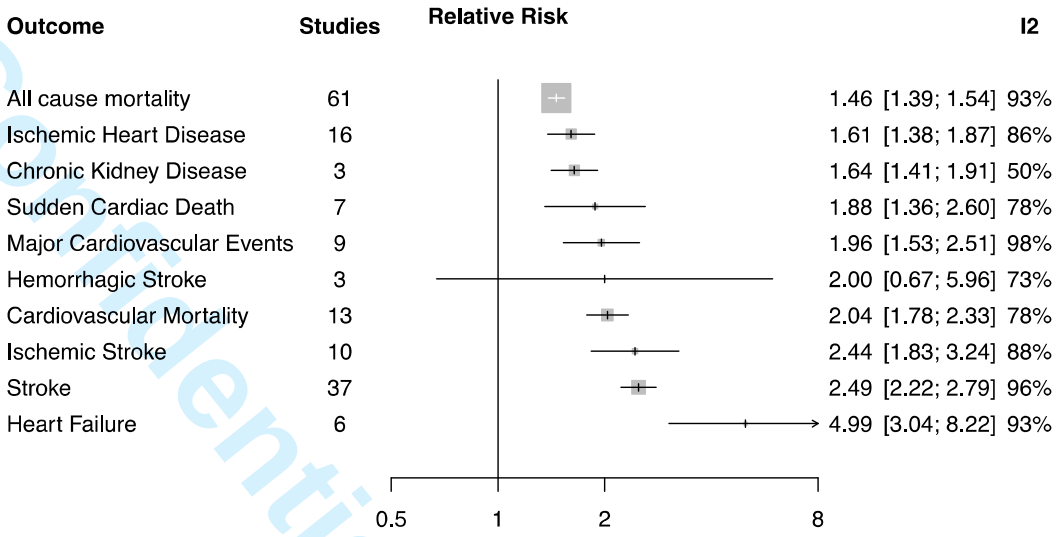
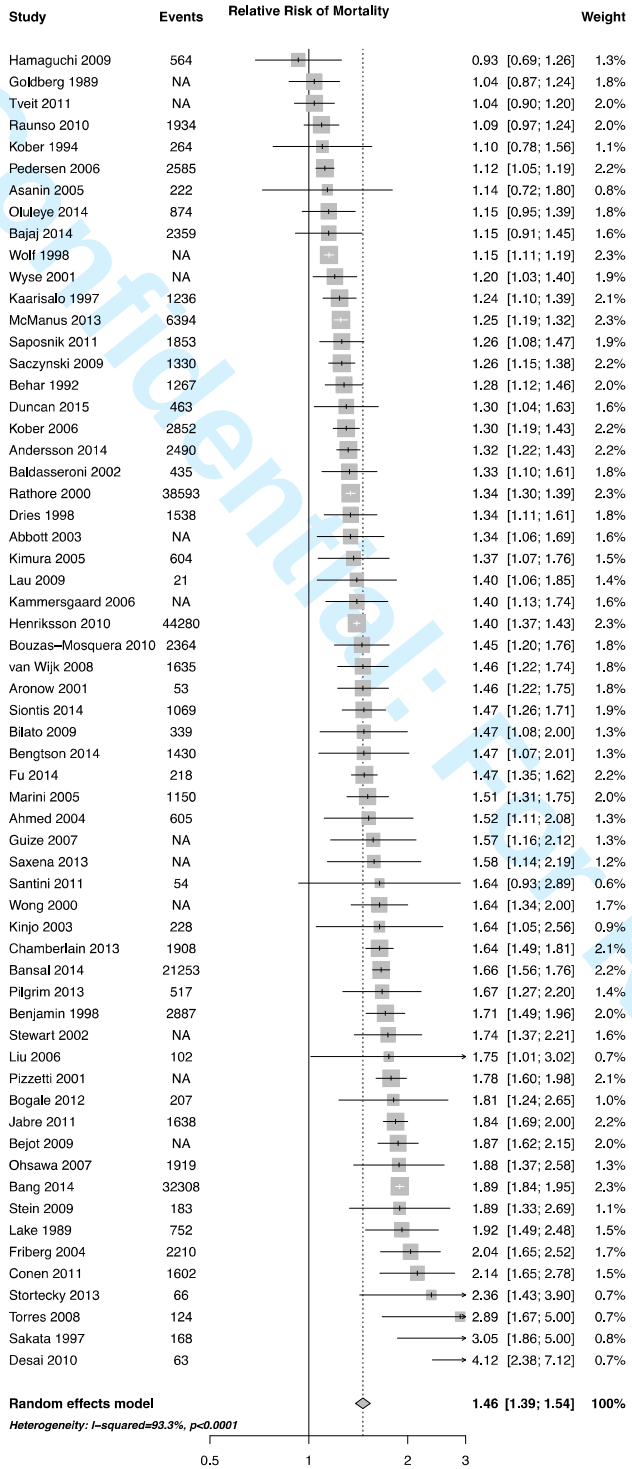


Figure 2. Association of Atrial Fibrillation with All-Cause Mortality



NA is not available

Figure 3. Association of Atrial Fibrillation with Mortality, Stratified by Patient Demographics and Baseline Clinical Characteristics

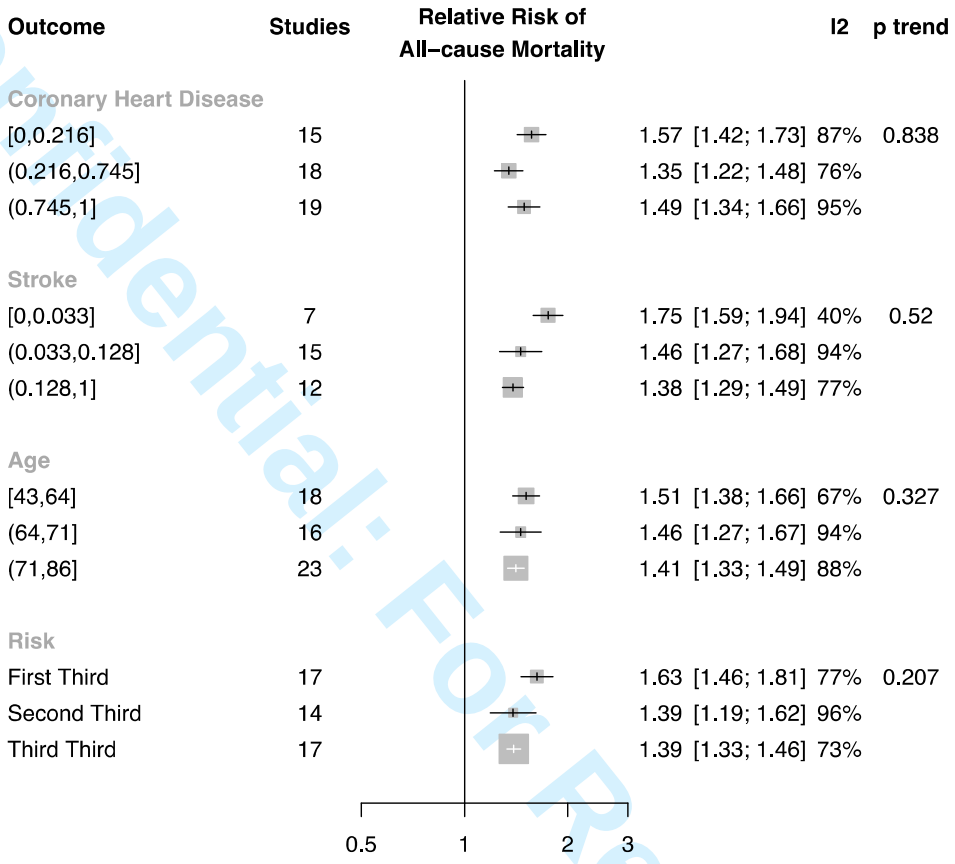
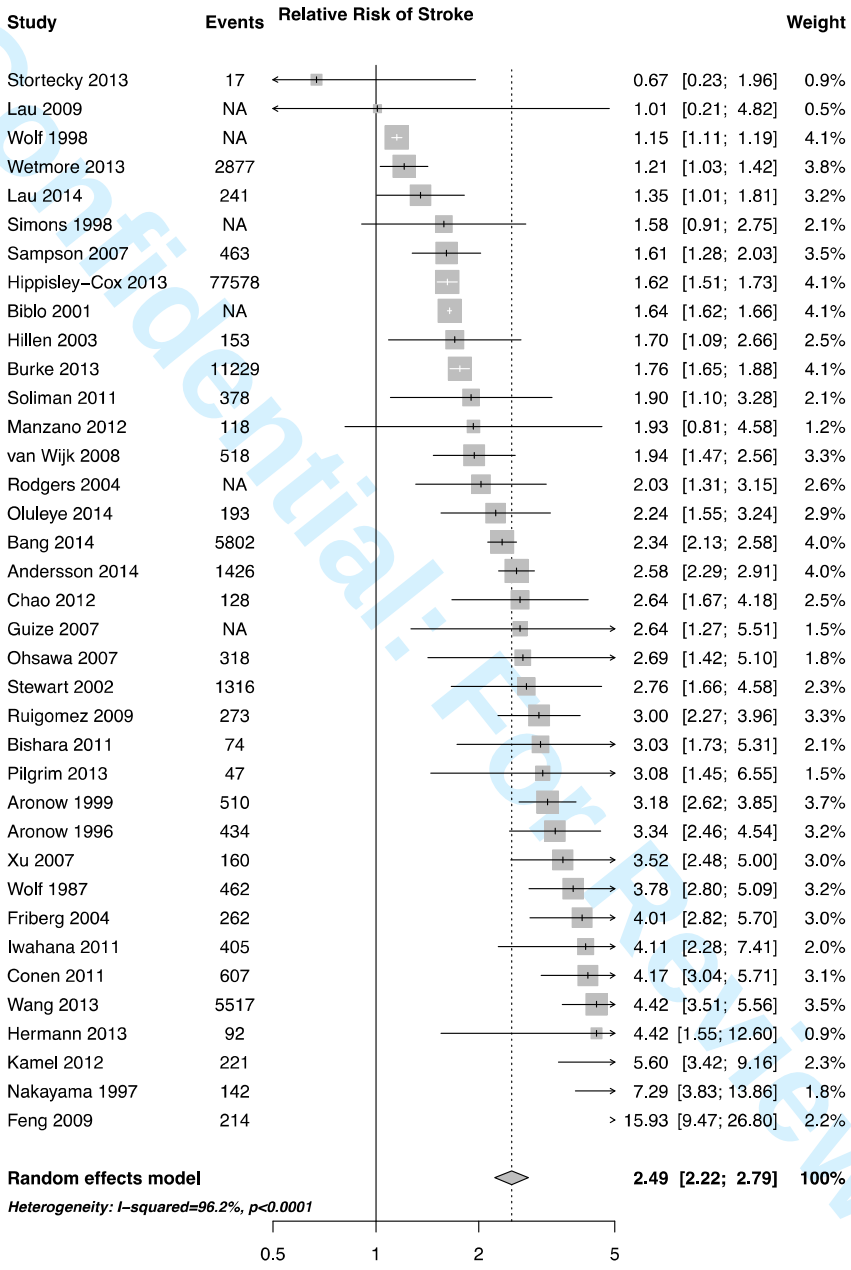
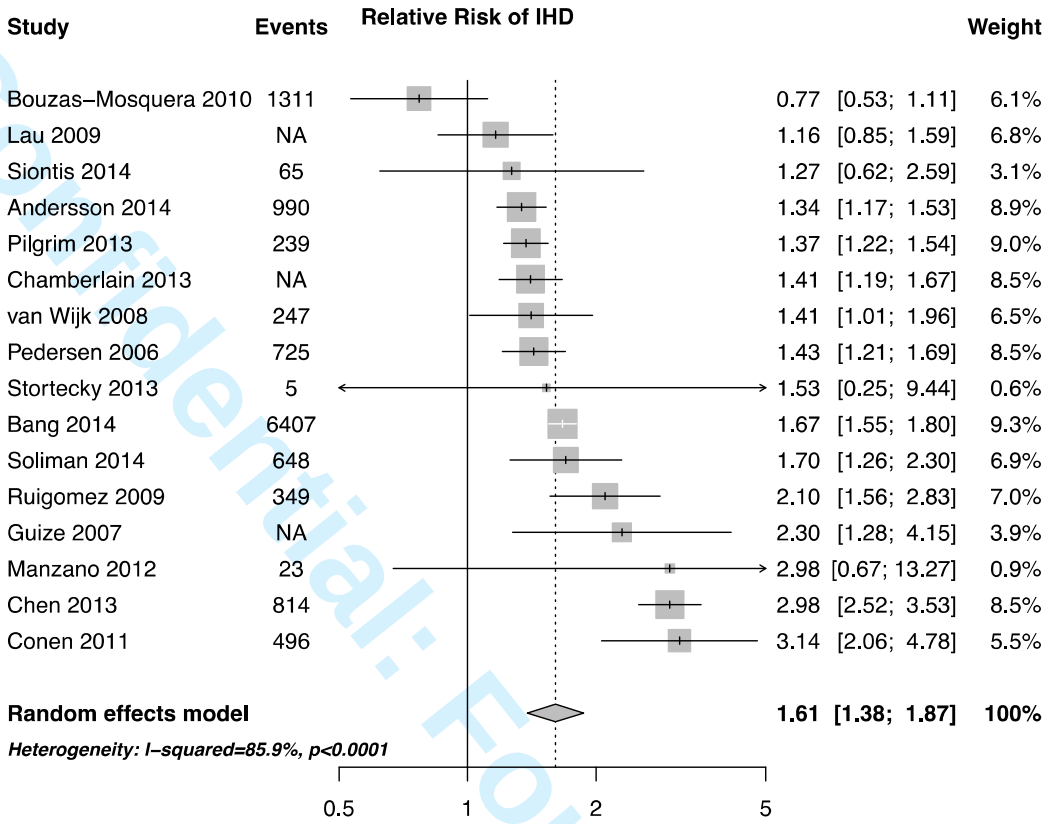


Figure 4. Association of Atrial Fibrillation with Stroke



NA is not available

Figure 5. Association of Atrial Fibrillation with Ischemic Heart Disease



NA is not available

Online-Only Supplement

Supplementary Table 1: Characteristics Of Included Studies by Method of AF Ascertainment.

