Stroke risk associated with atrial fibrillation: a Burden of Proof study.

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Abstract

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Atrial fibrillation (AF) is increasingly recognized as a significant predictor for stroke, carrying profound implications for morbidity and mortality globally. This study aims to explore the relationship between AF and stroke incidence and/or stroke mortality (in 30 days) by employing the Burden of Proof methodology.

Utilizing a systematic review and meta-analysis of published observational studies from PubMed and EMBASE databases and employing the Burden of Proof approach, this study identified a large dataset to estimate conservatively the mean AF-stroke risk functions and the Burden of Proof risk function (BPRF), estimating pooled mean relative risks (RR), evaluating systematic biases, quantifying heterogeneity, and assessing publication bias. The MR-BRT (Meta-regression-Bayesian, Regularized, Trimmed) model was utilized for its advanced capability to address systematic biases and heterogeneity.

After reviewing 6,447 de-duplicated articles from 8,527, we included and extracted 61 reported risk effect size measures from 49 articles and run the MR-BRT model. This analysis indicate that AF presents an increased risk factor for overall stroke, estimated mean relative risk (RR) for overall stroke incorporating between-study heterogeneity (γ) is 1.99 (95% uncertainty interval (UIs) 1.91, 2.08). The comprehensive Burden of Proof analysis also revealed the Risk-outcome score (ROS = 0.32), which suggests that AF contributes to an average increase in stroke risk by 38.29% compared to person with no-AF (the percentage of mean relative risk increases here revealed using (Exp (ROS) – 1) x 100) %. As per the ROS, the interpreted strength of this harmful relationship to be a moderate and three-star rating out of five. This analysis also considered publication biases (not found any, in this analysis) and interaction of significant bias covariates in the analysis for reporting conservatively estimated the BPRF (most conservative estimate of AF-stroke harmful association, 5^{th} percentile of mean RR) which is 1.92 (95% UIs 1.90, 1.99).

This study confirms the substantial role of AF in stroke outcome; however, the Burden of Proof framework facilitated a nuanced analysis that enhances our comprehension of the AF-stroke association. We anticipated this relationship to be stronger than a three-star rating (intuitive from the mean relative risk), emphasizing the need for synthesizing evidence for implementing public health strategies and informed policymaking to alleviate the burden of stroke attributable to AF.

BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice, with a significant impact on public health due to its association with an increased risk of stroke, and stroke mortality (in 30 days) [1]. The global prevalence of AF is rising, attributed to the aging population and improved survival rates from cardiac conditions [2]. Atrial fibrillation is characterized by rapid and disorganized atrial electrical activity, leading to ineffective atrial contractions and the potential for thrombus formation, particularly in the left atrial appendage, which may then embolize to the cerebral circulation, causing an ischemic stroke [2].

Stroke, a leading cause of disability and mortality worldwide, results from an obstruction to the blood supply to part of the brain, leading to cerebral infarction [3]. The relationship between AF and stroke was not well studied in aspect of their strength association, with AF significantly increasing the risk of stroke [3,4]. The pathophysiology underlying this association involves the formation of atrial thrombi during episodes of AF, which can embolize to the cerebral arteries, causing stroke. This risk is modulated by various factors, including the presence of additional stroke risk factors such as hypertension, diabetes mellitus, and cardiac, renal and pulmonary comorbidities, geography and use of antihypertensive, use of statins, oral anti-coagulants (OAC), smoking, drinking behavior and many others [1]. Given the substantial burden of AF-related stroke, accurate risk stratification and quantifying the strength of association is essential for effective stroke management strategies [2]. Anticoagulation therapy (OAC) has been shown to significantly reduce the risk of stroke in patients with AF, yet it is underutilized, partly due to concerns about bleeding risk [5]. Hence, there is a substantial need for synthesizing robust amount of evidence in published peer-reviewed literature analyzing association between AF-stroke risk-outcome pair while also comparing the study heterogeneity robustly, to guide clinical decision-making in the management of AF to prevent stroke.

Large epidemiological studies have provided valuable insights into the incidence and prevalence of AF and its contribution to the burden of stroke across different populations [2,6]. However, there remain gaps in our understanding this AF-stroke harmful association, particularly regarding the quantification of risk and the impact of various risk factors across different regions and demographics. Furthermore, the heterogeneity in study designs, methodologies, and quality among existing studies complicates the synthesis of evidence, necessitating advanced analytical

approaches to derive accurate and generalizable findings. To address these gaps, rather than using conventional meta-analytic, by employing a comprehensive meta-regression-Bayesian, regularized, trimmed (MR-BRT) approach [7] and by using data from systematically reviewed published observational studies, this study aimed to estimate the mean AF-stroke relative risks considering study-heterogeneity (γ), Burden of Proof risk function (BPRF), and to calculate risk-outcome scores (ROS) and interpreting the ROS into corresponding star ratings (one to five) for both all stroke and mortality (in 30 days) outcomes. Such insights are crucial for emphasizing the need for synthesizing evidence using statistically rigorous method for implementing effective public health strategies and informed policymaking to alleviate the burden of stroke attributable to AF.

Specific Aims:

1. To conduct a systematic review and meta-analysis using the Burden of Proof study method for the published observational studies reporting the association between AF and stroke.
2. To estimate the pooled mean AF-stroke, relative risks and the conservative BPRF from the collected data.
3. To calculate a risk outcome score (ROS) and corresponding star rating for AF-stroke risk-pair.

METHODS

Overview:

The study used the Burden of Proof approach to generate conservative estimations of the associations, BPRF between AF and stroke risks while also assessing the robustness of the evidence supporting these association. Developed by the Institute for Health Metrics and Evaluation (IHME), the Burden of Proof approach is comprehensively described by Zheng et al. [7]. This method has been utilized in the past to assess health risks linked to smoking, elevated systolic blood pressure, chewing tobacco and oral cancers, secondhand smoking, and health outcomes [8-10]. Mostly, the Burden of Proof approach incorporates a series of steps within a meta-analytic framework, which include:

1. Performing a comprehensive literature search of peer-reviewed sources to find and collect all relevant information regarding the association between AF and stroke.
2. Estimating a pooled mean relative risk for the AF-stroke dichotomous risk-pair.
3. Evaluating the presence of systematic biases, to understand if they affect the outcomes of the models and adjust for any significant biases with the inclusion of covariates.
4. Quantifying remaining unexplained between-study heterogeneity (γ) while accounting for within-study correlations (β) and incorporating their standard errors (SE) into analysis to calculate mean RR.
5. Evaluating potential publication bias based on visual examination of funnel plots and Egger's regression test.
6. Generate the BPRF, the conservative 5^{th} quantile estimates of mean relative risk (closest to the null) and resulting ROS and converting it into corresponding star ratings, one to five.

Steps 2 to 6 employ the MR-BRT model, an analytical tool that more effectively addresses systematic biases in the published literature, accounts for heterogeneity both within and among studies, and detects potential outliers more efficiently than conventional meta-analytic techniques [7]. These models are designed to be comprehensive, drawing on data from different geographic locations, and populations, rather than being specific to any one demographic. The protocol for the systematic review was registered with PROSPERO, underscoring our commitment to following the best practices for systematic reviews (Prospero registration number: CRD42023469924). [11].

Defining Exposure:

Atrial Fibrillation (AF)

This study considered AF as an exposure. Being aligned with the Global Burden of Disease (GBD) study case definition, we considered all types (paroxysmal, persistent/sustained, chronic and, unspecified) of AF.

