Screening, risk stratification, and management of atrial fibrillation

By

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To my wife and my son

These years of separation have been so difficult for our family. You have been my light in the darkness, my source of motivation. I am forever grateful for your support.

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ABBREVIATIONS AND ACRONYMS

95% CI: 95% confidence interval

AAD: anti-arrhythmic drug

ACS: acute coronary syndrome

AF: atrial fibrillation

AFSS: atrial fibrillation severity scale

aHR: adjusted hazard ratio

AMI: acute myocardial infarction

aOR: adjusted odds ratio

aPE: acute pulmonary embolism

BMI: body mass index

BNP: brain natriuretic peptide

CAD: coronary artery disease

CAS: carotid artery stenting

CEA: carotid artery endarterectomy

cIMT: carotid intima-media thickness

CKD: chronic kidney disease

COPD: chronic obstructive pulmonary disease

CP: carotid plaque

CRP: C-reactive protein

CS: cryptogenic stroke

CT: computed tomography

DALYs: disability adjusted life years

DNA: deoxyribonucleic acid

DOAC: direct oral anticoagulant

DVT: deep vein thrombosis

ECG: electrocardiogram

ECV: electrical cardioversion

EDD: enrolment disparity difference

eGFR: estimated glomerular filtration rate

ESUS: embolic stroke of undetermined source

FEV1: forced expiratory volume in one second

FGF-23: Fibroblast growth factor-23

FVC: forced vital capacity

GLI: Global Lung Initiative

GBD: Global Burden of Disease

HF: heart failure

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HR: hazard ratio

hsCRP: highly sensitive C-reactive protein

ICD-9: International Classification of Diseases, Ninth Revision

ICD-10: International Classification of Diseases, Tenth Revision

ICM: implantable cardiac monitor

IL: interleukin

INR: international normalized ratio

IQR: interquartile range

LA: left atrium

LAA: left atrial appendage

LAVI: left atrial volume index

LCL: lower confidence limit

LOS: length of stay

LVEF: left ventricular ejection fraction

LVH: left ventricular hypertrophy

MCOT: mobile cardiac outpatient telemetry

MD: mean difference

MET: metabolic equivalent of task

MI: myocardial infarction

NIS: national inpatient sample

NR: not reported

NSTEMI: non-ST myocardial infarction

NT-proBNP: N-terminal pro-B-type natriuretic peptide

OAC: oral anticoagulation

OppSTS: opportunistic single-time-point screening

OR: odds ratio

OSA: obstructive sleep apnea

PAC: premature atrial contractions

PA-TDI: total atrial conduction time assessed by tissue doppler imaging

PFG: proportion of females with AF among the general population

PFT: proportion of females enrolled in the trial

RCT: randomized controlled trial

RNA: ribonucleic acid

RoB: risk of bias assessment

RR: risk ratio

SD: standard deviation

SDI: sociodemographic index

SE: systemic embolism

SEC: spontaneous echo-contrast

STEMI: ST-elevation myocardial infarction

TIA: transient ischemic attack

TnI: troponin I

TnT: troponin T

UCL: upper confidence limit

uHR: unadjusted hazard ratio

uOR: unadjusted odds ratio

UKB: UK Biobank

VKA: vitamin-K antagonist

VTE: venous thromboembolism

WL: weight loss

ABSTRACT

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with high morbidity and mortality. Major improvements have been made in the diagnosis and management of AF in the past two decades. However, important questions pertaining to the screening, prognosis, risk stratification, and management of AF remain unanswered. This thesis presents original studies addressing knowledge gaps in these aspects of AF.

In **Chapter 2**, using a large cohort of individuals from the UK Biobank, we investigated the association between lung function and incident AF. We observed that reduced ventilatory function was associated with increased risk of AF independently of age, sex, smoking, and several other known AF risk factors. This suggests that individuals with substantial reduction of their lung function might represent an appropriate population for targeted AF screening and ventilatory parameters might improve AF risk prediction.

Chapter 3 assesses data related to implantable cardiac monitors (ICM). The first section reports AF diagnostic yield in a real-world cohort of patients receiving prolonged cardiac monitoring with ICM for stroke and unexplained syncope. It indicates that patients with stroke or transient ischemic attack (TIA) have a higher rate of AF detection compared with patients with unexplained syncope. However, this real-world study shows AF detection rates following stroke significantly lower than what has been previously reported. The second section of this chapter summarizes data on AF detection rates across different rhythm monitoring strategies (non-invasive and ICM) in patients with cryptogenic stroke (CS) or embolic stroke of undetermined source (ESUS). It shows that the yield of ICM increases with the duration of monitoring; more than a quarter of patients with CS or ESUS will be diagnosed with AF during follow-up. About one in seven patients have AF detected within a

month of mobile cardiac outpatient telemetry, suggesting that a non-invasive rhythm monitoring strategy should be considered before invasive monitoring.

Chapters 4 and 5 address risk stratification in patients with AF. **Chapter 4** has two sections. The first section is a meta-analysis that comprehensively summarizes data from prospective cohort studies on clinical predictors of stroke in anticoagulant-naïve patients with AF. It shows that although weighted similarly in most risk stratification schemes such as the CHA_2DS_2-VASc score, the absolute risk of stroke attributable to hypertension, diabetes, vascular disease, and heart failure may not be the same in individual patients. Furthermore, it shows that female sex seems not to be universally associated with stroke or systemic embolism, suggesting that the decision to initiate oral anticoagulation should not be made on the sole basis of female sex as currently recommended by some scientific societies. By compiling evidence from various studies, the second section of this chapter demonstrates that some anatomic and functional cardiac imaging parameters are associated with stroke in patients with AF and therefore, might improve stroke risk stratification in these patients. **Chapter 5** presents two systematic reviews and meta-analysis which show that AF and carotid artery disease frequently co-exist, with about one in ten patients with AF who has carotid stenosis, and vice versa; and non-stenotic carotid disease being much more frequent. Moreover, there is an association between carotid atherosclerosis and the risk of stroke in patients with AF, suggesting that the incorporation of carotid atherosclerosis and characteristics of carotid plaques into scoring systems might improve stroke prediction in patients with AF. Taking this further, the last section of this chapter investigates the potential added value of high-risk carotid plaques on stroke risk stratification compared to the classical CHA_2DS_2-VASc score in a prospective cohort of patients with AF. It shows a low prevalence (5.5%) of moderate to severe carotid stenosis ($\geq$ 50%), whereas one in three participants have carotid plaques considered vulnerable or high-risk. Neither the degree of carotid stenosis nor

the presence of vulnerable plaques is associated with incident ischemic stroke, suggesting that carotid disease is probably not an important cause of ischemic stroke in this group of patients with AF and therefore, vulnerable carotid plaques might not improve stroke risk stratification in patients with AF.

Chapter 6 presents two pooled analyses of data on the prognostic impact of AF on acute coronary syndromes (ACS) and acute pulmonary embolism (aPE). The first section of the chapter shows that AF is common in patients with ACS (one in nine) and that it (especially newly diagnosed AF) is associated with poor short-term and long-term outcomes including re-infarction, heart failure, stroke, acute kidney injury, heart failure, major bleeding, and death. Likewise, the second section of the chapter demonstrates that AF is frequent in patients with aPE (one in eight) and is associated with increased short-term and long-term mortality. Considering this strong prognostic impact of AF in patients with ACS and aPE, its incorporation into risk stratification schemes for these patients should be considered. Furthermore, considering the significant incidence of AF in patients with ACS and aPE, studies are needed to determine the appropriate rhythm monitoring strategies in these patients.

Chapters 7-9 focus on sex differences in the management of AF. **Chapter 7** analyses data from 142 randomized controlled trials (RCTs) of AF published in top tiers cardiovascular journals and shows that despite recent progress, females remain substantially less represented in RCTs of AF. This raises concern about the generalizability of these trials and the validity of the evidence guiding the treatment of females. Furthermore, primary outcomes are infrequently reported by sex in these RCTs of AF. Considering established benefit of risk factor modification on outcomes in patients with AF, **Chapter 8** assesses sex differences in weight-loss, cardiorespiratory fitness gain, and progression and recurrence of AF in patients undergoing aggressive risk factor modification. It shows that despite sex

differences in some baseline characteristics, the benefits of weight-loss and fitness gain were favourable for both males and females. However, improvement in fitness had a much greater benefit for total arrhythmia freedom for females, whereas there was a trend towards more common regression from persistent to paroxysmal AF in males. These findings reinforce the need to address lifestyle risk factors to minimize arrhythmia recurrence and reduce symptom severity for all individuals. Finally, **Chapter 9** investigates the impact of sex on the clinical profile, utilization of rhythm control therapies, in-hospital mortality, length of stay (LOS), and cost of hospitalization in patients admitted for AF in the United States. It shows similarities and disparities in risk factors for mortality between males and females, and that unlike what has been reported in several previous studies, although women had a relatively higher mortality rate, after risk adjustment, female sex was not a predictor of mortality.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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LIST OF ARTICLES, CONFERENCE PRESENTATIONS, AND AWARDS

PhD-related articles

Chapter 1. Literature review

Published

- Noubiap JJ, Sanders P, Nattel S, Lau DH. Biomarkers in Atrial Fibrillation: Pathogenesis and Clinical Implications. *Card Electrophysiol Clin*. 2021 Mar;13(1):221-233.

Chapter 2. Incident atrial fibrillation in relation to ventilatory parameters: a prospective cohort study

Published

- Noubiap JJ, Tu SJ, Emami M, Middeldorp ME, Elliott AD, Sanders P. Incident atrial fibrillation in relation to ventilatory parameters: a prospective cohort study. *Can J Cardiol*. 2023 Feb 9:S0828-282X(23)00082-X.

Chapter 3. Searching for atrial fibrillation after stroke

Published

- Noubiap JJ, Thomas G, Middeldorp ME, Fitzgerald JL, Harper C, Sanders P. Atrial fibrillation detection using insertable cardiac monitor after stroke: A real-world cohort study. *J Cardiovasc Electrophysiol*. 2023 Jan;34(1):142-146.

- Noubiap JJ, Agbaedeng TA, Kamtchum-Tatuene J, Fitzgerald JL, Middeldorp ME, Kleinig T, Sanders P. Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc*. 2021 Apr 16;34:100780.

Chapter 4. Clinical and cardiac predictors of stroke in patients with atrial fibrillation

Published

- Noubiap JJ, Feteh VF, Middeldorp ME, Fitzgerald JL, Thomas G, Kleinig T, Lau DH, Sanders P. A meta-analysis of clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation. *Europace*. 2021 Oct 9;23(10):1528-1538.

- Noubiap JJ, Middeldorp ME, Thomas G, Sanders P. CHA2DS2-VASc score is no longer enough-Authors' reply. *Europace*. 2022 Jul 21;24(7):1195.

Under review

- Noubiap JJ, Nyaga UF, Middeldorp ME, Thomas G, Sanders P. Cardiac imaging correlates and predictors of stroke in patients with atrial fibrillation: A pooled analysis

Chapter 5. Carotid and aortic atherosclerotic disease and stroke risk stratification in patients with atrial fibrillation

Published

- Noubiap JJ, Agbaedeng TA, Tochie JN, Nkeck JR, Ndoadoumgue AL, Fitzgerald JL, Kleinig T, Thomas G, Middeldorp ME, Sanders P. Meta-Analysis Comparing the Frequency of Carotid Artery Stenosis in Patients With Atrial Fibrillation and Vice Versa. *Am J Cardiol*. 2021 Jan 1;138:72-79.

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Chapter 6. Prognostic impact of atrial fibrillation on acute cardiovascular events

Published

- Noubiap JJ, Agbaedeng TA, Nyaga UF, Lau DH, Worthley MI, Nicholls SJ, Sanders P. Atrial fibrillation incidence, prevalence, predictors, and adverse outcomes in acute coronary syndromes: A pooled analysis of data from 8 million patients. *J Cardiovasc Electrophysiol*. 2022 Mar;33(3):414-422.

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Chapter 7. Sex disparities in enrolment and reporting of outcomes by sex in contemporary clinical trials of atrial fibrillation

Published

- Noubiap JJ, Thomas G, Nyaga UF, Fitzgerald JL, Gallagher C, Middeldorp ME, Sanders P. Sex disparities in enrollment and reporting of outcomes by sex in contemporary clinical trials of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2022 May;33(5):845-854.

Chapter 8. Sex differences in outcomes of an intensive risk factor modification program in patients with atrial fibrillation

Under review

- Noubiap JJ, Pathak RK, Thomas G, Elliot A, Sanders P, Middeldorp ME. Sex differences in outcomes of an intensive risk factor modification program in patients with atrial fibrillation

Chapter 9. Sex differences in clinical profile, management, and outcomes of patients hospitalized for atrial fibrillation in the United States

Published

- Noubiap JJ, Thomas G, Agbaedeng TA, Fitzgerald JL, Gallagher C, Middeldorp ME, Sanders P. Sex differences in clinical profile, management, and outcomes of patients hospitalized for atrial fibrillation in the United States. Eur Heart J Qual Care Clin Outcomes. 2022 Nov 17;8(8):852-860.

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CHAPTER 1:

Literature review

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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

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1.1 The burden of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia. It has become a major global health problem owing to its increasing prevalence and incidence, and to its associated morbidity and mortality. Atrial fibrillation currently affects approximately 0.5% of the global population [1]. The surge in the incidence and prevalence of AF has been driven by the aging of the population, increasing prevalence of established risk factors for AF, emergence of newer risk factors and improved survival of patients with cardiovascular disease [2].

1.1.1 Incidence and prevalence of atrial fibrillation

1.1.1.1 Global trends

The incidence and prevalence of AF have markedly risen in the last decades. The Framingham Heart Study was one of the first large cohorts that showed a substantial increase in the prevalence of AF [3]. In the Framingham Heart Study, between 1958 and 2007, the age-adjusted prevalence of AF increased from 20.4 to 96.2 cases per 1000 person-years in men, and from 13.7 to 49.4 cases per 1000 person-years in women. Additionally, the age-adjusted incidence of AF raised from 3.7 to 13.4 cases per 1000 person-years in men and 2.5 to 8.6 cases per 1000 person-years in women. This represents more than 3-fold increase in the incidence and prevalence of AF over a 50-year period [3].

The Global Burden of Disease (GBD) study also provides trend estimates in the prevalence and incidence of AF. According to the GBD, the global incidence of AF has increased from 1.83 million new cases (309 new cases per million inhabitants) in 1997 to 3.05 million new cases (403 new cases per million inhabitants) in 2017, representing a 31% increase [1]. The global prevalence of AF has increased by 33% during the same period, from 22.17 million cases (3751 cases per million inhabitants) in 1997 to 37.57 million cases (4977 cases per million inhabitants) in 2017 [1]. If the AF epidemic continue to follow the current

trends, predictions suggest that the absolute incidence and prevalence would also increase by 63% (4.95 million new cases) and 66% (62.51 million cases) respectively in the next 30 years [1].

1.1.1.2 Regional variations

Although there is wide variation in the incidence and prevalence of AF across the globe, increasing trends are observed in all regions and countries. In the United States, 1% to 2% of the population have AF [4]. This corresponds to between 3 to 6 million people with AF, and these numbers are expected to reach between 6 to 16 million by 2050 [4, 5]. In China, about 2% (3.9 million) of people aged ≥60 years have AF [6]; by 2050 the country is expected to have 460 million individuals aged ≥60 years, of whom about 9 million will have AF [7]. Overall in Asia, it is estimated that more than 72 million people will have AF by 2050, and this will be associated with up to 3 million AF-related strokes [8]. In the Europe Union, there were 8.8 million adults over 55 years with AF in 2010. This number is projected to double by 2060 to 17.9 million [9].

Estimates from low- and middle-income countries are less accurate. In Africa for instance, data on AF are scarce [10]. However, available data suggest that AF is not spared by the AF epidemic. According to some projections there will be more people with AF in Africa than in either China, the United States, or India by 2050 [11]. Much more, AF has become one of the risk factors with the sharpest rise in attributed cardiovascular mortality in Africa [12].

1.1.1.3 AF burden in Australia

Australia is one of the countries with the highest reported prevalence of AF [13]. In 2020, approximately 500,000 people had AF, representing approximately 2% of the general population [14]. This prevalence increases with age, with an estimated 5% of Australian adults aged ≥55 years who have AF [14]. In Australian Aboriginal and Torres Strait Islander communities the prevalence of AF has been estimated at 2.5% [14, 15].

In terms of hospitalizations with AF as the principal diagnosis, their burden has continuously risen over the past two decades [14, 16-19]. Between 2000–01 and 2017–18, the age-standardized rate of AF hospitalization increased by 42%, from 175 to 248 hospitalisations per 100,000 population [14]. This has been associated with an increase in AF-related procedures such as cardioversion and ablation, and in the overall cost of hospitalization [14, 16]. Strikingly, AF has surpassed myocardial infarction and heart failure in hospitalization numbers and cost [16]. In fact, there has been a relative increase in AF hospitalisations, from 0.5% of all hospitalisations and 8% of hospitalisations for cardiovascular disease (CVD) in 2000–01, to 0.7% of all hospitalisations and 12% of CVD hospitalisations in 2017–18 [14]. This increasing burden of AF hospitalizations is mainly driven by population aging and re-admissions [18, 19].

1.1.1.4 Accuracy of the AF incidence and prevalence estimates

These estimates of AF incidence and prevalence are most likely underestimated for at least two main reasons. First, up to one-third of people with AF are asymptomatic. These asymptomatic AF cases are more likely to remain undiagnosed. Second, paroxysmal AF (that self-terminates within 7 days) represents between 25% and 62% of cases of AF [20, 21]. Paroxysmal AF is largely underdiagnosed with single-time-point 12-lead electrocardiogram (ECG) [21]. The detection of paroxysmal AF can be improved using frequent screening or prolonged ambulatory monitoring. This is well demonstrated by the ASSERT study that enrolled 2580 patients, 65 years of age or older, with hypertension and no history of AF, in whom a pacemaker or defibrillator had recently been implanted [22]. The study found that by 3 months, subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) detected by implanted devices had occurred in 10.1% of patients. Furthermore, subclinical atrial tachyarrhythmias were associated with an increased risk of clinical AF (hazard ratio [HR], 5.56; 95% confidence interval [CI], 3.78 to 8.17; p <0.001) [22].

1.1.2 Mortality and disability attributable to atrial fibrillation

Atrial fibrillation is associated with high morbidity and mortality. According to data from the GBD study, AF accounted for 5976 million disability adjusted life years (DALYs) in 2017, increasing from 3371 million DALYs in 1997 (+77%). Countries with high sociodemographic index (SDI; calculated from on income per capita, education attainment and fertility) had the highest burden in terms of DALYs, followed by middle, high-middle, low-middle, and low SDI countries [1]. In 2017, there were 0.287 million deaths attributable to AF (0.51% of the global cumulative mortality), a proportion that increased from 0.140 million deaths in 2017 (+105%). The male/female ratio for mortality was 0.79 in 2017 [1].

1.2 Risk factors for atrial fibrillation

Several modifiable and non-modifiable risk factors for AF have been identified. Most of them are consistently associated with an increased risk of AF across all ethnic groups. With a cohort followed up for 38 years, the Framingham Heart Study was pioneer in providing strong data on risk factors for AF [23]. The study identified aging, male sex, hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, and valvular heart disease as independent risk factors [23]. Subsequent studies have uncovered additional risk factors such as white race, excessive alcohol consumption, cigarette smoking, obesity, obstructive sleep apnoea (OSA), chronic kidney disease, chronic obstructive pulmonary disease (COPD), hyperthyroidism, left ventricular hypertrophy, rheumatic and degenerative valvular diseases [2].

1.2.1 Ageing

Advancing age is the strongest and most consistent single independent risk factor for AF. This is partly explained by the accumulation of other risk factors for AF with advancing age.

But independent of these other risk factors, cellular ageing promotes the anatomical substrate required for the development of AF. In the Framingham Heart Study, the risk of AF increased by 2.1-fold (95% CI: 1.8–2.5) in men and 2.2-fold (95% CI: 1.9–2.6) in women per decade of age [23]. Furthermore, there is a sharp slope in the incidence of AF after age 65 years. More than 70% of patients with AF in Europe, North America and Australia are >65 years old [2, 11].

Importantly, ageing is not just a risk factor for the occurrence of AF but is also a main driver of adverse health outcomes in this population. For instance, advancing age is one of the strongest predictors of stroke in patients with AF as demonstrated by the weight attributed to age in stroke risk stratification schemes [24].

1.2.2 Male sex

Male sex is an independent risk factor for AF. In the Framingham Heart Study, males had had a 1.5 times (95% CI: 1.3-1.8) greater risk of developing atrial fibrillation than women [23]. The prevalence of AF is estimated at 3.3% (95% CI: 2.7–4.0%) in males and 2.4% in females (95% CI: 1.9–2.9%) [25]. A higher prevalence of AF in males is also observed in the Global Burden of Disease study, with a male/female ratio of 1.11 [1]. If the predominance of AF in males seems to be a global phenomenon, China is an exception, with the prevalence of AF reportedly similar in males and females [1, 2].

1.2.3 Race and ethnicity

Despite a higher prevalence of risk factors for AF, individuals of African ancestry have a lower incidence of AF compared with Caucasians. Asians and Hispanics also seem to have lower incidence of AF than Caucasians [2, 25-28]. For instance, in the Multi-Ethnic Study of Atherosclerosis (MESA), among participants aged 65 years or older, the AF incidence was

46% to 65% lower in Hispanics, Asians, and blacks compared with non-Hispanic whites [27]. In the 1999 Large Health Survey of Veteran Enrollees that included over 600,000 male patients, the age-adjusted prevalence of AF in whites was almost 2-fold higher than in other ethnicities [28].

These racial differences could be explained by genetic and anatomic parameters, and socioeconomic and environmental determinants of health. Blacks have lower access to healthcare and more commonly paroxysmal AF [29] resulting in AF underdiagnosis and apparent lower AF incidence and prevalence. Blacks also have smaller average left atrial dimensions compared to whites [30], implying a lower risk of AF as left atrial dilatation is a predictor of incident AF [31]. A genetic study involving three population-based cohorts in the US revealed that the single SNP rs10824026 (chromosome 10: position 73661450) substantially mediated the higher risk for AF in white individuals compared with black individuals [32]. Furthermore, because African Americans have varying degrees of European ancestry, the Candidate-Gene Association Resource (CARe) Study tested the hypothesis that European ancestry is an independent risk factor for using ancestry informative markers. The study confirmed that European ancestry predicts the risk of incident AF in African Americans [33].