First author, year	Name of Cohort	Method of AF Ascertainment	Participants (AF)	Median Follow Up (Yrs)	Median Age (Yrs)	Men (n)	Chronic AF (n)	Persistent AF (n)	Paroxysmal AF (n)	CHD (n)	Stroke (n)	AF on Anticoagulants (n)
Electrocardiogram												
Ahmed, 2004[1]	Medicare Alabama	Electrocardiogram	944 (233)	4.0	79	364	NA	NA	NA	245	NA	NA
Aronow, 1996[2]	NA	Electrocardiogram	2101 (283)	3.5	81	650	283	0	0	NA	554	NA
Aronow, 1999[3]	NA	Electrocardiogram	2384 (313)	3.7	81	724	313	0	0	NA	689	NA
Aronow, 2001[4]	NA	Electrocardiogram	355 (132)	0.5	80	141	NA	NA	NA	NA	NA	NA
Asanin, 2005[5]	Serbia Coronary Care Unit	Electrocardiogram	650 (320)	7.0	63	447	NA	NA	NA	650	14	144
Bajaj, 2014[6]	Cardiovascular Health Study	Electrocardiogram	5379 (116)	13.0	73	2272	NA	NA	NA	915	208	NA
Baldasseroni, 2002[7]	IN-CHF Registry	Holter (24 hrs)	4126 (798)	1.0	NA	3239	798	0	0	2039	NA	NA
Bang, 2014[8]	Denmark National Registry	Electrocardiogram	89412 (10708)	5.0	68	5749	NA	NA	NA	8941	3737	NA
Behar, 1992[9]	SPRINT Registry	Electrocardiogram	5803 (577)	5.5	63	4291	0	0	577	5803	NA	NA
Bejot, 2009[10]	NA	Electrocardiogram	3064 (572)	2.0	75	1449	NA	NA	NA	620	3064	NA
Benjamin, 1998[11]	Framingham	Electrocardiogram	1863 (621)	25.6	75	888	NA	NA	NA	252	213	NA
Bilato, 2009[12]	Progetto Veneto Anziani	Electrocardiogram	1576 (135)	4.0	74	607	NA	NA	NA	65	72	22
Bishara, 2011[13]	NA	Electrocardiogram	2402 (174)	1.0	61	1897	NA	NA	NA	2402	NA	32
Bogale, 2012[14]	European CRT Survey	Electrocardiogram	2111 (474)	1.0	70	1623	NA	NA	NA	1006	NA	NA
Bouzas-Mosquera, 2010[15]	NA	Electrocardiogram	17100 (619)	6.5	64	10101	NA	NA	NA	2963	NA	NA
Dries, 1998[16]	SOLVD	Electrocardiogram	6517 (419)	2.8	60	5604	NA	NA	NA	4855	412	145
Friberg, 2004[17]	Copenhagen City Heart Study	Electrocardiogram	29310 (276)	4.7	58	12996	NA	NA	NA	763	0	12
Fu, 2014[18]	From Chinese People's Liberation	Electrocardiogram	1050	1.1	86	937	47	44	128	1050	NA	NA

	Army General Hospital		(219)									
Guize, 2007[19]	NA	Electrocardiogram	154070 (298)	15.2	51	9896 1	NA	NA	NA	NA	NA	NA
Hamaguchi, 2009[20]	JCARE-CARD	Electrocardiogram	2659 (937)	2.4	71	1590	NA	NA	NA	851	399	657
Hermann, 2013[21]	Heinz Nixdorf Recall	Electrocardiogram	4180 (52)	NA	59	1968	NA	NA	NA	0	0	NA
Hillen, 2003[22]	The South London Community Stroke Register	Electrocardiogram	1626 (249)	1.2	71	792	NA	NA	NA	NA	1626	NA
Iwahana, 2011[23]	Jichi Medical School Cohort Study	Electrocardiogram	10929 (54)	10.7	56	4147	NA	NA	NA	NA	0	NA
Kammersgaard, 2006[24]	NA	Electrocardiogram	899 (155)	5.0	74	432	NA	NA	NA	202	899	90
Kinjo, 2003[25]	Osaka	Electrocardiogram	2475 (297)	1.0	64	1913	NA	NA	NA	2475	187	NA
Kober, 1994[26]	NA	ECG	584 (90)	6.2	61	430	NA	NA	NA	584	NA	NA
Kober, 2006[27]	VALIANT	Electrocardiogram	14660 (2151)	3.0	66	1010 4	NA	NA	NA	1466 0	893	414
Lake, 1989[28]	Busselton, Australia	ECG	1770 (87)	17.0	NA	920	NA	NA	NA	246	NA	NA
Lau, 2009[29]	ACACIA	Electrocardiogram	3230 (536)	1.0	65	2069	NA	NA	NA	1616	221	154
Marini, 2005[30]	L'Aquila district	Electrocardiogram	3530 (869)	1.0	79	1676	814	NA	55	929	3530	98
Nakayama, 1997[31]	Shibata Study	Electrocardiogram	2302 (N/A)	15.5	NA	961	NA	NA	NA	NA	0	NA
Ohsawa, 2007[32]	National Survey on Circulatory Disorders	Electrocardiogram	9483 (60)	19.0	51	4154	NA	NA	NA	NA	0	NA
Olsson, 2006[33]	CHARM	Electocardiogram	7599 (1148)	3.1	66	5199	NA	NA	NA	3904	663	863
Pedersen, 2006[34]	TRACE	Electrocardiogram	5983 (1149)	2.7	67	4131	NA	NA	NA	5983	NA	NA
Pedersen, 2006[35]	DIAMOND	Electrocardiogram	3479 (818)	8.0	73	2080	NA	NA	NA	1974	NA	NA
Pizzetti, 2001[36]	GISSI-3	Electrocardiogram	17944 (1386)	4.0	NA	1391 2	NA	NA	319	1794 4	NA	60
Rathore, 2000[37]	Cooperative Cardiovascular Project	Electrocardiogram	106780 (23565)	1.0	77	5278 4	NA	NA	NA	1067 80	NA	NA
Raunso, 2010[38]	ECHOS	Electrocardiogram	2881 (1175)	7.0	75	1749	681	NA	494	1322	335	658
Rodgers, 2004[39]	Cohort Study in Northumberland, UK	Electocardiogram	4351 (218)	5.0	76	1997	NA	NA	NA	1037	0	NA
Ruel, 2004[40]	Ottawa Heart Institute	Electrocardiogram	2317 (N/A)	6.3	62	1583	NA	NA	NA	841	49	NA

Ruel, 2006[41]	Ottawa Heart Institute	Electrocardiogram	848 (94)	5.4	64	570	94	NA	NA	289	NA	NA
Sakata, 1997[42]	NA	Electrocardiogram	1039 (100)	8.0	66	783	20	NA	80	1039	NA	NA
Santini, 2011[43]	Italian ClinicalService Project	Continuous monitoring	1193 (361)	1.1	66	939	NA	NA	NA	576	NA	NA
Simons, 1998[44]	Dubbo Study of the Elderly	Electrocardiogram	2805 (66)	8.2	69	1235	NA	NA	NA	607	155	NA
Soliman, 2011[45]	REGARDS	Electrocardiogram	27109 (360)	4.4	65	1219 9	NA	NA	NA	NA	NA	240
Stewart, 2002[46]	Renfrew	Electrocardiogram	15406 (100)	20.0	54	7052	NA	NA	NA	NA	197	NA
Stortecky, 2013[47]	Bern TAVI Registry	Continuous monitor	389 (131)	1.0	83	165	70	8	26	238	30	68
Torres, 2008[48]	Coronary Care Unit of Hospital de São Marcos	Electrocardiogram	1183 (140)	0.5	64	857	NA	NA	NA	1183	72	NA
Tveit, 2011[49]	Norwegian Heart Failure Registry	Electrocardiogram	4048 (1391)	2.3	70	2839	NA	NA	NA	2249	NA	1198
van Wijk, 2008[50]	LiLAC Cohort Study	Electrocardiogram	2659 (186)	10.1	66	1713	NA	NA	NA	277	2659	48
Watanabe, 2009[51]	Niigata Preventive Medicine Study	Electrocardiogram	235818 (1694)	5.9	61	7546 5	NA	NA	NA	NA	NA	NA
Wolf, 1987[52]	Framingham Heart Study	Electrocardiogram	5184 (303)	30.0	NA	NA	303	0	0	NA	0	NA
Electrocardiogram and Medical Records												
Chamberlain, 2013[53]	Olmsted County	Electrocardiogram and medical records	1664 (937)	4.0	76	759	NA	NA	NA	353	NA	NA
Chen, 2013[54]	ARIC and CHS	Electrocardiogram and medical records	20918 (2352)	13.1	59	9205	NA	NA	NA	1786	NA	NA
Conen, 2011[55]	Women's Health Study	Electrocardiogram and medical records	34722 (1011)	15.4	53	0	NA	355	656	0	0	536
Genovesi, 2009[56]	NA	Electrocardiogram and Medical Records	476 (127)	3.0	NA	277	68	43	16	112	NA	NA
Goldberg, 1990[57]	Worcester, Massachusetts, Standard Metropolitan Statistical Area	Electrocardiogram and medical records	4108 (659)	10.0	67	2529	NA	NA	NA	4108	NA	481
Jabre, 2011[58]	Olmsted County	Electrocardiogram and medical records	3220 (1033)	6.6	68	1852	NA	NA	NA	3220	NA	NA
Kaarisalo, 1997[59]	FINMONICA Stroke Study	Electrocardiogram and medical records	2635 (767)	1.0	82	755	NA	NA	NA	457	2635	NA
O'Neal, 2015[60]	REGARDS	Electrocardiogram and self report	24953 (2155)	7.4	65	1147 1	NA	NA	NA	NA	NA	NA
Okin, 2013[61]	LIFE	Electrocardiogram and adverse event reporting	8831 (701)	4.7	67	4023	NA	NA	NA	1353	367	NA
Oluleye, 2014[62]	I-PRESERVE	Electrocardiogram and	4128	4.4	72	1637	NA	NA	NA	2096	399	662

		medical history	(1227)									
Pilgrim, 2013[63]	Bern University Hospital, Switzerland	Electrocardiogram and medical records	6041 (323)	4.0	64	4555	NA	NA	NA	6041	NA	62
Saczynski, 2009[64]	Worcester Heart Attack Study	Electrocardiogram and medical records	7513 (999)	1.0	69	4282	NA	NA	NA	7513	738	763
Siontis, 2014[65]	Mayo Clinic	Electrocardiogram and medical records	3673 (650)	4.1	55	2012	NA	NA	NA	607	182	265
Soliman, 2014[66]	REGARDS	Electricardiogram and self reported history	23928 (1631)	4.5	64	9991	NA	NA	NA	0	NA	325
Wyse, 2001[67]	AVID Registry	Electrocardiogram or self report	3762 (917)	2.1	64	2869	NA	NA	NA	2865	NA	436
Medical records												
Abbott, 2003[68]	United States Renal Data System	Medical records (ICD9)	39628 (432)	1.9	43	2382 7	NA	NA	NA	NA	NA	NA
Andersson, 2014[69]	Swedish Registry	Medical records	21987 (9519)	N/A	59	1517 1	NA	NA	NA	NA	NA	NA
Bansal, 2013[70]	Kaiser California	Medical records (ICD9)	206229 (16463)	5.1	71	1008 46	NA	NA	NA	1237 4	3300	NA
Bansal, 2014[71]	Kaiser Permanente California	Medical records	81088 (6269)	4.8	73	3959 1	NA	NA	NA	5246	1622	257
Bengtson, 2014[72]	ARIC	Medical records (ICD9)	20049 (2717)	1.0	59	1284 1	NA	NA	NA	2004 9	1412	NA
Biblo, 2001[73]	Medicare	Medical records	749998 (337428)	8.0	NA	NA	NA	NA	NA	NA	NA	NA
Burke, 2013[74]	California State Inpatient Database	Medical records	1173353 (27061)	2.3	50	6058 45	NA	NA	NA	4150 3	NA	NA
Chao, 2012 [75]	Taiwan National Health Insurance Research Database	Medical records (ICD9)	9119 (829)	4.8	45	5599	NA	NA	NA	NA	NA	0
Duncan, 2015[76]	UK TAVI registry	Medical records	850 (202)	5.0	82	442	NA	NA	NA	381	NA	NA
Feng, 2009[77]	Western China	Medical records	1913 ()	1.0	64	1098	NA	NA	NA	NA	1913	NA
Henriksson, 2010[78]	Swedish Stroke Registry	Medical records	105074 (31821)	2.4	76	5272 9	NA	NA	NA	NA	2763 0	NA
Hippisley-Cox, 2010[79]	QResearch	Medical Records	2343759 (12031)	7.0	48	1153 914	NA	NA	NA	0	0	NA
Hippisley-Cox, 2013[80]	QStroke	Medical records	3549478 (15371)	7.0	45	1748 108	NA	NA	NA	9956 1	0	0
Kamel, 2012[81]	Kaiser Permanente	Medical records	5575 (113)	1.0	73	2619	NA	NA	NA	1624	5575	NA
Kimura, 2005[82]	NA	Medical records	10981 (2010)	0.7	70	6940	NA	NA	NA	NA	1098 1	NA
Manzano, 2012[83]	Singapore General Hospital	Medical records	1124 (96)	1.0	65	663	NA	NA	NA	266	1124	NA

Marijon, 2009[84]	EVADEF Cohort	Medical history	2296 (663)	1.7	60	1980	NA	NA	NA	1313	NA	NA
McManus, 2013[85]	NA	Medical records (ICD9)	23644 (11429)	1.8	74	1236 1	NA	NA	NA	3080	4990	5555
Ruff, 2014[86]	REACH Registry	Medical records	44518 (4582)	4.0	68	2880 3	NA	NA	NA	2595 4	1255 4	2484
Ruigomez, 2009[87]	CPRD	Medical records	9057 (831)	3.6	64	4221	539	NA	292	0	0	NA
Saposnik, 2011[88]	Registry of the Canadian StrokeNetwork	Medical records	8223 (1405)	1.0	72	4322	NA	NA	NA	1936	8223	NA
Saxena, 2013[89]	ANZSTCTS Cardiac Surgery Database	Medical records	2563 (322)	2.4	74	1748	NA	NA	NA	2563	453	NA
Smit, 2006[90]	University Medical Center of Goningen, Netherlands	Medical records	456 (122)	2.6	55	339	NA	43	78	262	NA	NA
Stein, 2009[91]	SERF Registry	Medical records	1655 (433)	1.0	67	1359	NA	NA	NA	1195	NA	NA
Wang, 2013[92]	Taiwan Longitudinal Health Insurance Database	Medical records	104094 (908)	3.0	49	4655 4	NA	NA	NA	1197 4	NA	NA
Wetmore, 2013[93]	Medicare/Medicaid	Medical records	56734 (5629)	1.8	61	2461 4	5629	0	0	1325 8	6155	NA
Wolf, 1998[94]	Hospitalised Medicare patients	Medical records	26753 (13558)	3.0	NA	1233 7	NA	NA	NA	NA	NA	NA
Wong, 2000[95]	GUSTO-III Trial	Medical records	13858 (906)	1.0	63	1018 2	NA	NA	NA	1385 8	0	12
Ascertainment not Specified												
Desai, 2010[96]	NA	N/A	549 (70)	3.4	73	434	NA	NA	NA	322	NA	NA
Lau, 2014[97]	NA	N/A	1105 (239)	6.3	72	548	NA	NA	NA	188	1105	NA
Liu, 2006[98]	Nanjing Stroke Registry Program	N/A	752 (72)	1.0	67	498	NA	NA	NA	75	752	NA
Sampson, 2007[99]	VALIANT	N/A	14703 (960)	2.1	65	1013 3	NA	NA	NA	1470 3	895	NA
Xu, 2007[100]	Nanjing Stroke Registry Program	Unclear	834 (128)	1.0	69	556	NA	NA	NA	NA	834	NA

Supplementary Table 2: Adjustments Of Included Studies by by Method of AF Ascertainment.