Atrial fibrillation was characterized by disorganized atrial electrical activity leading to irregular heart rhythms, is identified through diagnostic criteria including electrocardiogram (ECG)

findings of irregular R-R intervals (in the absence of complete atrioventricular block) and absence of distinct P waves.

For the purposes of this study, atrial fibrillation cases are defined using the International Classification of Diseases (ICD) [12], ICD-10 codes: I48.0 for paroxysmal atrial fibrillation, I48.1 for persistent atrial fibrillation, I48.2 for chronic atrial fibrillation, and I48.91 for unspecified atrial fibrillation. ICD-9 codes: 427.31 (for all paroxysmal, persistent and chronic atrial fibrillation), and 427.31 for unspecified atrial fibrillation. We did not consider any type of atrial flutter as an exposure thus excluded ICD-10 codes, I48.3, I48.4 and ICD-9 code 427.32.

Defining Outcomes:

Stroke

This study primarily considered any type of incident stroke and/or stroke mortality (in 30 days) as the outcome. Being aligned with the Global Burden of Disease (GBD) study case definition, we considered all types of (ischemic or hemorrhagic, unspecified) stroke. Incident stroke was defined as the occurrence of first-ever diagnosis of any stroke except minor strokes, transient ischemic attack (TIA), and minor/lacunar bleedings, based on clinical diagnosis by a physician using diagnostic imaging. Strokes and/or stroke mortality (in 30 days), especially ischemic stroke was mostly considered to include all vascular events leading to limited blood flow to brain tissue, with resulting infarction, including atherosclerotic and thromboembolic strokes, but excluding strokes in which the underlying cause is intracranial hemorrhage (cerebral infarction, brain infarction).

This study considered ICD-10 codes: I63 and I60, ICD-9 codes: 430, 431, for ischemic and hemorrhagic stroke, respectively. There are three ICD10 codes for unspecified stroke - I62 is unspecified hemorrhagic stroke, I64 is an unspecified stroke, and I63.9 is for ischemic stroke of unspecified origin; these are also included. Any transient ischemic attack (TIA), ICD-10 code G45.9 and ICD-9 code 435, and/or minor bleedings (e.g.: lacunar bleeding) were not considered as an outcome for analyses.

Steps of meta-analytic process:

1. **Performing systematic reviews to identify relevant peer-reviewed literature:**

In this research, systematic literature review was carried out to gather all relevant studies listed in PubMed and EMBASE from January 1, 1970, to April 31, 2024, up until May 15, 2024. The aim was on identifying studies related to any form of stroke, including ischemic stroke, and/or stroke mortality (in 30 days) as an outcome, with exposure to any type of AF. Tailored search queries were developed for each database (Appendix Table 2) consulting with health science librarian, and the retrieved records were then managed using DistillerSR (DistillerSR. Version 2.35. DistillerSR Inc.; 2024. Accessed January-June 2024.), a systematic review software [13]. The software was utilized to eliminate duplicate entries across databases. Title-and-abstract review was finished utilizing the DAISY automation feature after the initial 54% completion by human reviewer. All title- eliminated records were also reviewed by human reviewer to confirm the accuracy of the automation feature of DistillerSR. EndNote version 20 was used to manage references and citations throughout the analysis and report writing [14].

In brief, this systematic review was focused on including studies that specifically investigated patients with any types of atrial fibrillation described above, characterized by arrhythmias due to electrical conduction abnormalities in the atria of the heart, leading to irregular and often rapid heart rates and diagnosed by based on ECG findings. Eligible studies were those reporting on clinical outcomes: stroke, ischemic stroke, or stroke not further specified, with an interest in observational studies, either cohort or case-control, that provided relative risk assessments including hazard ratios (HR), risk ratios (RR), and odds ratio (OR) values. Conversely, we excluded studies if they involved cases of systemic embolism, transient ischemic attack (TIA), cerebral microbleeds, or lacunar syndromes. Furthermore, studies were ineligible if they included patients with atrial fibrillation alongside conditions that may increase the risk of stroke such as acute myocardial infarction (AMI), left ventricular dysfunction, sepsis or chronic kidney disease requiring dialysis, multiple myeloma, type 2 diabetes, liver disease, and COVID-19, dementia, or if patients had a

history of stroke at study inception. We also excluded studies not reflective of the general population, those comparing the risk of stroke in atrial fibrillation patients under different medical (only considered few studies with guideline directed medical therapy for AF patients with oral anti-coagulants (OAC)) or surgical treatments, controlled trials for comparing interventions for AF management, duplicate publications, and literature in the form of reviews, conference abstracts, editorials, books or book chapters, case reports, and cross-sectional studies. This inclusion and exclusion criteria framework were designed to ensure the synthesis of data relevant to the real-world risk of stroke in patients with atrial fibrillation, excluding confounding factors or conditions that could skew the understanding of this risk.

Adhering to the pre-determined inclusion and exclusion criteria, a sub-set of randomly selected (n=100) records were initially screened by a pair of researchers during the title-and-abstract review phase. The concordance value was 84% between two reviewers for the subset of title-and-abstract screening and the main author carried out the remaining title-and-abstracts phase to completion. In this process, DistillerSR used automation to screen 46% of the title-and-abstracts. Subsequently, any records that passed the initial screening were subjected to a more detailed full-text review phase. Conflicts at either the title-and-abstract screening phase or during the full-text review phase were resolved by consulting a third reviewer. Every record, irrespective of language, underwent screening for eligibility. Detailed descriptions of the search strings for each database are provided in the Appendix section. Data extraction from the selected studies was conducted by a single reviewer utilizing a customized DistillerSR extraction template (adapted from the risk ratio template developed for MR-BRT model). This process involved gathering study metadata such as location, study design, methods of determining exposure and outcomes, and demographics of the study population. Both the most and least adjusted risk effect sizes (including RR, HR, and/or OR), complete with 95% Confidence Intervals (CIs), alongside the definitions of outcomes used, sample sizes, and the covariates adjusted for in each analysis were extracted. The accuracy of these extractions was subsequently verified through manual review by a second reviewer. Data cleaning and preparation process for modeling was done using R version 4.2 as per the MR-BRT model instructions.

Throughout the processes of data collection, analysis, and report writing, this study-maintained adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations as much as possible, including the use of PRISMA figures [15].

2. Estimating the mean association between AF and stroke:

This analysis employed the MR-BRT tool for conducting meta-regression analyses, where the log-transformed relative risk of stroke served as the dependent variable, and the diagnosis of AF was the binary independent variable (AF vs. non-AF). This approach produced a pooled mean relative risk reflecting the relationship between AF and stroke, based on the effect sizes extracted from the studies. To mitigate the impact of potential outliers that could skew the analysis, the model incorporated a default (10%) trimming. The trimming process within the MR-BRT framework utilizes the least trimmed squares technique to eliminate data points that deviate significantly from the overall dataset pattern, determined by the number of standard error intervals separating the data points from the average estimate. In cases where studies presented multiple effect sizes for the AF and stroke associations, the analysis prioritized the selection of data points that closely aligned with the defined outcomes and exposures. The most-adjusted effect size from these selections was then chosen for inclusion. Each study contributed at least one effect size to the model.

There are several existing methods for addressing within-study covariance in meta-analyses; however, these typically necessitate either a known within-study covariance matrix or access to individual-level data [16]. Given the lack of such data in our analysis, we utilized the limited information at hand to implement a cautious and plausible adjustment for within-study covariance. Although this approach may result in a very conservative estimation of the correlation between estimates, it is important for ensuring that no single study unduly influences the overall model outcomes. The effect sizes and standard errors employed in our principal analysis are documented in Appendix 3. Study Characteristics Table.