1.2.4 Hypertension

Hypertension is one of the most common chronic diseases. It affects about 1.28 billion adults aged 30-79 years globally [34]. In the US for instance, one-third of adults have hypertension, with a prevalence of 26% in adults <45 years and 80% in those >65 years [35]. Hypertension is the most common and strongest modifiable risk factor for AF worldwide [2, 5]. In the Framingham Heart Study, people on treatment for hypertension had a 1.8-fold (95% CI: 1.48-

2.18) increased risk of AF [36]. In the Atherosclerosis Risk in the Community (ARIC) study, whereas common cardiovascular risk factors such as cigarette smoking, diabetes mellitus, elevated blood pressure, overweight/obesity, and prior cardiac disease contributed to 57% of incident AF, elevated or borderline blood pressure alone explained 20-25% of AF cases [37]. Indeed, in large registries of AF, hypertension is found in 60-80% of patients with AF [38-41].

Despite the close link between hypertension and AF, the underlying pathophysiology of AF in patients with hypertension is not fully elucidated. Two major mechanisms have been proposed to explain the development of AF in hypertension: hemodynamic and structural changes in atria due to hypertension, and activation of renin-angiotensin-aldosterone system (RAAS) [42]. On one hand, in the setting of long-standing hypertension, the excessive afterload imposing onto the left ventricle leads to progressive left ventricular hypertrophy (LVH), left ventricular diastolic and systolic dysfunction, and ultimately a rise in left atrial pressure, left atrial enlargement with reduced contractility and compliance [43]. This left atrial and left ventricular remodelling is accompanied by profibrotic changes [42-44]. Chronic atrial stretch may lead to atrial structural and electrophysiological changes that constitutes a substrate for AF development [43, 44].

On the other hand, activation of the RAAS is the main driver of remodelling in hypertension through upregulated TGF-ß1 expression, increased aldosterone production, activation of nicotinamide adenine dinucleotide phosphate oxidase, and apoptosis [44]. Angiotensin II induces atrial fibrosis and hypertrophy, changes in expression of ion channels, gap junction and calcium handling, as well as increased oxidative stress and inflammation [45]. Angiotensin II also has direct cellular electrophysiological effects on cardiomyocytes that promote the development of AF [42, 46].

1.2.5 Obesity

There is a global epidemic of obesity. The World Health Organization estimated that in 2016, more than 1.9 billion adults (aged 18 years or older) were overweight and 650 million were obese, representing 39% and 13% of the global adult population, respectively [47]. Similar estimates were reported by the Global Burden of Disease study which, additionally, showed that between 1980 and 2015, the age-standardized prevalence of obesity increased by a factor of 2 or more in 13 of the 20 most populous countries in the world [48].

Body mass index (BMI) is linearly associated with AF risk, with a 4.7% (95% CI: 3.4–6.1%) increased risk per kg m^2 [2]. In the Atherosclerosis Risk in Communities (ARIC) study, obesity or overweight was the second strongest modifiable risk factor for AF after hypertension, accounting for nearly 18% of the population-attributable risk of AF [37]. In a large meta-analysis (626,603 individuals from 51 studies), incremental increases in BMI were associated with a significant excess risk of AF. There were 29% greater excess risks of incident AF and 10% greater excess risks of post-operative and post-ablation AF for every 5-unit increase in BMI.[49] With the burgeoning obesity epidemic, obesity is becoming a major driver of the increase in the prevalence of AF worldwide [11].

Long-standing obesity may indirectly favour the development of AF through other cardiometabolic disorders such as diabetes mellitus, hypertension, obstructive sleep apnoea, and coronary artery disease which are known risk factors for AF and with which obesity frequently co-exists [2, 50]. Additionally, a direct causal role of obesity for AF has been demonstrated in a Mendelian randomization study, which showed a link between a genetic risk score comprised of 39 polymorphisms associated with BMI and incident AF [51].

From a mechanistic point of view, there are robust evidence supporting the association between obesity and atrial structural and electrophysiological changes that

constitute a substrate for AF development [5, 52]. Such changes include left ventricular hypertrophy, diastolic dysfunction, increased left atrial volume, fibrosis and fat content, reduced left atrial conduction velocity, and increased AF vulnerability and AF duration [52-56]. Moreover, obesity is associated with low-grade inflammation and larger epicardial fat, which impair atrial electrophysiology [56-58].

1.2.6 Diabetes mellitus

Diabetes mellitus is a major global health problem owing to its increasing prevalence and to its complications. According to International Diabetes Foundation, there were 425 million adults (aged 20-79 years) affected by diabetes globally in 2017, a number that has increased by 26.4% to reach 537 million adults in 2021 [59]. Additionally, in 2021, 541 million adults had impaired glucose tolerance (IGT), which places them at high risk of type 2 diabetes [59]. Diabetes was responsible for 6.7 million deaths in 2021 [59].

Diabetes is a very common risk factor in patients with AF, with around 20% presenting with diabetes [2, 11]. In the Framingham Heart Study, diabetes was associated with a 40% and 60% increased risk of AF in males and females, respectively [23]. A meta-analysis of cohort studies revealed that prediabetes and diabetes increase the risk of AF by 20% and 28%, respectively [60]. Furthermore, there is a dose-response relationship between increasing blood glucose and AF, with an 11% increased risk of AF per 20 mg/dl increase of blood glucose [60].

Diabetes contributes to AF substrate development through several mechanisms. Glucose intolerance and insulin resistance that are components of diabetes mellitus modulate electro-anatomical changes in the atria [61]. In metabolic stressed heart, oxidative stress and inflammation have been shown to play a central role in mitochondrial dysfunction and

consequent DNA damage, generating a substrate for AF initiation [62-64]. Other mechanisms that contribute to AF development in animals with induced diabetes mellitus include decreased atrial connexin 43 phosphorylation [64], activated TGF-β1 and RhoA–Rho-associated protein kinase [65], increased expression of the advanced glycation end products and their receptors [66], atrial fibrosis [67], increased AF vulnerability and atrial conduction slowing [68].

1.2.7 Heart failure

Heart failure (HF) and AF frequently co-exist and impact reciprocally on each other [69]. In the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF), 22.6% of patients with AF had HF [39]. In another international registry, rates of HF were 33% in paroxysmal, 44% in persistent and 56% in permanent AF [20]. Patients with HF have an increased risk of AF (HR 3.2, 95% CI: 2.0–5.2) [70]. Both HF with reduced left ventricular ejection fraction and HF with preserved ejection fraction are associated with an increased risk of AF. The incidence of AF increased with the severity of HF [2, 25, 37, 70]. The co-existence of AF and HF is partly explained by shared risk factors. Hypertension, diabetes, obesity, obstructive sleep apnoea, and coronary artery disease are all associated with an increased risk of developing both HF and AF [71].

Atrial fibrillation can contribute to the development of HF by several established mechanisms. Loss of atrial systole in AF impairs LV filling and can decrease cardiac output by up to 25%, especially in patients with diastolic dysfunction [71]. This is worsened by increased heart rate which causes shortening of diastolic filling time [71]. Furthermore, irregular and/or rapid ventricular conduction in AF can result in a tachycardia-induced cardiomyopathy [71].

Reciprocally, HF can also promote AF via several mechanisms. Heart failure increases atrial filling pressure and atrial dilatation, leading to atrial scarring and fibrosis, and ultimately to structural and electrical remodelling that promotes AF [69, 71]. Additionally, stretching of the atria in HF induces acute electrophysiological arrhythmogenic changes that could trigger AF in a vulnerable substrate [69]. Left atrial dilatation is associated with significant shortening of the atrial refractory period which can induce AF [69].

1.2.8 Coronary artery disease

Coronary artery disease (CAD) is the foremost single cause of mortality and disability globally. According to the Global Burden of Disease study, the total number of DALYs due to CAD has risen steadily since 1990, reaching 182 million DALYs and 9.14 million deaths in the year 2019. It is estimated that 197 million people had CAD in 2019 [72].

Patients with CAD are prone to develop AF, especially new-onset AF (NOAF), following acute myocardial infarction (AMI). In some series, the rate of NOAF following AMI has been reported at up to 50% [73]. The full spectrum of CAD is consistently associated with increased risk of AF in all populations [2, 25, 36]. Acute myocardial infarction has a risk ratio of 3.62 (95% CI: 2.59–5.07), angina pectoris has a risk ratio of 2.84 (95% CI: 1.91–4.21), and ST-T wave abnormalities have a risk ratio of 2.21 (95% CI: 1.62–3.00) [2].

There seems to be a relationship between the lesions and severity of CAD and the occurrence of AF [73]. A significant correlation was shown between ischemia or infarction in the territory of the right coronary artery and NOAF [74-76]. This might be explained by the fact that the atrial arteries that supply blood to the atria usually originate from the right coronary artery. However, other studies have reported that NOAF is more likely to develop in patients with left main CAD [77]. It was shown that severe disease in the right coronary artery and the

left circumflex predicts early onset AF, whereas disease in the left main and left anterior descending coronary arteries is associated with late onset AF [78].

Reciprocally, studies have demonstrated that patients with AF are more likely to have CAD than those without AF. In one study, coronary atherosclerosis and obstructive CAD (≥50% luminal narrowing) were more frequently detected in patients with AF, and the lesions were more common in the left main or proximal left anterior descending artery [79].

The association between CAD and AF can be explained on one hand by shared risk factors and on the other hand by direct interactions between the two conditions. Coronary artery disease has many identified risk factors, including hypertension, obesity, diabetes mellitus, dyslipidemia, obstructive sleep apnoea, smoking, age, and decreased physical activity [80]. All these conditions are highly prevalent in patients with CAD, AF, or both [73]. Coronary artery disease contributes to AF through three main mechanisms including re-entry formation, focal ectopic activity, and neural remodelling [73, 81]. Re-entry formation is due to connexins fibrosis, shortening of the atrial effective refractory period, and atrial dilatation from HF and diastolic dysfunction [73]. Focal ectopic activity is generated by CAD through enhanced automaticity, prolonged action potential duration, and delayed after-polarizations [81]. Coronary artery disease also causes sympathovagal imbalance from hyperparasympathetic and hyposympathetic activies which lead to neural remodelling [82]. All these mechanisms lead to a structural and electrical substrate that generates AF [73].

1.2.9 Obstructive sleep apnoea

There is a strong association between obstructive sleep apnoea (OSA) and AF [2, 83]. Obstructive sleep apnea is also an important risk factor for the occurrence and progression of

AF [84-86]. Patients with OSA and without other cardiovascular co-morbidities have an increased risk of AF (HR 1.5, 95% CI: 1.17–2.01) [2].

Obstructive sleep apnea contributes to atrial arrhythmogenesis through several mechanisms in the short- and long-terms. Acutely, negative intrathoracic pressure swings during obstructed inspiration lead to a dilatation of the atria that shortens the atrial effective refractory period, slows conduction, and favors intermittent conduction delay [84]. Furthermore, the sympathovagal activation caused by obstructed breathing efforts induces acute electrophysiological arrhythmogenic changes that could trigger AF in a vulnerable substrate [84].

In the long-term, OSA is associated with substantial atrial structural and electrical changes. Intermittent episodes of deoxygenation and reoxygenation induce oxidative stress that, along with chronic neurohormonal activation contribute to atrial fibrosis [84]. Frequent stretching of the atria from recurrent obstructive respiratory episodes also causes myocardial injury and remodeling, as well as local conduction slowing and re-entry [84]. All these OSA-induced changes are worsened by associated conditions such as hypertension, obesity, and diabetes mellitus, and ultimately constitute a complex and dynamic arrhythmogenic substrate for AF [84].

Obstructive sleep apnea also substantially impacts on AF outcomes. Although the evidence is limited, OSA has been reported as an independent predictor of stroke in patients with AF [87]. Obstructive sleep apnea significantly alters the effectiveness of rhythm control strategies including antiarrhythmic drug therapy and catheter ablation [88-90]. Furthermore, several non-randomized observational studies and meta-analyses showed that treatment of OSA by continuous positive airway pressure (CPAP) may improve success rates after catheter ablation in patients with AF [88, 91].

1.2.10 Alcohol consumption

Alcohol consumption is prevalent in many parts of the globe, especially in western countries. In 2016, a total of 2.4 billion people were current drinkers, representing 32.5% of the global population [92]. In the same year, alcohol consumption was the 7th leading risk factor for premature mortality and health loss. It led to 2.8 million deaths, which corresponds to 2.2% of age-standardized female deaths and 6.8% of age-standardized male deaths [92]. In terms of overall disease burden, alcohol consumption accounted for 1.6% of total DALYs globally among females and 6.0% among males in 2016 [92].

Alcohol consumption is associated with an increased risk of AF [93]. Back in 1978, AF was coined as Holiday Heart syndrome, due to its recognized association with binge alcohol drinking [94]. In fact, a physician, Ettinger, noted that his patients presented with AF and other cardiac arrhythmias following weekend or holiday binge drinking episodes [94]. This association between binge alcohol consumption and AF has later been observed in several studies [95]. Besides alcoholic binges, data on the relationship between chronic alcohol consumption and AF has recently emerged.

An analysis of data from the UK Biobank showed a J-shaped association between total alcohol consumption and AF [96]. It also showed that low consumption of red and white wine and very low consumption of spirits may not be associated with increased AF risk, whereas any consumption of beer/cider may be associated with harm [96]. The association of alcohol intake and AF seems less clear in females [2]. Furthermore, abstinence from alcohol has been shown to reduce arrhythmia recurrences in regular drinkers with AF [97].

1.2.11 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) defined by irreversible airflow obstruction is very common in patients with AF, with a prevalence estimated at nearly 25% [98]. COPD has been shown to be an independent predictor of AF, to promote AF progression from paroxysmal to sustained forms, to increase AF recurrence after electrical cardioversion, and to reduce the efficacy of catheter ablation [98]. Furthermore, previous studies have shown an association between lung function measured by forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) and incident AF [23, 99-102]. However, these studies were mostly based on old cohorts of patients initially recruited in the 1970s and 1980s, with old spirometry standards [103], implying that their findings might not be as accurate as those from contemporaneous studies. Hence, there is a need for new studies on the association between respiratory function and AF.

1.3 Risk prediction models for incident atrial fibrillation

It is estimated that 30% of patients living with AF are undiagnosed, these patients usually have asymptomatic AF [2]. Unfortunately, in up to 10% of these patients AF will be first manifest as a stroke [104, 105]. Ischemic stroke due to AF is associated with higher mortality and disability compared to stroke of other etiology [106, 107]. AF-related strokes can largely be prevented by oral anticoagulation [104]. Early identification and management of AF before complications occurs is therefore crucial.

It is still unclear what is the most appropriate strategy to identify patients with AF in the general population. Few strategies have been proposed for the identification of patients with AF, including opportunistic single-time-point screening (OppSTS), or systematic screening [105]. A major argument against population-level systematic screening is the low overall prevalence of AF in the general population. Indeed, a recent systematic review of

OppSTS reported a prevalence of undetected AF of 1.4% in adults aged ≥65 years old in the general population [108]. Accurate identification of individuals at higher risk of AF could help reducing the number of needed to screen through targeted screening. Several risk prediction models have been proposed to identify people at high risk of developing AF in the general population (**Table 1**).

1.3.1 The Framingham Heart Study risk score for AF (FHS-AF)

The Framingham Heart Study risk score for AF (FHS-AF) was designed on a Cox regression model to assess the 10-year risk of AF based on a model including clinical and electrocardiographic parameters. It identified 10% of study participants with incident AF after a 10-year follow-up [36]. The model was later recalibrated and subsequently externally validated for 5-year risk of incident AF [109]. Secondary analyses showed that the incorporation of echocardiographic parameters slightly improved the performance of the initial model [110]. The FHS-AF score is reasonably accurate for stratification of individuals into risk categories. It shows similar accuracy across both sexes, young adults and elderly. The score was developed in a white population. A secondary analysis demonstrated that the FHS-AF score could be reliably used in whites and African Americans [111].

1.3.2 The Atherosclerosis Risk in the Community (ARIC)

The Atherosclerosis Risk in Communities (ARIC) is a prospective biracial (whites and blacks) community-based cohort study. The study was used to develop a point-based risk score that incorporates commonly identified risk factors to estimate a 10-year risk of incident AF [112]. It showed a moderately good discrimination under the Cox regression model. Interestingly, the study found a higher incidence of AF in whites compared with blacks.

Nevertheless, a comparison between the ARIC risk score and the FHS-AF score showed that the ARIC risk score predicted AF by race in a similar manner, whereas the FHS-AF score performed better in whites than blacks [112].

1.3.3 The CHARGE-AF score

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF score was developed from a diverse population combined from 3 large cohorts in the United States, including the Cardiovascular Health Study, the FHS, and the ARIC study [113]. The score estimates a 5-year risk of AF based on a Cox regression model including various parameters readily available in clinical practice, with good discrimination [113]. The addition of electrocardiographic parameters was shown to improve the predictive ability. The score was externally validated, including in the Age, Gene and Environment-Reykjavik study and the Rotterdam Study, where it showed acceptable discrimination and adequate calibration [113].

1.3.4 The Malmö diet and cancer study (MDCS)

The Malmö Diet and Cancer Study (MDCS) is a prospective cohort study. The AF risk model from this study includes age, sex, hypertension, history of diabetes mellitus and related cardiovascular disease, laboratory biomarkers and individual habits [114]. The model had acceptable accuracy in predicting 5-year risk of AF. The addition of natriuretic peptides in the initial model improved its accuracy [110].

1.3.5 The HATCH score

Previous studies that were done to develop risk scores for AF, such as the FHS-AF and ARIC scores, have included mostly whites and black individuals, excluding several other

populations such as Asians [111, 112]. Hence, recent studies evaluated incident AF prediction in participants from Asian countries such as China, Korea, and Taiwan. The evaluation of the $CHADS_2$ score in a cohort of 702,502 Chinese individuals from Taiwan, aged more than 18 years, with no prior history of cardiac arrhythmias or valvular heart disease, showed that the $CHADS_2$ was good in predicting AF, with an incidence of 1.5 per 1,000 patients [115].

The HATCH score was developed as a score to predict the progression from paroxysmal to persistent AF in the Euro Heart Survey [116]. It was later evaluated as a predicting tool for incident AF in Asian individuals. Over 9 years of follow up, 1.4% of the 670,804 participants developed AF [117]. The HATCH score had a acceptable performance in risk estimation and stratification of Asian individuals [117]. Moreover, it proved to be useful for risk prediction in patients with different comorbidities, better than risk models like FHS-AF and ARIC risk scores [110].

1.3.6 The Suita study

The Suita study in Japan included 6,898 participants aged 30-79 years, without history of cardiac arrhythmia. A score was developed to evaluate a 10-year risk of incident AF. However, the score is somewhat complex, and it still needs an external validation in populations other than Japanese [118].

1.3.7 The C2HEST

The C_2HEST score was developed as a simple clinical tool, using parameters available in routine clinical practice, to estimate the risk of incident AF. In a study using data from 471,446 individuals from the Chinese Yunnan Insurance Database and 451,199 individuals from the Korean National Health Insurance Service, the C_2HEST score was found to be

superior to the $CHADS_2$ and CHA_2DS_2-VASc in predicting incident AF [119]. The utility of the C_2HEST score as a possible opportunistic screening tool for incident AF was also demonstrated in a healthy population from the National Danish Cohort study.[120]

1.4 Screening for atrial fibrillation

In many people AF remains asymptomatic until a thromboembolic event, mostly stroke, occurs [105]. Stroke is preventable through oral anticoagulation (OAC), it is crucial to identify AF as soon as possible to initiate primary prevention for stroke when indicated. Unrecognized AF can be detected incidentally, by opportunistic single-time-point screening (OppSTS), or by systematic screening of targeted populations [105]. Several new technologies have become available for the detection of AF in the general population or in targeted populations.

1.4.1 Devices for atrial fibrillation screening or monitoring

1.4.1.1 New technologies for screening

A range of new technologies have been developed to help improving the accuracy and rates of AF detection. One of the advantages of these technologies is their flexibility, allowing people to periodically self-test anywhere and capture their heart rhythm at any time or during symptoms. These technologies include photoplethysmography via smartwatch or watch (AppleWatch, applications compatible with wide range of smartphones such as FibriCheck), blood pressure monitor to detect AF [WatchBP Home A (Microlife), Omron M6 (Omron)], handheld device or smartphone compatible electrocardiogram (ECG) recorder [(Kardia (Alivecor), Zenicor ECG (Zenicor), MyDiagnostik (Applied Biomedical Systems BV)], Patch ECG monitors [Zio (iRhythm), Cardiostat (Icentia), Nuvant (Corventis)] [105, 121]. Some of

these technologies have been evaluated in large studies such as the AppleWatch study [122] or the Huawei Heart Study [123], showing that extended monitoring or more frequent screening is likely to result in increased rates of AF detection [105, 121]. However, their accuracy, benefits and potential harms, and cost-effectiveness still need to be determined [105, 121].

1.4.1.1.1 Implantable cardiac monitors

Implantable cardiac monitors (ICMs) are increasingly being used for prolonged monitoring in some group of patients such as those with recent embolic stroke of undetermined source (ESUS) or after rhythm control procedures such as catheter ablation [105, 121]. Pacemakers, implanted cardioverter defibrillators and cardiac resynchronization therapy devices, which have the ability to detect high-frequency atrial activity, can also be used for the detection of AF [105, 121]. In several studies, high-rate atrial episodes detected on these devices have been shown to be due to AF [2, 22, 124, 125]. Furthermore, these high-rate atrial episodes have been associated with almost doubling the risk of stroke[22, 124, 125]. However, it remains uncertain what duration and burden of episodes should be used to determine eligibility to OAC prophylaxis.