First author, year	Adjustments	Adjustment
Electrocardiogram		
Ahmed, 2004[1]	Age, sex, race, history of heart failure, admission pulse, SBP, LVSD, discharge use of ACE inhibitors and digoxin, diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, care by cardiologist	Adequate
Aronow, 1996[2]	Age, sex, prior stroke	Adequate
Aronow, 1999[3]	Age, sex, LVH, previous stroke	Adequate
Aronow, 2001[4]	Age, sex, hypertension, diabetes, abnormal LVEF	Well
Asanin, 2005[5]	Age, sex, history of hypertension, history of diabetes mellitus, previous myocardial infarction, history of angina pectoris, thrombolysis, peak creatinine kinase level, and beta blocker therapy	Well
Bajaj, 2014[6]	Age, sex, race, smoking, acute myocardial infarction, hypertension, diabetes mellitus, stroke, chronic obstructive pulmonary disease, cancer, arthritis, left ventricular ejection fraction, instrumental activity of daily living, time to walk 15 feet, serum creatinine, and serum C-reactive protein.	Well
Baldasseroni, 2002[7]	Age, ischaemic heart disease, previous hospitalization for congestive heart failure, NYHA class III–IV, reduced systolic blood pressure, third heart sound, ventricular tachycardia, and renal failure	Adequate
Bang, 2014[8]	Age, sex, calendar year, re-infarction, concomitant pharmacotherapy, cerebral vascular disease, peripheral vascular disease, cancer, cardiac arrhythmias, acute renal failure, chronic renal failure, diabetes with complications, pulmonary edema, shock, peptic ulcer	Adequate
Behar, 1992[9]	Age, sex, history of myocardial infarction, diabetes mellitus, congestive heart failure, serum lactate dehydrogenase level, inclusion in the SPRINT trial	Adequate
Bejot, 2009[10]	Age and sex	Adequate
Benjamin, 1998[11]	Stratified by sex, adjusted for age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack	Well
Bilato, 2009[12]	Age, sex, heart failure, peripheral arterial disease, myocardial infarction, diabetes, disability in activity daily living, chronic obstructive pulmonary disease, cognitive impairment, angina pectoris, and stroke	Adequate
Bishara, 2011[13]	Age, sex, history of prior infarction, history of diabetes, history of hypertension, serum creatinine, Killip class at admission, ST-elevation infarction, anterior location of infarction, coronary revascularisation, LVEF categorised as preserved (≥45%) or reduced (<45%) and left atrial dimension	Adequate
Bogale, 2012[14]	Age, sex, heart failure, peripheral arterial disease, myocardial infarction, diabetes, disability in activity daily living, chronic obstructive pulmonary disease, cognitive impairment, angina pectoris, and stroke	Adequate

Bouzas-Mosquera, 2010[15]	Age, sex, diabetes mellitus, hypertension, hypercholesterolemia, smoking habit, family history of CAD, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, typical angina, left bundle branch block, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, nitrates, calcium channel blockers, digoxin, diuretics, exercise-induced chest pain, exercise electrocardiographic results, metabolic equivalents, peak systolic blood pressure, and percentage of maximum age-predicted heart rate	Well
Dries, 1998[16]	Age, ejection fraction, NYHA class, diabetes, stroke, diuretic use, antiarrhythmic use, beta-blocker, anticoagulant, antiplatelet, randomization to enalapril, prior myocardial infarction, history of angina, history of hypertension, etiology of heart failure and simultaneous use of antiplatelet and anticoagulant therapy	Well
Friberg, 2004[17]	Stratified by sex, adjusted for age, arterial hypertension, systolic blood pressure, diabetes, myocardial infarction, electrocardiographic left ventricular hypertrophy, smoking, and forced expiratory volume	Well
Fu, 2014[18]	Age, sex, history of smoking, BMI, heart failure, hypertension, diabetes mellitus, systolic blood pressure, diastolic blood pressure, heart rate, left ventricular ejection fraction, interventricular septum, left ventricular posterior wall, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular mass index, hemoglobin, serum albumin, glucose, triglycerides, HDL cholesterol, LDL cholesterol, serum sodium, potassium, calcium and phosphorus.	Well
Guize, 2007[19]	Stratified by sex, adjusted for age, cardiopathy, LVH, blood pressure, cholesterol, glycemia, body mass index, smoking, alcohol, and vital capacity	Adequate
Hamaguchi, 2009[20]	Stratified by sex, adjusted for age, cause of heart failure (ischemic, hypertensive or valvular heart disease), diabetes, hyperlipidemia, hyperuricemia, prior stroke, serum creatinine, hemoglobin and BNP levels, LVEF, and medication use (diuretics, nitrates, aspirin, antiplatelet, warfarin, statin)	Well
Hermann, 2013[21]	Age, sex, systolic blood pressure, LDL and HDL cholesterol, diabetes mellitus, and smoking	Well
Hillen, 2003[22]	Age, sex, ethnicity, stroke subtype, Glasgow coma stroke scale, previous TIA, ischemic heart disease, hypertension, diabetes, alcohol and smoking.	Well
Iwahana, 2011[23]	Age, sex, smoking status, drinking status, obesity, hypertension, dyslipidemia, and diabetes mellitus	Well
Kammersgaard, 2006[24]	Stepwise regression: age, sex, initial stroke severity, living alone, daily alcohol intake, smoking, ischemic heart disease (IHD), arterial hypertension (HA), diabetes, previous stroke, intermittent claudication, and pre-existing disability	Well
Kinjo, 2003[25]	Age, sex, diabetes mellitus, hypertension, current smoking, prior acute MI, prior cerebrovascular disease, systolic blood pressure 100 mm Hg, heart rate 100 beats/min, Killip class IV, left anterior descending artery, multivessel disease, and final TIMI flow grade 3	Well
Kober, 1994[26]	Age, sex, LVEF, digoxin, furosemide, diabetes, calcium antagonist, heart failure, ventricular fibrillation	Adequate

Kober, 2006[27]	Age, pulse pressure, baseline creatinine, heart rate, weight, anterior MI, new left bundle branch, block, smoking status, Killip class at qualifying MI, history of angina, history of HF, history of unstable angina, history of peripheral arterial disease, history of alcohol abuse, history of stroke, history of chronic obstructive pulmonary disease, prior MI, use of percutaneous intervention or coronary artery bypass grafting, or thrombolytics prior to randomization, previous hospitalizations, renal function, diabetes status, country of enrollment, and randomized treatment (sex considered in selection, not significant predictor)	Well
Lake, 1989[28]	Age, sex, history of MI, electrocardiograph, angina, cholesterol, SBP and Quetelet's index	Adequate
Lau, 2009[29]	Age, increased heart rate, elevated cardiac biomarkers, ST-segment changes on the electrocardiogram, cardiogenic shock, impaired renal function, history of ischemic heart disease or heart failure, and the absence of in-hospital percutaneous coronary intervention (sex considered but excluded after forward selection)	Adequate
Marini, 2005[30]	Age, sex, hypertension, coronary heart disease, hypercholesterolemia, smoking, peripheral arterial disease	Adequate
Nakayama, 1997[31]	Stratified by sex, adjusted for age, mean arterial blood pressure, cholesterol, hematocrit, BMI, ECG abnormality, urinary albumin, urinary glucose, optic fundus abnormality, daily cigarettes, daily alcohol, physical activity, and history of IHD	Well
Ohsawa, 2007[32]	Stratified by sex, adjusted for age, body mass index, systolic blood pressure, blood glucose level, total cholesterol level, history of valvular heart disease, existence of left ventricular hypertrophy, regular drinking and current smoking status.	Well
Olsson, 2006[33]	Age, sex, ethnicity, ejection fraction, heart rate, blood pressure, BMI, HF, prior cardiovascular disease, medical treatment	Well
Pedersen, 2006[34]	Age, sex, LVEF, previous myocardial infarction, HF, angina pectoris, diabetes, hypertension, and bundle branch block	Well
Pedersen, 2006[35]	Age, sex, wall motion index, diabetes, IHD	Adequate
Pizzetti, 2001[36]	Age, sex, site of myocardial infarction, previous myocardial infarction, history of hypertension, history of diabetes mellitus, Killip class, systolic blood pressure, history of angina, time from onset of symptoms, heart rate, in-hospital administration of anti-arrhythmic treatment, and randomised treatment	Well
Rathore, 2000[37]	Age, sex, race, heart rate, systolic blood pressure, Killip class, hypertension, time to presentation, current smoking status, anterior MI, prior cerebrovascular disease, prior acute MI, and antiarrhythmic agent use on admission, during hospitalization, and at discharge	Well
Raunso, 2010[38]	Age, sex, LVEF, history of IHD, diabetes, smoking status, body mass index, history of chronic obstructive pulmonary disease, NYHA class at discharge, and serum creatinine levels at baseline	Well
Rodgers, 2004[39]	Age, history of TIA, smoking, cardiovascular disease, history of hypertension, systolic blood pressure (sex considered but removed after stepwise modeling)	Well

Ruel, 2004[40]	Age, sex, comorbidities, valve type, history of cerebrovascular accident, left ventricular grade 3 or 4 at the time of surgical referral, diabetes mellitus, primary indication of aortic insufficiency versus stenosis, redo status, aortic prosthesis, and aspirin use.	Adequate
Ruel, 2006[41]	Age, LVEF, operative indication, FMR grade, bioprosthetic implant (sex considered, but excluded after univariate analysis)	Adequate
Sakata, 1997[42]	Stepwise regression: age, sex, peak creatine phosphokinase levels, left ventricular ejection fraction, presence or absence of AF, hypertension (blood pressure .160/90 mm Hg), diabetes mellitus, hypercholesterolemia, history of acute MI, and cigarette smoking	Well
Santini, 2011[43]	Age, sex, NYHA class, LVEF, beta-blocker use, secondary prevention status, oral anticoagulation	Adequate
Simons, 1998[44]	Age, sex, prior stroke, SBP, HDL, BMI, peak expiratory flow, disability, depression	Adequate
Soliman, 2011[45]	Age, sex, race, use of antihypertensive medications, systolic blood pressure, current smoking, diabetes, left ventricular hypertrophy, and previous heart disease	Well
Stewart, 2002[46]	Stratified by sex, adjusted for age, stroke, chest pain, cholesterol, DBP, cardiothoracic ratio, glucose, forced expiratory volume, bronchitis, Q waves, ST segment, LBBB	Well
Stortecky, 2013[47]	Age, sex, BMI, hypertension, diabetes, past medical history, symptoms, cardiovascular risk (stepwise removed)	Well
Torres, 2008[48]	Stepwise regression:Age, sex, dyslipidemia, smoking, diabetes, hypertension, obesity, angina, myocardial infarction, and myocardial revascularization	Well
Tveit, 2011[49]	Stepwise regression: Age, sex, EF, NYHA, coronary artery disease, hypertension, valvular heart disease, heart rate, beta blockers, ACEI/ARB, frusemide, bumetanide, any loop diuretic, thiazide, warfarin, hemoglobin, creatninie	Adequate
van Wijk, 2008[50]	Age, sex, hypertension, smoking, diabetes, modified Rankin Scale, any infarct and white matter lesions on computed tomography scan	Well
Watanabe, 2009[51]	Age, sex, body mass index, systolic and diastolic blood pressure, treated hypertension, and diabetes in all subjects and were adjusted for age, sex, body mass index, and systolic and diastolic blood pressure in subjects without treated hypertension or diabetes	
Wolf, 1987[52]	Age, sex, cardiac failure, coronary heart disease, hypertension	Adequate
ECG and Medical Records		
Chamberlain, 2013[53]	Age, sex, body mass index, year of heart failure diagnosis, smoking status, derived NYHA class, estimated glomerular filtration rate, anemia, hypertension, diabetes mellitus, COPD, MI, and beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics at the index visit.	Well
Chen, 2013[54]	Age, sex, race, field center, heart rate, smoking status, body mass index, hypertension, diabetes mellitus, coronary heart disease, heart failure, LVH, use of beta-blockers, use of digoxin, and use of antiarrhythmic drugs	Well
Conen, 2011[55]	Age, height, body mass index, diabetes, hypertension, systolic blood pressure, hypercholesterolemia, smoking, alcohol	Well

	consumption, education, randomized treatment assignment, and race/ethnicity, intercurrent myocardial infarction, stroke, and congestive heart failure (women only)	
Genovesi, 2009[56]	Stratified by age, adjusted for hemodialysis duration, ischemic heart disease, dilated cardiomyopathy, valvular heart disease, hypertension, diabetes, left ventricular hypertrophy, LVEF, QRS interval duration, hyperkalaemia, HD mode, C-reactive protein (sex considered, but excluded after univariate analysis)	Well
Goldberg, 1990[57]	Age, sex, myocardial infarction, heart failure, cardiogenic shock, ventricular tachycardia, ventricular fibrillation/cardiac arrest, and drug therapy	Adequate
Jabre, 2011[58]	Age, sex, heart failure, and comorbidity, as measured by the Charlson index	Adequate
Kaarisalo, 1997[59]	Age, sex, recent MI, previous MI, hypertension	Adequate
O'Neal, 2015[60]	Age, sex, race/ethnicity, region of residence, systolic blood pressure, total cholesterol, HDL cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, and aspirin	Well
Okin, 2013[61]	Age, sex, race, diabetes mellitus, history of heart failure, myocardial infarction, ischemic heart disease, stroke, smoking, baseline serum high-density lipoprotein cholesterol, creatinine and glucose, and urine albumin/creatinine ratio as standard risk factors, and for incident myocardial infarction, in-treatment digoxin use, diastolic and systolic blood pressure, heart rate, QRS duration, Cornell product, and Sokolow-Lyon voltage LVH as time-varying covariates	Well
Oluleye, 2014[62]	Age, sex, race, history of ischemic heart disease, COPD hypertension, hyperlipidemia, stroke, renal artery disease, diabetes mellitus, hospitalization for HF in previous 6 months, heart block, and other arrhythmias, chronic kidney disease, anemia, systolic blood pressure, left ventricular hypertrophy on ECG, albumin, platelet count, and treatment with irbesartan, antiarrhythmic, antiplatelet agent, antithrombotic agent, calcium channel blocker, beta-blocker, angiotensin converting enzyme inhibitor, digoxin, diuretic, spironolactone, nitrate, lipid lowering drugs, and an ICD/pacemaker	Well
Pilgrim, 2013[63]	Age, sex, hypertension, hyperlipidaemia, diabetes, smoking, renal impairment, LVEF and acute coronary syndrome	Well
Saczynski, 2009[64]	Age, sex, history of angina, hypertension, diabetes, stroke, heart failure, AMI-associated characteristics, development of heart failure, cardiogenic shock, and stroke during hospitalization, and length of hospital stay	Well
Siontis, 2014[65]	Age, sex, family history of sudden cardiac death, NYHA class, obstructive phenotype, aspirin and warfarin	Adequate
Soliman, 2014[66]	Age, sex, race, region of residence, education level, and income, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, body mass index, diabetes, blood pressure–lowering drugs, warfarin use, aspirin use, statin use, history of noncardiac vascular disease, estimated glomerular filtration rate lower than 60 mL/min/1.73m2, log-transformed C-reactive protein, and log-transformed albumin to creatinine ratio.	Well
Wyse, 2001[67]	Age, sex, race, presenting ventricular tachyarrhythmia, remote myocardial infarction, heart failure, hypertension, diabetes, cigarette smoking, use of antiarrhythmic drugs at entry, LVEF, presence of coronary artery disease or dilated cardiomyopathy, hyperlipidemia, use of a pacemaker or implantable cardioverter debrillator, revascularization after the	Well

	qualifying event, and discharge medications	
Medical records		
Abbott, 2003[68]	Stepwise regression: Age, sex, race, weight, pretransplant dialysis, duration of dialysis prior to transplantation, total follow-up time, repeat transplant, donor cytomegalo-virus serology, dialysis in the first week after transplant (delayed graft function, yes/no), rejection (either treatment or diagnosis) occurring at any time in the study period, induction antibody therapy, maintenance immunosuppressive medications at time of discharge after transplant surgery, graft loss, and cause of ESRD (diabetes, systemic lupus erythematosus). Only hospitalizations occurring after the approximate date of rejection were considered in analysis. Maintenance immunosuppressive medication use, in particular cyclosporine and tacrolimus, at the time of discharge after transplantation was also analyzed as a pre-existing covariate.	Adequate
Andersson, 2014[69]	Matched by sex, adjusted for age, comorbidities excluded	Adequate
Bansal, 2013[70]	Age, sex, race, education, income level, eGFR level, albuminuria, hemoglobin level, diabetes mellitus, hypertension, coronary heart disease, ischemic stroke, transient ischemic attack, heart failure, peripheral arterial disease, dyslipidemia, chronic lung disease, chronic liver disease, hyperthyroidism, and baseline medication use (βblockers, ACE inhibitors/ARBs, calcium channel blockers, diuretics, statins, other lipid-lowering agents, warfarin	Well
Bansal, 2014[71]	Age, sex, race, household income status, educational attainment, diabetes mellitus, dyslipidemia, chronic lung disease, chronic liver disease, thyroid disease, eGFR category, proteinuria, hemoglobin category, systolic blood pressure, history of stroke or transient ischemic attack, history of heart failure, history of coronary heart disease, history of peripheral artery disease, and baseline use of medications (beta blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, diuretics, statins, other lipid-lowering agents, warfarin, and antiplatelet agents	Well
Bengtson, 2014[72]	Age, sex, race, field center, year, ST-elevation MI, non ST-elevation MI and unclassified, systolic blood pressure, pulse, modified PREDICT score, aspirin, beta-blockers, calcium channel blockers, ACE or angiotensin II inhibitors, warfarin, lipid-lowering medications, anti-platelet agents other than aspirin, percutaneous coronary intervention and coronary artery bypass graft	Well
Biblo, 2001[73]	Age, sex, race, myocardial infarction, heart failure, rheumatic heart disease, hypertension, diabetes, atrial flutter	Adequate
Burke, 2013[74]	Age, sex, race, hypertension, hyperlipidemia, diabetes, CHD, PVD, epilepsy, injury severity, traumatic brain injury, injury mechanism, admittance, Charlson comorbidities	Well
Chao, 2012 [75]	Age, sex, dyslipidemia, CKD, asthma, malignancy, liver cirrhosis, autoimmune diseases (stepwise inclusion)	Adequate
Duncan, 2015[76]	Age, sex, creatinine, COPD, CHD, EuroScore, LVEF, diabetes,	Well
Feng, 2009[77]	Age, sex	Adequate