3. Testing and adjusting for bias related to variation in study characteristics:

In this analysis, 26 binary covariates were generated to identify potential dimensions of systematic bias, drawing upon the for bias identification and the distinct attributes of our dataset. These covariates aimed to capture the representativeness of both the study population and the analytical sample, the precision of methods used to determine a participant's exposure and outcome status, variations in the definitions of exposure and outcomes, and the extent of adjustment for potential confounders, including age, sex, education, smoking and drinking habits, study designs, follow-up time, comorbidities, and medication use. A more comprehensive exposition of these bias covariates, alongside other considered but ultimately excluded potential sources of bias, is provided in Appendix 5. Additionally, the specific values of these bias covariates for each study were also catalogued. For a covariate to qualify for testing, it was requisite that at least two data points in the model corresponded to each value of the covariate. The selection of eligible covariates for inclusion was conducted using a covariate selection algorithm that employs a stepwise Lasso technique to select bias covariates that significantly influence on the outcomes when incorporated as interaction terms within the primary linear meta-regression analysis. Covariates identified as significantly biasing were accordingly adjusted for in the ultimate mixed-effects model, which was structured with Gaussian priors to preclude model overfitting [7].

4. Quantifying residual between-study heterogeneity:

This analysis further incorporated a study-level random slope (γ) to account for the residual heterogeneity across studies, in addition to a study-level random intercept to accommodate within-study correlation. Given the analysis's reliance on a relatively limited number of input studies, which may lead to an underestimation of between-study heterogeneity, the uncertainty associated with γ was calculated using the inverse Fisher Information Matrix. This calculation facilitates the generation of γ draws, which are then utilized to ascertain the uncertainty estimate for our relative risk inclusive of γ. This estimate is derived considering both the uncertainty enveloping the mean effect and the 95^{th} quantile of the heterogeneity draws between studies. The reported relative risk excluding γ, as documented in Table 1,

presents an uncertainty that does not fully encapsulate between-study heterogeneity, reflecting the estimates typically disclosed in conventional meta-analyses. Conversely, the relative risk inclusive of γ offers a more accurate reflection of the consistency level among the underlying studies [7].

5. Evaluating the possibility of publication and reporting bias:

To assess the likelihood of publication and reporting bias within this study, Egger's regression method was employed [17]. The findings from this regression were further corroborated by examining modified funnel plots (Figure 2), which depict the model outcomes and associated uncertainties in conjunction with the residual mean and standard deviations of the dataset. In this analysis no included records were revealed as reporting or publication biases.

6. Estimating the Burden of Proof risk function (BPRF):

Using the final MR-BRT models for stroke and AF, we estimated the BPRF for each outcome. The BPRF reflects the most conservative estimate of the harmful association between AF and stroke that is consistent with the evidence, given the variation between data inputs. It is defined as the 5^{th} quantile/percentile of the relative risk estimates closest to null. From the BPRF, this analysis also derived the risk-outcome score (ROS) for dichotomous risk factors as the signed natural log(BPRF) divided by two. The value of the ROS reflects the estimated strength of the association between the risk factor and the outcome, with a moderate strength positive ROS indicating that there is a large effect size and strong, consistent evidence of the association between the risk factor and the outcome, a small positive ROS indicating a small effect and inconsistent evidence, and a negative ROS suggesting that there is weak evidence of any significant association. The ROS for a risk-outcome association can be then translated into a star rating ranging from a one-star pair (weak evidence of association with an ROS less than 0.0) to a five-star pair (very strong evidence of an association with an ROS greater than 0.62) [18]. The ROS thresholds for two-, three-, and four-star pairs are 0.0–0.14, >0.14–0.41, and >0.41–0.62, respectively. The

conservative percentage of increased stroke risk associated with AF can be quantified from the ROS as the ((exp(ROS)-1)-1)x100) [7].

Model validation:

MR-BRT has been extensively and rigorously validated by Zheng and colleagues for its use in conducting Burden of Proof meta-analysis [7].

RESULTS

Systematic review

This systematic review and meta-analysis examined the robustness of evidence and the association between stroke outcomes and AF. Initially, a total of 6,447 records were identified through searches in PubMed and EMBASE databases, following the removal of 2080 duplicates from an original count of 8,527 records. Utilizing DistillerSR for title-and-abstract screening 5,961 records were discarded based on pre-defined exclusion criteria. This title-and-abstract screening forwarded 486 studies for full-text review. This systematic review only considered prospective cohorts, retrospective cohorts, case-cohorts, or case-control studies that provided data for the association between an overall stroke outcome or stroke mortality (in 30 days) and AF in a general population context. Subsequent to a thorough full-text review, data reporting the AF-stroke risk association were extracted from a total of 49 studies, yielding 61 data-points suitable for model input and analysis. Comprehensive information on each study including study design, participant numbers, definitions of exposure and outcomes, final or the most confounder adjusted risk effect size (OR, HR, RR), and their standard errors, and bias covariates extracted and analyzed. These are described in the Appendix 3, Study Characteristics Table. Additionally, a PRISMA diagram explaining the systematic review process for each study is available in Appendix 1.