1.4.1.1.1.1 Description

Implantable cardiac monitors (ICMs), also known as implantable or insertable loop recorders are small devices that are implanted in the subcutaneous tissue of the anterior chest through a minimally invasive procedure. Most current models of ICM have a weigh of less than 5g, have a size of approximately 7mm in width, 45 mm in length, and 4 mm in thickness, and offer continuous monitoring with a life span up to 4.5 years [126-129]. Devices are inserted near the left 4th intercostal space corresponding to the V2-V3 ECG lead location, and an ECG tracing is measured between 2 electrodes at the ends [127]. Examples of available ICMs include the Reveal XT and Reveal LINQ models (Medtronic, Minneapolis, Minnesota), the

BioMonitor2 model (Biotronik, Berlin, Germany) and the SJM Confirm and Confirm Rx models (Abbott, Chicago, IL, USA).

Implantable cardiac monitors record and wirelessly transmit automatically detected arrhythmia episodes and manual patient-activated symptom episodes to a remote monitoring data server and notifies the clinician. They are used to detect occult cardiac arrhythmias in a variety of clinical situations including post-stroke monitoring, unexplained syncope, palpitations, and management of AF, for example for arrhythmia detection following catheter ablation.

1.4.1.1.1.2 Atrial fibrillation detection algorithms

Arrhythmia detection accuracy is the most important feature of ICMs. Below are the detection algorithms of few of the most used ICMs:

- The AF detection algorithm in the Reveal LINQ uses a three-step process. First, it considers the patterns of incoherence of R-R intervals in a Lorenz plot and attributes an AF score to specific arrhythmia events. Second, it looks for the presence of P waves and calculates a P wave evidence score, and then finally, an AF evidence score is computed [130]. The accuracy of the AF detection algorithm is dependent on the AF prevalence in the population, the programmed sensitivity of the algorithm, as well as the duration of detected AF episodes [131, 132].
- The TruRhythm Detection, the 5th-generation innovation in AF detection in Reveal™ ICMs, learns and adapts to the patient's rhythm over time, and applies an adaptive P wave evidence algorithm to further reduce false AF detection with minimal reduction in sensitivity [133].
- The AF detection algorithm in Confirm Rx detects irregularity in the R-R intervals [134]. For each beat, the algorithm considers at the previous 64 beats and obtains two

probabilities. The first uses a Markov Chain model to compare the similarity of R-R interval transitions in the previous 64 beats to both AF and non-AF templates. The second probability is based on the computed R-R variance to differentiate between random and patterned changes in R-R interval such as bigeminy. These two probabilities are combined into an AF probability score to determine whether an AF episode has begun. AF onset is declared if 1) the AF probability score exceeds a threshold, and 2) the onset of the rhythm is sudden. During an AF episode, the algorithm continues to monitor the 64-beat window and will consider the AF terminated when the Markov Chain model indicates a probability that the rhythm is no longer AF. The algorithm will detect AF episodes based on a programmed minimum episode length, with options of 30 seconds, 1, 2, 5, and 10 minutes [134].

- In SharpSense™ Technology, is an upgradable software enhancement introduced to the Confirm Rx ICM. A P wave detection algorithm is activated when the base algorithm triggers AF detection. The P wave detection algorithm analyzes the electrogram signal prior to the trigger and rejects the initial detection if consistent P waves are found [130].
- The RhythmCheck is the detection algorithm in the BIOMONITOR IIIm (Biotronik, Berlin, Germany). This AF detection algorithm is based on continuous checks of the R-R interval variability according to programmable parameters [135]. The RhythmCheck recognizes every single ectopic beat and avoids them being misinterpreted as AF, since 52% of false positive detections are due to ectopic beats. As a results, the algorithm reportedly eliminates 72% of false positive AF detections of patients with ectopic beats. Furthermore, the algorithm dynamically adjusts to each patients' unique rhythm [135].

1.4.1.1.1.3 Accuracy

Few studies have investigated the accuracy of ICMs. Most of them were of small sample size and funded by the owning companies. They showed good performance in detecting AF compared with Holter monitoring as the reference standard, with expert adjudication of events [134, 136]. The XPECT trial evaluated the performance of the REVEAL XT ICM compared with a Holter device. The sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with any AF were 96.1%, 85.4%, 79.3%, and 97.4%, respectively [136]. The DETECT AF study evaluated the performance of the Confirm DM2102 ICM to accurately detect and monitor AF (episodes of at least 2 minutes in length), with Holter as the reference [134]. Using a per patient analysis sensitivity was 100%, positive predictive value was 64.0%, specificity was 85.7%, and negative predictive value was 100%. Using a per episode analysis, sensitivity was 94.0% and positive predictive value was 64.0% [134]. Nevertheless, several recent studies have shown that the diagnostic yield of ICMs for AF detection remains suboptimal [130, 137, 138]. For instance, a recent randomized controlled trial comparing the efficiency of data transmissions and arrhythmia detection accuracy of the Reveal LINQ with TruRhythm Detection with the Confirm Rx with SharpSense Technology found that accuracy of arrhythmia detection in both ICMs was suboptimal [130]. Patient-averaged true positive detection rates were not statistically significant in the two groups (Reveal LINQ vs Confirm Rx, AF: 52% vs 38%). Compared to the Reveal LINQ, Confirm Rx has shorter event transmission time, more frequent event detections, shorter duration to diagnose true arrhythmic events, and higher percentage of diagnosed patients [130]. Another study reporting the real world diagnostic yield and accuracy of remote ILR monitoring in high risk patients with cryptogenic stroke found that at least 84% of AF alerts were false positive [137]. In another study using Reveal LINQ, the incidence of false positive transmissions was 46%, 86%, and 71% in patients implanted for AF surveillance,

cryptogenic stroke, and syncope, respectively [138]. Therefore, event adjudication by a specialist remains crucial. A new AF detection technology was recently released (Medtronic, Minneapolis, Minnesota), the AccuRhythm™ artificial intelligence algorithms [139]. These algorithms use deep learning based on over one million professionally adjudicated ECGs to improve AF detection accuracy. A 74% reduction in false AF alerts has been reported by the manufacturer [139]. However, independent studies reporting the diagnostic accuracy of AccuRhythm™ are still lacking.

1.4.1.1.1.4 Advantages and drawbacks

Implantable cardiac monitors have important advantages including device miniaturization, simplified implant procedures, safety, and enhanced automation and wireless data transmission to patient care networks and physicians. For the new devices, the implantation usually requires about 5 minutes including wound dressing [128]. The minimally invasive procedure is also associated with low rate of complications. The RIO (Reveal In-Office) and RIO 2 (Reveal LINQ In-Office 2) assessed the feasibility of ICM implants in a non-hospital setting (office) compared to in-hospital [140, 141]. They demonstrated excellent safety profile of the Reveal LINQ ICM insertion, irrespective of the insertion environment. In RIO 2, the untoward event rate (composite of unsuccessful insertion and ICM- or insertion-related complications) was 0.8% (2 of 244) in the office and 0.9% (2 of 227) in the hospital (95% confidence interval, -3.0% to 2.9%; 5% noninferiority: $p < 0.001$) [140]. This finding suggests that ICM insertion can be safely performed outside the electrophysiology lab, for instance in an outpatient setting.

Implantable cardiac monitoring has a substantial cost, for the device, the insertion procedure, and long-term monitoring. However, there are data suggesting that long-term monitoring with ICMs is cost-effective. One study evaluated the cost-effectiveness of ICM in a population with cryptogenic stroke in the United States [142]. They modelled lifetime costs

and quality-adjusted life years for three monitoring strategies post cryptogenic stroke: ICM starting immediately, ICM starting after Holter monitoring (delayed ICM) and standard of care involving intermittent ECG and Holter monitoring. They found that early ICM was found to be cost-effective versus standard of care and cost-saving versus delayed [142].

As shown above, AF detection algorithms are prone to a high number of false positive alters and misclassification from ectopic beats. False positive are mostly due to motion and myopotential artifacts [127]. For this reason, a cardiologist or a certified cardiac technician should adjudicate all possible AF tracings. The adjudication of many tracings for the increasing number of patients receiving ICM monitoring might overload clinicians.

1.4.1.1.2 External monitors

External monitors include Holter, event, and mobile cardiac telemetry monitors. These devices have short monitoring duration and the monitoring with them might not be continuous. Hence, their benefit may be limited in cases of rare events. In practice, they might be used as first option for short-term non-invasive monitoring before ICM is considered [2, 143].

1.4.2 Opportunistic single-time-point screening

In the clinical setting, AF can be detected incidentally or by OppSTS during in-person clinic visits made for reasons other than screening for AF [105]. In OppSTS, healthcare providers systematically screen for AF during routine consultations by pulse palpation, auscultation, or blood pressure checks in patients at increased risk for AF (eg, patients ≥65 years of age); if an irregular pulse is detected, a follow-up ECG is obtained to confirm AF [105]. Opportunistic single-time-point screening is recommended by several international taskforces based on its feasibility in selected clinical settings and its potential cost-effectiveness [105, 143-145].

1.4.3 Systematic screening

In systematic screening, a target population at high risk of AF (eg, patients ≥65 years of age or with heart failure, etc) undergoes screening for AF using single or intermittent testing or continuous recordings of variable duration [105]. In its 2022 report, the US Preventive Services Task Force concluded although screening can detect more cases of unknown AF, evidence regarding effects on health outcomes is limited [146]. The current evidence is still insufficient to recommend routine systematic electrocardiographic screening for AF [105, 121, 146]. The STROKESTOP was a multicentre, parallel group, unmasked, randomised controlled trial (RCT) that investigated the clinical outcomes in systematic screening for AF in an older population [147]. All 75-76-year-olds residing in Halland and Stockholm (Sweden) were randomly assigned (1:1) to be invited to screening for AF or to a control group. Participants attended local screening centres and those without a history of AF were asked to register intermittent ECGs for 14 days. Treatment with oral anticoagulants was offered if AF was detected or untreated. All participants were followed up for a minimum of 5 years. The primary endpoint was a combination of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death. Of those invited to screening, 7165 (51·3%) of 13 979 participated. After a median follow-up of 6·9 years (IQR 6·5-7·2), significantly fewer primary endpoint events occurred in the intervention group (4456 [31·9%] of 13 979; 5·45 events per 100 years [95% CI 5·52-5·61]) than in the control group (4616 [33·0%] of 13 996; 5·68 events per 100 years [5·52-5·85]; hazard ratio 0·96 [95% CI 0·92-1·00]; p=0·045). In this trial, screening for AF showed a small net benefit compared with standard of care, indicating that screening is safe and beneficial in older populations. However, there is a need for more RCTs to evaluate the benefits and harms of systematic AF screening. Systematic population-level screening in asymptomatic patients is

not recommended by current international taskforces due to high cost and a lack of evidence that it is more effective than usual care [105, 121].

1.4.4 Searching for atrial fibrillation post-stroke

Searching for AF following ischemic stroke is crucial as secondary prevention with OAC can be initiated in case of newly detected AF. Patients who do not have detectable AF during hospital admission by in-hospital telemetry, on repeated 12-lead ECG, or Holter ECG can undergo prolonged monitoring with external monitors for one month or implanted devices for a much longer period up to several years [2, 143]. The proportion of AF detected using prolonged monitoring increases with increasing duration of monitoring [2, 143]. However, brief episodes of AF detected after many months or even years of monitoring may not be the cause of the index stroke.

1.4.4.1 Major trials of post-stroke atrial fibrillation monitoring

Two landmarks randomized trials explored long-term monitoring versus shorter-term monitoring after cryptogenic stroke: CRYSTAL-AF and EMBRACE [148, 149]. Before CRYSTAL AF and EMBRACE, guidelines recommended at least 24 hours of ECG monitoring after an ischemic stroke to rule out AF. However, there was no data on the most effective duration and type of monitoring.

1.4.4.1.1 The EMBRACE trial

In EMBRACE, 572 patients aged ≥55 years, without known AF, who had had a cryptogenic ischemic stroke or TIA within the previous 6 months (cause undetermined after standard tests, including 24-hour electrocardiography [ECG]) were randomized to undergo additional non-invasive ambulatory ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hour monitor (control group) [149]. The primary

endpoint was newly detected AF lasting 30 seconds or longer within 90 days after randomization. Atrial fibrillation lasting 30 seconds or longer was detected in 45 of 280 patients (16.1%) in the intervention group and 9 of 277 (3.2%) in the control group (absolute difference, 12.9 percentage points; 95% CI, 8.0-17.6, p <0.001; number needed to screen, 8). Atrial fibrillation lasting 2.5 minutes or longer was present in 28 of 284 patients (9.9%) in the intervention group, as compared with 7 of 277 (2.5%) in the control group (absolute difference, 7.4 percentage points; 95% CI 3.4-11.3; p<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group than in the control group (52 of 280 patients [18.6%] vs. 31 of 279 [11.1%]; absolute difference, 7.5 percentage points; 95% CI 1.6-13.3, p = 0.01). The EMBRACE study demonstrated that compared with the standard practice of short-duration ECG monitoring, 30 days non-invasive ambulatory ECG monitoring substantially increased AF detection after a recent cryptogenic stroke or TIA, and was associated with increased uptake of anticoagulant treatment [149].

1.4.4.1.2 The CRYSTAL AF trial

The CRYSTAL AF study assessed whether long-term monitoring with an ICM was more effective than conventional follow-up (control) for detecting AF in patients with cryptogenic stroke [148]. A total of 441 patients aged ≥40 years without evidence of AF during at least 24 hours of ECG monitoring underwent randomization within 90 days after the index event. The primary end point was the time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months. By 6 months, AF had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients) (HR 6.4; 95% CI 1.9-21.7; p<0.001). By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients) (HR 7.3, 95% CI 2.6-20.8, p<0.001) [148]. The CRYSTAL AF study showed that ECG monitoring with

an ICM is superior to conventional follow-up for detecting AF in patients after cryptogenic stroke [148].

Following CRYSTAL AF, several studies have reported real-world data on prolonged continuous monitoring using ICM. They showed variable AF detection rates with ICM in patients with cryptogenic stroke depending on the length of monitoring or other potential factors such as the duration of qualifying AF episodes, or patient characteristics [137, 143, 150-161]. The highest yield of AF occurs when monitoring is performed very early after stroke, i.e., during the stroke admission or soon after discharge [162]. Monitoring such as inpatient telemetry or Holter-monitoring performed before ICM implantation is likely to impact AF detection rates. There might be a much higher AF incidence if extended inpatient ECG monitoring has not occurred [162].

In this thesis, we will explore AF detection rates according to different durations to define an episode of AF, and factors associated with AF detection in a large population of patients with stroke monitored with ICM in the United States. Furthermore, we will perform a systematic review and meta-analysis to summarize data on AF detection rates across different rhythm monitoring strategies (non-invasive and ICM) at precise time points (e.g. 1 month, 12 months or 24 months) in patients with cryptogenic strokes, and to explore factors influencing these detection rates.

1.4.4.1.2 The LOOP study

Although CRYSTAL AF and real-world cohort studies showed increased detection of AF with ICM compared with standard of care in patients with cryptogenic stroke, it remained unknown whether screening for AF, if AF is detected and subsequent treatment with anticoagulants can prevent stroke. The LOOP study investigated whether AF screening and use of anticoagulants can prevent stroke in individuals considered at high risk [163]. This

clinical trial, enrolled individuals aged 70-90 years, without AF, with at least one additional stroke risk factor (ie, hypertension, diabetes, previous stroke, or heart failure) who were randomly assigned in a 1:3 ratio to ICM monitoring or usual care (control). In the ICM group, anticoagulation was recommended if AF episodes lasted 6 min or longer. The primary outcome was time to first stroke or systemic arterial embolism. A total of 6004 individuals (mean age 74·7 (SD 4·1) years, 47.3% women, and 90·7% with hypertension) were randomized. During a median follow-up of 64.5 months, AF was diagnosed in 477 participants (31·8%) in the ICM group versus 550 participants (12·2%) in the control group (HR 3.17, 95% CI 2.81-3.59, p<0.0001). Oral anticoagulation was initiated in more participants in the ICM group (445 [29·7%] in the ICM group versus 591 in the control group [13·1%]; HR 2.72, 95% CI 2.41-3.08, p<0.0001). There was no difference in the primary outcome between both groups (67 [4.5%] in the ICM group versus 251 [5.6%] in the control group; HR 0.80, 95% CI 0.61-1.05, p=0.11). There was also no difference in major bleeding between groups (65 [4.3%] in the ICM group versus 156 [3.5%] in the control group; HR 1.26, 95% CI 0.95-1.69, p=0.11). In summary, although monitoring with ICM resulted in a three-fold increase in AF detection and OAC initiation in individuals with stroke risk factors, it did not lead to a significant reduction in incident thromboembolism [163]. These findings suggest that not all AF is worth screening for, and not all screen-detected AF should lead to OAC.

1.4.4.2 Recommendations on atrial fibrillation screening in stroke survivors

Apart from a baseline ECG, recommendations on the length and type of monitoring remain unclear. The 2016 European Society of Cardiology AF guidelines recommend AF monitoring for 72 hours in all patients with ischemic stroke without known AF (Class I recommendation), and additional ECG monitoring with either long-term non-invasive ECG monitors or implanted loop recorders (Class IIa recommendation) [164]. The 2019 American

Heart Association/American College of Cardiology/Heart Rhythm Society update of the 2014 guideline states that in patients with cryptogenic stroke in whom external ambulatory monitoring is inconclusive, ICM implantation is reasonable to optimize detection of silent AF (Class IIa recommendation) [165]. According to the Canadian Stroke Best Practice Recommendations, prolonged ECG monitoring for at least 14 days is recommended in selected patients aged ≥55 years with cryptogenic stroke or TIA of suspected cardioembolic source, who are not already receiving anticoagulant therapy but would be potential anticoagulant candidates (Level A Evidence) [166]. The Australian Heart Foundation and Cardiac Society of Australia and New Zealand 2018 guidelines recommend that, for patients with embolic stroke of undetermined source, longer-term ECG monitoring (external or implantable) should be used [145].

1.5 Complications of atrial fibrillation

1.5.1 Stroke

Atrial fibrillation is associated with increased risk of stroke and transient ischemic attack (TIA), and this risk increases with age [167]. In the Framingham Heart Study, the attributable risk of AF for stroke was 1.5% and 23.5% among people aged 50-59 years and 80-89 years, respectively [167]. The risk of stroke is also increased by asymptomatic AF detected as high-rate atrial episodes by implantable cardiac devices. High-rate atrial episodes longer than 6 minutes has been associated with an increased risk of ischemic stroke (HR, 2.50; 95% CI, 1.28–4.89) [22].

Atrial fibrillation-related strokes are associated with higher morbidity and mortality compared with strokes from non-AF causes. In the Copenhagen Stroke Study, patients with AF-related strokes had higher in-hospital mortality (OR 1.7; 95% CI: 1.2–2.5), longer

hospital stay (50 days verse 40 days, $p<0.001$), and lower rates of discharge home (versus care facility, OR 0.60; 95% CI: 0.44–0.85) [168]. Congruently, in the Framingham Heart Study, compared with non-AF strokes, AF-related strokes were associated with increased 30-day mortality (OR 1.84; 95% CI: 1.04–3.27) [169].

1.5.2 Extracranial systemic embolism

Extracranial systemic embolism is much less common than stroke in patients with AF [170]. In a pooled analysis of four AF antiplatelet and anticoagulation trials including 37,973 patients from more than 40 countries, during a mean follow-up of 2.4 years, 221 systemic embolic events occurred, representing 11.5% of total clinically apparent embolic events [171]. These systemic embolic events involved mostly the lower limbs (58%) and the mesenteric circulation (22%). Furthermore, systemic embolism was associated with increased morbidity and mortality, as 64% of affected patients required an interventional procedure or amputation and 24% died within 30 days [171].

1.5.3 Venous thromboembolism

Due to shared risk factors such as ageing, obesity, hypertension, heart failure, and smoking, AF and venous thromboembolism frequently co-exist [172]. Atrial fibrillation is strongly associated with an increased risk of venous thromboembolism (VTE) including pulmonary embolism, especially during the first months after AF diagnosis [173, 174]. Conversely, multiple arrhythmias including new-onset AF occur after an acute pulmonary embolism [172]. In a Swedish Nationwide Registry study, in males and females, VTE rates were higher among patients with AF the first 30 days after an AF diagnosis [40.2 vs. 5.7 in males and 55.7 vs. 6.6 in females per 1000 person-years at risk, respectively; HR 6.64, 95% CI: 5.74–7.69; and HR

7.56, 95% CI: 6.47–8.83)]; and then decreasing, simultaneously with an increasing number of patients with AF receiving OAC [175]. In an analysis of the national administrative database of Taiwan, AF was associated with an increased risk of VTE (HR 1.74; 95% CI: 1.36–2.24) and pulmonary embolism (HR 2.18; 95% CI: 1.51–3.15) [176].

1.5.4 Dementia

Atrial fibrillation is associated with a heightened risk of cognitive impairment, dementia, Alzheimer's disease, and vascular dementia, independently of common risk factors for dementia such as age, hypertension, diabetes, obesity, or stroke [170, 177]. In a recent systematic review and meta-analysis of 61 studies including 2.8 million individuals, AF was associated with 39% increased risk of cognitive impairment compared to the general population (HR 1.39, 95% CI: 1.25-1.53; follow-up 3.8-25 years). In the post-stroke cohort, AF was associated with a 2.7-fold increased risk of cognitive impairment [adjusted OR 2.70, 95% CI: 1.66-3.74; follow-up 0.25-3.78 years] [177]. Mechanisms of dementia in patients with AF include silent brain infarcts and cerebral hypoperfusion due to disturbed hemodynamic caused by AF [170, 177].

1.5.5 Heart failure

The relationship between AF and HF is bidirectional. Heart failure is both a risk factor and a complication of AF [2, 170]. AF and HF frequently co-exist, in part due to shared risk factors such as hypertension, diabetes, CAD, and valvular disease [2, 170]. In the Framingham Heart Study, 24% of participants had prior or concurrent AF and 17% subsequently developed AF [70]. One fifth of participants had AF and HF detected on the same day [70], demonstrating their interconnection. However, it seems that AF begets HF more than HF begets AF [170]. Indeed,

in the Framingham Heart Study, the incidence of HF was substantially higher in participants with AF than the incidence of AF in those with HF [178]. In terms of HF subtypes, in patients with AF in the Framingham Heart Study, the risk of incident HF with preserved ejection fraction (HR 2.34; 95% CI: 1.48–3.70) was higher than that of HF with reduced ejection fraction (HR 1.32; 95% CI: 0.83–2.10) [178].