Henriksson, 2010[78]	Age, sex, heart failure, diabetes, hypertension, previous stroke	Well
Hippisley-Cox, 2010[79]	Stratified by sex, adjusted for age,body mass index, systolic blood pressure, cholesterol, Townsend score, smoking, ethnicity, family history of CHD, diabetes, rheumatoid arthritis, renal disease	Well
Hippisley-Cox, 2013[80]	Stratified by sex, adjusted for age, BMI, blood pressure, total:HDL cholesterol ratio, Townsend deprivation score, smoking status, ethnicity, family history of coronary artery disease, coronary heart disease, congestive cardiac failure, type 1 diabetes, type 2 diabetes, treated hypertension, rheumatoid arthritis, chronic renal disease, and valvular heart disease	Well
Kamel, 2012[81]	Age, sex, race, hypertension, dyslipidemia, diabetes, previous stroke, and use of antithrombotic and statin medications	Well
Kimura, 2005[82]	Age, sex, hypertension, diabetes, hypercholesterolemia, smoking, stroke severity at hospital discharge, stroke subtype and residence after hospital discharge	Well
Manzano, 2012[83]	Age, sex, hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking, ankle brachial index, severe ECD and ICLAD	Well
Marijon, 2009[84]	Age, sex, NYHA, diabetes, obesity, hypertension, smoking, coronary artery disease, dilated cardiomyopathy, QRS, beta-blocker, ACE-inhibitor/ARB, primary vs. secondary prevention	Well
McManus, 2013[85]	Age, sex, race, systolic blood pressure, hypertension, cholesterol, diabetes left ventricular ejection fraction, heart failure, acute myocardial infarction, unstable angina, coronary artery bypass graft surgery, percutaneous coronary intervention, ischemic stroke, other thromboembolic event, ventricular fibrillation or ventricular tachycardia, peripheral arterial disease, cardiac resynchronization therapy, implantable cardioverter defibrillator, dyslipidemia, hospitalized bleeds, diagnosed dementia, diagnosed depression, chronic lung disease, chronic liver disease, mechanical fall, systemic cancer, estimated GFR, hemoglobin, site	Well
Ruff, 2014[86]	Age, sex, prior ischemic event, vascular disease, congestive heart failure, diabetes, smoking, body mass index, region, aspirin and statin use	Well
Ruigomez, 2009[87]	Age, sex, BMI, alcohol, primary care physician visits, smoking, hypertension, hyperlipidaemia, peripheral vascular disease, venous thromboembolism, COPD, diabetes, other cardiac diseases group	Well
Saposnik, 2011[88]	Age, sex, severe stroke, nonlacunar stroke subtype, glucose, coronary artery disease, congestive heart failure, cancer, dementia, dialysis, and dependency before stroke	Adequate
Saxena, 2013[89]	Age, sex, COPD, diabetes, cholesterol, hypertension, PVD, renal failure, cardiac surgery, myocardial infarction, triple vessel disease, ejection fraction, obesity, smoking, NYHA class, status, criticical peroperative state	Well
Smit, 2006[90]	Age, sex, LVEF, baseline drug therapy, and cumulative RV pacing	Adequate
Stein, 2009[91]	Age, BMI, diabetes, LVEF, physical activitiy, mean arterial pressure, NYHA, diuretic, digitalis, lipid lowering medications (sex considered, but unassociated in univariate analysis)	Well
Wang, 2013[92]	Age, sex, urbanization level, the year of index date, propensity score, hypertension, diabetes, CAD, hyperlipidemia,	Well

	income, region	
Wetmore, 2013[93]	Age, sex, race, BMI, smoking, substance abuse, employment, comorbidities, Liu index, dialysis	Well
Wolf, 1998[94]	Matched for age and sex, adjusted for AMI, unstable angina, stable angina, heart failure, hypertension, diabetes, valvular disease, stroke and COPD	Well
Wong, 2000[95]	Age, systolic blood pressure, weight, Killip class, heart rate, infarct location, diabetes mellitus, hypercholesterolemia, prior MI, angina, heart failure, cerebrovascular disease, prior angioplasty, and prior bypass surgery (sex unassociated in univariate analysis)	Well
Ascertainment Not Specified		
Desai, 2010[96]	Stepwise regression: Age, sex, ischemic cardiomyopathy, nonischemic cardiomyopathy, LVEF, pacing, QRS duration, NYHA class, smoking, systemic hypertension, diabetes, dyslipidemia, use of statins, beta-blockers, ACE-inhibitors or ARBs, amiodarone, sotalol, and digoxin	Well
Lau, 2014[97]	Stepwise regression: Age, diabetes, chronic kidney disease, cancer (sex unassociated in univariate analysis)	Adequate
Liu, 2006[98]	Age, hypertension, hyperlipidemia, diabetes, history of TIA, history of MI, cigarette smoking, drinking and family history of stroke (sex unassociated in univariate analysis)	Well
Sampson, 2007[99]	Stepwise regression: Age, sex, race, weight, height, body mass index, body surface area, SBP, DBP, MAP, pulse pressure, heart rate, estimated eGFR, time to randomization, region, heart failure, LV systolic dysfunction, LV failure, Killip class, ECG type and site, previous hospitalization, smoking status, diabetes, history of angina, unstable angina pre-qualifying MI, history of MI, other comobridities, GP IIb/IIa inhibitor use, ACE-inhibitor use, amiodarone use at randomization, ARB use, aspirin use, other medications	Well
Xu, 2007[100]	Subtype of stroke, hypertension, AF, history of TIA, smoking and antiplatelet treatment (age and sex considered, but non-significant in univariate analysis)	Well

Abbrevations: SBP: systolic blood pressure; DBP: diastolic blood pressure LVSD: left ventricular systolic dysfunction, ACE inhibitor: Angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, LVH: left ventricular hypertrophy, NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; HDL: high density lipoprotein; LDL: low density lipoprotein; BMI: body mass index; MI: myocardial infarction; HF: heart failure; ECG: electrocardiogram; TIA: transient ischemic attack; CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate

Supplementary Table 3: Sensitivity Analyses Of Relative Risk Of All-Cause Mortality.

Strata	Number of Studies	HR (CI)	I2	Test for Interaction/Trend
Type of Population				
General Population	13	1.6 (1.4, 1.84)	92	p interaction: 0.112
Specific Population	48	1.42 (1.34, 1.51)	93	
Method of AF Ascertainment				
ECG Only	36	1.49 (1.37, 1.62)	93	p interaction: 0.455
ECG and Medical Records	10	1.42 (1.24, 1.62)	90	
Medical Records	13	1.39 (1.28, 1.5)	92	
Level of Adjustment				
Adequately Adjusted	22	1.42 (1.27, 1.59)	95	p interaction: 0.597
Well Adjusted	39	1.47 (1.39, 1.55)	88	
Year of Publication				
[1987,2006]	27	1.41 (1.32, 1.51)	86	p trend: 0.447
(2006,2011]	19	1.5 (1.36, 1.65)	87	
(2011,2015]	15	1.49 (1.33, 1.67)	94	
Median Follow Up (Years)				
[0.5,2.23]	23	1.42 (1.34, 1.5)	67	p trend: 0.162
(2.23,5.4]	20	1.47 (1.33, 1.62)	97	
(5.4,30]	17	1.47 (1.3, 1.68)	90	
Location				
Asia	8	1.48 (1.26, 1.74)	71	p interaction: 0.306
Europe	27	1.46 (1.34, 1.6)	95	
International	5	1.31 (1.18, 1.44)	50	
Other	4	1.5 (1.22, 1.83)	63	
United States	17	1.49 (1.37, 1.63)	94	

Supplementary Table 4. Sensitivity Analyses Of Relative Risk Of Cardiovascular Mortality.

Strata	Number of Studies	HR (CI)	I2 (%)	Test for Interaction/Trend
Type of Population				
General Population	5	2.55 (1.79, 3.62)	79	p interaction: 0.086
Specific Population	8	1.83 (1.58, 2.11)	77	
Method of AF Ascertainment				
ECG Only	7	2 (1.58, 2.53)	81	p interaction: 0.191
ECG and Medical Records	4	2.11 (1.68, 2.66)	79	
Medical Records	1	5.83 (1.89, 18)	-	
Level of Adjustment				
Adequately Adjusted	4	2.06 (1.94, 2.2)	14	p interaction: 0.804
Well Adjusted	9	2.14 (1.62, 2.82)	84	
Year of Publication				
[1987,2006]	1	2.89 (2.23, 3.74)	-	p trend: 0.296
(2006,2011]	5	2.18 (1.47, 3.23)	87	
(2011,2015]	7	1.86 (1.6, 2.18)	67	
Median Follow Up (Years)				
[0.5,2.23]	2	3.19 (1.39, 7.3)	53	p trend: 0.303
(2.23,5.4]	5	1.86 (1.51, 2.3)	87	
(5.4,30]	6	2.16 (1.65, 2.84)	75	
Location				
Asia	4	1.93 (1.02, 3.64)	85	p interaction: 0.926
Europe	6	2.12 (1.78, 2.53)	62	
United States	3	2.2 (1.67, 2.91)	86	

Supplementary Table 5. Sensitivity Analyses Of Relative Risk Of Major Cardiovascular Events.

Strata	Number of Studies	HR (CI)	I2 (%)	Test for Interaction/Trend
Type of Population				
General Population	4	2.71 (1.82, 4.04)	99	p interaction: 0.002
Specific Population	5	1.39 (1.18, 1.63)	75	
Method of AF Ascertainment				
ECG Only	3	1.58 (1.11, 2.23)	93	p interaction: 0.579
ECG and Medical Records	3	2.45 (0.8, 7.49)	99	
Medical Records	3	1.87 (1.64, 2.14)	80	
Level of Adjustment				
Well Adjusted	9	1.96 (1.53, 2.51)	98	
Year of Publication				
[1987,2006]	2	1.64 (0.87, 3.09)	96	p trend: 0.927
(2006,2011]	3	2.61 (1.18, 5.77)	99	
(2011,2015]	4	1.69 (1.21, 2.36)	92	
Median Follow Up (Years)				
[0.5,2.23]	1	2.25 (1.04, 4.87)	-	p trend: 0.11
(2.23,5.4]	4	1.5 (1.1, 2.05)	97	
(5.4,30]	4	2.53 (1.38, 4.65)	99	
Location				
Asia	1	2.25 (1.04, 4.87)	-	p interaction: <0.001
Europe	4	1.77 (1.55, 2.02)	62	
International	3	1.42 (0.98, 2.06)	98	
United States	1	6.94 (5.75, 8.38)	-	

Supplementary Table **6. Sensitivity Analyses Of Relative Risk Of Stroke.**

Strata	Number of Studies	HR (CI)	I2 (%)	Test for Interaction/Trend
Type of Population				
General Population	20	2.59 (2.23, 3.01)	97	p interaction: 0.571
Specific Population	17	2.4 (1.93, 2.98)	93	
Method of AF Ascertainment				
ECG Only	19	2.69 (2.28, 3.16)	69	p interaction: 0.309
ECG and Medical Records	3	3.09 (1.97, 4.84)	68	
Medical Records	12	2.32 (1.96, 2.74)	98	
Level of Adjustment				
Adequately Adjusted	13	2.71 (2.15, 3.43)	96	p interaction: 0.475
Well Adjusted	24	2.44 (2.04, 2.91)	96	
Year of Publication				
[1987,2006]	11	2.45 (2, 2.99)	98	p trend: 0.566
(2006,2011]	12	3.05 (2.18, 4.27)	87	
(2011,2015]	14	2.2 (1.83, 2.64)	93	
Median Follow Up (Years)				
[0.5,2.23]	10	2.47 (1.5, 4.06)	93	p trend: 0.287
(2.23,5.4]	13	2.53 (1.93, 3.3)	98	
(5.4,30]	12	2.34 (1.99, 2.75)	90	
Location				
Asia	9	3.09 (2.14, 4.46)	84	p interaction: 0.054
Europe	14	2.65 (2.13, 3.31)	92	
International	2	1.84 (1.34, 2.52)	55	
Other	2	1.5 (0.89, 2.53)	0	
United States	9	2.12 (1.76, 2.55)	99	

Supplementary Table 7. Sensitivity Analyses Of Relative Risk Of Ischemic Stroke.

Strata	Number of Studies	HR (CI)	I2 (%)	Test for Interaction/Trend
Type of Population				
General Population	6	2.96 (2.38, 3.68)	41	p interaction: 0.007
Specific Population	4	1.75 (1.28, 2.39)	80	
Method of AF Ascertainment				
ECG Only	5	2.89 (2.01, 4.15)	56	p interaction: 0.303
ECG and Medical Records	1	3.08 (1.45, 6.55)	-	
Medical Records	4	2 (1.41, 2.86)	91	
Level of Adjustment				
Adequately Adjusted	4	2.51 (1.84, 3.43)	52	p interaction: 0.917
Well Adjusted	6	2.45 (1.7, 3.53)	89	
Year of Publication				
[1987,2006]	4	2.65 (1.74, 4.02)	61	p trend: 0.424
(2006,2011]	2	3.25 (2.37, 4.46)	15	
(2011,2015]	4	1.86 (1.34, 2.57)	84	
Median Follow Up (Years)				
[0.5,2.23]	2	1.52 (1.06, 2.18)	91	p trend: 0.073
(2.23,5.4]	4	3.07 (2.65, 3.55)	0	
(5.4,30]	4	2.83 (1.61, 4.95)	62	
Location				
Asia	3	3.5 (2.29, 5.35)	23	p interaction: 0.061
Europe	2	3.01 (2.32, 3.9)	0	
Other	2	1.82 (1.19, 2.77)	0	
United States	3	1.93 (1.21, 3.09)	96	