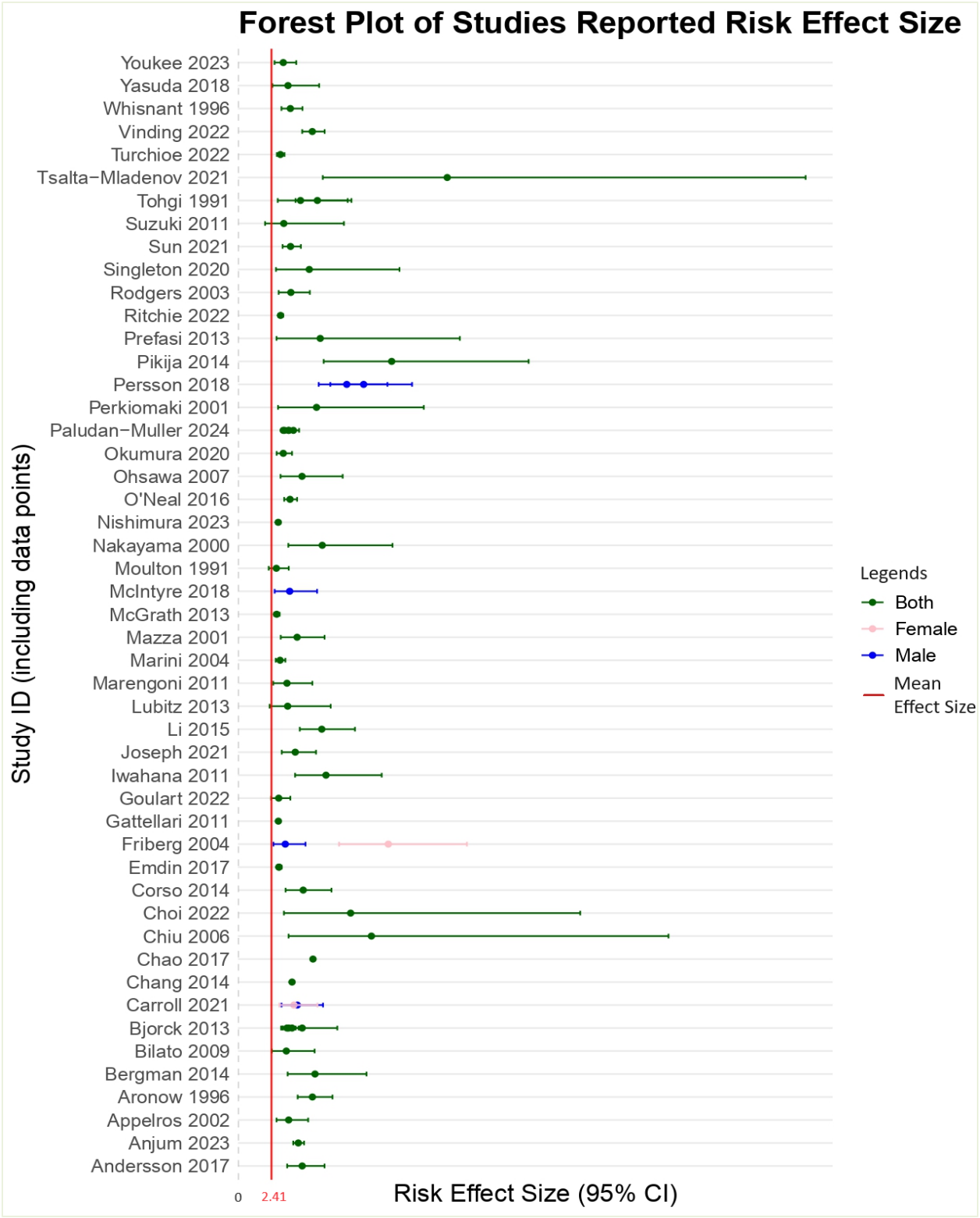

Figure. 1: Forest plot showing study reported risk effect size measures and pooled mean of risk effect size measures.

Included studies were published from 1991 to 2024. Except for three studies, (Carroll 2021, Friberg 2004, Persson 2018) [19-21], one of which Carroll 2021 [19] reported sex specific risk estimates on 502493 individuals, separately on both sexes (highest sample size for sex specific risk effect sizes), all other 46 studies reported either OR, or HR, or RR for both sexes combined. Study sample ages ranged from 18 to 99 years. Study sample sizes varied from 250 to 4269194 (for sex adjusted values).

We found one large multi-county, multi-center study [1] which analyzed 153,152 patient's data and which was geographically adjusted (with age, sex and CHADS2 score) reported HR of 2.29 (95% CIs 1.49, 3.52) for AF-stroke association. Other studies were not geographically multi-national; these are from 19 countries: USA, Japan, Finland, UK, Sweden, Italy, Denmark, Taiwan, Australia, Spain, Canada, Brazil, Hong Kong, South Korea, Sierra Leone, Norway, China, Croatia, Bulgaria.

The mean of pooled risk effect size from selected studies was 2.41. Figure 1 describes the study specific risk effect sizes and their pooled mean in a forest plot. Our analysis did not uncover any evidence of publication bias (Figure 2).

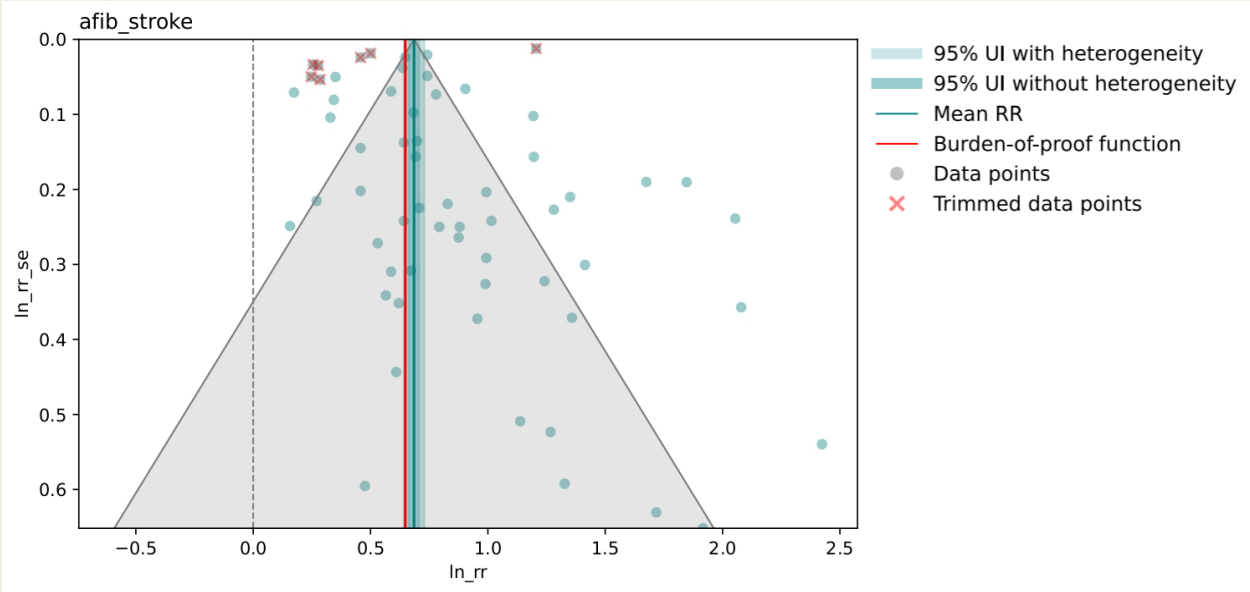

Figure. 2: Modified funnel plots for atrial fibrillation vs. stroke. This modified funnel plot shows the residuals of the reported mean relative risk (RR) relative to 0, the null value, on the x-axis and the residuals of the standard error, as estimated from both the reported standard error and gamma, relative to 0 on the y-axis for the association between **AF** vs. **stroke**. The light blue vertical interval corresponds to the 95% uncertainty interval incorporating between-study heterogeneity; the dark blue vertical interval corresponds to the 95% uncertainty interval without

between-study heterogeneity; the dots are each included observation; the red X's are outlier observations if relevant; the grey dotted line reflects the null log(RR); the blue line is the mean log(RR) for [risk factor] and the outcome of interest; the red line is the BPRF function at the 5th quantile for these harmful risk-outcome associations.

Atrial Fibrillation and Stroke: Burden of Proof Analysis

In this Burden of Proof meta-analytic procedure, the study quantified and assessed the consistency of results across the included studies, thereby measuring the between-study heterogeneity (γ). The observations demonstrated consistency, with a γ value of 1.69×10^{-9} (SE 0.00018), indicating a harmful relationship between atrial fibrillation (AF) and stroke. The within-study correlations (β), as measured by the model, were 0.69 (SE 0.01). The calculated mean relative risk (RR), accounting for between-study heterogeneity, stood at 1.99 (UIs of 1.91, 2.08) as presented in Table 1 and Figure 2. This RR of 1.99 suggests that individuals with AF have twice the risk of stroke compared to those without AF, representing about 100% relative increase in risk.

This analysis offers a nuanced perspective, where the ROS score of 0.324 can be inferred that the presence of AF elevates the risk of stroke by a conservative estimate of at least 38.29% (using the formula: % increased = (exp(ROS) - 1)*100)). This evidence categorizes this as a **three-star** risk-outcome association (Table 1). In other words, while traditional RR meta-analysis might indicate a risk increase ranging between 91% and 108%, the Burden of Proof approach is more conservative, suggesting a minimum 38.29% increase in risk as supported by the evidence from the included studies. This integrated approach underscores the significant, yet cautiously interpreted, association between AF and an increased risk of stroke, highlighting the importance of methodological rigor in synthesizing evidence across diverse studies.