Heart failure is associated with increased mortality in patients with AF [2, 70, 170]. In the Framingham Heart Study, among participants with AF, incident HF increased all-cause mortality (HR 1.25; 95% CI: 1.04–1.51) [178]. Indeed, HF has been reported to be the leading cause of mortality, accounting for about a third of death, in patients newly diagnosed with AF [179].

1.5.6 Coronary artery disease

There is also a bidirectional association between AF and CAD including myocardial infarction (MI) [2, 170]. As mentioned above, CAD is a risk factor for AF [2]. Atrial fibrillation is also a risk factor for MI [2, 170]. For instance, In the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, AF was associated with doubling of MI risk, with a greater risk in females (HR 2.16; 95% CI: 1.41–3.31) than males (HR 1.39; 95% CI: 0.91–2.10) [180]. The risk of mortality is increased by AF after an acute coronary syndrome [181]. Among patients with newly diagnosed AF, the risk of death after coronary ischemic events was increased in both females (HR 2.99; 95% CI: 2.53–3.53) and males (HR 2.33; 95% CI: 1.94–2.81) [181].

1.5.7 Death

Atrial fibrillation is associated with a substantial increased risk of death [2, 170]. In a systematic review and meta-analysis of 64 studies including over a million patients, with 14.8% of them having AF, AF increased the risk of death (pooled relative risk 1.6, 95% CI:1.39–1.53) [182]. In a subgroup analysis, the risk of cardiovascular mortality was also increased by AF (pooled relative risk 2.03, 95% CI: 1.79–2.3) [182]. A pooled analysis of the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study showed that AF was associated an increased risk of sudden cardiac death (HR 2.47; 95% CI: 1.95–3.13) [183].

1.6 Biomarkers in atrial fibrillation

Although the exact mechanisms underlying AF are not fully understood, significant advances have been made in elucidating its pathogenesis. The milieu leading to AF in each individual is often driven by risk factors that alter inflammation, oxidative stress, cardiomyocyte damage, atrial fibrosis and thrombogenesis, amongst others, while modulated by background risk of ageing and underlying genetic predisposition. Various molecules involved in these mechanisms have the potential to be robust markers of AF risk, progression and complications including thromboembolism and death (**Figure 1, Table 2**).

1.6.1 Inflammation

Many studies have suggested a pivotal role of inflammation in the development and perpetuation of AF. Inflammation is directly involved in several pathological processes underlying the atrial substrate for AF, including oxidative stress, myocyte injury and fibrosis. Inflammation seems to have prognostic implications in AF patients, as it has been linked to

mortality and adverse cerebrovascular and coronary events. The link between inflammation and AF is detailed in another paper of this issue.

1.6.1.1 C-reactive protein

C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to inflammatory cytokines. CRP has been shown to be associated with incident AF, the progression from paroxysmal to permanent AF.[184, 185] Moreover, CRP levels have been shown to be positively correlated with AF recurrence after catheter ablation or electrical cardioversion.[186] A systematic review and meta-analysis showed that an elevation between baseline and postoperative CRP levels is associated with the onset of AF following cardiac surgery.[187] In terms of adverse outcomes, CRP and highly sensitive CRP (hsCRP) have been associated with risk of stroke, myocardial infarction, bleeding and cardiovascular death in AF patients.[188, 189]

1.6.1.2 Interleukins

Interleukins (IL) are cytokines produced by various types of cells, mostly leucocytes, and that participate in the regulation of immune responses, inflammatory reactions, hematopoiesis and thrombogenesis. IL-6 is the most investigated interleukin in association with AF and outcomes. Elevated serum IL-6 levels were reported to be associated with an increased risk of AF, and with AF recurrence after catheter ablation or electrical cardioversion.[190] Elevated serum IL-6 were also shown to be predictors of thromboembolic events, major bleeding, and vascular death.[188, 189, 191]

1.6.2 Oxidative stress

Oxidative stress refers to the damage of cell components, including proteins, lipids and DNA, caused by excess reactive oxygen species. Oxidative stress results from an imbalance between oxidant production and endogenous antioxidant defences. It is involved in many diseases, including AF. Oxidative stress is one of the links between atrial fibrosis, as a result of cell damage, and AF, with an interplay of other mechanisms including inflammation and the renin-angiotensin system.[192] Numerous mechanistic pathways linking oxidative stress to AF have been identified. These include the XO pathway, NADPH Oxidase (through the NOX2, NOX4, Small G-protein Rac1), mitochondrial damage (via the Nuclear Factor-kappa B, LOX-1, ICAM-1, Heme Oxygenase-1) and calcium overload and disrupted myocytes electrical activity.[192]

In a cohort study with long follow-up (median 6.3 years) , redox potentials of glutathione (Eh GSH) and cysteine (Eh CySH) were associated with prevalent and incident AF.[193] Similarly, high asymmetric dimethylarginine (ADMA) levels were associated with an increased risk of AF recurrence within 1 month after electrical cardioversion,[194] while malondialdehyde (MDA) and nitrotyrosine predicted 1-year sinus rhythm maintenance following cardioversion.[195] Similarly, plasma derivatives of reactive oxygen metabolites (DROMs) and myeloperoxidase (MPO) have been shown to be an independent predictors of AF recurrence after catheter ablation.[196]

The prognostic value of oxidative stress on cardiovascular events and mortality in AF patients was well demonstrated in the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) biomarker sub-study.[197] Growth differentiation factor 15 (GDF-15), a marker of oxidative stress and inflammation was shown to be an independent predictor of major bleeding, death, and stroke. Specifically, compared to patients within the lowest quartile of GDF-15 levels, those in the highest quartile had a two-fold higher risk of

stroke or systemic embolism, a 3.5-fold higher risk of major bleeding, a 4- to 5-fold higher risk of all-cause and cardiac mortality. These associations between baseline GDF-15 level and adverse outcomes remained stable over time and significant after adjustment for clinical risk factors and the CHA_2DS_2-VASc score.[197]

1.6.3 Cardiomyocyte stress and injury

1.6.3.1 Troponin

Troponins (subunits I, T and C) are a group of proteins found in skeletal and heart (cardiac) muscle fibers that, together with tropomyosin, regulate the interaction between actin and myosin filaments leading to muscular contraction. Cardiac troponin is a sensitive and specific marker of myocardial damage and a powerful diagnostic and prognostic tool in acute coronary syndrome. Recent systematic review and meta-analysis found TnT but not TnI, to be associated with both incident AF and AF recurrences after radiofrequency ablation.[198] Further, high-sensitivity cardiac troponins T (hsTnT) and I (hsTnI) have been shown to predict incident AF and AF-related hospitalizations, although they did not improve risk stratification.[199, 200] Interesting, early positive cardiac troponins may help identify among patients with acute stroke those who have a cardioembolic source subtype that might benefit from oral anticoagulation.[201]

Pertaining to adverse events, the first major study to demonstrate the prognosis importance of troponin in AF patients was the Randomized Evaluation of Long -Term Anticoagulant Therapy (RE-LY) biomarker sub-study. The study performed in 6,189 patients with AF and ≥1 risk factor for stroke, and treated with either warfarin or dabigatran, showed that nearly half of the patients had detectable levels of TnI (≥0.01 μg/L).[202] Furthermore, persistent elevation (over 3 months) of TnI was associated with a higher risk of thromboembolic events and cardiovascular mortality, as compared to none or transient elevation.[202] In hospitalized patients with AF, others have shown that circulating TnI levels

were associated with mortality and major adverse cardiac events where cumulative 3-year survival rates were 78% in patients with non-detectable TnI, 62% in those with a minor elevation, and 57% in the those with a significant TnI elevation (log-rank $P < 0.001$).[203] A more recent retrospective cohort study of 957 patients with newly diagnosed AF reported increased mortality and readmission rates for heart failure and revascularization associated with elevated hsTnI.[204] Similar results were observed with TnT. In the ARISTOTLE biomarker study performed in 14,892 AF patients with increased stroke risk treated with either apixaban or warfarin, hsTnT level was independently associated with an increased risk of stroke, cardiac death, and major bleeding.[205] Consistent findings have been reported in a cohort of 930 AF patients who were effectively anticoagulated (INRs 2.0-3.0) for at least 6 months, whereby elevated hsTnT level was associated with increased rates of cardiovascular events and death.[191] A study using electronic health records from five tertiary centers in the UK also reported the association of increased troponin levels with increased mortality.[206]

1.6.3.2 B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a hormone secreted by cardiomyocytes in response to stretch in the setting of volume or pressure overload. It is synthesized as a precursor protein, pro-B-type natriuretic peptide, which is then cleaved into the bioactive BNP and the amino terminal N-terminal pro-B-type natriuretic peptide (NT-proBNP). Levels of BNP are increased in various cardiac conditions including left ventricular hypertrophy, cardiomyopathy, heart failure and acute coronary events. The Cardiovascular Health Study (CHS) was one of the first large community-based cohort studies to establish that NT-proBNP was predictive of incident AF in a community-based population of older adults independent of established risk factors.[207] An association between pre-operative BNP and postoperative AF in patients undergoing thoracic surgery has also been shown in a meta-analysis.[208] Furthermore, others have shown that BNP is elevated in AF patients, and that this

elevation normalizes after restoration of sinus rhythm, indicating a potential predictive role on AF recurrences after rhythm control intervention.[209, 210]

Biomarker sub-studies of two large randomized controlled trials provided firm evidence on the prognostic value of NT-proBNP in AF patients. In the RE-LY biomarker sub-study which analyzed data from 6,189 AF patients, in comparison with normal NT-proBNP levels, the highest quartile of NT-proBNP levels was associated with a two-fold and five-fold increased risk of stroke or systemic embolism and cardiovascular death respectively.[202] The ARISTOLE biomarker sub-study involving 14,892 AF patients confirmed the association between increased NT-proBNP levels and stroke or systemic embolism and cardiac death.[211] More recently, the US multicenter nationwide Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) showed among 13,375 AF patients that BNP levels were associated with the risk of AF progression and predicted a composite of major adverse cardiovascular or neurological events.[212]

1.6.4 Atrial fibrosis

Atrial fibrosis is a key structural abnormality in different substrates for AF involving different signaling pathways.[213, 214] The atrial structural remodeling includes apoptosis of cardiomyocytes, proliferation of fibroblasts, differentiation to myofibroblasts and increased production of extracellular matrix. All these pathological processes seem to be driven by an overlap of myocyte injury, oxidative stress and inflammation, amongst others.[213] Ultimately, the fibrotic myocardial tissue can result in conduction slowing and increased conduction heterogeneity that favor wavefront re-entry and perpetuation of AF. Studies on some biomarkers of atrial fibrosis have yielded promising results, highlighting their potential use in clinical practice to guide AF management.

1.6.4.1 Relaxin

Relaxin is a hormone that downregulates the deposition of collagen and other extracellular matrix proteins, reduces oxidative stress and inflammatory response. Therefore, it has anti-inflammatory and anti-fibrotic properties. Relaxin has been shown to reduce the susceptibility to AF in a murine hypertensive model by reversing atrial fibrosis, improving atrial conduction and increasing sodium ions current density in cardiomyocytes.[215] Interestingly, clinical studies have shown that relaxin level was higher in patients with AF than those in sinus rhythm and that higher circulating relaxin level was associated with higher AF recurrence after catheter ablation and higher occurrence of heart failure.[216, 217]

1.6.4.2 Galectin-3

Galectin-3 is an inflammatory β-galactoside-binding lectin secreted by activated macrophages that, when bound to the matrix, exerts matricellular functions. It has been shown to contribute to atrial fibrosis in AF patients and has emerged as a potential prognostic marker in AF. Indeed, galactin-3 levels were shown to independently correlate with the extent of left atrial fibrosis detected with magnetic resonance imaging and assessed from atrial appendage tissue samples.[218] There are evidence suggesting an association of galactin-3 levels with incident AF, higher AF burden, and AF recurrence following rhythm control therapies.[218, 219] Serum galectin-3 is also a potential marker of thrombogenicity in AF. Indeed, studies have shown that serum galectin-3 levels correlate with left atrial appendage remodelling and predict left atrial appendage thrombus formation in AF patients.[220, 221]

1.6.4.3 Fibroblast Growth Factor-23

Fibroblast growth factor-23 (FGF-23) is a bone-derived hormone that plays a central role in phosphate homeostasis, vitamin D metabolism and bone mineralization. Meta-analytical data suggests that higher FGF-23 levels is associated with increased risk of stroke, myocardial infarction, heart failure, cardiovascular and all-cause mortality.[13] Additionally, higher serum

FGF-23 levels was associated with incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA) study and the Cardiovascular Health Study (CHS).[222] However, in the Atherosclerosis Risk in Communities (ARIC) study, a larger community-based cohort, baseline FGF-23 levels were not associated with AF risk independently of renal function.[223] In the Chronic Renal Insufficiency Cohort (CRIC) study, FGF-23 was independently associated with prevalent and incident AF in patients with mild to severe chronic kidney disease.[224] These data suggest that serum FGF-23 may be a useful biomarker of AF in patients with renal dysfunction. Nevertheless, findings from recent mechanistic studies suggested both pro-fibrotic and pro-arrhythmic role of FGF-23,[225, 226] although there is limited data on the link between FGF-23 and AF outcomes following rhythm control intervention.[227, 228]

1.6.5 Thrombogenesis

1.6.5.1 D-dimer

D-dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. D-dimer is therefore a marker of fibrin turnover, and its elevated plasma levels suggest the presence of hypercoagulability or prothrombotic state. Recent meta-analysis data found high plasma D-dimer to be associated with left atrial spontaneous echo contrast and left atrial thrombus.[229] In the RE-LY sub-study, the risk of stroke or systemic embolism and of cardiovascular death was 3-fold and 3.5-fold higher in AF patients in the highest quartile of D-dimer levels compared to those in the lowest quartile.[230] Similarly, in the ARISTOTLE sub-study, higher baseline D-dimer levels were associated with an increased risk of stroke, bleeding and death.[231] Further, a recent study which enrolled 1,441 patients with AF-related stroke and atherosclerosis, showed that high

D-dimer levels (≥2 μg/mL) were significantly associated with higher risk of recurrent ischemic stroke [232].

1.6.5.2 von Willebrand factor

von Willebrand factor (vWF) is a blood glycoprotein synthesized by endothelial cells, that plays a pivotal role in hemostasis after vascular injury through platelet adhesion and aggregation. A recent meta-analysis of prospective cohort studies showed that high vWF levels were associated with increased risks of all-cause death (RR 1.56; 95% CI 1.16-2.11), cardiovascular death (RR 1.91; 95% CI 1.20-3.03), major adverse cardiac events (RR 1.83; 95% CI 1.28-2.62), stroke (RR 1.69; 95% CI 1.08-2.64) and bleeding (RR 2.01; 95% CI 1.65-2.45) in patients with AF.[233] This suggest that vWF may also be a clinically useful risk marker in AF.

1.6.6 Non-coding RNAs

Non-coding RNAs are functional ribonucleic acid (RNA) molecules that are transcribed from DNA but not translated into proteins. They are derived from non-coding genes which represent about 98% of the human genome and which were previously considered as "genetic junk" or "transcriptional noise" due to presumed non-involvement in cellular function. However, in recent years, non-coding RNAs have emerged as crucial regulators in cellular processes and key contributors in the pathogenesis of several disease states. Non-coding RNAs are mainly classified as either linear RNAs or circular RNAs. Linear RNAs can be sub-classified based on the length of transcripts (<200 nucleotides vs. ≥200 nucleotides) into microRNAs (miRNAs) or long non-coding RNAs (lncRNAs). miRNAs have been the most studied and have to date the strongest evidence on the pathogenic link between non-coding

RNAs and AF, although there are increasing data regarding lncNRAs.[234, 235] This section will focus on miRNAs.

Table 3 summarizes the data from human studies on key miRNAs involved in AF. Several miRNAs contribute to electrical remodeling in AF by affecting the conductance of L-type Ca2+ current (I_{CaL}) and of inward rectifier current (IK_1), as well as triggering changes in the electrical properties of Ca2+-activated K+ channels and connexin 40 & 43 . These include miR-1 which promotes cardiomyocyte arrhythmogenicity and proliferation; miR-499 which contributes to the remodeling of L-type Ca2+ currents and; miR-328 which plays a pivotal role in cardiomyocyte calcium handling and electrical remodeling.[234, 236, 237] Both miR-208 and miR-106 expression have been shown to have an impact on calcium handling in cardiomyocytes, through the downregulation of the sarcoplasmic reticulum Ca2+ adenosine triphosphates type 2a (SERCA2a) protein and the upregulation of RYR2 protein, respectively. These proteins are involved in Ca^{2+} transport between the cytosol and the sarcoplasmic reticulum.[236, 237]

miRNAs are also involved in atrial structural remodeling by regulating the genes that encode proteins forming the extracellular matrix. For instance, the upregulation of miR-21 promotes atrial remodeling and fibrosis by activating the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) and the PI3K signalling pathways. miR-29b upregulates the collagen-1A1, collagen-3A1 and fibrillin genes leading to increased production of the extracellular matrix proteins.[236, 237] Additionally, miR-126, miR-150, miR-483, miR-409 and miR432 are involved in various cellular processes including inflammation, oxidative stress, platelet function and aggression, angiogenesis and ultimately atrial fibrosis.[236] Few miRNAs have been shown to contribute to the occurrence and progression of AF via autonomic remodeling. For instance, miR-30 and miR-206 cause

autonomic nerve remodeling by downregulating acetylcholine-dependent potassium current, and enhancing the production of reactive oxygen species, respectively.[236, 237]

The involvement of these miRNAs in the pathogenesis of AF underpins their potential as biomarkers to predict the occurrence or recurrence of AF. For instance, miR-1 and miR-483 were suggested to potentially predict post-operative AF, while miR-125 may play a role in post-ablation AF recurrence.[236] Some microRNAs could be therapeutic targets for the treatment of atrial cardiomyopathy and AF. However, because a single non-coding RNA can be involved in the regulation of a large number of genes, the specificity and safety of therapeutic targeting of non-coding RNAs can be problematic while further research is warranted.[237]

1.6.7 Clinical implications

AF accounts for up to a third of ischemic strokes and biomarkers that can improve detection of AF in high-risk individuals or those with embolic stroke of unknown source will be of clinical significance in both primary and secondary stroke prevention. For example, such biomarkers may guide patient selection for more prolonged ECG monitoring or implantation of insertable cardiac monitor to maximize cost-effectiveness especially in the context of limited resources.[143] Natriuretic peptides, BNP and NT-proBNP, are the most promising biomarkers to improve the prediction of AF detection after ischemic stroke. It has been suggested that BNP values of >100 pg/mL and NT-proBNP values >400 pg/mL have a predictive value for the occurrence of AF in stroke patients.[238] A sub-analysis of the Find-$AF_{RANDOMISED}$ trial showed that BNP measured early after ischemic stroke identified a subgroup of patients with stroke at increased risk for AF, in whom enhanced and prolonged Holter-ECG is very useful with significantly reduced number needed to screen.[239] A BNP-

based prediction model is being investigated for post-thoracic surgery AF and this may improve management and reduce complications in this patient group.[240]

Natriuretic peptides have also shown a potential benefit in improving community screening of AF. The CHARGE-AF Consortium of community-based cohort studies reported that adding BNP to the CHARGE-AF risk score which is purely based on clinical factors, substantially improved its predictive performance.[241] In the STROKESTOP II study, NT-proBNP-stratified systematic screening for AF increased the detection of AF in high risk elderly from the community (from 8.1% to 10.5%), with 94.5% of the participants with newly diagnosed AF who accepted the initiation of oral anticoagulation.[242] A recent study using data-driven discovery through logistic regression and machine learning identified BNP and FGF-23, along with three clinical risk factors (age, sex and body mass index), as robustly associated with AF.[243] These biomarkers could therefore be used to risk stratify patients and select those who are more likely to develop AF for more targeted electrocardiographic screening.

The incremental value of cardiac troponins and NT-proBNP in predicting adverse events in patients with AF was convincingly demonstrated in the ARISTOTLE and RE-LY biomarker sub-studies. Indeed, the addition of NT-proBNP, TnI (RE-LY)/TnT (ARISTOTLE) or both to the CHA_2DS_2-VASc score significantly improved its performance in predicting thromboembolic events and major bleeding in AF patients.[202, 205] These findings underpinned the development of the first hybrid score, the ABC (Age, Biomarkers [high-sensitivity troponin and N-terminal fragment B-type natriuretic peptide], and Clinical history of prior stroke/transient ischemic attack)-stroke risk score.[244] The ABC-stroke risk score has been externally validated in independent cohorts (**Table 4**). Similar scores for the prediction of major bleeding, the ABC (Age, Biomarkers [growth differentiation factor-15, hsTnT, and haemoglobin], and clinical history [previous bleeding])-bleeding risk score,[245] and of death,

the ABC (Age, Biomarkers [growth differentiation factor-15, hsTnT, NT-proBNP], Clinical history of heart failure)-death risk score,[246] have been developed and validated (**Table 4**). Specifically, the ABC-stroke score and the ABC-bleeding score were shown to outperform the CHA_2DS_2-VASc and HAS-BLED scores, respectively.[244, 245, 247-249] However, one real-world study showed better performance of the HAS-BLED score[250], and network meta-analysis revealed that although the ABC-bleeding score has a high sensitivity, the HAS-BLED is a more balanced bleeding risk assessment tool with higher specificity.[251]

1.7 Risk stratification in patients with atrial fibrillation

1.7.1 Stroke risk assessment

Several clinical stroke risk scores have been developed over time to guide pharmacological and interventional stroke prevention strategies in AF patients (**Table 5**). The most popular include the $CHADS_2$ score, the CHA_2DS_2-VASc score and the ATRIA stroke risk score, released in 2001, 2010 and 2013, respectively [252-254]. The number of risk factors included in these scores varies considerably, from four in the ABC-Stroke score to eight in the GARFIELD-AF and ATRIA-Stroke scores, with all stroke risk scores including age and previous stroke or transient ischaemic attack (TIA) and/or thromboembolism [244, 252-254]. More recently, the GARFIELD-AF risk calculator was released. It is a computer-based risk calculator that simultaneously provides risk estimates for mortality, ischemic stroke or systemic embolism and major bleeding for up to 24 months [255]. Table 2 summarizes the characteristics of the most used stroke risk stratification scores. The CHA_2DS_2-VASc score remains the most commonly used risk stratification tool for AF patients [256].