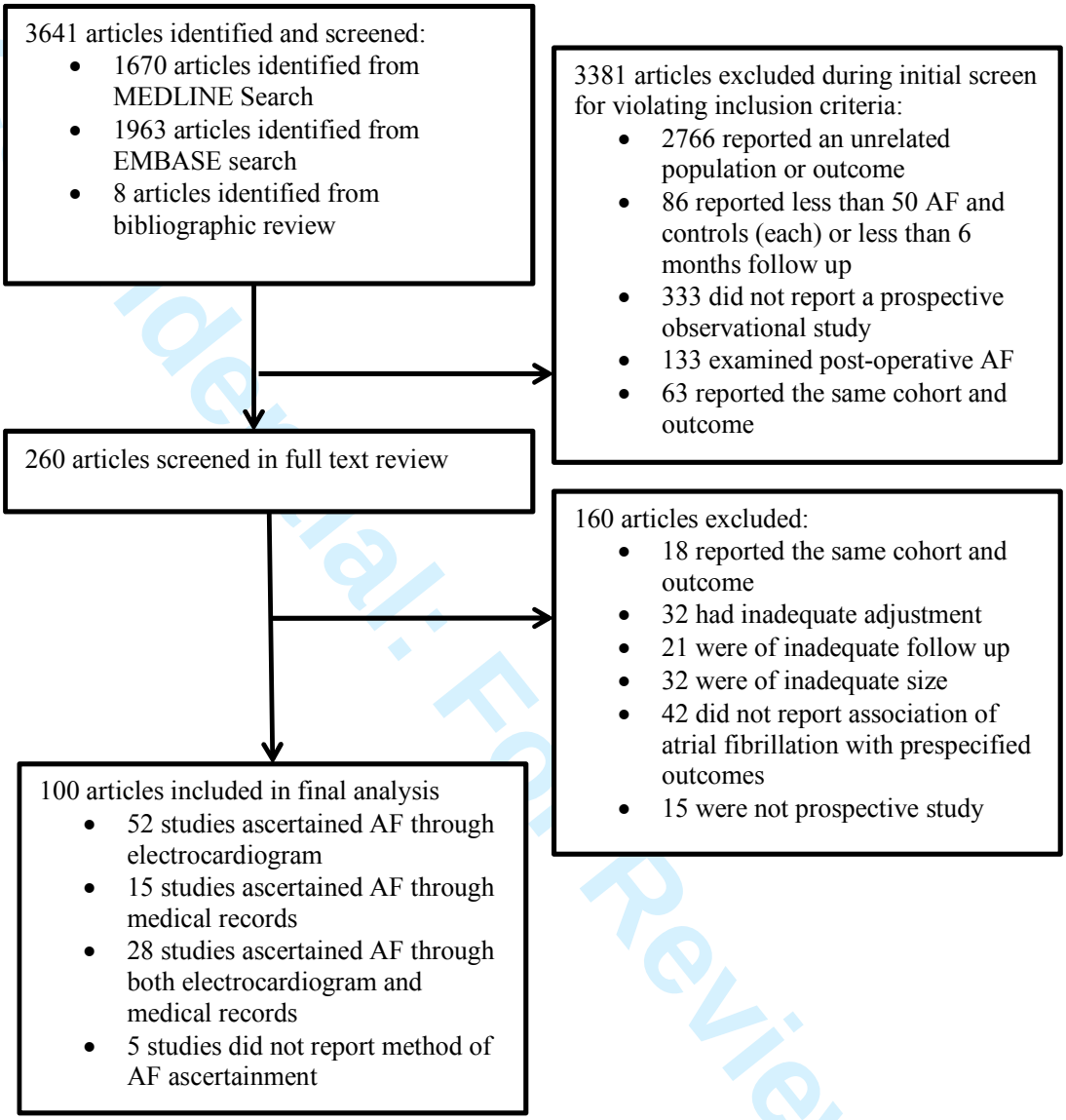
Supplementary Table 8. Sensitivity Analyses Of Relative Risk Of Ischemic Heart Disease.

Strata	Number of Studies	HR (CI)	I2 (%)	Test for Interaction/Trend
Type of Population				
General Population	6	2.14 (1.49, 3.06)	92	p interaction: 0.022
Specific Population	10	1.36 (1.2, 1.55)	67	
Method of AF Ascertainment				
ECG Only	7	1.37 (1.12, 1.68)	75	p interaction: 0.261
ECG and Medical Records	6	1.86 (1.33, 2.61)	93	
Medical Records	3	1.71 (1.13, 2.59)	76	
Level of Adjustment				
Adequately Adjusted	5	1.47 (1.22, 1.77)	71	p interaction: 0.377
Well Adjusted	11	1.68 (1.33, 2.14)	89	
Year of Publication				
[1987,2006]	1	1.43 (1.21, 1.69)	-	p trend: 0.801
(2006,2011]	6	1.61 (1.09, 2.38)	85	
(2011,2015]	9	1.65 (1.36, 2.01)	89	
Median Follow Up (Years)				
[0.5,2.23]	3	1.22 (0.9, 1.64)	0	p trend: 0.012
(2.23,5.4]	7	1.54 (1.39, 1.71)	59	
(5.4,30]	5	1.88 (1.09, 3.24)	93	
Location				
Asia	1	2.98 (0.67, 13.27)	-	p interaction: 0.156
Europe	9	1.46 (1.27, 1.67)	76	
Other	1	1.16 (0.85, 1.59)	-	
United States	5	2 (1.33, 3)	91	

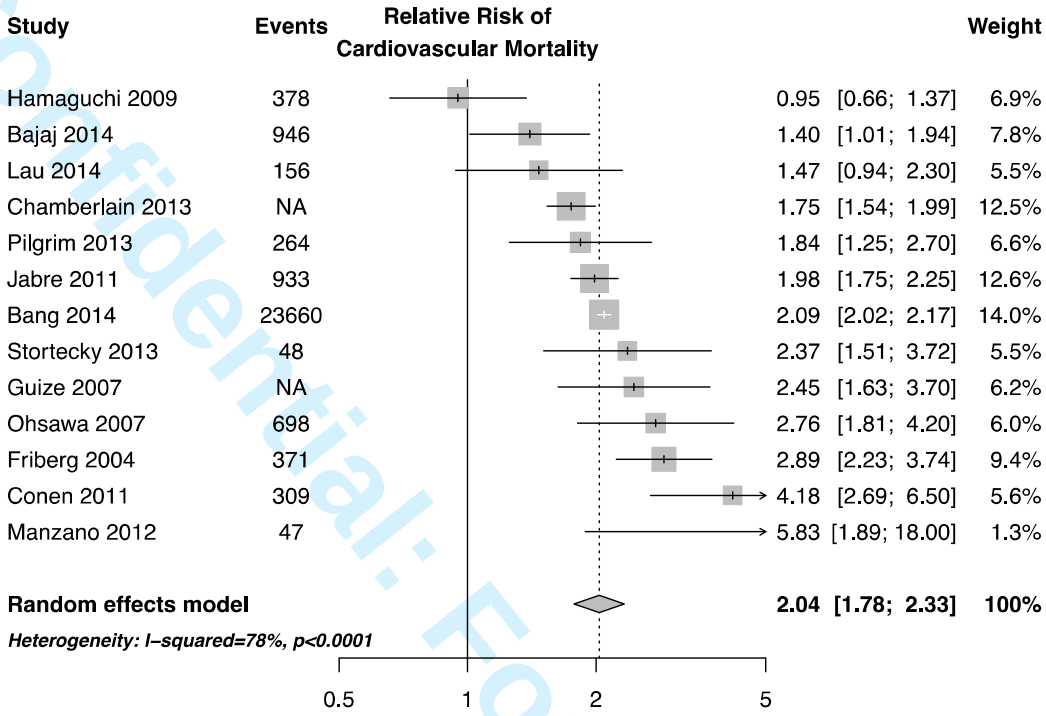
Supplementary Table 9. Sequential Exclusion of Studies to Assess the Impact of Heterogeneity

Outcome	Number of Studies Excluded	Number of Studies Included	Original RR (CI)	Original I2 (%)	New RR (CI)	New I2 (%)
All-cause mortality	19	42	1.46 (1.39, 1.54)	93	1.42 (1.36, 1.48)	48
Cardiovascular Mortality	4	9	2.04 (1.78, 2.23)	78	2.02 (1.80, 2.27)	46
Major Cardiovascular Events	5	4	1.96 (1.53, 2.51)	98	1.72 (1.63, 1.83)	6
Ischemic Heart Disease	4	12	1.61 (1.38, 1.87)	86	1.46 (1.34, 1.59)	46
Ischemic Stroke	2	8	2.44 (1.83, 3.24)	88	2.92 (2.61, 3.41)	25
Stroke	16	21	2.49 (2.22, 2.79)	96	2.71 (2.41, 3.05)	43

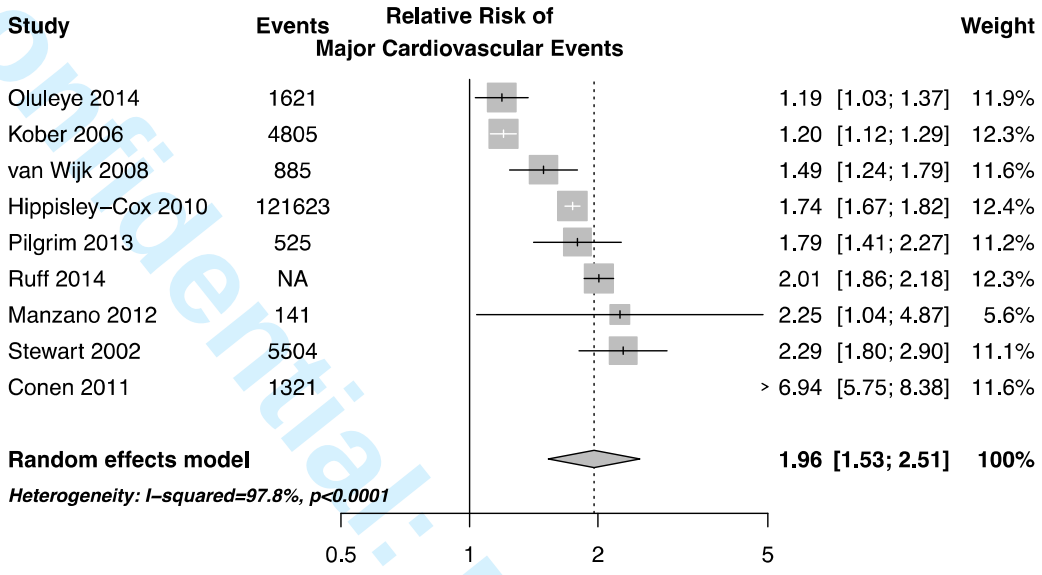
Supplementary Figure 1. Identification of Included Studies



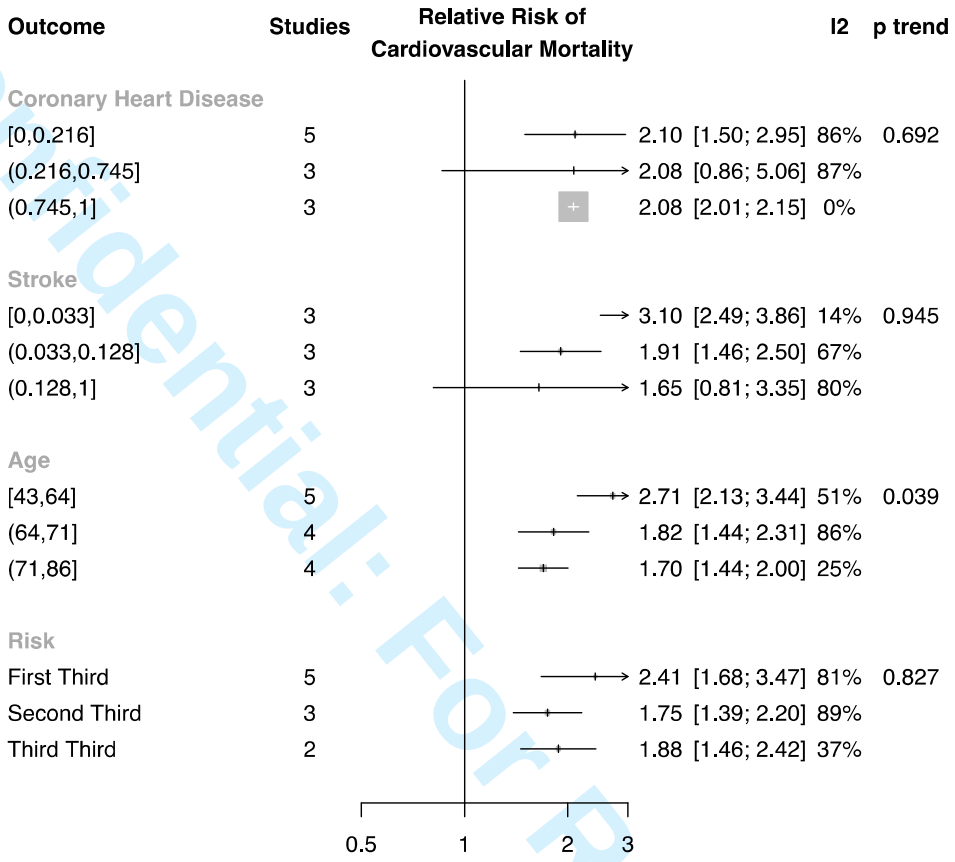
Supplementary Figure 2. Association Between Atrial Fibrillation and Cardiovascular Mortality



Supplementary Figure 3. Association Between Atrial Fibrillation and Major Cardiovascular Events

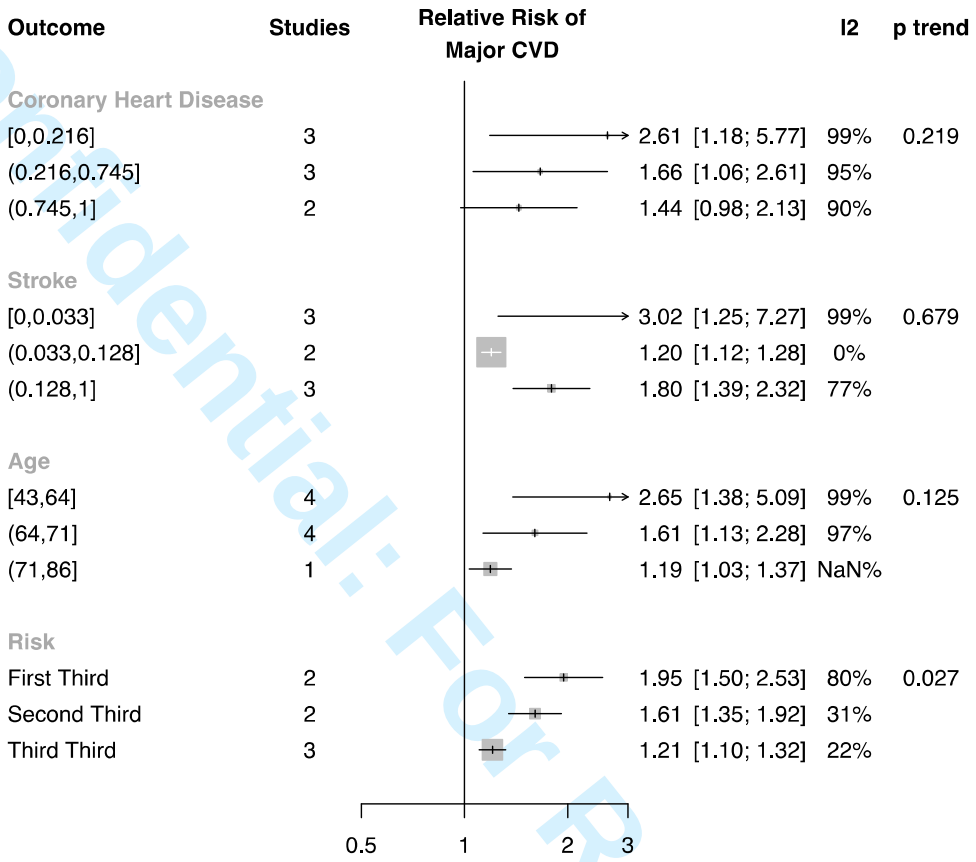


Supplementary Figure 4. Association Between Atrial Fibrillation and Cardiovascular Mortality, Stratified by Patient Demographics and Baseline Clinical Characteristics



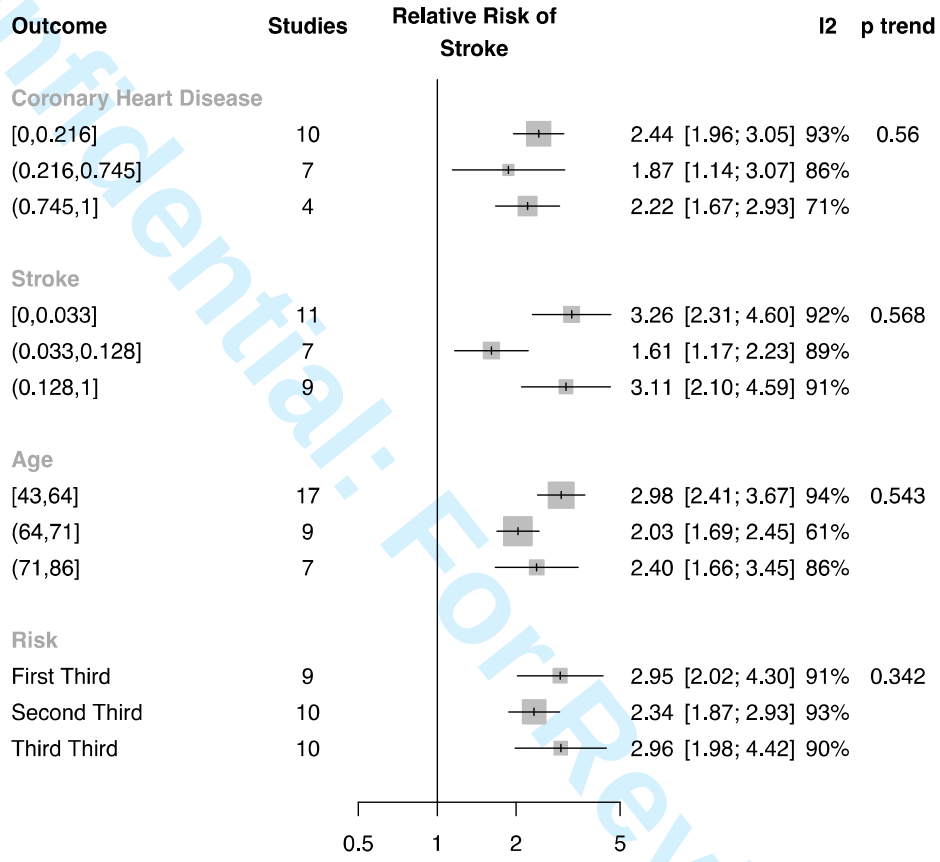
First risk third is from 0.6 events/1000 patient years to 0.9, second third from > 0.9 to 4.3, third third from > 4.3 to 12.3.