The covariate selection process identified - Stroke mortality (in 30 days) outcome, case-cohort study design, cohort study design, age, smoking, alcohol use, hypertensive disease, renal disease, dementia, and CNS score as significant (β SE = 0.001) bias covariates listed in Appendix 5. Bias covariate's table.

Table. 1. Strength of the evidence for the relationship between AF and all stroke outcomes analyzed.

Health outcome	RR (95% UI without γ)	RR (95% UI with γ)	BPRF	ROS	Star rating	No. of studies (data)	Selected bias covariates
Stroke	1.98 (1.94, 1.98)	1.99 (1.91, 2.08)	1.92	0.32	★★★	49 (61)	Stroke mortality (in 30 days) outcome, Case-Cohort study design, Cohort study design, Age, Smoking, alcohol use, hypertensive disease, renal disease, dementia, and CNS score was as significant bias covariates

The reported relative risk (RR) and its 95% uncertainty interval (UI) reflect the risk an individual who has AF and of developing the stroke outcome relative to that of someone who does not have AF. Gamma (γ) quantifies the estimated between-study heterogeneity of included observations. We report two separate 95% UIs, one that is estimated without incorporating between-study heterogeneity (γ) and one that does account for this source of uncertainty—"95% UI with γ." The Burden of Proof Risk Function (BPRF) is calculated for risk-outcome pairs that were found to have significant relationships at an 0.05 level of significance when between-study heterogeneity is not incorporated. The BPRF corresponds to the 5th quantile estimate of relative risk accounting for between-study heterogeneity closest to the null for each risk–outcome pair, and it reflects the most conservative estimate of excess risk associated with chewing tobacco that is consistent with the available data. Since we define chewing tobacco exposure as a dichotomous risk factor, i.e., an individual either with or without AF, the risk-outcome score (ROS) is calculated as the signed value of natural log(BPRF) divided by two. For ease of interpretation, we have transformed the ROS and BPRF into a star rating (1–5) with a higher rating representing a larger effect with stronger evidence. A zero-star rating is assigned to risk-outcome pairs whose RR 95% uncertainty interval without consideration of between-study heterogeneity crosses 1. The potential existence of publication bias, which, if present, would affect the validity of the results, was tested using Egger's Regression. Included studies represent all available relevant data identified through our systematic reviews from January 1970 through April 2024. The selected bias covariates were chosen for inclusion in the model using an algorithm that systematically detects bias covariates that correspond to significant sources of bias in the observations included. If selected, the observations were adjusted to better reflect the gold standard values of the covariate.

DISCUSSION

This Burden of Proof investigation systematically collected and analyzed existing research to understand the stroke risks associated with AF, utilizing a methodological framework that assessed the uniformity of findings across a wide array of studies. The results indicate a moderate level of evidence supporting a harmful association between AF and the risk of stroke, as demonstrated by the mean relative risk (RR). The pooled mean RR was found to be 1.99 (95% UIs, 1.91 to 2.08), is nearly aligned but less strong with the calculated and aggregated mean risk effect size of 2.41 derived from the forest plot analysis depicted in Figure 1. This analysis reported a BRPF function and an ROS value for the AF-stroke association. The main implication of this meta-analytic process using a MR-BRT model compared to conventional meta-analysis is that the BRPF and ROS score can be interpretable to quantify the increased risk of stroke (38.29%) comparing between the AF and no-AF groups. The ROS score denoted this association as a three-star risk-outcome pair, suggesting a moderate amount of evidence of association based on our conservative interpretation of the current evidence. This rating emphasizes the quality of this study findings and point to the possibility that future studies could shift our current perspective on the relationship between AF and ischemic stroke. We acknowledge that our assessment could evolve with the advent of new evidence.

The rationale for employing the Burden of Proof analysis over conventional meta-analytic processes in this study merits particular attention. Unlike traditional meta-analyses that often aim to provide a singular pooled estimate of effect size, the Burden of Proof approach is designed to offer a more nuanced and conservative estimation of risk association. This methodology is particularly adept at accounting for between-study heterogeneity and potential systematic biases, thereby yielding a more refined understanding of the risk relationship. This analysis, through its incorporation of the BPRF and the subsequent star rating system, allows for a cautious interpretation of the data, acknowledging the complexities and variability inherent in the studies reviewed. This approach is crucial for developing effective public health strategies and clinical guidelines, as it provides a conservative yet informative perspective on the AF-stroke relationship, which is especially valuable in the absence of gold-standard evidence [7].

Our analysis, by focusing exclusively on any type of AF as exposure, minimizes the impact of clinical variation and accounting for heterogeneity in types and durations of AF, thereby reducing potential confounding factors. Despite this focus, which introduced a high degree of sensitivity to model parameters and data point inclusion, leading to more uncertainty in our relative risk estimates than might be seen in more homogeneous analyses. This heterogeneity underscores the need for a cautious approach, such as that provided by the Burden of Proof analysis, in interpreting the data and deriving conclusions about the AF-stroke association.

Considering the existing clinical evidence and epidemiological studies that identify AF as the most frequent underlying cause of cardioembolic stroke, with a reported increase in stroke risk by 3 to 5 times [22,23], the analysis's failure to achieve a rating stronger than three-stars highlights several limitations needing further exploration. This discrepancy suggests a limitation in identifying AF in participants labeled as having "no AF", and possibly neglects to account for minor strokes. It also points to the variability in the incidence rates of cardioembolic strokes versus other types across different populations and geography (see study locations in Appendix Figure 4). The majority of the studies were from Scandinavian country's population-based registries and also from Japan.

Additionally, the impact of age as a strong modifier is emphasized by the variation in age groups among the studies which reported age stratified risk measures [24-26]. Moreover, the duration of follow-up is identified as a pivotal factor that could alter the strength of the observed association between AF and cardioembolic strokes. Furthermore, methodological differences between studies, such as variations in population selection criteria, may explain the differences in risk estimates. The extent of adjustment for confounding factors and the heterogeneity in the populations studied (for example, differences in age, comorbidities, and medication use, especially oral anticoagulants) could also affect the observed risk. Lastly, there might be selection or misclassification bias related to this analysis, as we checked concordance only with the 100 randomly selected articles from both title-and-abstract, and full text screening phase. The automation feature in DistillerSR eliminated about 46% of the articles after human reviewer screening at the threshold level of 76.6%.

This Burden of Proof analysis offers two distinct types of estimates: a traditional mean RR incorporating γ, and a conservative estimate through the BPRF and ROS. The traditional RR is crucial for a deeper insight into the proportion of stroke cases attributable to AF, a necessary understanding given the frequent omission of causality in stroke data. This omission likely leads to an underestimation of the true impact of AF on stroke incidence and/or stroke mortality. Meanwhile, the ROS score and its associated star rating reflect the comparatively weaker evidence base for the harmful relationship between AF and stroke, as derived from our studies, indicating that less research has been conducted on this important topic. This insight underscores the importance for further comprehensive prospective cohort studies that thoroughly examine all the complex confounders within this risk-outcome dynamic, which might not be captured if we conducted a conventional meta-analytic approach.

In conclusion, the comprehension of the risk of stroke associated with AF remains incomplete. Preliminary evidence suggests that AF may increase the likelihood of stroke by double. However, based on the current evidence and applying statistically robust but conservative Burden of Proof methodology, we can confidently affirm that there is an approximate 40% increase in stroke risk attributable to AF. Such research is crucial to fully explain and can inform public health policies correctly.