These current stroke risk stratification tools have modest performance in predicting stroke and systemic embolic events in real-world cohorts. Hence, there is a need for new risk

predictor tools incorporating both clinical factors and non-clinical factors such as left atrial imaging features, electrocardiographic markers, and biomarkers.

1.7.2 Bleeding risk assessment

Several scores have been validated for the assessment of bleeding risk in patients with AF, the most recent and popular ones being HAS-BLED [257], ATRIA-bleeding score [258], ABC-bleeding risk score [245], and ORBIT [259] (**Table 6**). The HAS-BLED is the most commonly recommended score by international guidelines [256]. The bleeding risk on OAC is assessed to identify patients at high risk of bleeding, who may require more intensive follow-up and those with modifiable bleeding risk factors which can be addressed to remove or reduce the risk to the patient (controlling blood pressure, cessation of non-essential antiplatelet therapy or non-steroidal anti-inflammatory drugs, improving international normalized ratio (INR) control if patient is receiving a vitamin K antagonist, and reduction/cessation of alcohol intake) [256]. Assessing bleeding risk on OAC therapy allows to discuss with the patient about the benefit/risk of the therapy, ways of reducing the risk of bleeding, and symptoms of bleeding and adequate management [256]. The use of validated bleeding risk scores to assess bleeding risk in AF patients is better than an assessment using modifiable bleeding risk factors alone. Indeed, a prospective cluster-randomized trial showed that appropriate use of the HAS-BLED score as part of structured care, based on the ABC pathway, to address and mitigate modifiable bleeding risk factors, was associated with lower bleeding rates and an increase in OAC use when compared with usual care [260].

1.8 Management of atrial fibrillation

There are four pillars in the management of AF: stroke prevention mainly with OAC, rate control, rhythm control, and risk factor management.

1.8.1 Stroke prevention

Stroke is the most common and devastating complication of AF. People with AF have a five-fold increased risk of stroke [167], and AF-related cardioembolism accounts for up to a third of all ischemic strokes [143]. The main strategies for stroke prevention include OAC with either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), and percutaneous left atrial appendage occlusion [261].

Oral Anticoagulation can reduce stroke rate by up to two-third [262], with DOACs slightly more effective and much safer pertaining to the bleeding risk, than the VKA warfarin [263]. The decision to start OAC in patients with AF is guided by risk stratification schemes that help balancing the benefit of OAC for preventing stroke against the risk of bleeding. Several clinical stroke risk scores have been developed over time including the $CHADS_2$ score, the CHA_2DS_2-VASc score, the ATRIA stroke risk score and recently, the GARFIELD-AF risk calculator [252, 255, 264, 265]. The CHA_2DS_2-VASc score is best at identifying low-risk patients and is at least as good as the $CHADS_2$ score in identifying high-risk patients [261]. Several guidelines, mainly from the American Heart Association/American College of Cardiology and Heart Rhythm Society, consider that a patient is eligible for OAC when the CHA_2DS_2-VASc score is ≥ 2 for males and ≥ 3 for females [266]. However, other guidelines, including from the Japanese Circulation Society, the Canadian Cardiovascular Society, and the National Heart Foundation of Australia Consensus Statement, do not apply a sex-specific cut-off, and consider eligible for OAC all patients with a CHA_2DS_2-VASc score of ≥ 1 [267-269].

1.8.1.1 Vitamin K antagonists

The target therapeutic range on adjusted-dose VKAs is an INR of 2.0–3.0 [2, 144, 266]. However, VKAs have important limitations, including significant inter- and intra-patient variability in international normalized ratio (INR) which can be influenced by factors such as illness, genetics, consumption of alcohol or vitamin K-rich food, and drug interactions. This imposes the requirement for regular monitoring. The measure of good-quality anticoagulation control with VKAs is the time in therapeutic range (TTR) [2]. A high TTR is associated with maximum efficacy and safety [2].

1.8.1.2 Direct oral anticoagulants

Direct oral anticoagulants are a new class of non-vitamin K antagonist oral anticoagulants that includes apixaban, dabigatran, edoxaban, and rivaroxaban. Supported by international guidelines [266-269], DOACs are becoming the main therapeutic option for stroke prevention in patients with AF. Compared with VKAs, DOACs have attractive characteristics including no need for regular laboratory monitoring, easier dosing, and less frequent drug–drug or drug-food interactions [270]. Pivotal trials have demonstrated the non-inferiority and better safety profile of DOACs for stroke prevention when compared with VKAs [271]. This has been corroborated by real-world data from large-scale registries [272].

1.8.2 Rate control

Rate control therapy aims to reduce symptoms, improve quality of life, lessen the development of heart failure and prevent thromboembolic complications. Rate-controlling drugs include β-blockers, non-dihydropyridine calcium antagonists, digoxin and (rarely used) amiodarone [2]. It is uncertain which rate control drug or combination is the most effective. Based on the available data, digoxin seems to be the least effective, and β-blockers or rate-

limiting calcium channel blockers seem to be the most affective [2]. The choice of these drugs alone or in combination for rate control is guided by age, lifestyle, symptoms, comorbidities, heart rate, and potential adverse effects [2].

1.8.3 Rhythm control

A rhythm-control strategy uses antiarrhythmic drug therapy, electrical cardioversion, catheter ablation of the left atrium, and/or an ablation procedure performed at the time of open-heart surgery to maintain sinus rhythm. Many patients who remain in sinus rhythm require long-term rate-slowing drugs (in the event of return to atrial fibrillation).

1.8.3.1 Pharmacological and electrical cardioversion

Antiarrhythmic drugs (AADs) are the most common therapeutic approach for the restoration of sinus rhythm and/or the prevention of AF recurrence. Antiarrhythmic drugs can be categorized into classes depending on their predominant mode of action. Class I agents are Na+ channel blockers and include flecainide and propafenone; class II agents are β-blockers; class III agents are multichannel blockers, such as amiodarone; and class IV agents are calcium channel blockers [2].

Most of AF episodes spontaneously reverse to sinus rhythm. Pharmacological or electrical cardioversion (ECV) should be considered in patients with persistent AF, especially for those who have new-onset AF or remain symptomatic after rate control and adequate anticoagulation therapy [2]. Pharmacological cardioversion using AADs is usually the first option in order to avoid potential risk of ECV, reduce the risk of AF recurrence after successful cardioversion, and it has a lower cost than ECV [2]. Long-term AADs can be used to prevent the recurrence of AF in patients with paroxysmal AF and to maintain sinus rhythm

after successful cardioversion or relapse after non-pharmacological therapies (catheter or surgical ablation) [2].

Although patients with recent-onset AF commonly undergo immediate restoration of sinus rhythm by pharmacologic cardioversion or ECV, until recently, it was unclear whether immediate restoration of sinus rhythm is necessary, since AF often terminates spontaneously. The RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7–Acute Cardioversion versus Wait and See) showed that in patients presenting to the emergency department with recent-onset (<36 hours), symptomatic atrial fibrillation, a wait-and-see approach (delayed cardioversion) was noninferior to early cardioversion in achieving a return to sinus rhythm at 4 weeks [273].

1.8.3.2 Catheter and surgical ablation

Ablation of AF has become an alternative to AADs for rhythm control in patients with AF. Catheter ablation is indicated in patients with paroxysmal, persistent or long-standing persistent AF that is refractory or intolerant to AADs, and in some patients with symptomatic paroxysmal AF [2, 144]. The goal of ablation procedure is to make tissular lesions that prevent AF by eliminating the triggers that initiate it or modifying the substrate that maintains it.

Catheter ablation of AF is mainly performed in the left atrium, which is accessed from the right atrium by trans-septal puncture. Ablation is achieved through the application of radiofrequency energy. Radiofrequency ablation causes myocardial necrosis through tissue heating by delivering a low voltage alternating electrical current from the tip of the ablation catheter. Cryoablation or laser ablation are used as alternative ablation techniques applied through balloon-tipped catheters that are inflated at the opening of the pulmonary veins and ultimately, electrically isolate the pulmonary veins from the left atrium by circumferential lesions [2].

The effectiveness of catheter ablation of AF varies widely, depending on several factors including the type of AF, comorbidities, the experience of the operator, and the duration and intensity of follow up [2]. Ablation success rates for a single procedure are higher in patients with paroxysmal AF and a relatively normal heart (60–75%) than in those with persistent and long-standing persistent AF (45–60%) [2].

Catheter ablation also carries a risk, with an overall incidence of major complications of 4.5% [274]. Such complications include cardio-embolism, myocardial perforation with subsequent cardiac tamponade, pulmonary vein stenosis, phrenic nerve and vagal plexus injury, gastroesophageal hypomobility or atrio-oesophageal fistula [2]. Strategies to prevent these complications include periprocedural anticoagulation, intracardiac echocardiography, titration of power and contact force during ablation, and monitoring the oesophageal temperature [2].

Surgical ablation is an alternative to catheter ablation. It is usually performed in patients undergoing cardiac surgery [2]. The mainstay of surgical ablation is the Maze procedure, which is a form of substrate modification that involves producing a bi-atrial set of transmural linear lesions in order to interrupt all possible re-entrant circuits [2]. Surgical ablation has evolved over time. It now uses modern techniques such as radiofrequency or cryoablation to create lesions, and can be performed through minimally invasive approaches [2].

1.8.4 Rate versus rhythm control strategies

Several randomized clinical trials have compared rate and rhythm control strategies in patients with AF [275-281]. Most of the older studies showed similar outcomes in terms of death and thromboembolism. However, in one trial quality of life was improved by rhythm control

[280]. The most recent trial, the EAST-AFNET 4 trial, which included patients with early AF (diagnosed within a year of enrolment) demonstrated a reduced risk of cardiovascular adverse outcomes, including death, when catheter ablation was allowed in the rhythm control arm, compared with the rate control strategy [281].

1.8.4.1 AFFIRM AND RACE trials

These are the first major randomized controlled trials comparing rhythm control to rate control for the management of patients with AF.

1.8.4.1.1 The AFFIRM trial

In this trial, 4060 patients aged at least 65 years (mean [SD] age, 69.7[9.0] years) with recurrent AF, a high risk of stroke or death, and no contraindications to antiarrhythmic or anticoagulation therapy were randomly assigned to a rate control strategy (using digoxin, beta blocker, and/or calcium channel blocker) and anticoagulation with warfarin or to rhythm control with the most effective AAD, with the use of warfarin left up to the discretion of the investigator [275]. All patients initially received OAC, but those in the rhythm control arm who maintained sinus rhythm could be withdrawn from warfarin. The primary endpoint was all-cause mortality.

After a mean follow-up of 3.5 years, there were 356 deaths among the patients assigned to rhythm control therapy and 310 deaths among those assigned to rate control therapy (mortality at five years, 23.8% and 21.3%, respectively; HR 1.15, 95% CI: 0.99-1.34, p=0.08). There was no significant difference in the composite secondary end point of death, ischemic stroke, anoxic encephalopathy, major bleeding, or cardiac arrest. More patients in the rhythm control group than in the rate control group were hospitalized, and there were more adverse drug effects in the rhythm control group as well [275]. Two prespecified subgroups had a significant reduction in mortality with rate control: those aged ≥65 years and those without a history of congestive heart failure, coronary artery disease, or abnormal

LVEF [282]. A subsequent analysis of the AFFIRM trial suggested that the trend toward increased mortality with rhythm control was probably due to the adverse effects of AADs [283].

In conclusion, in the AFFIRM trial AADs were not associated with improved survival, suggesting that any beneficial antiarrhythmic effects of AADs were offset by their deleterious effects. An effective method for maintaining sinus rhythm with fewer adverse effects could have been beneficial [275, 282, 283].

1.8.4.1.2 The RACE trial

The RACE trial recruited 522 patients (mean age 68 years) with recurrent persistent AF or atrial flutter (defined as non–self-terminating arrhythmia requiring electrical cardioversion to obtain sinus rhythm) of less than one year in duration, without contraindication to OAC [276]. Patients were randomly assigned to rate control or rhythm control. Patients in the rate-control group received oral anticoagulant drugs and rate-slowing medication. Patients in the rhythm-control group underwent serial cardioversions and received antiarrhythmic drugs and oral anticoagulant drugs. The end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs [276].

After a mean 2.3-year follow-up, 39% percent of the 266 patients in the rhythm-control group had sinus rhythm, as compared with 10% of the 256 patients in the rate-control group. The primary endpoint occurred in 44 patients (17.2%) in the rate-control group and in 60 (22.6%) in the rhythm control group, representing an almost significant trend toward a lower incidence of the primary endpoint with rate control (HR 0.73, 90% CI: 0.53-1.01). There was no difference in cardiovascular mortality (6.8% versus 7%). However, there was a trend toward a higher incidence of nonfatal endpoints in the rhythm control arm, including heart failure, thromboembolism, pacemaker insertion, and adverse drug reactions[276]. A sub-

study of RACE showed that quality of life was comparable between the rate control and rhythm control groups [284].

1.8.4.1.3 Limitations of the AFFIRM and RACE trials

The AFFIRM and RACE trials have a couple of issues that limit their applicability. First, participants in these trials were relatively old (mean age 70 years in AFFIRM and 68 years in RACE) [275, 276]. Hence, whether younger and healthier patients might benefit from more aggressive rhythm control was unclear. Second, symptom burden was relatively low among participants in AFFIRM, with nearly half of them who had symptomatic episodes of AF less than once per month in average [285]. Such patients are unlikely to have substantial benefit from rhythm control. Furthermore, the results of the AFFIRM might have limited applicability in patients with higher symptom burden [286]. Third, in both trials OAC could be stopped four weeks after documentation of sinus rhythm. This led to a higher rate of stroke. It has been postulated that continued OAC might have led to a lower mortality in the rhythm control group [26]. Fourth, these trials were conducted before the catheter ablation era. Hence, these trials could not provide information on the potential benefit of catheter ablation as an option for rhythm control.

1.8.4.2 The EAST-AFNET 4 trial

Unlike the AFFIRM and RACE trials [275, 276], the EAST-AFNET 4 trial included catheter ablation in the rhythm control arm and included patients with AF of much shorter duration from first presentation [281]. The EAST-AFNET 4 was an international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial that randomly assigned 2789 patients who had early AF (diagnosed ≤1 year before enrolment; median time since diagnosis, 36 days) and cardiovascular conditions to receive either early rhythm control (with antiarrhythmic drugs or catheter ablation) or usual care [281].

The trial was stopped prematurely for efficacy at the third interim analysis after a median of 5.1 years of follow-up per patient. A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (HR 0.79, 95% CI: 0.66-0.94, p=0.005). Death from cardiovascular causes occurred less often in the rhythm control group (67 [1.0%] versus 94 [1.3%] events, respectively; HR 0.72, 95% CI: 0.52-0.98). Stroke occurred less often in the rhythm-control group (40 [0.6%] versus 62 [0.9] events, respectively; 0.6 versus 0.9 percent, HR 0.65, 95% CI: 0.44-0.97). The mean (±SD) number of nights spent in the hospital did not differ significantly between the groups (5.8±21.9 and 5.1±15.5 days per year, respectively; p=0.23). There was no significant difference between the two arms in the rate of the primary safety outcome (death, stroke, and serious adverse event related to the rhythm-control strategy). Serious adverse events related to rhythm control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care [281].

1.8.4.3 Choice of therapy

The choice between rhythm control and rate control should be thoroughly discussed with the patients, notably the benefits and risks of each strategy [287].

A rate control strategy should be preferred in [287]:

- Asymptomatic patients with AF, particularly long-standing, recurrent AF. This is mostly based on the findings of the AFFIRM and RACE trials that showed similar or even a trend towards improved outcomes with rate control compared with rhythm control in patients with persistent AF [275, 276]. Furthermore, AADs were associated with a high burden of side effects [283].
- Elderly because they are often asymptomatic, with more commonly present with permanent AF, and they are more sensitive to the proarrhythmic effects of AADs.

A rhythm control strategy should be preferred in [287]:

- Patients with high cardiovascular risk. This is mostly based on the findings of the EAST-AFNET 4 trial that showed a lower risk of adverse cardiovascular outcomes than usual care among patients with early AF (diagnosed within one year);
- Patients who failed rate control (persistent symptoms or inability to reach an appropriate heart rate);
- Patients with heart failure;
- Patients aged <65 years, or those who have daily activities requiring optimal cardiac performance.

1.8.5 Risk factor modification

Obesity, physical inactivity, obstructive sleep apnea, diabetes mellitus, hypertension, dyslipidemia, alcohol abuse, and smoking are risk factors for the development and progression of AF [55]. Most of these AF drivers can potentially be reversed or controlled, and compelling evidence supports that addressing these modifiable risks contribute to primary and secondary AF prevention [55, 144, 288]. Indeed, patients with AF who comprehensively managed their risk factors demonstrate greater reduction in symptoms, AF burden, more successful ablations and improved outcomes with greater AF freedom [289-291]. The management of AF has long focused on OAC, rhythm control, and ventricular rate control [55]. Risk factor management is now integrated in major clinical guidelines as an additional pillar of AF management [55, 144, 288], and one of the domains covered by quality indicators for the care and outcomes of adults with AF [292].

1.8.5.1 Impact of risk factor modification on symptoms

Cardiometabolic risk factor modification and weight loss in overweight or obese patients with AF were shown to result in a substantial reduction in patient symptoms and AF burden determined by ambulatory monitoring in a randomized controlled trial [289]. The intervention group who received risk factor modification and weight loss had marked improvements in in patient well-being, blood pressure, glycaemic control and cholesterol [289].

1.8.5.2 Impact of risk factor modification on catheter ablation outcomes

The Aggressive Risk Factor Reduction Study for Atrial Fibrillation (ARREST-AF) cohort study demonstrated the benefits of risk factor modification (RFM) on the outcomes of AF ablation [290]. The study showed an improvement in AF frequency, symptoms, and duration in the group who underwent RFM compared with the controls. Furthermore, there were more favourable ablation outcomes with 62% AF freedom in the RFM group compared with 26% in the control group following single procedure. This was replicated in multiple procedural outcomes with 87% in the RFM group and 48% in the control group free from AF at final follow-up.

1.8.5.3 Long-term outcomes of risk factor modification

The LEGACY (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up) study provided evidence of the long-term benefits of aggressive risk factor modification and weight loss in overweight and obese individuals with symptomatic AF [291]. Achieving and maintaining weight loss was facilitated by a dedicated physician-led clinic that was focused on the management of weight and risk factors. The study demonstrated that progressive weight loss has a dose-dependent effect on long-term freedom from AF. In the group who achieved a ≥10% loss of their initial body mass, 46% of them remained free from AF without the use of rhythm control strategies over 5-year follow-up. Furthermore, weight fluctuation of >5% had an adverse effect on overall

freedom from AF, with a 2-fold greater likelihood of recurrent arrhythmia. Weight loss was also associated with beneficial structural remodelling, including substantial decrease in left atrial volumes and left ventricular hypertrophy [291].

1.8.5.4 Impact of risk factor modification on AF progression

Higher AF burden is associated with increased morbidity and mortality. Compared with paroxysmal AF, persistent AF is associated with lower success rates for rhythm control strategies. Delaying the natural progression of AF from paroxysmal to more persistent forms is crucial for improving AF outcomes. This has been demonstrated by the REVERSE-AF (The PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation) study which showed that in overweight and obese individuals with symptomatic AF, sustained obesity is associated with progression of the AF disease whereas significant weight loss (≥10%) is associated with less progression from paroxysmal to persistent AF and with increased reversal from persistent to paroxysmal AF or no AF [293]. This improvement in AF burden may be due to reversed structural remodelling of the LA with weight loss. Reversal of atrial remodelling and improved outcomes of AF catheter ablation were also observed in patients with OSA treated with continuous positive airway pressure (CPAP) [294].

1.8.5.5 Benefits of improvement in cardiorespiratory fitness

Few studies have provided evidence on the impact of exercise and cardiorespiratory fitness in the management of AF. The CARDIO-FIT (Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation) study evaluated the role of cardiorespiratory fitness and the incremental benefit of cardiorespiratory fitness improvement on rhythm control in obese individuals with AF. It showed that participation in a dedicated risk factor management clinic was associated with increased cardiorespiratory fitness gain. In overweight and obese individuals with symptomatic AF, preserved baseline

cardiorespiratory fitness predicts long-term freedom from AF. There was a significant dose-response relationship between baseline cardiorespiratory fitness with a 20% reduction in the risk of AF recurrence for each metabolic equivalent (MET) increase in baseline cardiorespiratory fitness. Furthermore, cardiorespiratory fitness gain with a structured exercise program has an additive effect to weight loss in improving the long-term outcome of AF. METs gain in cardiorespiratory fitness ≥2 on top of weight loss was associated with 2-fold increased chance of freedom from AF. Another randomised clinical trial demonstrated that aerobic interval training reduces AF symptoms, AF burden, hospital admissions, and cardioversions resulting in improved quality of life. These studies stress the importance of exercise in the management of AF, particularly as a strategy for rhythm control and AF symptoms improvement.

1.8.5.6 Cost-effectiveness of risk factor modification

One study addressed the cost-effectiveness of risk factor modification through face-to-face counselling in a dedicated clinic. The CENT (Cost-Effectiveness and Clinical Effectiveness of the Risk Factor Management Clinic in Atrial Fibrillation) study showed that lifestyle and risk factor modification in a dedicated clinic reduces the need for emergency department attendances, unscheduled specialist appointments, hospitalisations, cardioversions, ablation procedures and additional medications, leading to significant health economic benefits.