Supplementary Figure 5. Association Between Atrial Fibrillation and Major Cardiovascular Events, Stratified by Patient Demographics and Baseline Clinical Characteristics



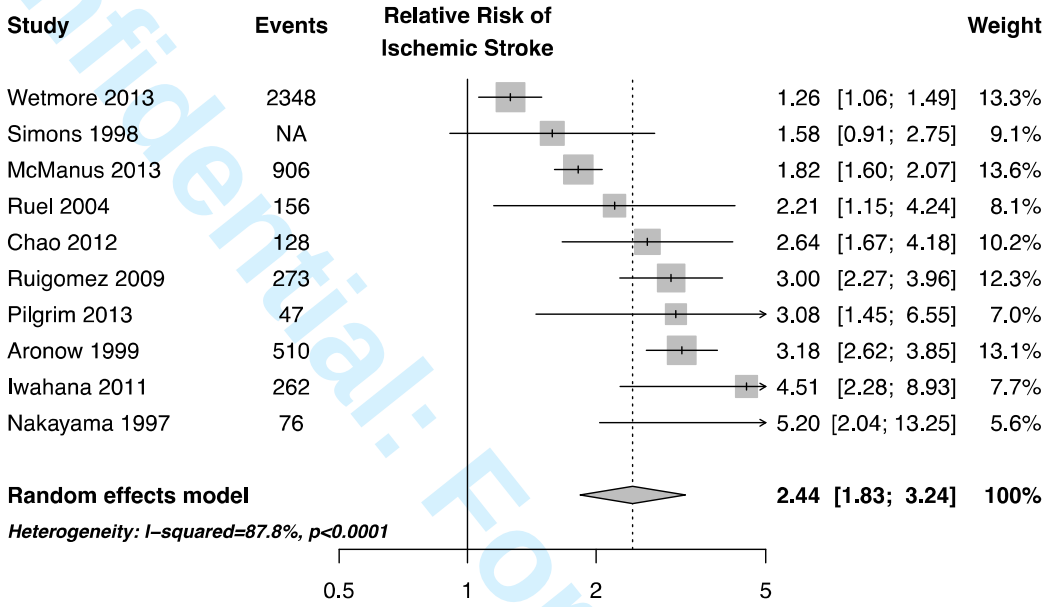
First risk third is from 2.5 events/1000 patient years to 19.2, second third from > 19.2 to 70.3, third third from > 70.3 to 125.

Supplementary Figure 6. Association Between Atrial Fibrillation and All Stroke, Stratified by Patient Demographics and Baseline Clinical Characteristics

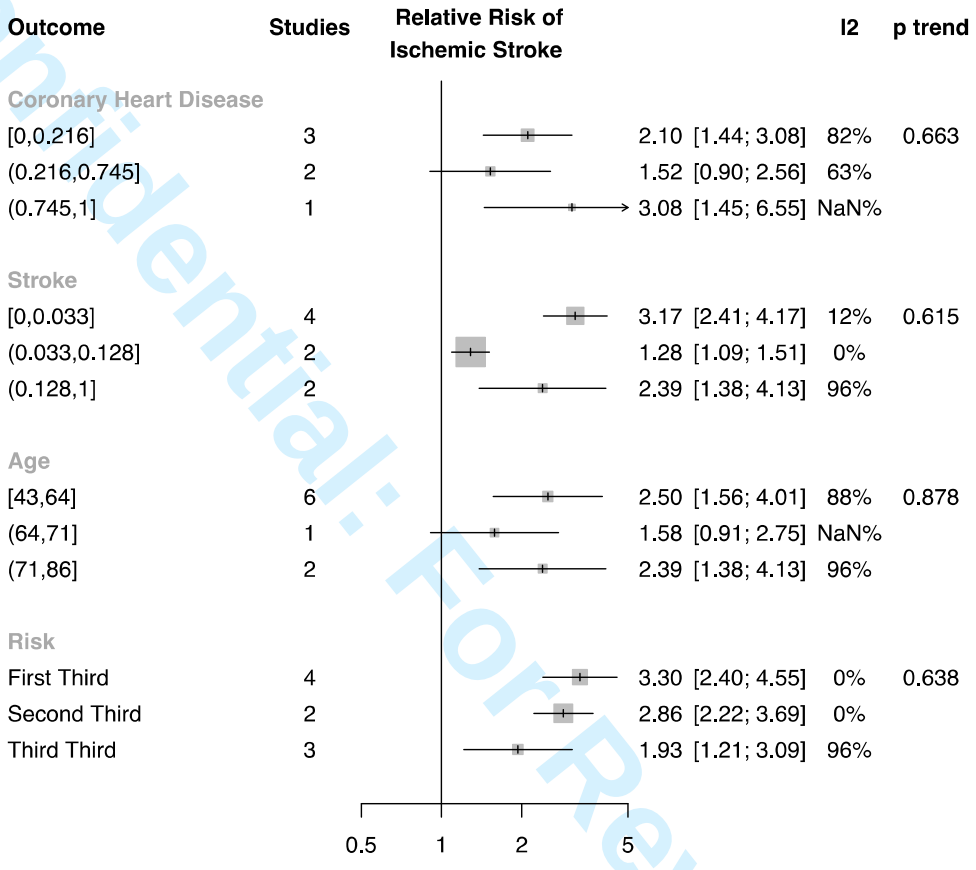


First risk third is from 1.1 events/1000 patient years to 3.8, second third from > 3.8 to 29.1, third third from > 29.1 to 192.

Supplementary Figure 7. Association Between Atrial Fibrillation and Ischemic Stroke

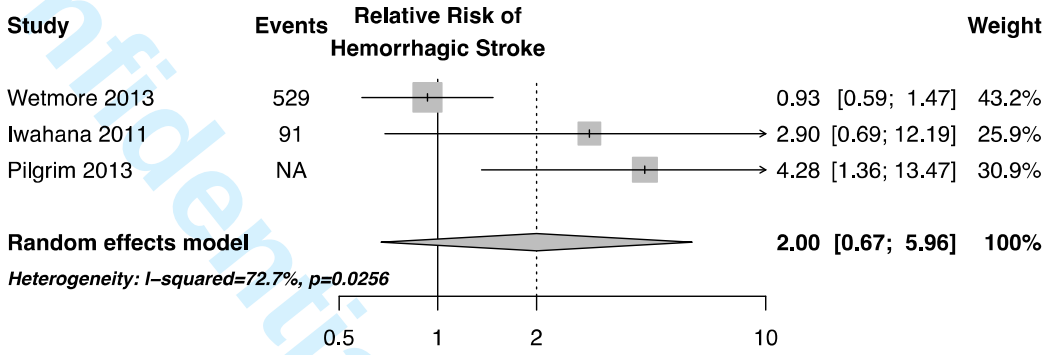


Supplementary Figure 8. Association Between Atrial Fibrillation and Ischemic Stroke, Stratified by Patient Demographics and Baseline Clinical Characteristics

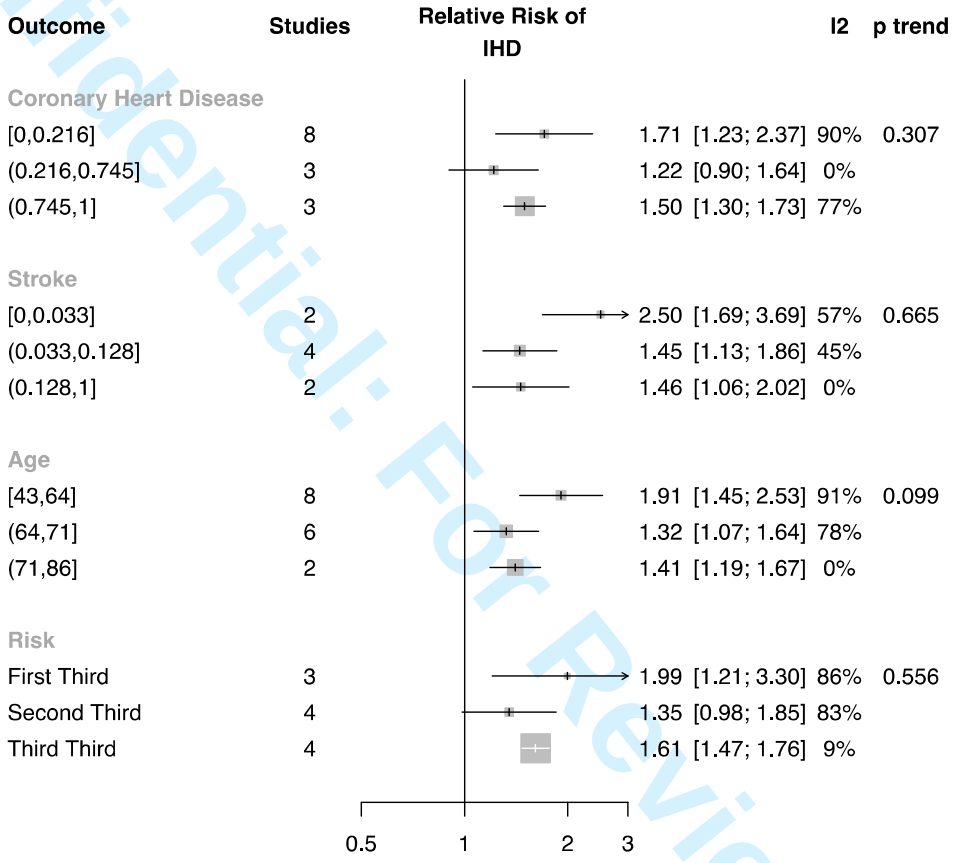


First risk third is from 2.0 events/1000 patient years to 3.3, second third from > 3.3 to 17.8, third third from > 17.8 to 59.

Supplementary Figure 9. Association Between Atrial Fibrillation and Haemorrhagic Stroke

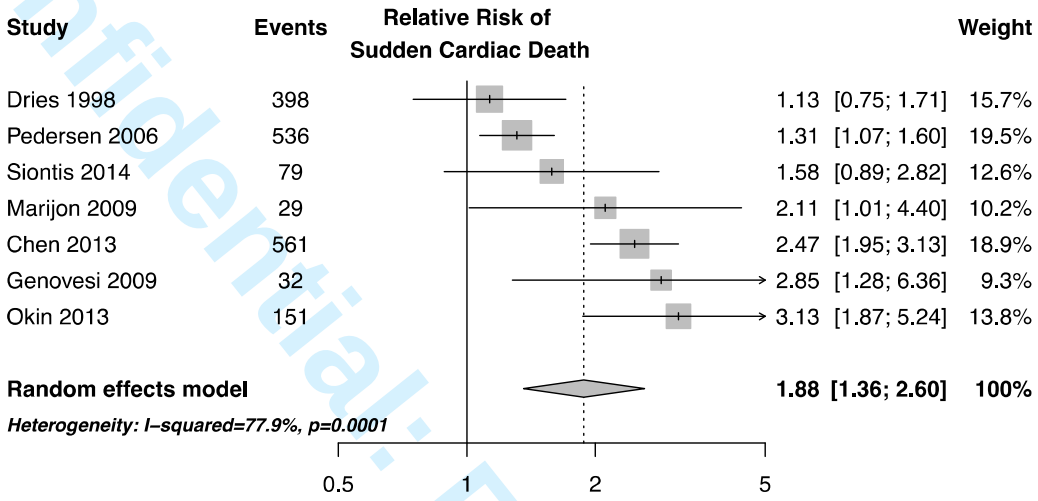


Supplementary Figure 10. Association Between Atrial Fibrillation and Ischemic Heart Disease, Stratified by Patient Demographics and Baseline Clinical Characteristics

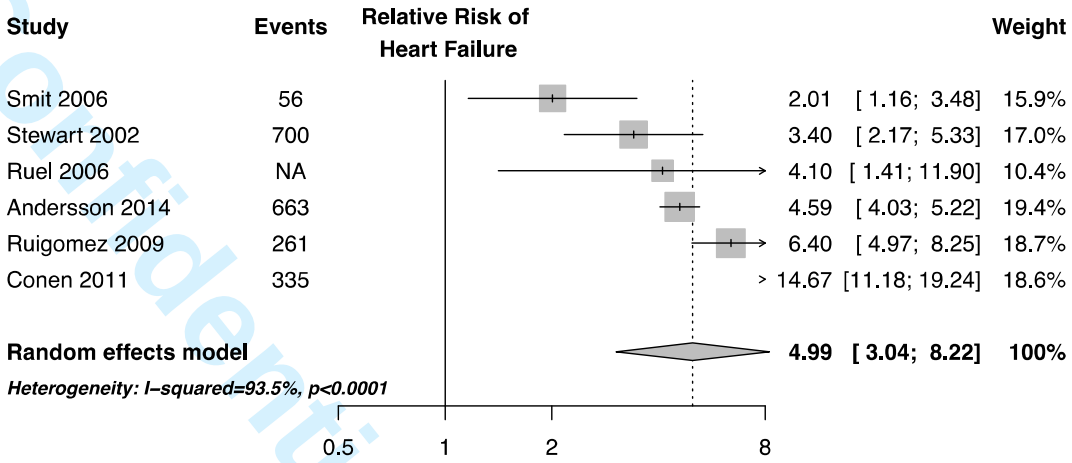


First risk third is from 0.9 events/1000 patient years to 8.1, second third from > 8.1 to 12.1, third third from > 12.1 to 45.