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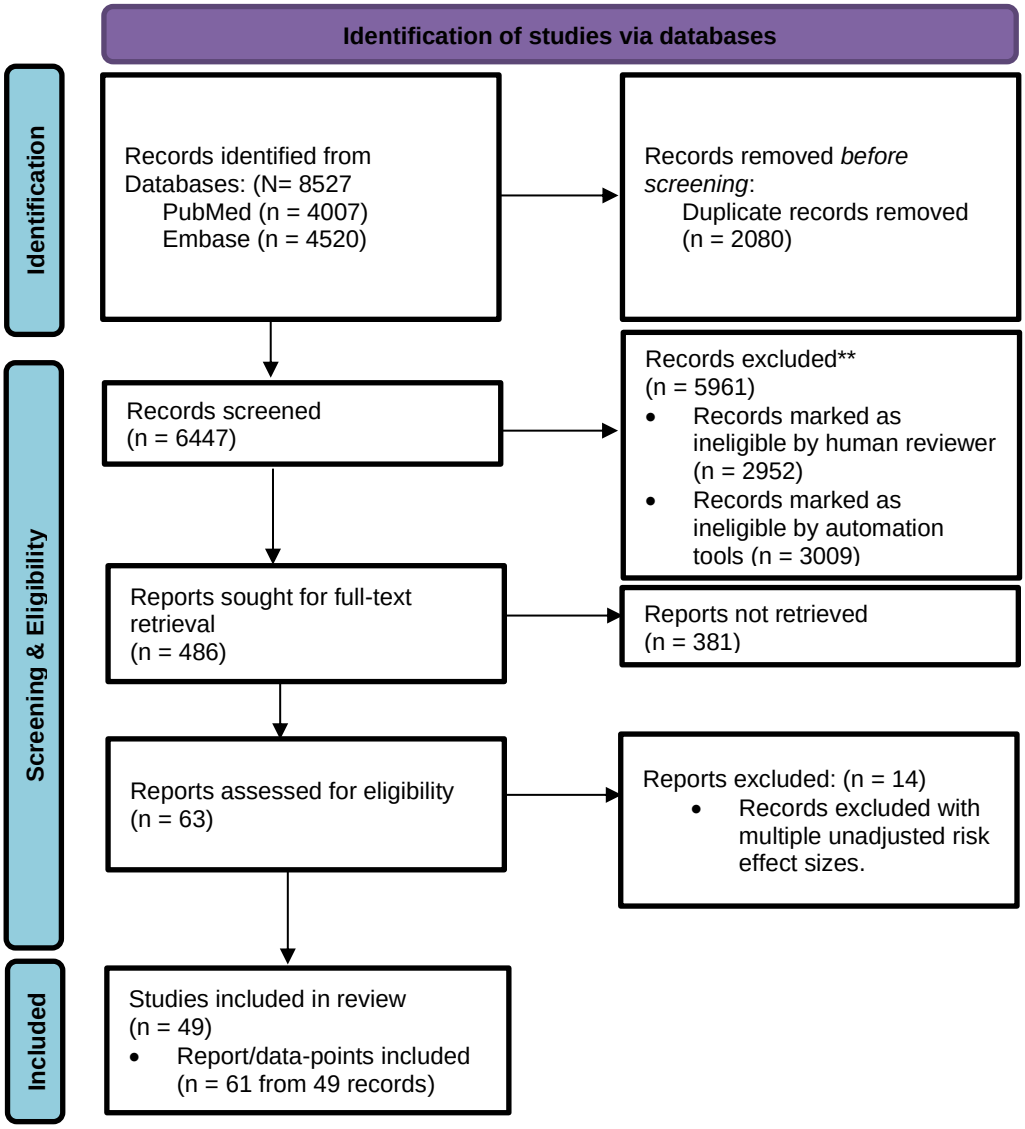
APPENDIX

Appendix 1. PRISMA 2020 flow diagram [15] for systematic reviews:



Appendix 2. Search Strings and hits:

Sl.	Database	Search strings	Date of search, Hits
1	PubMed	(("Stroke"[MeSH Terms] OR "ischemic stroke"[Title/Abstract] OR "ischaemic stroke"[Title/Abstract] OR "cerebral infarction*"[Title/Abstract]) AND ("atrial fibrillation"[MeSH Terms] OR "atrial fibrillation"[Title/Abstract] OR "Atrial flutter"[Title/Abstract]) AND ("risk ratio"[Title/Abstract] OR "rate ratio"[Title/Abstract] OR "relative risk*"[Title/Abstract] OR "hazard ratio*"[Title/Abstract] OR "odds ratio"[MeSH Terms] OR "odds ratio*"[Title/Abstract])) NOT ("pubmed books"[Filter] OR "meta analysis"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) AND ("1970/01/01"[PDAT] : "2024/05/31"[PDAT])	May 15, 2024 4007
2	EMBASE	('cerebrovascular accident'/exp OR 'cerebrovascular accident' OR 'ischemic stroke':ti,ab,kw OR 'ischaemic stroke':ti,ab,kw OR 'cerebral infarction*':ti,ab,kw) AND ('atrial fibrillation'/exp OR 'atrial fibrillation' OR 'atrial fibrillation':ti,ab,kw OR 'atrial flutter':ti,ab,kw) AND ('risk ratio':ti,ab,kw OR 'rate ratio':ti,ab,kw OR 'relative risk*':ti,ab,kw OR 'hazard ratio*':ti,ab,kw OR 'odds ratio'/exp OR 'odds ratio' OR 'odds ratio*':ti,ab,kw) AND [article]/lim AND [humans]/lim AND [embase]/lim AND [1970-2024]/py AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'correlational study'/de OR 'evidence based medicine'/de OR 'intention to treat analysis'/de OR 'longitudinal study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'outcomes research'/de OR 'population based case control study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND ([adult]/lim OR [aged]/lim) AND 'article'/it	May 15, 2024 4520

Appendix 3. Study Characteristics Table

Study ID	Location	Sample sex	Sample age range	Effect size	Effect size UIs (lower, upper)	Study design	Total sample size	Adjusted for covariates	Citation
Moulton 1991	USA	Both	79-99	1.17	0.72, 1.91	Case-control	417	Matched 1:1	[27]
Tohgi 1991	Japan	Both	71-80	2.60	1.30, 5.60	Retrospective cohort	100600	Sex	[24]
Tohgi 1991	Japan	Both	61-70	3.60	2.30, 5.60	Retrospective cohort	100600	Sex	[24]
Whisnant 1996	USA	Both	50-90	2.00	1.49, 2.75	Case-control	2888	Matched 1:1, model adjusted for age, date of stroke, transient ischemic attacks, hypertension, current smoking, atrial fibrillation, ischemic heart disease, mitral valve disease (other than prolapse), and diabetes mellitus.	[28]
Nakayama 2000	Japan	Both	65-99	3.89	1.88, 8.05	Prospective cohort	582	Age, sex	[29]
Perkiomaki 2001	Finland	Both	65-99	3.55	1.27, 9.88	Prospective cohort	330	Age, sex	[30]
Carroll 2001	UK	Male	45-99	2.41	NA	Prospective cohort	502493	Age	[19]
Carroll 2001	UK	Female	45-99	2.21	NA	Prospective cohort	502493	Age	[19]
Appelros 2002	Sweden	Both	65-99	1.90	1.20, 3.10	Case-cohort	377	Age, sex, comorbidities, prestrike dementia	[31]
Mazza 2001	Italy	Both	65-91	2.40	1.42, 4.00	Prospective cohort	3282	Age, sex	[32]
Rodgers 2004	UK	Both	65-99	2.03	1.31, 3.16	Prospective cohort	4351	Age, sex	[33]
Marini 2004	Italy	Both	80-99	1.39	1.13, 1.70	Case-cohort	3594	Age, sex	[34]