1.8.5.7 Implementation of a risk factor modification program

Lifestyle and risk factor modification can be implemented in different ways. When patients are managed in a dedicated risk factor clinic, the results are substantial [188, 295]. Patients with AF should be ideally managed in an AF management clinic with a focus on arrhythmia management covering OAC, rate and rhythm control, and a risk factor management clinic focused on risk factors, with a close collaboration between both clinics [188]. A lifestyle and risk factor modification programme should be implemented through a process [188]:

- Initial RFM clinic visit: this should build a good relationship between the caregivers and the patient, assess patient behaviour and motivation, discuss each individual risk factor, and advise to maintain a lifestyle journal.
- Second RFM clinic visit: on this occasion, patient lifestyle journal should be reviewed, and achievable targets set; patient behaviour and motivation should be reassessed, and regular appointments should be established to monitor progress.
- Subsequent RFM clinic visit: the lifestyle journal should be reviewed; medication adherence should be assessed; an evaluation of the progress should be performed to determine barriers and set new goals.
- AF management clinic visit: if symptomatic AF persists, AF ablation and/or AAD as per AF guidelines; if there is no symptomatic AF, consider AAD if required as per AF guidelines.
- Ongoing RFM and AF management: both RFM and AF management teams should continue treating risk factors and help maintaining lifestyle changes and sinus rhythm as much as possible. Clinic visits should be done as required.

Patient education is pivotal to establish importance for the individual in the health behaviour change process, to empower the individual to self-monitor and manage their condition, and ultimately to improve outcomes. There are several tools that can be used to assist in achieving the goals set in the RFM program. These include the use of a food diary, exercise record, home blood pressure monitoring, an AF symptom diary, monitoring of downloads from continuous positive airway pressure machines, and referral to other members of the multidisciplinary team [188].

1.9 Sex differences in atrial fibrillation

1.9.1 Incidence and prevalence

The development of AF is highly influenced by age and sex. After accounting for age and other risk factors, male sex is associated with a 1.5-fold increased risk of AF [296]. For instance, the incidence of AF was 3.8 cases per 1000 person years in men versus 1.6 cases per 1000 person-years in women in FHS [3]. Similarly, men had a higher incidence of AF compared with women (4.7 cases per 1000 person years versus 2.7 cases per 1000 person years) in the Olmstead County study [297]. This finding has been consistently reported across European and Asian populations [296]. In the age groups at higher risk, males also have a higher incidence of AF. An analysis of 8.3 million individuals showed that age 85-89 years, the incidence of AF reaches a peak at 32.9 cases per 1000 person-years in men and 30.4 cases per 1000 person-years in women. Consequently, the age-adjusted prevalence of AF is higher in men compared with women. For example, in US Medicare beneficiaries, the prevalence of AF was reported to be 10.3% in men and 7.4% in women [298]. In randomized controlled trial of systematic screening for AF using intermittent ECG recordings among 75- to 76-year-old individuals in Sweden, the prevalence of AF was 15.0% in men and 9.2% in women [299].

Overall, men have a slightly higher lifetime risk of AF compared with women the lifetime (25.8% versus 23.4% at 60 years of age in the FHS [300], and 23.8% versus 22.2% at 55 years of age in the Rotterdam study [301]). However, because women live much longer, the absolute number of women with AF is higher than that of men, despite the higher incidence, prevalence, and lifetime risk of AF in men [296].

1.9.2 Risk factors

There is conflicting evidence as to whether sex plays a role in the association of various risk factors and the development of AF. The magnitude at which some risk factors increase the risk of AF varies between sexes. The risk of AF attributable to heart failure (OR 5.9 [95% CI: 4.2-8.4] in women and 4.5 [95% CI: 3.1-6.5] in men) and valvular disease (OR 3.4 [95% CI: 2.5-4.5] in women and 1.8 [95% CI: 1.2-2.5] in men) is much higher in women than in men [23]. On the contrary, postoperative AF is more common in men than in women [302]. The risk of AF conferred by increased BMI seems to be higher in men [303]. However, there is no substantial difference between the sexes in the risk of AF attributable to diabetes mellitus (OR 1.4 [95% CI: 1.0-2.0]in men and 1.6 [95% CI: 1.1-2.2] in women), hypertension (OR 1.5 [95% CI: 1.2-2.0] in men and 1.4 [95% CI: 1.1-1.8] in women), and myocardial ischemia (OR 1.4 [95% CI: 1.0-2.0] in men and 1.2 [95% CI: 0.8-1.8] in women) [23, 296, 304, 305].

There are data supporting the role of pregnancy in the development of AF. In the Women's Health Study there was a linear increase in the risk of AF with increasing parity, ranging from a hazard ratio of 1.15 (95% CI: 0.87-1.53) for a single pregnancy to 1.46 (95% CI: 1.10-1.94) for ≥6 pregnancies, as compared to no pregnancies. This association might be due to the impact of hemodynamic, inflammatory, and hormonal stresses on the left atrium during repeated pregnancies [306].

1.9.3 Pathophysiology

Several mechanisms have been postulated to explain the sex-related differences in the development of AF. Men have larger LA dimensions, which have been associated in an increased risk of AF [307]. The burden of atrial fibrosis, a structural change that promote AF, is

higher in women than in men, In a study using delayed-enhancement magnetic resonance imaging, left atrial fibrosis was 29.9 ± 6.2% in women versus 23.0 ± 7.9% in men (p=0.003)[308]. Men seem to have greater expression of repolarizing ion channel subunits, which could accelerate atrial repolarization and favour re-entry [296] Female sex has been associated with a more negative resting membrane potential in pulmonary vein tissue in rabbit models, as well a preponderance of non-pulmonary vein AF-initiating foci [296, 309].

Sex hormones seem to play a significant role in the development of AF. In a study in castrated mice, testosterone deficiency was associated with increased calcium leak from the sarcoplasmic reticulum leading to enhanced atrial arrhythmogenicity. This was corrected by testosterone replacement [310]. A human study showed an inverse association between testosterone levels and the risk of AF (HR 3.53, 95% CI: 1.69-6.37, for each SD decrease in testosterone) [311]. Administration of oestrogen has been shown to prolong atrial conduction time, atrioventricular nodal conduction time, action potential duration, and the atrial effective refractory period, possibly through downregulation of potassium channel proteins or increased calcium influx (weaker repolarizing currents), eventually promoting atrial arrhythmogenicity [296, 312-315].

1.9.4 Clinical presentation

There are major sex differences in the clinical profile of AF. Hypertension, heart failure, and valvular disease, seem to be more common in women, whereas obstructive sleep apnoea, diabetes mellitus, vascular disease including coronary artery disease seem more frequent in men [296, 316-322].

Compared with men, women tend to present with higher heart rates in AF, and longer AF episodes [323]. Women are more symptomatic (~40% difference in symptom frequency and

severity scores); they have more atypical symptoms, more functional impairment, more depression, and worse quality of life (~ reduction in objective quality of life scores) [296, 319, 322, 324-327]. Consequently, women are more likely to seek care for AF [324]. However, quality of life scores have been reported to improve similarly after catheter ablation for AF in men and women [328].

1.9.5 Outcomes

1.9.5.1 Mortality

Studies investigating sex differences in mortality in patients with AF have yielded contradictory results. In a meta-analysis including 30 studies and a pooled population of 4,371,714 participants, AF was associated with a higher risk of all-cause mortality in women (ratio of relative risks for women compared with men 1.12, 95% CI: 1.07-1.17) and a significantly stronger risk of stroke (1.99, 95% CI: 1.46-2.71), cardiovascular mortality (1.93, 95% CI: 1.44 -2.60), cardiac events (1.55, 95% CI: 1.15-2.08), and heart failure (1.16, 95% CI: 1.07-1.27) [329].

1.9.5.2 Stroke and systemic embolism

Although some studies have shown that female sex is a risk factor for stroke and systemic embolism in patients with AF, this observation has not been replicated in other studies. For instance, female sex was associated with an increased risk of stroke and systemic embolism in the Euro Heart Survey on Atrial Fibrillation, the FHS, the Copenhagen City Heart Study, the Swedish Atrial fibrillation Cohort Study, and the ATRIA study[320, 330-333]. As a result, female sex was included in the CHA_2DS_2-VASc score and the ATRIA risk score, whereas it is not a component of the older $CHADS_2$ score [252, 264, 265]. However, the absent significant association of female sex with thromboembolism in other individual studies motivated the

revision of several AF management guidelines, including those of the Japanese Circulation Society, the Canadian Cardiovascular Society, and the National Heart Foundation of Australia Consensus Statement which excluded female sex as a risk factor.[267-269]

Furthermore, strokes due to AF are more severe in women than in men. Indeed, AF-related stroke in women are of larger size and are associated with higher residual disability [334].

1.9.5.3 Dementia

In a recent systematic review and meta-analysis AF was associated with increased risk of cognitive impairment in the general population and in stroke survivors. This risk of cognitive impairment might be increased even in the absence of clinical stroke [177]. In an analysis of the Taiwan's National Health Insurance Research Database, female sex increased the risk of developing dementia compared to male sex in patients with AF. However, the magnitude of this association varied according to age groups. The difference was not significant for ≤55 years (sub distribution hazard ratio (SHR) 0.89, 95% CI: 0.73-1.07), but increased between 56-65 years (SHR 1.13, 95% CI: 1.02-1.25), 66-75 years (SHR 1.14, 95% CI: 1.09-1.20), 75-85 years (SHR 1.11, 95% CI: 1.07-1.15) and >85 years (SHR 1.10, 95% CI: 1.04-1.16) for females.

1.9.5.4 Heart failure

The risk of heart failure attributable to AF seem similar between men and women. Few studies have reported a higher likelihood to develop HFpEF in men compared that women [335, 336]. In one study in patients who presented to the emergency department due to AF, women exhibited a higher rate of HF events than men (OR 2.73, 95% CI: 1.04-5.89) and shorter mean time-to-HF hospitalization (87.45±8.74 vs 164.5±18.80; HR 5.72, 95% CI: 1.30–25.05) [337].

1.9.6 Management

1.9.6.1 Stroke prevention

Sex-specific differences have been reported in the patterns of OAC prescription and use. Women tend to receive antiplatelet therapy more commonly than OAC compared to men [338]. Women are also more likely to be prescribed DOAC than VKA [339, 340], and when receiving OAC, it is more frequently lower approved doses compared with men [339, 341].

In terms of effectiveness and safety of OAC, in one meta-analysis of sex differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with OACs, women with AF treated with warfarin have a greater residual risk of stroke or systemic embolism and an equivalent major bleeding risk. Those treated with DOACs deemed superior to warfarin are at equivalent residual risk of stroke or systemic embolism and less major bleeding risk compared with men [342]. Another meta-analysis of randomized controlled trials comparing the efficacy and safety of DOACs with warfarin in patients with AF showed no sex interaction in the superiority of DOACs over warfarin [343]. No sex-specific difference was observed in the overall rates of bleeding with warfarin [344-347]. However, major and clinically relevant nonmajor bleeding were substantially lower in women with AF treated with DOACs [344-347].

1.9.6.2 Rate and rhythm control

Several survey reported that women are treated more conservatively with less rhythm control than men [320, 322]. In the Euro Heart Survey on Atrial Fibrillation, although women received less rhythm control therapy than men, long-term changes in quality of life and other morbidities and mortality were similar [320]. In Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE) trial, women treated with rate control had lower

incidence of the composite primary end point (cardiovascular mortality, heart failure, thromboembolism, adverse antiarrhythmic drug effects, and pacemaker implantation) compared with women treated with rhythm control (10.5% vs 32.0%) [276]. Similarly finding was observed in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial with the primary endpoint of overall mortality [275]. This difference was driven predominantly by the need for pacemaker implantation, and adverse drug effects of AADs.

1.9.6.3 Catheter ablation

Several studies have also shown a lower utilization of rhythm control procedures for AF in women [348-353]. In most studies, women represented about only a third of patients who underwent catheter ablation [348-350, 352]. Women are more commonly managed with AAD therapy compared with men [348-350, 352]. For instance, in the ORBIT-AF registry, despite having more symptoms, more functional impairment, and worse quality of life, women had lower crude rates of catheter ablation [319]. An analysis of Quebec administrative databases showed that the annual proportion of women who had received AF ablation between 2003 and 2021 had not surpassed 30%, and that men had a 54% higher likelihood of undergoing ablation than did women [348]. Women usually undergo catheter ablation after a longer course of disease (with advanced AF), with higher disease burden (higher proportion of persistent AF), higher symptoms burden, after failing larger number of AADs [296, 319, 354]. Furthermore, these women are usually older, with more comorbidities, have larger LA dimensions and higher prevalence of non-pulmonary vein triggers compared with men [328, 352, 353]. Similar catheter ablation outcomes have been reported between men and women, despite the later having higher-risk clinical profile before ablation [296, 354, 355].

In terms of complications, several studies have suggested that women have higher rates of procedural complications during or following catheter ablation [352, 356-358]. Putative explanations for this include smaller cardiac and venous structures making venous access and

catheter manipulation more prone to vascular complications and cardiac perforation with tamponade [355]. However, other studies reported no sex difference in catheter ablation complications [296, 355].

1.10 Gaps in knowledge and aims of the thesis

1.10.1 Gaps in knowledge

There are persisting grey areas in the epidemiology and management of AF. This thesis tackles a few knowledge gaps:

- The current screening strategies for AF needs substantial improvement. There is a need to identify new clinical factors and biomarkers that can be incorporated into the current prediction tools to improve their performance.
- The seminal Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial revealed significantly increased AF detection with prolonged continuous cardiac monitoring with ICM over standard-of-care monitoring in patients with cryptogenic stroke [148]. Real-world data of AF detection in cryptogenic stroke are needed.
- The current stroke risk stratification tools have modest performance in predicting stroke and systemic embolic events in real-world cohorts. Hence, there is a need for new risk predictor tools incorporating both clinical factors and non-clinical factors such as left atrial imaging features, electrocardiographic markers, and biomarkers.
- Atrial fibrillation is common in patients with acute cardiovascular events such as myocardial infarction or pulmonary embolism. The prognostic impact of AF in such patients remain unclear. Indeed, it is uncertain whether AF is a true prognostic factor or just a marker of co-morbidities or myocardial infarction or pulmonary embolism

severity. It is possible that AF could improve risk stratification of patients with these conditions.

- Several studies have shown sex differences in the pathophysiology and clinical patterns of AF. However, the impact of sex on the response to various treatments in patients with AF is largely unknown.

1.10.2 Aims

This thesis aimed to:

- Investigate the risk of AF associated with decline in lung function
- Evaluate the AF diagnostic yield using prolonged cardiac monitoring in patients with cryptogenic stroke
- Summarize data on clinical, biomarkers and imaging predictors of stroke in patients with AF
- Determine the potential added value of occlusive and non-occlusive carotid artery disease in stroke risk stratification in patients with AF
- Determine the prognostic impact of AF on patients with acute cardiovascular events such as myocardial infarction and acute pulmonary embolism
- Identify sex differences in the management and outcomes of AF

1.11 Tables and figures

Table 1. Clinical scores for the prediction of incident atrial fibrillation

Clinical score	Characteristics of the study population	Variables included
FHS[36]	▪ 4,764 individuals ▪ Age: 45-95 years ▪ Race: Caucasians ▪ 10 year-risk score assessment	Age, sex, body mass index, systolic blood pressure, Pulse pressure, hypertension medication, PR interval duration, ECG left ventricular hypertrophy, heart failure, clinically significant heart murmur
ARIC[112]	▪ 15,792 individuals ▪ Aged 45–64 years ▪ Race: African descent, Caucasians ▪ 10-year risk prediction	Age, race, height, smoking status, systolic blood pressure, hypertension treatment, diabetes, coronary heart disease, heart failure, left atrial enlargement, cardiac murmur, ECG left ventricular hypertrophy, prolonged P wave duration
CHARGE-AF[113]	▪ 18,556 individuals ▪ Age: 6-94 years ▪ Race: African descent, Caucasians ▪ 5-year risk prediction	Age, race, anthropometric data, systolic blood pressure, diastolic blood pressure, smoking status, hypertension medication, diabetes, previous myocardial infarction, heart failure, PR interval duration
MDCS[114]	▪ 30,447 individuals ▪ Age: 44-73 years ▪ Race: Caucasian	Age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, body mass index, low-density lipoprotein, high-density lipoprotein, current smoking, diabetes mellitus, previous myocardial infarction, heart failure
Suita[118]	▪ 6,898 individuals ▪ Age: 30-79 years ▪ Race: Asian ▪ 10-year risk prediction model	Age, sex, systolic hypertension, weight, drinking status, coronary artery disease, smoking status, lipoprotein-cholesterol level, history of arrhythmia, presence of cardiac murmur
HATCH[117]	▪ 670,804 individuals ▪ Age: >20 years ▪ Race: Asian ▪ 10-year risk prediction model	Hypertension, age more than 75 years, stroke or transient ischemic attack, chronic obstructive pulmonary

		disease, heart failure
C2HEST[119]	▪ 471,446 individuals ▪ Age: 31-63 years ▪ Race: Asian ▪ 11-year prediction	Coronary artery disease, chronic obstructive pulmonary disease, hypertension, Age >75 years, systolic heart failure, hyperthyroidism

Table 2. List of biomarkers with a potential role in atrial fibrillation

Mechanism	Biomarkers
Inflammation	C-reactive protein, IL-2, IL-6, IL-8, IL-10, IL-17A, IL-18, IL-27, IL-37, TNF-α, monocyte chemoattractant protein-1 (MCP-1), Growth differentiation factor 15 (GDF-15)
Oxidative stress	NOX2, NOX4, Small G-protein Rac1, asymmetric dimethylarginine, reduced glutathione (Eh GSH), reduced cysteine (Eh CySH), isoprostanes, biopyrrin, malondialdehyde (MDA), nitrotyrosine, derivatives of reactive oxidative metabolites (DROMs), Growth differentiation factor 15 (GDF-15)
Cardiomyocyte stress	B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Cardiomyocyte injury	Cardiac troponin T and I
Atrial fibrosis	Relaxin, galectin-3, fibroblast growth factor-23 (FGF-23), Procollagen type III N-terminal propeptide (PIIINP), type I collagen carboxy-terminal telopeptide (ICTP)
Thrombogenesis	D-dimer, von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), thrombin-antithrombin (TAT)
Epigenetic regulation	microRNAs, long non-coding RNAs

IL: interleukin; RNA: ribonucleic acid

Table 3. MicroRNAs involved in the pathogenesis of atrial fibrillation

MicroRNA	Source	Target gene	Remodeling mechanism	Regulatory mechanism
miR-1	Right atrial appendage	KCNE1, KCNB2, KCNJ2, HCN2, HCN4	Structural	Up
miR-1	Plasma	KCNE1, KCNB2, KCNJ2, HCN2, HCN4	Electrical	Down
miR-21	Atrial tissue	Spry1, Rac1-GTPase, CTGF	Structural	Up
miR-26a	Right atrial appendage	KCNJ2, NFAT	Electrical	Down
miR-26a	Right atrial appendage	TRPC3	Structural	Down
miR-26a	Right atrial appendage	KIR2.1, KCNJ2	Electrical/structural	Down
miR-29b	Rapid pacing model	COL1A1, COL3A1, fibrillin	Structural	Down
miR-30d	Right atrial appendage	KCNJ3/Kir3.1	Electrical	Up
miR-30	Atrial tissue	I_{KACh}, snail 1	Electrical/structural	Down
miR-31	Right atrial tissue	nNOS	Electrical	Up
miR-34	Right atrial tissue	Ank-B	Structural	Up
miR-106	Atrial tissue, plasma	RYR2, klf2a	Electrical	Down
miR-125	Atrial tissue/plasma	IL-6R, TNFa	Structural	Down
miR-126	Serum	EGFL7	Structural	Down
miR-133	Right atrial appendage	TGF-β1, TGF-β receptor-ll	Structural	Down
miR-138-5p	Right atrial appendage	CYP11B2	Structural	Down
miR-146	Left atrial appendage	TIMP-4	Structural	Up
miR-150	Serum, plasma	IL-6, IL-18, TNF-a/b	Structural	Down
miR-199a	Right atrial appendage	SIRT1	Structural	Down
miR-206	Rapid pacing model	SOD1	Electrical	Up
miR-208a	Plasma	CACNA1C, CACNB2, MYH7, Cx40	Electrical/structural	Up
miR-208b	Right atrial appendage	CACNA1C, CACNB1, SERCA2	Electrical	Up
miR-328	Rapid pacing model	CACNA1C, CACNB1	Electrical	Up
miR-409	Plasma	SMAD2, ITGB3, ACE, CDKN2B	Structural	Down
miR-432	Plasma	SMAD2, ITGB3, ACE, CDKN2B	Structural	Down
miR-499	Right atrial appendage	CACNA1C, CACNB2	Electrical	Up
miR-483	Plasma	IGF2	Structural	Up
miR-590	Right atrial appendage	TGF-β1, TGF-β receptor-ll	Structural	Down

Table 4. Studies comparing the predictive performance of the biomarker-based ABC scores with clinical risk scores

Study	Biomarker-based score	Endpoint	Comparator	Cohort (external)	C-statistics
Hijazi Z et al.[244]	ABC-stroke score	Stroke	CHA_2DS_2-VASc	STABILITY trial: 1400 participants with AF or atrial flutter (689 on oral anticoagulation) with a median follow-up was 3.4 years and a total of 48 events.	ABC-stroke score: 0.66 (0.58-0.74) CHA_2DS_2-VASc: 0.58 (0.49-0.67)
Oldgren et al.[247]	ABC-stroke score	Stroke & systemic embolism	CHA_2DS_2-VASc, ATRIA	RE-LY trial: 8356 patients with AF randomized to dabigatran versus warfarin, median follow-up of 1.9 years and a total of 219 events.	ABC-stroke score: 0.65 (0.61-0.69) CHA_2DS_2-VASc: 0.60 (0.57-0.64) ATRIA: 0.61 (0.58-0.65)
Rivera-Caravaca et al.[249]	ABC-stroke score	Ischemic stroke	CHA_2DS_2-VASc	Murcia AF Project: 1125 consecutive patients with AF stable on vitamin K antagonists, median follow-up of 6.5 years and a total of 114 events.	ABC-stroke score: 0.662 (0.633-0.690) CHA_2DS_2-VASc: 0.620 (0.590-0.648)
Berg et al.[248]	ABC-stroke score	Stroke & systemic embolism	CHA_2DS_2-VASc	ENGAGE AF-TIMI 48: 8705 patients with AF and $CHADS_2$ score ≥2 randomized to edoxaban versus warfarin, median follow-up of 2.8 years and a total of 139 events.	ABC-stroke score: 0.66 (0.63-0.68) CHA_2DS_2-VASc: 0.59 (0.57-0.62)
Berg et al.[248]	ABC-bleeding score	Major bleeding	HAS-BLED	ENGAGE AF-TIMI 48: 8705 patients with AF and CHADS2 score ≥2 randomized to edoxaban versus warfarin, median follow-up of 2.8 years and a total of 251 events.	ABC-bleeding: 0.67 (0.65-0.70) HAS-BLED: 0.62 (0.60-0.64)
Hijazi et al.[245]	ABC-bleeding score	Major bleeding	HAS-BLED, ORBIT	RE-LY trial: 8468 patients with AF randomized to dabigatran versus warfarin, median follow-up of 1.9 years and a total of 463 events.	ABC-bleeding: 0·71 (0·68-0·73) ORBIT: 0·68 (0·65-0·70) HAS-BLED: 0·62 (0·59-0·64)
Esteve-Pastor et	ABC-bleeding	Major bleeding	HAS-BLED	Murcia AF Project: 1120 consecutive patients with AF stable on vitamin K antagonists,	ABC-bleeding: 0.518 (0·488-0·548)

al.[250]	score			median follow-up of 6.5 years and a total of 207 events.	HAS-BLED: 0·583 (0·554-0·612)
Hijazi et al.[246]	ABC-death score	Death	CHA_2DS_2-VASc	RE-LY trial: 8548 patients with AF randomized to dabigatran versus warfarin, median follow-up of 1.9 years and a total of 594 events.	ABC-death: 0.74 (0.72-0.76) CHA_2DS_2-VASc: 0.58 (0.56-0.61)