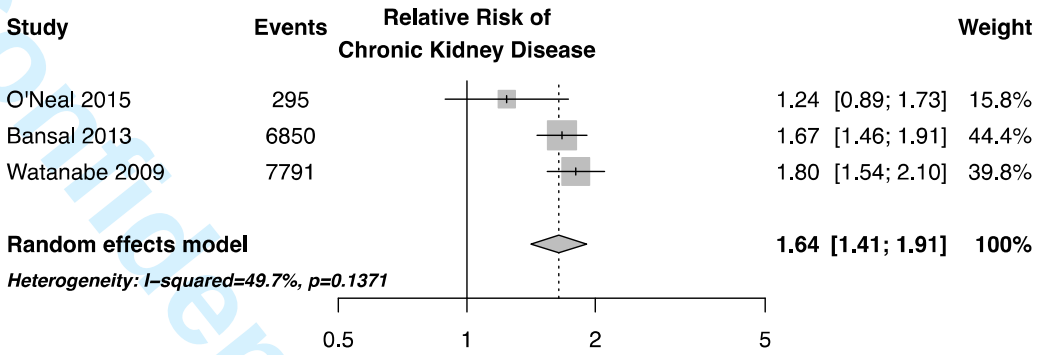
Supplementary Figure 11. Association Between Atrial Fibrillation and Sudden Cardiac Death



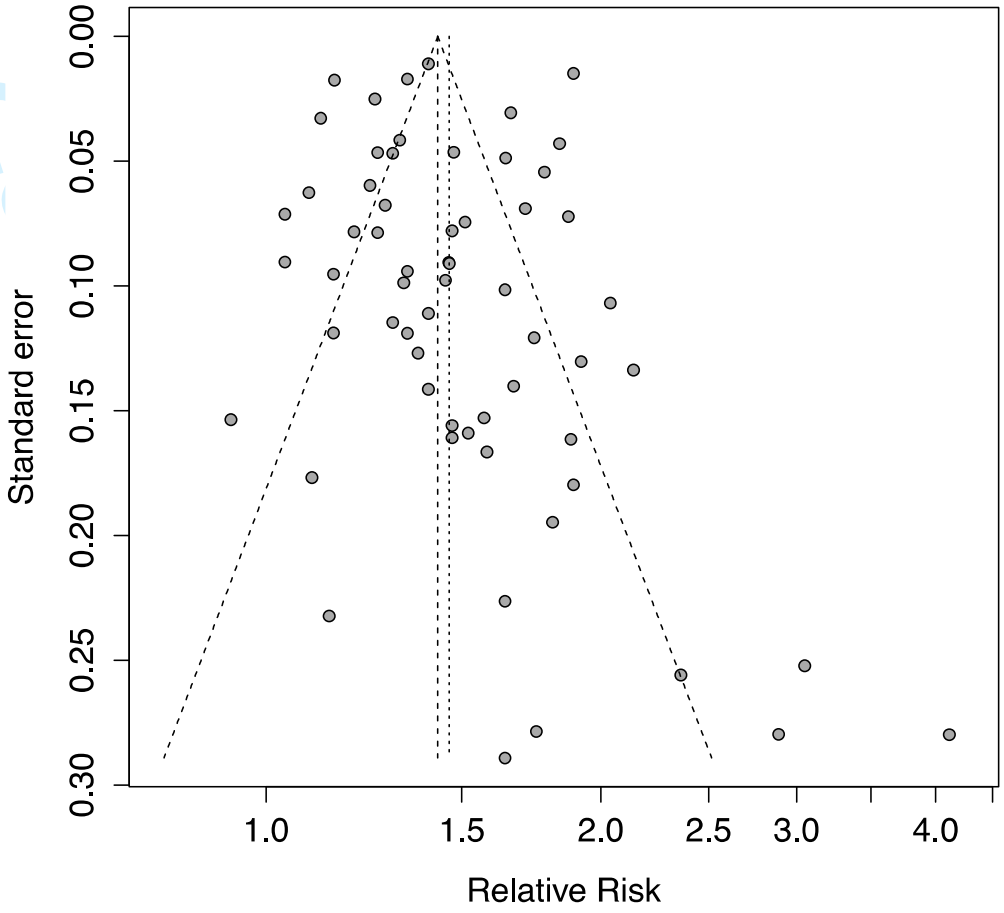
Supplementary Figure 12. Association Between Atrial Fibrillation and Incident Congestive Heart Failure



Supplementary Figure 13. Association Between Atrial Fibrillation and Chronic Kidney Disease