Friberg 2004	Denmark	Female	40-99	7.80	4.90, 12.5	Prospective cohort	14655	Age	[20]
Friberg 2004	Denmark	Male	40-99	1.70	1.00, 2.90	Prospective cohort	14655	Age	[20]
Chiu 2006	Taiwan	Both	18-87	6.80	1.90, 24.45	Case-control	476	Age, sex	
Ohsawa 2007	Japan	Both	30-99	2.69	1.42, 5.10	Prospective cohort	9483	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	[35]
Marengoni 2011	Sweden	Both	75-99	1.80	1.01, 3.40	Prospective cohort	685	Age, sex, education, hypertension, antithrombotic medications	[36]
Iwahana 2011	Japan	Both	60-71	4.11	2.28, 7.41	Prospective cohort	10929	Geographical area, age, sex, age, smoking status, drinking status, obesity, hypertension, dyslipidemia, and diabetes mellitus	[37]
Gattellari 2011	Australia	Both	18-99	1.29	1.21, 1.38	Retrospective cohort	28304	Age, sex, marital status, country, co-morbidities (MI, CHF, DM, Pulmonary diseases, PUD, renal diseases, HTN, Senility, HDL, Smoking)	[38]
Prefasi 2013	Spain	Both	18-50	3.77	1.18, 12.03	Case-cohort	157	Age, sex, and dyslipidemia	[39]
McGrath 2013	Canada	Both	18-99	1.19	1.03, 1.36	Case-cohort	10528	Age, sex, comorbidities, OAC nonuse, CNS score, TE therapy, other complications	[40]

Bjorck 2013	Sweden	Both	50-59	2.70	1.50, 4.70	Case-cohort	193817	Sex	[25]
Bjorck 2013	Sweden	Both	60-69	1.90	1.40, 2.40	Case-cohort	184134	Sex	[25]
Bjorck 2013	Sweden	Both	70-79	1.80	1.60, 2.10	Case-cohort	112733	Sex	[25]
Bjorck 2013	Sweden	Both	80-89	2.10	1.90, 2.30	Case-cohort	69672	Sex	[25]
Lubitz 2013	USA	Both	18-99	1.84	0.77, 4.38	Prospective cohort	162	Age, sex, smoking status, systolic blood pressure, diabetes mellitus, history of heart failure, history of myocardial infarction, clinically significant murmur, and electrocardiographic left ventricular hypertrophy	[41]
Chang 2014	Taiwan	Both	40-99	2.10	2.02, 2.19	Retrospective cohort	24612	Age, sex and comorbidities (such as hypertension, hyperlipidemia, diabetes, coronary artery disease, peripheral artery disease, chronic kidney disease, HTN, HF)	[42]
Bergman 2014	Sweden	Both	15-44	3.46	1.84, 6.51	Case-control	8186	Controls 1:1 matched, age, sex, and all other ICD-10 chapters (CVDs)	[43]
Aronow 1996	USA	Both	60-100	3.31	2.43, 4.49	Prospective cohort	1476	Age, sex	[44]
Emdin 2017	UK	Both	30-90	1.32 (any stroke)	1.23, 1.41	Retrospective cohort	4269194	Age, BMI, smoking status, sex, baseline diabetes, baseline antihypertensive use, baseline lipid-lowering drug (statin) use, baseline anticoagulant usage,	[45]

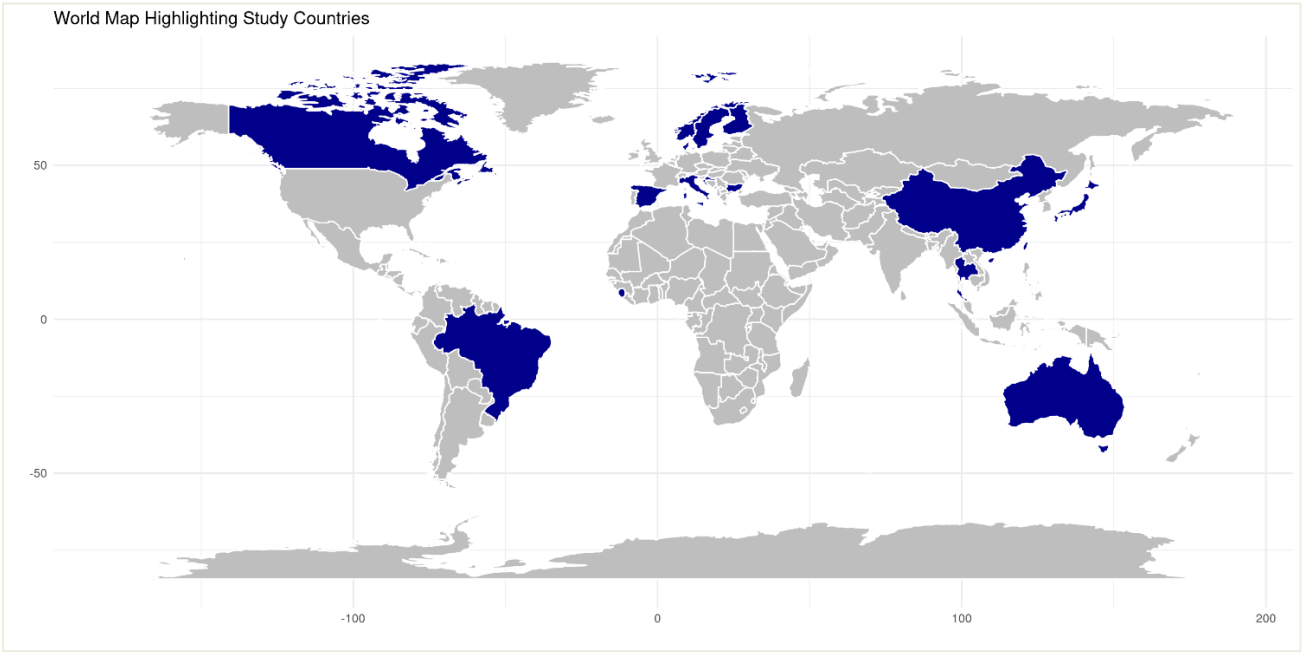
								baseline antiplatelet usage and baseline atrial fibrillation	
Emdin 2017	UK	Both	30-90	1.33 (IS)	1.20, 1.48	Retrospective cohort	4269194	Age, BMI, smoking status, sex, baseline diabetes, baseline antihypertensive use, baseline lipid-lowering drug (statin) use, baseline anticoagulant usage, baseline antiplatelet usage and baseline atrial fibrillation	[45]
O'Neal 2016	USA	Both	65-99	1.98	1.63, 2.39	Prospective cohort	1321	Age, sex, race, education, and income, smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, aspirin, and antihypertensive medications.	[46]
Corso 2014	Italy	Both	60-99	2.76	1.72, 4.44	Case-cohort	1057	Age, sex	[47]
Andersson 2017	Sweden	Both	39-99	2.7	1.8, 4.0	Case-control	21987	Age, Sex	[48]
Chao 2017	Taiwan	Both	20-99	3.34	3.26, 3.42	Case-cohort	579118	Age, sex	[49]
Yasuda 2018	Japan	Both	65-99	1.86	0.96, 3.81	Case-cohort	3343	Age, CHADS2 score components, sex, body weight loss (per 10 kg), prevalence of sustained AF, CKD, and OAC prescription at baseline	[50]
McIntyre 2018	Canada	Male	20-99	1.96	1.07, 3.58	Prospective cohort	3974	Age, Heart failure, Diabetes mellitus, Antihypertensive therapy, Cancer, Smoking, Antithrombotic therapy	[51]