ORBIT score: Older age (≥75 years), Reduced hemoglobin/hematocrit/history of anemia, Bleeding history, Insufficient kidney function, and Treatment with antiplatelet; and HAS–BLED is Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly)

ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation): prior stroke, age categories (≥85, 75–84, 65–74, <65 years), sex, diabetes mellitus, chronic

CHA2DS2-VASc: cardiac failure or dysfunction, hypertension, age (≥75, 65 to 74, <65 years) diabetes mellitus, previous stroke, vascular disease and sex

ABC-stroke score: Age, Biomarkers (high-sensitivity troponin T and N-terminal fragment B-type natriuretic peptide), and Clinical history of prior stroke/transient ischemic attack

ABC-bleeding score: Age, Biomarkers (growth differentiation factor-15, hsTnT, and hemoglobin), and Clinical history (previous bleeding)

ABC-death score: Age, Biomarkers (growth differentiation factor-15, hsTnT, NT-proBNP), Clinical history of heart failure

Table 5. Characteristics of the main clinical stroke risk stratification tools in patients with non-valvular atrial fibrillation

Score	Data source	Definition	Evidence
$CHADS_2$ Gage et al. [252]	Medicare Database N = 1,733	CHF, hypertension, age (≥65 yrs = 1 point, ≥75 yrs = 2 points), diabetes, and stroke/TIA (2 points)	$CHADS_2$ was superior to existing risk classification schemes AFI scheme: C-statistic = 0.68 (0.65–0.71) SPAF-III scheme: C-statistic = 0.74 (0.71–0.76) $CHADS_2$ score: C-statistic = 0.82 (0.80–0.84)
CHA_2DS_2-VASc Lip et al. [253]	Euro Heart Survey for AF N = 1,084	CHF, hypertension, age ≥75 yrs, diabetes, stroke, or TIA, vascular disease, age 65–74 yrs, sex	C-statistic was 0.606 (0.513–0.699) for CHA_2DS_2-VASs vs. 0.561 (0.450–0.672) for $CHADS_2$. Patients were classified as low (9.2% vs. 20.4%), intermediate (15.1% vs. 61.9%), or high (75.7% vs. 17.7%) risk with CHA_2DS_2-VASs vs. $CHADS_2$.
CHA_2DS_2-VA Tomita et al. [359]	J-RHYTHM registry N =997	CHA_2DS_2-VASc excluding the sex category	CHA_2DS_2-VA superior to CHA_2DS_2-VASc overall [C-statistic = 0.029; p = 0.02, NRI = 11% (1%–20%)] and in low-risk patients: [C-statistic = 0.053; p < 0.001, NRI = 11% (7%–14%)]
ATRIA Singer et al. [254]	ATRIA, ATRIA-CVRN cohort N = 10,927	Age (65–74 yrs = 3 points, 75–84 yrs = 5 points, ≥85 yrs = 6 points), hypertension, diabetes, CHF, proteinuria, GFR <45 ml/min/1.73 m^2, sex	ATRIA was superior to CHA_2DS_2-VASc: C-statistics = 0.708 (0.704–0.713) vs. 694 (0.690–0.700), NRI 16% (14%-17%).
ABC Hijazi et al. [244]	ARISTOTLE trial, STABILITY trial N = 18,201	Age, biomarkers (hs-troponin T, NT-proBNP), prior history of stroke	The ABC score yielded higher C-statistics than CHA_2DS_2-VASs in the derivation cohort (0.68 vs. 0.62; p < 0.001) and the external validation cohort (0.66 vs. 0.58; p < 0.001)
GARFIELD-AF Fox et al. [255]	GARFIELD-AF, ORBIT-AF registry N = 39,898	Computed machine learning model (web-based)	The GARFIELD-AF score yielded higher C-statistics than CHA_2DS_2-VASs 0.69 (0.67–0.71) vs. 0.64 (0.61–0.66) in the derivation cohort. In the validation cohort, GARFIELD-AF C-statistic was 0.68 (0.62–0.74)

Modified from [261]

ABC = age, biomarker, clinical history; AFI = Atrial Fibrillation Investigators; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BNP = B-type natriuretic peptide; CHF = congestive heart failure; CVRN = Cardiovascular Research Network; GARFIELD = Global Anticoagulant Registry in the FIELD; GFR = glomerular filtration rate; hs = high-sensitivity; NRI = net reclassification index; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NVAF = nonvalvular atrial fibrillation; ROCKET-AF = Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation trial; SPAF III = Stroke Prevention in Atrial Fibrillation III trial; STABILITY = The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial; TIA = transient ischemic attack.

Table 6. Characteristics of the main clinical bleeding risk stratification tools in patients with non-valvular atrial fibrillation

Risk score	Risk factors (score for each risk factor)	Risk categories			Bleeding events in validation cohort (per 100 patient years)		
		Low	Intermediate	High	Low	Intermediate	High
ABC [†], Hijazi et al. [245]	Age(†); biomarkers (†) (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, & Hb); Previous bleed (†)	<1%	1–2%	>3%	0.62	1.67	4.87
ATRIA Fang et al. [258]	Anaemia (3); severe renal disease (3); Age ≥75 (2); prior bleed (1); hypertension (1)	0–3	4	5–10	0.83	2.41	5.32
HAS-BLED Pisters et al. [257]	↑SBP (1); severe renal/hepatic disease (1 each); stroke (1); bleeding history or predisposition (1); labile INR (1); Age >65 (1); APT/NSAIDs (1); alcohol excess (1)	0–1	2	≥3	1.02–1.13	1.88	≥3.74
ORBIT O'Brien et al. [259]	Age ≥75 (1); ↓Hb/Hct/anaemia (2); Bleeding history (2); ↓ renal function (1); APT (1)	0–2	3	≥4	2.4[*]	2.0% [a]	5.4% [a]

Modified from [256]

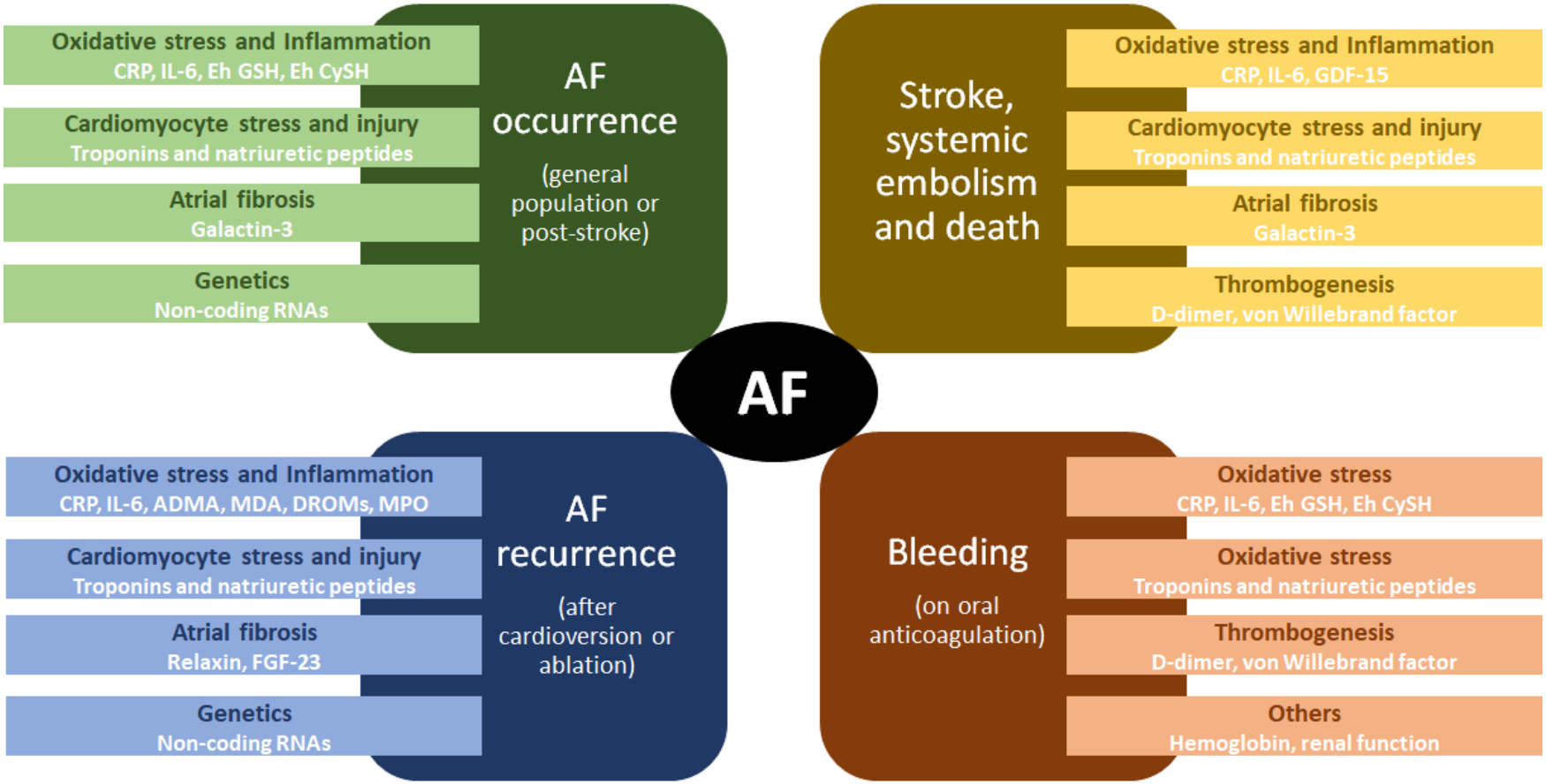
ABC, Age, biomarkers, clinical history; APT, antiplatelet therapy; ATRIA, Anticoagulation and Risk Factors in Atrial fibrillation; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cTnT-hs, high-sensitivity cardiac troponin T; GDF-15 = growth differentiation factor-15; HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; Plt, platelet count or function; SBP, systolic blood pressure.

*Bleeding event in original derivation cohort;

[a] At 3 months; ↓ reduced/decreased; ↑ elevated/increased;

† Score for each variable in ABC score is based on a nonogram

Figure 1. Summary of biomarkers according to mechanistic pathways and clinical utility.



Legend. ADMA: asymmetric dimethylarginine; CRP: C-reactive protein; DROMs: derivatives of reactive oxidative metabolites; EhCySH: reduced cysteine; Eh GSH: reduced glutathione; FGF-23: fibroblast growth factor 23; GDF-15: growth differentiation factor 15; IL-6: interleukin 6; MDA: malondialdehyde; MPO: myeloperoxidase

CHAPTER 2:

Incident atrial fibrillation in relation to ventilatory parameters: a prospective cohort study

Statement of Authorship

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Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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2.1 Introduction

Atrial fibrillation (AF) has become an important global health problem owing to its increasing prevalence and to its complications including stroke, heart failure, dementia, and death [11, 72]. In 2019, nearly 60 million individuals were affected (0.51% of global population), representing about a doubling compared to prevalent cases in 1990 [72]. This surge in the prevalence of AF is driven mainly by aging, cardiometabolic risk factors such as hypertension, obesity, diabetes mellitus, and cardiac disease [55]. However, these traditional risk factors represent only about half of the attributable risk of AF [37], indicating that there might be other important factors contributing to the risk of AF.

Chronic obstructive pulmonary disease (COPD) defined by irreversible airflow obstruction is very common in patients with AF, with a prevalence estimated at nearly 25% [98]. COPD has been shown to be an independent predictor of AF, to promote AF progression from paroxysmal to sustained forms, to increase AF recurrence after electrical cardioversion, and to reduce the efficacy of catheter ablation [98]. Furthermore, previous studies have shown an association between lung function measured by forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) and incident AF, where reduced ventilatory function is associated with increased risk [23, 99-102]. However, these studies were mostly based on former cohorts of patients initially recruited several decades ago, in the 1970s and 1980s. Furthermore, these studies used standards of spirometry that differ from the current recommendations [103], implying that their findings might not have the external validity of contemporaneous studies.

The UK Biobank (UKB) represents one of the largest contemporaneous cohorts that allow the study of factors associated with the development of disease [360]. Its cohort with spirometry is larger than the combined number of participants in previous large studies on the association between lung function and AF [23, 99-102], and is considered the most inclusive

sample with usable spirograms [361]. In the current study, we assessed the relationship between incident AF and several ventilatory function parameters including FEV1, FVC, FEV1/FVC ratio, and the corresponding Global Lung Initiative 2012 (GLI-2012) z-scores for each of them, in the UKB. We hypothesized that decline in ventilatory function would be associated with incident AF.

2.2 Methods

2.2.1 Study population

The UKB recruited over 500,000 volunteers aged 40-69 years in 22 recruitment centres throughout England, Wales and Scotland between 2006 and 2010. At enrolment, sociodemographic and lifestyle information was collected via a questionnaire; anthropomorphic measurements and verbal interviews for comorbidities were recorded. A various set of investigations including spirometry were also performed. Death and hospital records were available through linkage with national databases. For this analysis, we included all participants with available spirometry measurements, and excluded those with a prior diagnosis of AF. Non-White participants did not have available spirometry data in the UK Biobank data fields utilised for this study and were therefore excluded.

2.2.2 Assessment of ventilatory function

Spirometry was performed using a handheld pneumotachograph spirometer (Pneumotrac 6800) from which volume–time arrays were stored for each blow, and FEV1 and FVC were recorded. The cohort had 81% of participants who performed two blows with acceptable start and measures of FEV1 reproducible within 250 mL, making it the most inclusive sample of usable spirograms [361]. Furthermore, based on end-blow quality, 58% of the cohort had a good plateau and both FEV1 and FVC reproducible within 150 mL as recommended by the

American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Standardisation of Spirometry [103, 361]. UK Biobank data fields 20150 and 20151 were used in the current analysis, which correspond to the best measure of FEV1 and FVC respectively. They were measured at baseline. FEV1/FVC was derived as the ratio between the two values.

The Caucasian-specific GLI-2012 reference equations were used to calculate predicted FEV1, and FEV1, FVC and FEV1/FVC z-scores in this cohort. The GLI-2012 reference equations predict the estimated spirometry values for a standardised person of the same gender, age, ethnicity and height, who has no history of lung disease and is a lifelong non-smoker [362]. The z-score corresponds to the relative position of a participant in this standardised distribution.

2.2.3 Covariates

The following covariates were self-reported at baseline: age, sex, race, education, assessment center attended, and smoking status. The Townsend deprivation index, a measure of material deprivation, was calculated based on census data and each participant's postcode [363]. Body mass index (BMI) was measured according to a standard protocol. Total metabolic equivalent of task (MET)-minutes/week was calculated from a modified International Physical Activity Questionnaire [364]. As previously described [96], comorbidities at baseline were identified from: 1) self-report on the baseline questionnaire; 2) standardized verbal interview at enrolment; 3) hospital inpatient diagnosis codes; or 4) hospital operation/procedure codes.

2.2.4 Outcome

The outcome was incident AF (including atrial flutter), identified by the first occurrence of a relevant: 1) hospital inpatient diagnosis: 2) hospital ablation procedure; or 3) AF-related death, as previously described [365].

2.2.5 Statistical analysis

Baseline characteristics were expressed as frequencies and percentages while continuous variables were expressed as mean and standard deviation. We assessed differences between participants with and without incident AF using the Pearson's Chi square test and unpaired t-tests as appropriate. Standardised differences between participants with and without incident AF were measured using Cohen's *D* and Cramer's *V* for continuous and categorical variables, respectively. The greater the number, the greater the effect size; however, values between the two statistics are not comparable. Cox proportional hazards models were used to assess the association between ventilatory parameters and the first occurrence of AF. Age was used as the timescale, and individuals were considered at risk from the date of enrolment into the UK Biobank, until the: 1) date of incident AF; 2) date of death; 3) date lost to follow-up; or 4) end of available follow-up, whichever came first. Ventilatory parameters including FEV1, FEV1 percentage predicted, FEV1/FVC ratio, FEV1 z-score, FVC z-score, and FEV1/FVC z-score were each included in the model separately as restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles, which provided the best fit for most models (**Supplementary Table 1**). The reference value was defined as the median value of the ventilatory parameter except for the z-scores, where zero (median value in the predicted distribution) was the reference.

The regression model was stratified by sex and assessment centre attended at baseline (1 of 22 centres) and included education (college or university degree, vocational qualifications, optional national examinations at ages 17 to 18 years, national examinations at age 16 years, none of the above, unknown), Townsend deprivation index (in quintiles), lifestyles factors including smoking status (never, past, current, unknown), smoking pack-years (0, 1–10, 10–20, >20, or unknown), alcohol drinker status (never, past, current, unknown), alcohol amount (<7, 7–14, 14–28 or >28 UK standard drinks/week, or unknown),

BMI (<18, 18–25, 25–30, >30 kg/m^2), and total MET-minutes/week (<500, 500-1500, >1500, or unknown), and baseline comorbidities including hypertension, diabetes mellitus, dyslipidemia, heart failure, coronary artery disease, heart failure, valvular disease, obstructive sleep apnoea, and chronic kidney disease. Hazard ratio (HR) and 95% confidence interval (CI) were estimated by general contrasts of regression coefficients, using the median values of covariates. Furthermore, we assessed the association between COPD, identified by self-report or hospital inpatient diagnosis, and incident AF using multivariable regression analyses in the model defined above (excluding ventilatory parameters due to potential collinearity). The proportional hazards assumption was tested using Schoenfeld residuals and interaction with time, and no major violations were present after stratifying the model by sex and assessment centre. A two-tailed p-value of ≤ 0.05 was considered significant. All analyses were conducted using the R statistical software (version 4.0.2, The R Foundation for statistical computing, Vienna, Austria).

2.2.6 Ethical considerations

This project was performed under UK Biobank application number 76720. The UKB has ethical approval from the North West Multi-centre Research Ethics Committee. This secondary analysis of de-identified data from the UKB was also granted approval by the Central Adelaide Local Health Network (CAHLN) Human Research Ethics Committee (reference number 16606).

2.3 Results

2.3.1 Baseline characteristics

From the 502,490 participants initially recruited in the UKB, after stepwise exclusion of 29,810 non-White participants (spirometry data not available), 119,380 additional participants

who did not have valid spirometry measurements and 5,081 who had AF at baseline, we included a total of 348,219 participants (**Figure 1**). Compared to participants with spirometry data (**Supplementary Table 2**), participants without spirometry data were more likely women (55.9 vs 53.8%, difference in proportion 2.1% [95% CI: 1.8–2.4]), had more cardiovascular risk factors, more likely had AF (1.8 vs 1.4%, difference in proportion 0.3% [95% CI: 0.2–0.4]) and COPD (3.2 vs 1.8%, difference in proportion 1.4% [95% CI: 1.3–1.5]) but not asthma (12.0 vs 12.2%, difference in proportion 0.2% [95% CI: 0.0–0.4]) at baseline.

After a median follow-up of 11.5 years (IQR 11.0-12.6), there were 18,188 cases of incident AF. The baseline characteristics of the study population are summarized in **Table 1**. Compared with participants without incident AF, those that developed incident AF during follow-up were older (62.4 vs 56.6 years, mean difference 5.8 years [95% CI: 5.7–5.9]), had more cardiovascular risk factors, had lower FEV1 (2.74 vs 2.86 L, mean difference 0.12 L [95% CI: 0.11–0.13]), FVC (3.72 vs 3.78 L, mean difference 0.07 L [95% CI: 0.05–0.08]), and FEV1/FVC ratio (0.735 vs 0.756, mean difference 0.020 [95% CI: 0.019–0.022]) at baseline (**Table 1**). FVC between the two groups were materially the same (3.65L) despite statistically significant comparison. The characteristics of the study population by diagnosis of asthma and/or COPD at baseline are presented in **Supplementary Table 3**. Participants with a diagnosis of asthma and/or COPD at baseline were more comorbid and had lower ventilatory parameters compared to those who were disease free.

2.3.2 FEV1, FEV1 percentage predicted, FEV1 z-score and incident AF

There was a U-shaped relationship between FEV1 and AF risk (**Figure 2, Panel A**). The nadir of risk was at an FEV1 value at 2.97L, which was near the median FEV1 value. The point estimates were, for FEV1 of 1.5L, adjusted HR (aHR) 1.36 (95% CI: 1.29-1.43); FEV1 of 3.0L, aHR 0.99 (95% CI: 0.98-1.01); and FEV1 of 4.5L, aHR 1.21 (95% CI: 1.13-1.29).

There was a strong, almost negative linear association between FEV1 percentage predicted and incident AF (**Figure 2, Panel B**). Similarly, the risk of AF increased with decreasing GLI-2012 FEV1 z-score standardized for age, sex, and height (**Figure 2, Panel C)**.