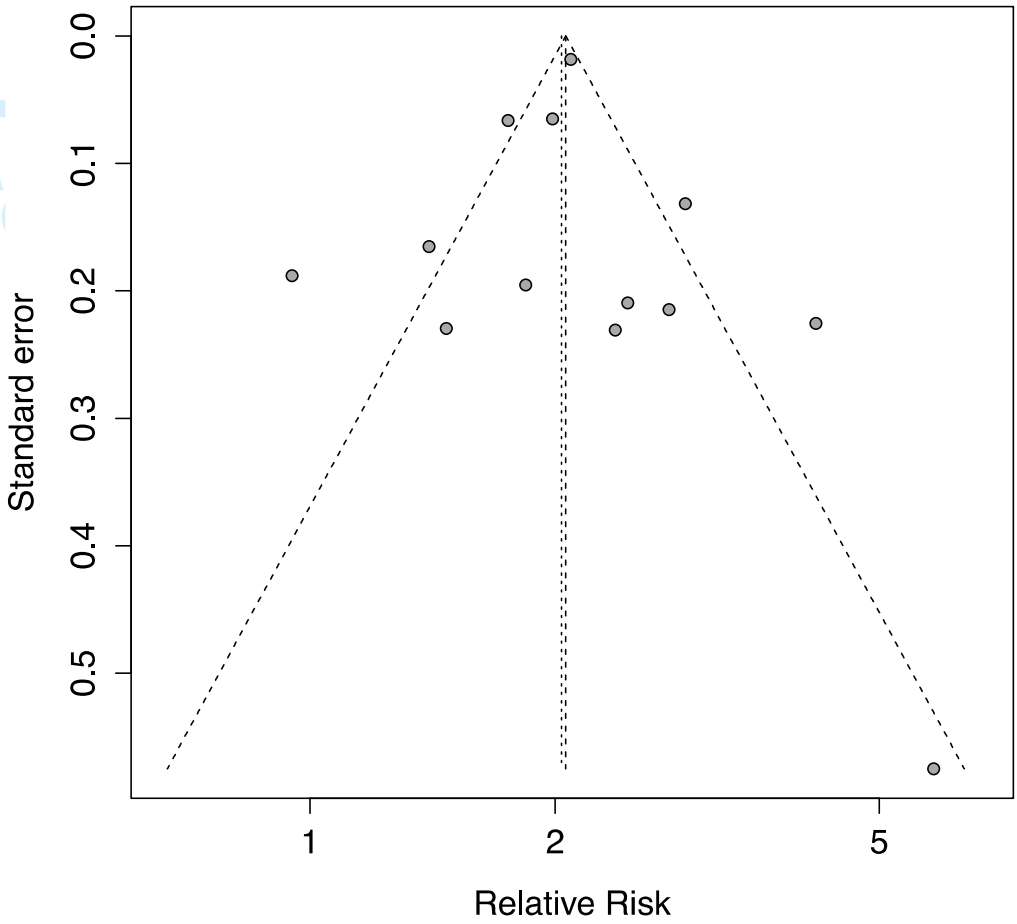


Supplementary Figure 14. Funnel Plot for All-cause Mortality



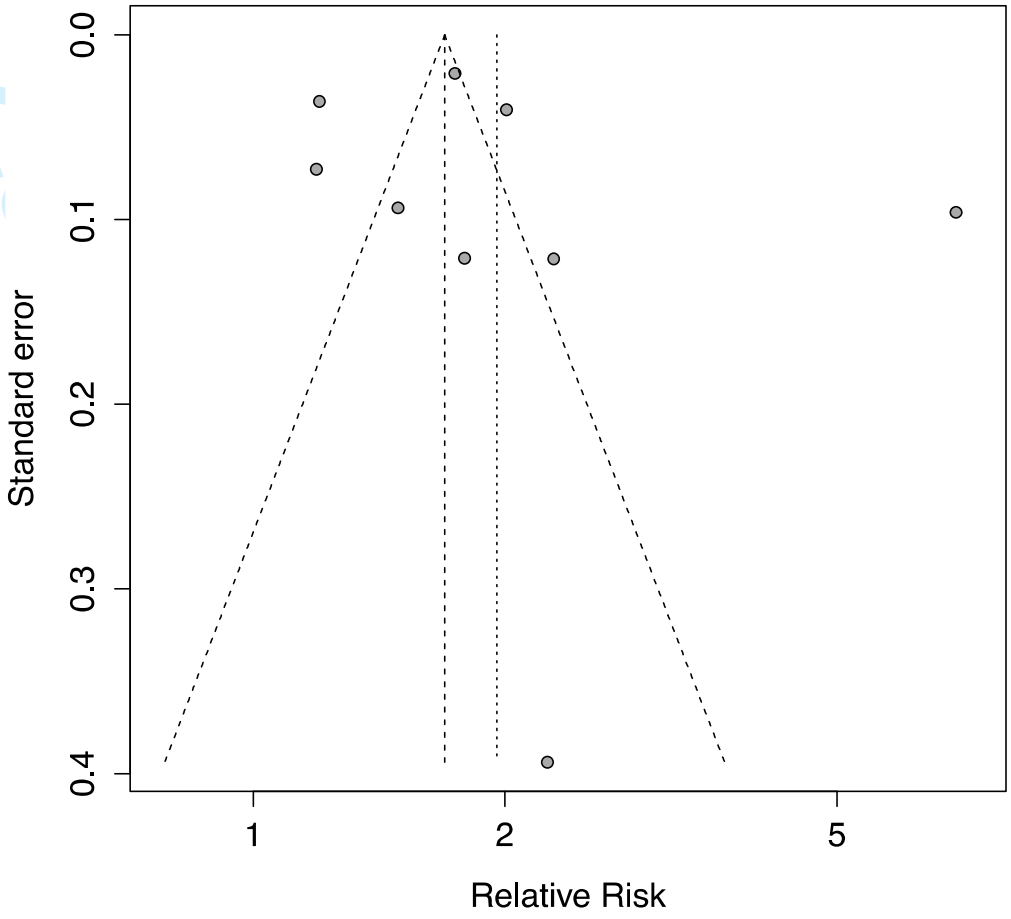
Egger's test p-value = 0.7

Supplementary Figure 15. Funnel Plot for Cardiovascular Mortality



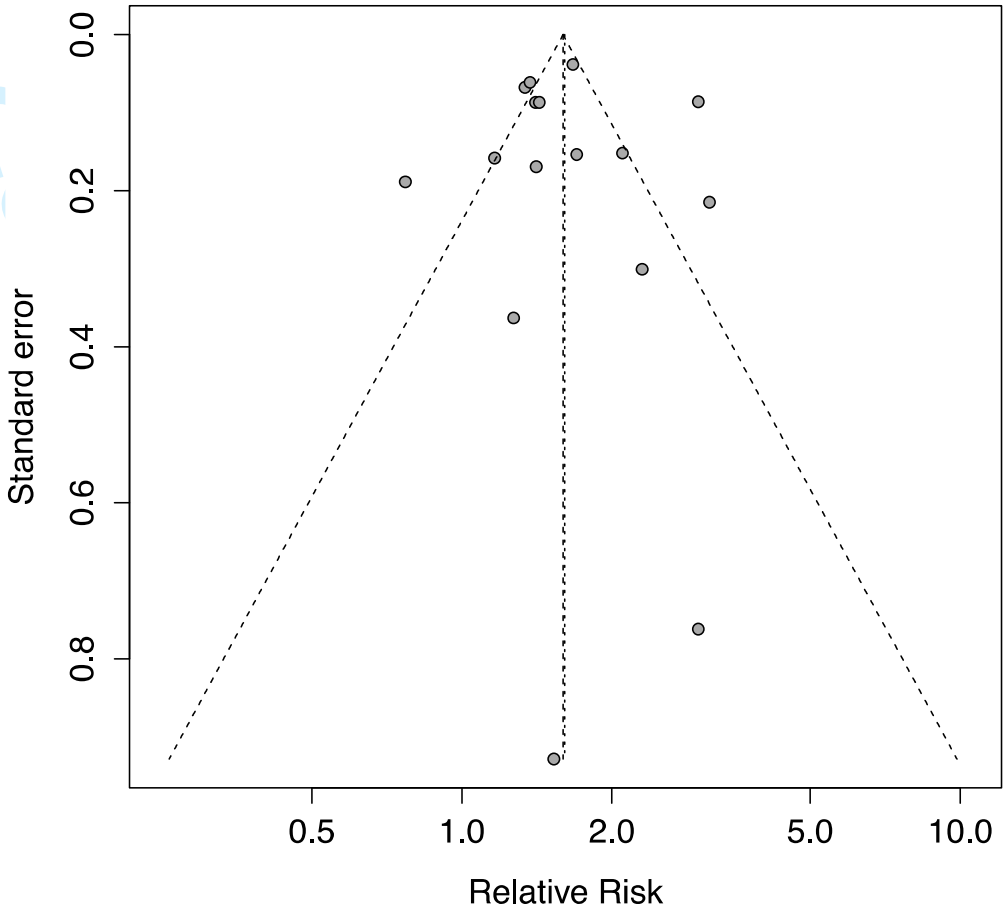
Egger's test p-value = 0.94

Supplementary Figure 16. Funnel Plot for Major Cardiovascular Event



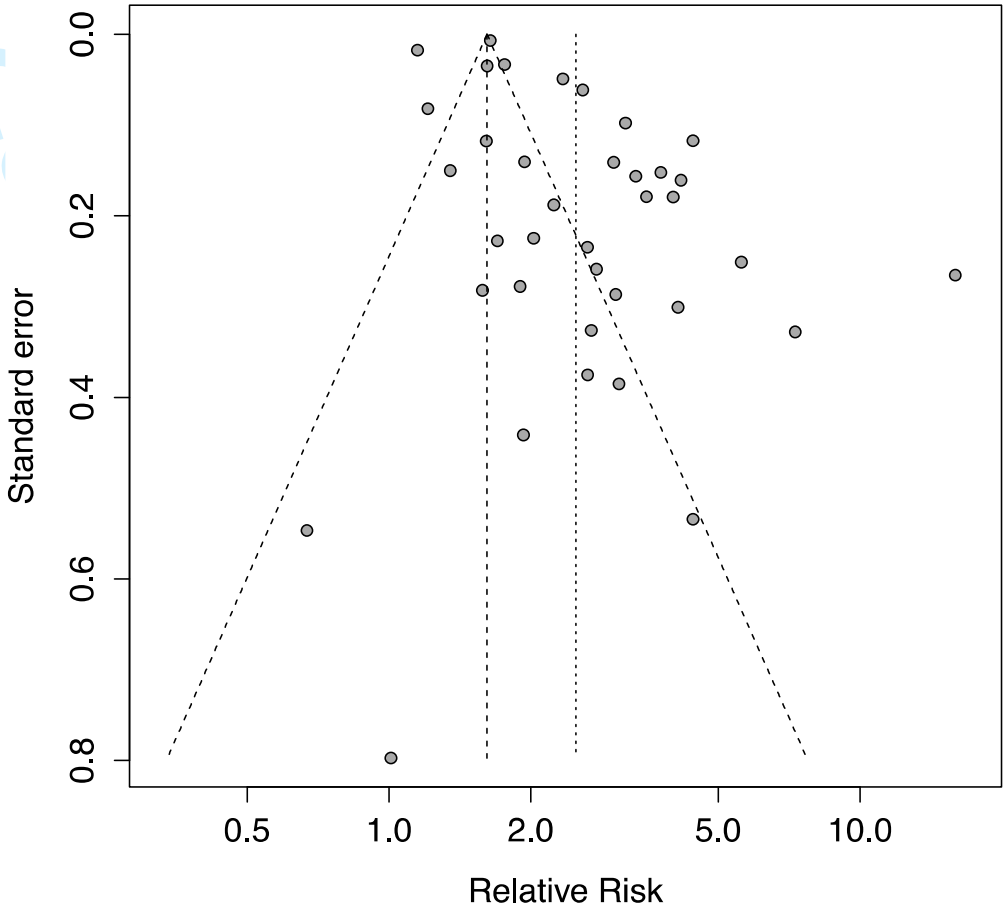
Egger's test p-value = 0.95

Supplementary Figure 17. Funnel Plot for Ischemic Heart Disease



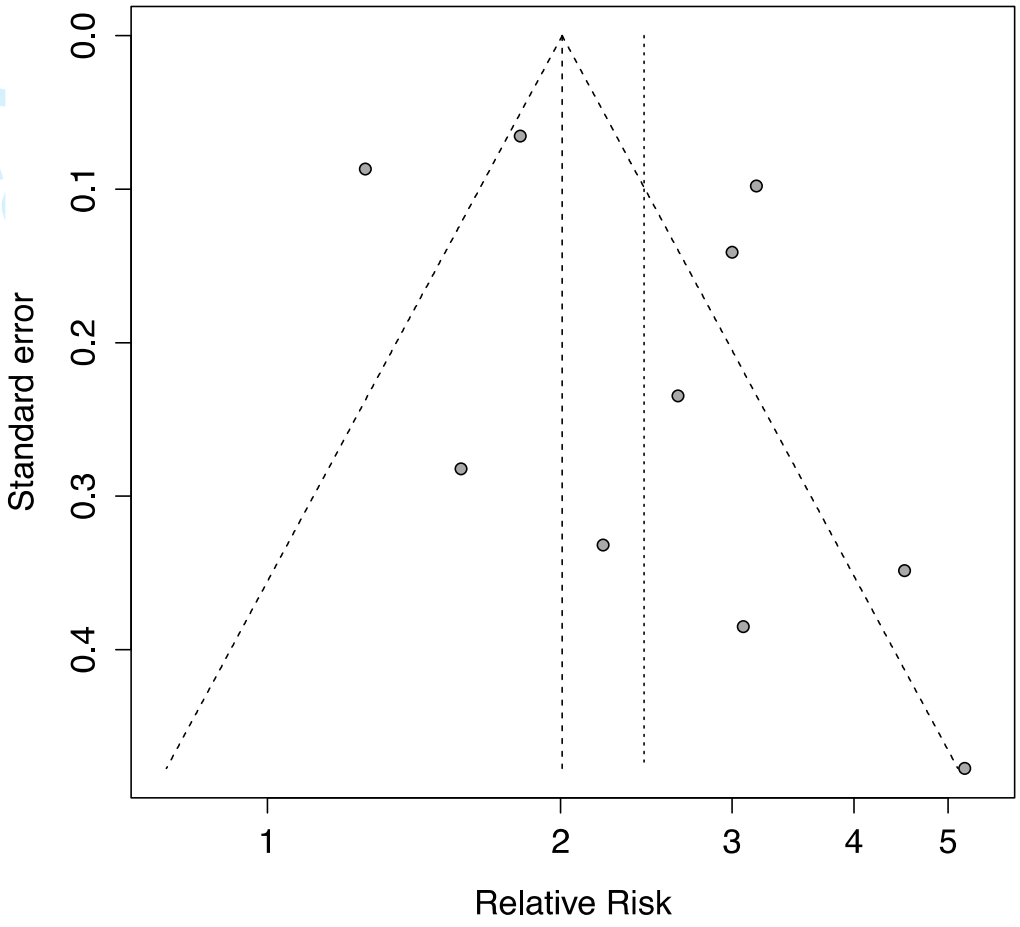
Egger's test p = 0.91

Supplementary Figure 18. Funnel Plot for Stroke



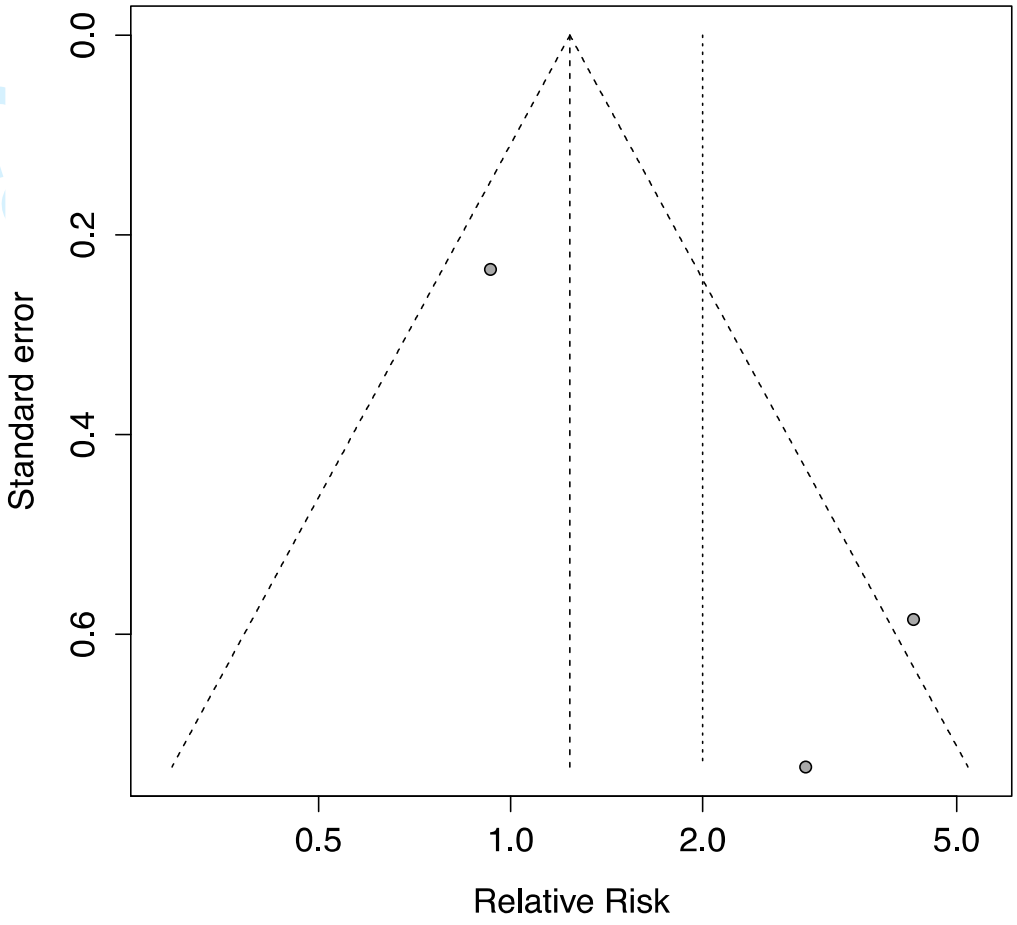
Egger's test p = 0.004
Trim-and-fill Estimate: RR 1.68 (1.51, 1.87)

Supplementary Figure 19. Funnel Plot for Ischemic Stroke



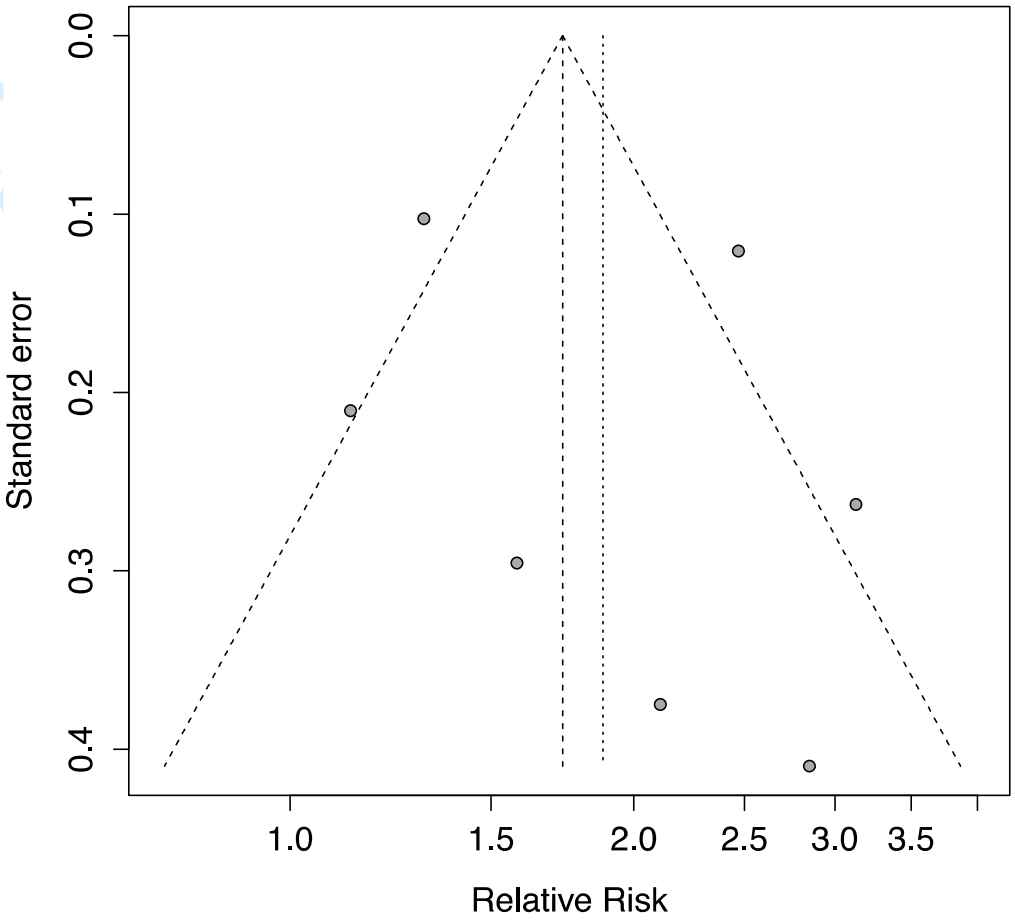
Egger's test p = 0.21

Supplementary Figure 20. Funnel Plot for Hemorrhagic Stroke



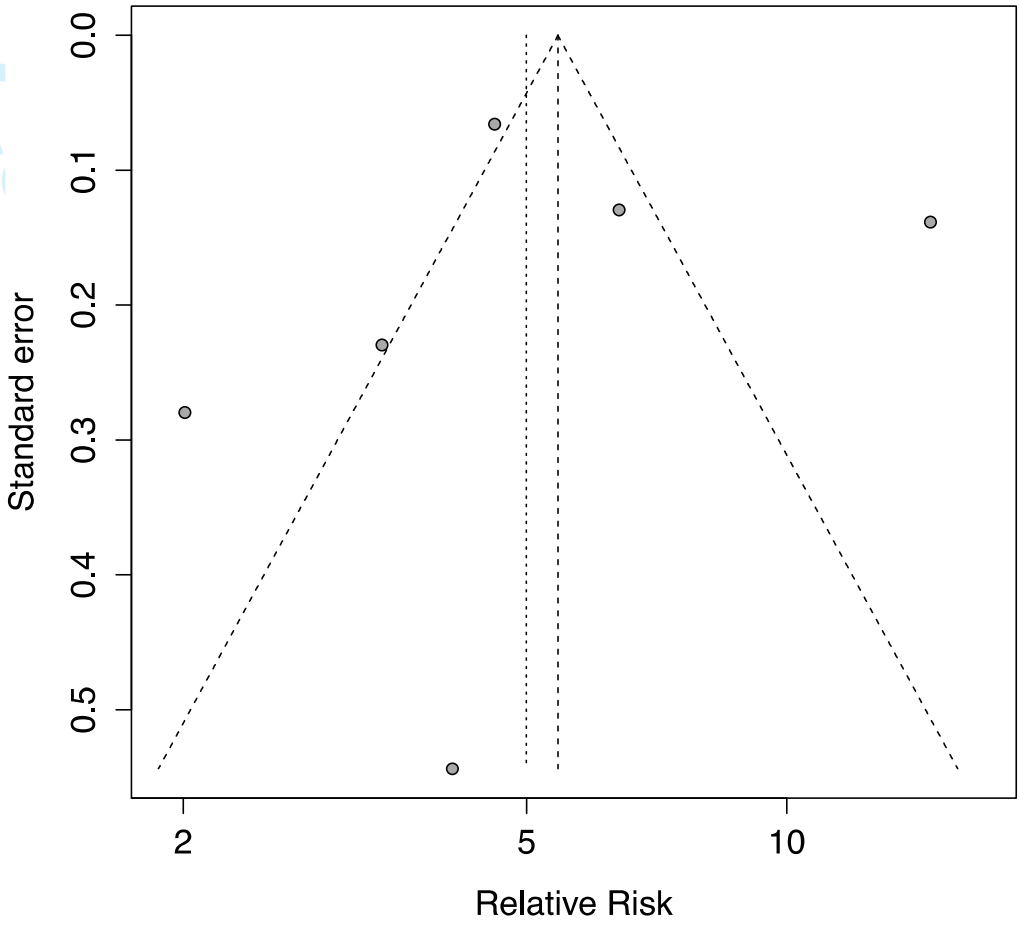
Egger's test p = 0.22

Supplementary Figure 21. Funnel Plot for Sudden Cardiac Death



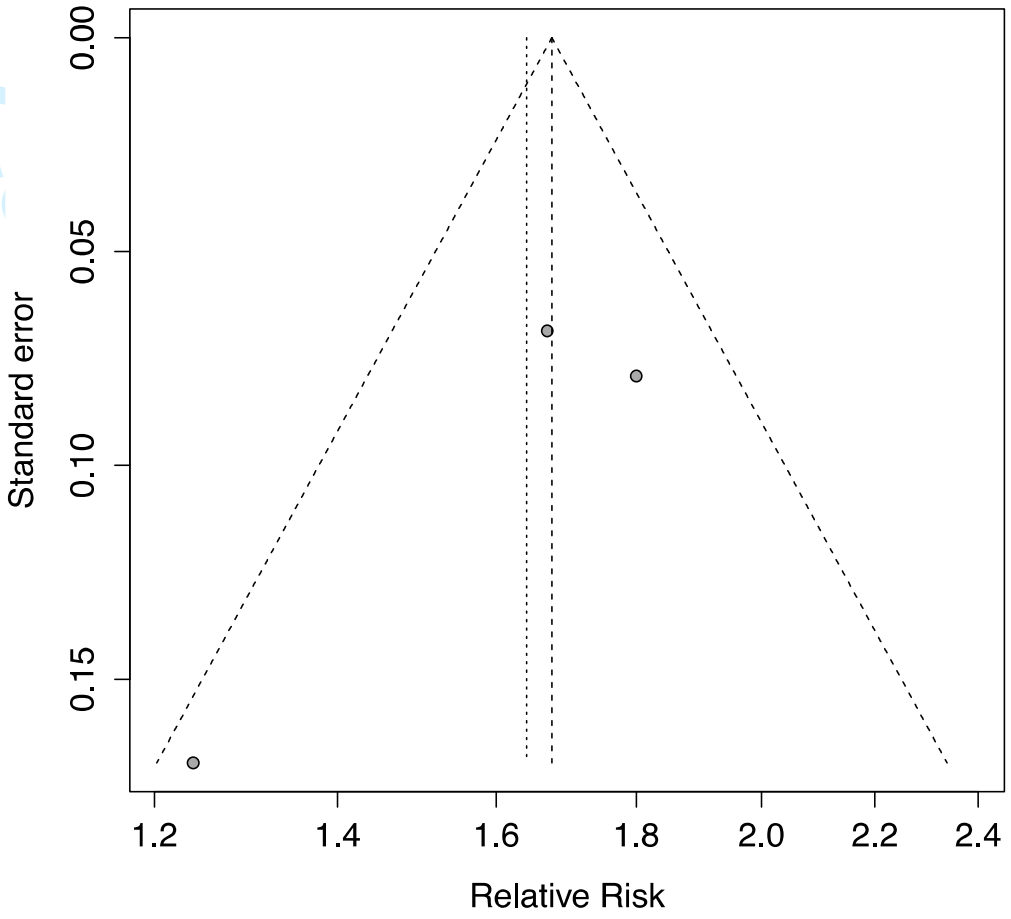
Egger's test p = 0.53

Supplementary Figure 22. Funnel Plot for Congestive Heart Failure



Egger's test p = 0.97

Supplementary Figure 23. Funnel Plot for Chronic Kidney Disease



Egger's test p = 0.35

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