Okumura 2020	Japan	Both	40-99	1.58	1.19, 2.10	Prospective cohort	12289	Age, sex, CHD, HTN, DM, h/ stroke, VD, BMI, Cr, Hb, OAC	[52]
Singleton 2020	USA	Both	40-99	3.12	1.15, 8.46	Prospective cohort	386	Age, sex, race, education, income, and geographic region. Model 2 adjusts for the covariates in model 1, with the addition of high-density lipoprotein cholesterol, total cholesterol, body mass index, and smoking. Model 3 adjusts for the covariates in model 2, with the addition of regular aspirin use and warfarin use	[53]
Joseph 2021	Global	Both	18-99	2.29	1.49, 3.52	Prospective cohort	153152	Age, sex, and CHADS2, and geographic regions	[1]
Goulart 2022	Brazil	Both	18-103	1.31	0.86, 2.00	Prospective cohort	1121	Age, sex, oral anticoagulant therapy time-dependent variable, hypertension, heart failure and CHD	[54]
Sun 2021	Hong Kong	Both	65-108	2.01	1.54, 2.62	Prospective cohort	2438	Age, sex, standardized, on pt without OAC	[55]
Turchioe 2022	USA	Both	45-99	1.41	1.21, 1.66	Prospective cohort	2124	Age, race, sex, income, education, hypertension, diabetes, current smoking, left ventricular hypertrophy, history of heart disease, and hyperlipidemia), and region of residence	[56]
Vinding 2022	Denmark	Both	18-99	3.30	2.70, 4.03	Prospective cohort	29328	30-day mortality adjusted with AF	[57]

								and stroke severity and also adjusted for chronic obstructive lung disease, chronic kidney disease, liver disease, cancer, alcohol abuse, prior bleeding, dementia, and prior use of statins	
Ritchie 2022	UK	Both	80-99	1.42	1.29, 1.57	Prospective cohort	3072	Age, sex, WIMD, AF, eGFI, smoking, dementia, pulmonary disease, cancer, peptic ulcer disease, prescription of oral anticoagulation (with or without antiplatelet therapy) within 6 months prior to care home entry, CHA2DS2VASc and HAS-BLED risk assessment scores	[58]
Choi 2022	South Korea	Both	50-99	5.57	1.62, 19.18	Prospective cohort	542	Age, sex	[59]
Youkee 2023	Sierra Leone	Both	18-99	1.58	1.06, 2.34	Prospective cohort	986	Age, sex	[60]
Nishimura 2023	Japan	Both	65-89	1.28	1.16, 1.41	Retrospective cohort	25352	Age, sex, comorbidity (diabetes mellitus, hypertensive disease, ischemic heart disease, other arrhythmias, other types of heart disease, pneumonia, chronic obstructive pulmonary disease, lower limb joint disorder, spinal disorder, renal failure, fracture, malignant tumor, and dementia and dependency level	[61]

Anjum 2023	Norway	Both	18-74	2.47	2.17, 2.81	Prospective cohort	1118762	Age, sex	[62]
Paludan-Muller 2024	Denmark	Both	81-99	1.91	1.82, 2.00	Retrospective cohort	1082895	Sex	[26]
Paludan-Muller 2024	Denmark	Both	71-80	1.65	1.59, 1.71	Retrospective cohort	1082895	Sex	[26]
Paludan-Muller 2024	Denmark	Both	61-70	1.58	1.51, 1.66	Retrospective cohort	1082895	Sex	[26]
Paludan-Muller 2024	Denmark	Both	51-60	1.89	1.75, 2.03	Retrospective cohort	1082895	Sex	[26]
Paludan-Muller 2024	Denmark	Both	20-50	2.18	1.89, 2.52	Retrospective cohort	1082895	Sex	[26]
Suzuki 2011	Japan	Both	18-99	1.61	0.50, 5.16	Case-cohort	13228	Age, sex	[63]
Bilato 2009	Italy	Both	65-99	1.76	0.90, 3.43	Case-control	1599	Unmatched	
Li 2015	China	Both	60-99	3.86	1.69, 3.85	Prospective cohort	13727	Age, sex, body mass index, current smoking, alcohol intake and hypertension	[64]
Pikija 2014	Croatia	Both	68-80	8.00	3.97, 16.10	Case-control	329	Age, sex	[65]
Persson 2018	Sweden	Male	50-98	5.34 (IS)	3.68, 7.75	Retrospective cohort	854	Age	[21]
Persson 2018	Sweden	Male	50-98	6.61 (all stroke)	4.47, 9.77	Retrospective cohort	854	Age	[21]
Tsalta-Mladenov 2021	Bulgaria	Both	18-99	11.29	3.92, 32.51	Case-cohort	250	Age, sex	[66]

Appendix 4. Figure. Geographical distribution of included studies:



Appendix 5. Study covariates assessed in the analysis:

List of bias covariates included in the analysis, coding and their significance in model

Name	Description	Coding
cov_representativeness	Generalizability	0 = Representative 1 = Not representative
cov_outcome_stroke	Any stroke	0 = Any stroke, 1 otherwise
cov_outcome_sm	Stroke mortality (in 30 days)	0 = Stroke mortality (in 30 days), 1 otherwise
cov_uncontrolled	Adjusted for confounders	0 = Adjusted, 1 = Unadjusted
cov_age	Age adjusted	0 = Adjusted, 1 = Unadjusted
cov_sex	Sex adjusted	0 = Adjusted, 1 = Unadjusted
cov_edu	Education adjusted	0 = Adjusted, 1 = Unadjusted
cov_smoking	Smoking adjusted	0 = Adjusted, 1 = Unadjusted
cov_alcohol	Drinking behavior adjusted	0 = Adjusted, 1 = Unadjusted
cov_bmi	BMI adjusted	0 = Adjusted, 1 = Unadjusted
cov_cvd	Cardiac comorbidities	0 = Adjusted, 1 = Unadjusted
cov_comrb	Other comorbidities	0 = Adjusted, 1 = Unadjusted
cov_dlp	Dyslipidemia adjusted	0 = Adjusted, 1 = Unadjusted
cov_dm	Diabetes Mellitus adjusted	0 = Adjusted, 1 = Unadjusted
cov_bp	Hypertension adjusted	0 = Adjusted, 1 = Unadjusted
cov_htn_med	Anti-hypertensive medication use adjusted	0 = Adjusted, 1 = Unadjusted
cov_statin	Statin use adjusted	0 = Adjusted, 1 = Unadjusted
cov_oac	Oral Anti Coagulants adjusted	0 = Adjusted, 1 = Unadjusted
cov_cha2ds2	CHA2DS2 adjusted	0 = Adjusted, 1 = Unadjusted
cov_renal	Renal disease adjusted	0 = Adjusted, 1 = Unadjusted
cov_lung	Pulmonary disease adjusted	0 = Adjusted, 1 = Unadjusted
cov_cns	CNS score and dementia adjusted	0 = Adjusted, 1 = Unadjusted
cov_c-cntrl	Case-control design	0 = Case-control design, 1 otherwise
cov_c-cohort	Case-Cohort (prospective/retrospective)	0 = Case-cohort design, 1 otherwise
cvov_cohort	Cohort (prospective/retrospective)	0 = Cohort study, 1 otherwise
cov_fu5	Minimum follow-up for 5 years	0 = Minimum follow-up for 5 years, 1 otherwise