2.3.3 FVC, FVC z-score and incident AF

There was a U-shaped relationship between FVC and AF risk, (**Figure 3, Panel A**). The point estimates were, for FVC of 2.0L, 1.27 (95% CI: 1.19-1.35); FVC of 4.0L, 1.01 (95% CI: 0.99-1.03); and FVC of 6.0L, 1.34 (95% CI: 1.26-1.44). For age, sex, and height standardized GLI-2012 FVC z-scores and risk of incident AF, there was a strong, almost negative linear association in those with z-score of less than 0 (**Figure 3, Panel B**). For those with z-scores above 0, there was an association with reduced incident AF, though the association flattened between a z-score of 0 and 1, such that there were no material differences in effect size with increasing z-score above this.

2.3.4 FEV1/FVC, FEV1/FVC z-score and incident AF

There was a near-linear relationship between FEV1/FVC and AF risk (**Figure 4, Panel A**). Every 0.05 decrease in the ratio appeared to be associated with an approximate 10% increase in the risk of AF. The cut-off of < 0.70 of FEV1/FVC is used to define airway obstruction. When this cut off is used to dichotomise FEV1/FVC, those with an FEV1/FVC ratio of < 0.70 had a 23% increased risk of AF (aHR 1.23, 95% CI: 1.19-1.28), compared to those with an FEV1/FVC ratio of ≥ 0.70. Regarding age, sex, and height standardized GLI-2012 FEV1/FVC z-score, the risk of incident AF was increased for z-scores < 0, but there was no significant association with incident AF for z-scores > 0 (**Figure 4, Panel B**).

2.3.5 COPD status and incident AF

Participants with baseline COPD and asthma had an increased risk of incident AF. There was a 36% increased risk of AF (aHR 1.40, 95% CI 1.29-1.51) in participants with COPD compared to those without COPD, and an 17% increased risk of incident AF in participants with baseline asthma (aHR 1.17, 95% CI 1.12-1.22) compared to those without asthma (**Table 2**).

2.4 Discussion

In this study we investigated the relationship between several ventilatory function parameters and incident AF. First, we observed a U-shaped relationship between FEV1, FVC and incident AF, with an increased risk of AF for both high and low FEV1 and FVC. However, after standardization to sex, age, and height, we observed that the risk of AF consistently increased with decreasing FEV1 percentage predicted, FEV1 z-score, and FVC z-score (**Figure 5**). Second, the risk of AF almost linearly increased with decreasing FEV1/FVC ratio. When considering the cut-off of < 0.70 of FEV1/FVC to define airway obstruction, we observed that participants with FEV1/FVC < 0.70 had a 23% greater risk of incident AF. Furthermore, patients with FEV1/FVC z-score < 0 had an increased risk of incident AF, whereas there was no significant association with incident AF for FEV1/FVC z-score > 0. Third, patients with identified COPD and asthma had respectively a 40% and a 17% increased risk of incident AF compared to those without these conditions at baseline.

Overall, our observation of increasing risk of AF with declining ventilatory function independent of smoking and other known risk factors for AF is consistent with findings from previous studies such as the Atherosclerosis Risk in Communities (ARIC) Study [99], the Malmö Preventive Project [100], Copenhagen City Heart Study [101], the Cardiovascular Health Study [102], and the Framingham Heart Study (FHS) [23]. Our study adds to what is already

known by providing contemporaneous and more accurate estimates from a large cohort and with more potential confounders accounted for compared to previous studies. Furthermore, we provide for the first time an analysis of the association of ventilatory function and incident AF using z-scores derived from the GLI-2012 reference equations. These population-standardised comparisons are independent of age, gender, ethnicity, and height, all of which are known strong risk factors for atrial fibrillation [2].

Several potential mechanisms contribute to the onset and progression of AF in the setting of decreased lung function or airway obstruction. Hyperinflation which is characteristic in patients with airflow obstruction increases end-expiratory pressures leading to pulmonary vascular resistance and subsequently to left ventricular interventricular septum encroaching and compromised inflow, and to increased left atrial and pulmonary venous pressures [98, 366]. Fibrosis and stretching of pulmonary veins due to increased intra-atrial pressure may trigger ectopic beats in the walls of the pulmonary veins where AF frequently originate [367]. Hypoxaemia and hypercapnia resulting from impaired gas exchanges can also cause pulmonary vasoconstriction and subsequent pulmonary hypertension and ultimately right ventricular hypertrophy and diastolic dysfunction [98, 368]. Animal studies have shown that induced right heart disease produced a substrate for AF maintenance prominently involving right atrial fibrosis and atrial arrhythmogenesis conduction [369, 370]. In addition, chronic hypoxaemia leads to systemic inflammation and oxidative stress promoting pro-fibrotic remodelling of the atrial tissue [98]. Individuals with airflow obstruction also have sympathetic overactivity which is involved in AF progression [98]. In patients with COPD, while atrial structural remodelling provides an AF-maintaining substrate, AF onset and paroxysms are frequently temporally related to acute exacerbations of COPD [98, 371]. All these changes induced by reduced lung function may be exacerbated by concomitant conditions such as hypertension, diabetes mellitus, obesity, obstructive sleep apnoea, and cardiac disease, and

ultimately constitute a complex and dynamic arrhythmogenic substrate for AF [98]. We also observed an increased risk of AF at high FEV1 and FVC values. This likely due to the confounder effect of height in predicting AF. Indeed, height is a well-known predictor of AF [2].This is further supported by the fact that the U shape curves of FEV1 and FVC flatten when using FEV1% predicted and FVC z-score that are both adjusted for height. In addition to these potential mechanisms, genome-wide association studies should explore coheritability between lung function and AF.

The finding of an association between reduced ventilatory function and incident AF implies that ventilatory parameters might be used to improve prediction of AF. Validated clinical risk scores to predict AF include the FHS, ARIC, CHARGE-AF, C_2HEST, and HATCH scores [372]. They use readily obtainable clinical variables, such as age, ethnicity, height, weight, blood pressure, smoking status, antihypertensive medication use, history of diabetes, heart failure, and myocardial infarction [372]. With area under the receiver operator curve (AUC) generally around 0.70 (AUC of 0.5 indicating no discrimination) [372], these scores need to be improved. Among the ventilatory parameters evaluated in our study, those standardized for age, sex, ethnicity, and height had a more consistent relationship with the risk of AF. Because of their U-shape relationship with incident AF, non-standardized FEV1 and FVC are unlikely to fit well in risk prediction models. A similar U-shape relationship was observed between FEV1/FCV z-score and incident AF whereby patients with FEV1/FVC z-score < 0 had an increased risk of incident AF, whereas there was no significant association with incident AF for FEV1/FVC z-score > 0. This also suggests that FEV1/FVC z-score might not be appropriate for risk prediction. However, the ratio FEV1/FVC seem to have the best association with incident AF as suggested by its nearly linear association. This suggest that airway obstruction is more predictive of AF rather than isolated reduced lung volumes. Notably, the significance of airway disease towards AF risk is already appreciated in the

C_2HEST and HATCH scores, where a diagnosis of COPD is a variable in these risk stratification models.

Our data also suggest that the FEV1/FVC cut-off of 0.70 which is used to define airway obstruction [373] does not appropriately predict AF risk as some participants with values ≥ 0.70 would still be at increased risk, compared to those with even higher FEV1/FVC ratios. Further studies are needed to evaluate the added value of ventilatory function parameters in AF risk prediction models.

Considering the increased risk of AF associated with COPD as shown in this study and the reported high prevalence of AF in patients with COPD in some cohorts (up to 25%) [98], searching for AF in patients with COPD is crucial. This can be done using 12-lead electrocardiogram during routine clinic visits and hospital admissions. Appropriate rhythm monitoring strategies in patients with COPD should be determined. We also observed an increased risk of AF associated with asthma. There is limited data on potential mechanisms underlying the association between asthma and AF. Proposed mechanisms include shared inflammatory pathways of asthma and AF [374], and dysfunction of the airway autonomic nervous observed in patients with asthma that may induce atrial electrical changes leading to AF [375]. A previous study showed that asthma and lack of asthma control were associated with moderately increased risks of AF in a dose-response manner [376]. This stress the importance of asthma control for AF prevention. Further investigations should determine whether asthma could have an added value in AF risk prediction.

Our study has some limitations. First, participants included in our analysis were exclusively white and relatively healthy which may compromise its generalizability. However, it offers a cohort of patients with spirometry measurements of an unprecedented size, larger than the combined number of participants in previous major studies on the association between lung function and AF [23, 99-102]. A previous study on the association of

ventilatory function with mortality using several British cohorts demonstrated that the findings from the UKB were similar to those from more representative cohorts, hence generalizable to the British population [361]. Second, although we performed extensive adjustment in multivariable regression analyses, unmeasured and residual confounders may not have been accounted for. Third, because this study was retrospective and the assessment of comorbidities were at least partly done by self-report and ICD code identification, there is a potential of self-report bias and ascertainment bias from coding errors and disease misclassification. Furthermore, the definition of incident AF in our study could have excluded cases of paroxysmal AF that might not have been detected by ECG or by hospital diagnosis.

2.5 Conclusion

Our findings indicate that reduced ventilatory function is associated with increased risk of AF independently of age, sex, smoking, and several other known AF risk factors. However, there was increased risk of AF at high FEV1 and FVC values, likely representing the confounder of height in predicting AF. Future studies should assess the added value of ventilatory parameters in AF risk prediction models. Considering the high risk of AF associated with COPD and the frequent co-existence of these conditions, appropriate rhythm monitoring strategies for AF detection in patients with COPD should be determined.

2.6 Tables and figures

Table 1. Baseline characteristics of the study population

Table 2. Association between chronic obstructive pulmonary disease, asthma and incident atrial fibrillation

Figure 1. Participant selection

Figure 2. Incidence of AF in relation to FEV1 (Panel A), FEV1 percentage predicted (Panel B) and GLI-2012 z-score for FEV1 (Panel C)

Figure 3. Incidence of AF in relation to FVC (Panel A) and GLI-2012 z-score for FVC (Panel B)

Figure 4. Incidence of AF in relation to FEV1/FVC (Panel A) and GLI-2012 z-score for FEV1/FVC (Panel B)

Figure 5. Graphical abstract

Supplementary Table .1. Akaike information criterion (AIC) of the regression model using different numbers of knots for each ventilatory parameter

Supplementary Table 2. Characteristics of the participants excluded

Supplementary Table 3 Baseline characteristics of study population by asthma and/or chronic obstructive pulmonary disease diagnosed at baseline

Table 1. Sociodemographic characteristics of the study population

Variables	Total (n = 465225)	Incident AF (n = 25592)	No incident AF (n = 439633)	P value
Sociodemographic				
Age, years	58.5 (50.8, 63.7)	63.9 (59.7, 67.1)	58.0 (50.5, 63.4)	<0.001
• Females	54.8	38.0	55.8	<0.001
Lifestyles				
• Current smokers	10.5	11.3	10.5	<0.001
• Current alcohol drinkers	93.2	91.5	93.3	<0.001
• Physical activity (MET-min/week)	1780 (813, 3570)	1790 (756, 3680)	1780 (813, 3570)	<0.001
Anthropomorphic parameters				
• BMI, kg/m^2	26.7 (24.1, 29.8)	28.2 (25.3, 31.8)	26.6 (24.1, 29.7)	<0.001
Co-morbidities (in percentage)				
• Hypertension	27.8	48.8	26.6	<0.001
• Diabetes mellitus	4.9	10.8	4.6	<0.001
• Hyperlipidemia	13.5	24.6	12.8	<0.001
• Chronic kidney disease	0.3	1.0	0.3	<0.001
• Heart failure	0.4	1.8	0.3	<0.001
• Valvular heart disease	1.0	3.7	0.8	<0.001
• Coronary artery disease	5.4	15.6	4.8	<0.001
• Obstructive sleep apnea	0.7	1.5	0.6	<0.001
• COPD	1.7	3.9	1.5	<0.001
• Asthma	11.6	12.9	11.5	<0.001
Ventilatory function				
• FEV1 (L)	2.77 (2.30, 3.36)	2.69 (2.16, 3.27)	2.77 (2.31, 3.36)	<0.001
• FEV1 percentage predicted (%)	96.6 (85.9, 107)	91.7 (79.0, 103)	96.8 (86.2, 107)	<0.001

• FVC (L)	3.65 (3.06, 4.42)	3.65 (2.97, 4.40)	3.65 (3.06, 4.42)	<0.001
• FEV1/FVC	0.765 (0.724, 0.798)	0.749 (0.703, 0.785)	0.766 (0.725, 0.799)	<0.001

Data are expressed as proportions (%) or as median (Q1, Q3)

BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MET: metabolic equivalent of task

Table 2. Association between chronic obstructive pulmonary disease and incident atrial fibrillation

Adjusted models	HR	LCL	UCL	P value
Model 1	1.61	1.48	1.75	<0.001
Model 2	1.45	1.33	1.58	<0.001
Model 3	1.36	1.24	1.48	<0.001

HR: hazard ratio; LCL: 95% lower confidence limit; UCL: 95% upper confidence limit
Model 1: sex, age, race, education, Townsend deprivation index, and assessment centre
Model 2: all variables from model 1, as well as smoking status, smoking pack-years, alcohol drinker status, alcohol amount, BMI, and total MET-minutes/week.
Model 3: all variables from model 2, as well as comorbidities including hypertension, diabetes mellitus, dyslipidemia, heart failure, coronary artery disease, heart failure, valvular disease, obstructive sleep apnea, and chronic kidney disease

Figure 1. Participant selection

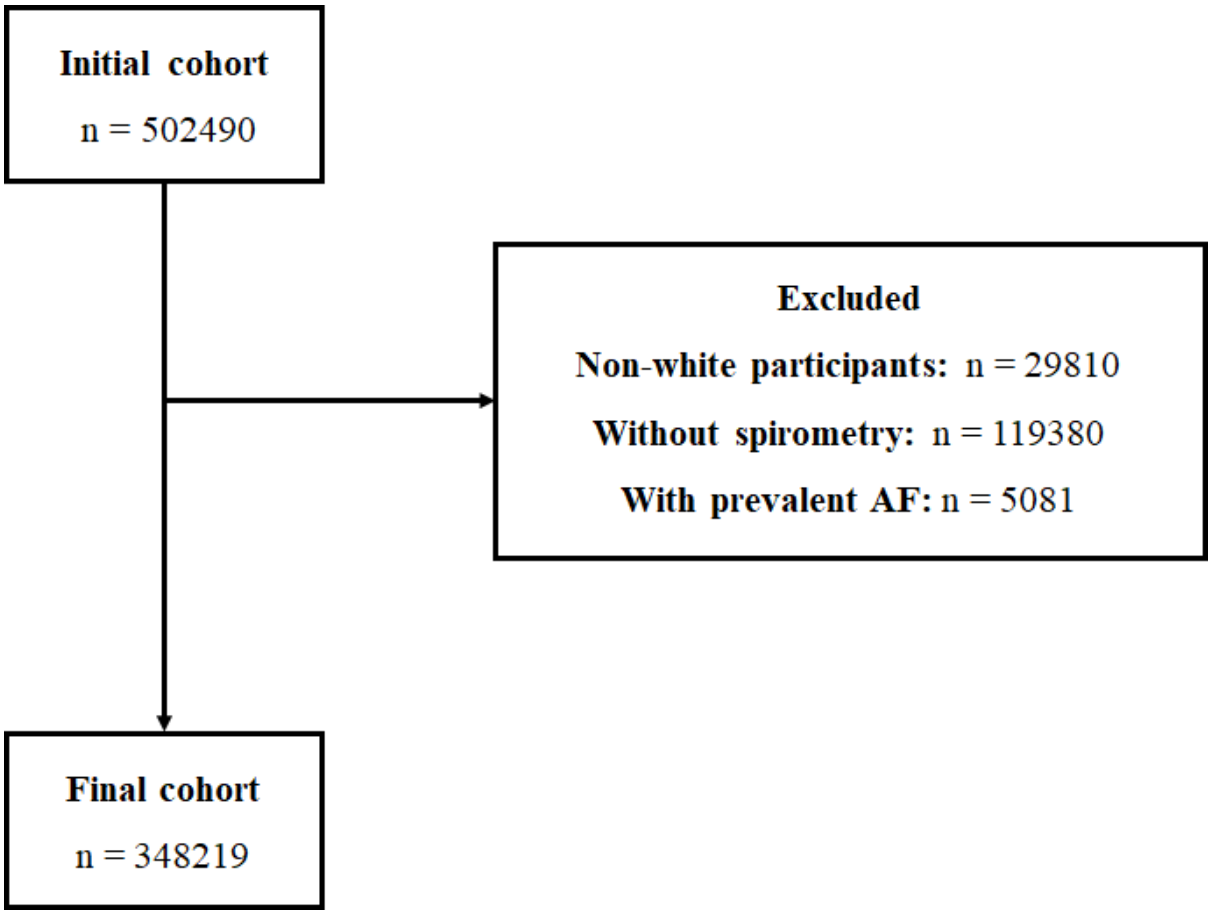


Figure 2. Incidence of AF in relation to FEV1 (Panel A), FEV1 percentage predicted (Panel B) and GLI-2012 z-score for FEV1 (Panel C)

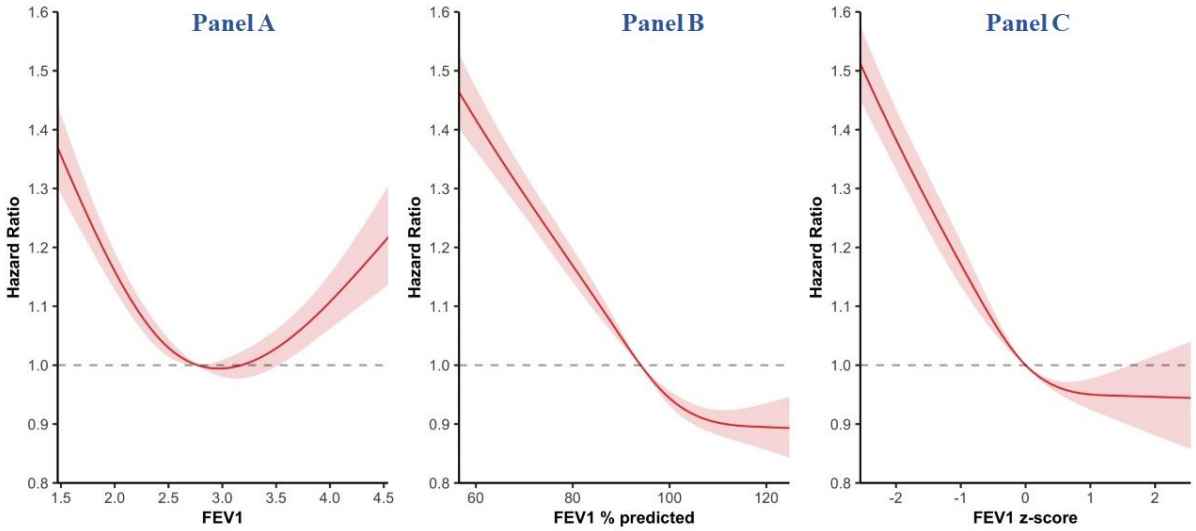


Figure 3. Incidence of AF in relation to FVC (Panel A) and GLI-2012 z-score for FVC (Panel B)

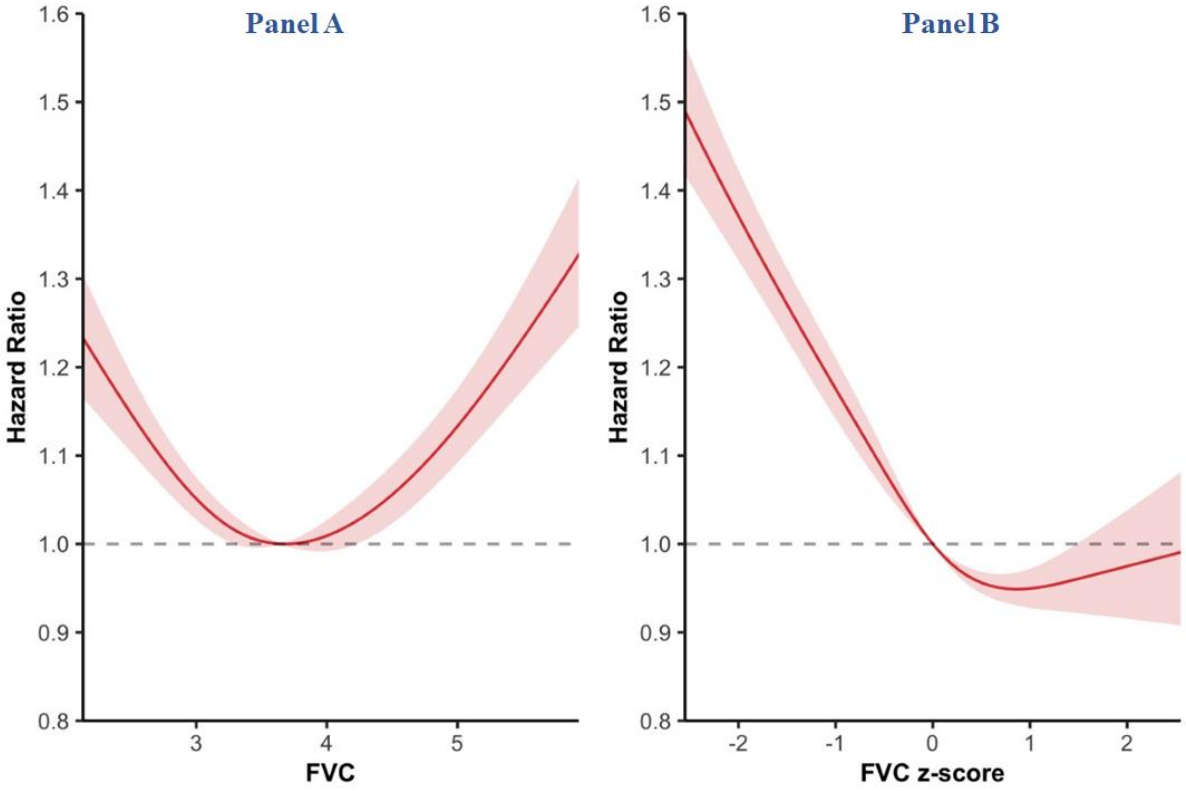


Figure 4. Incidence of AF in relation to FEV1/FVC (Panel A) and GLI-2012 z-score for FEV1/FVC (Panel B)

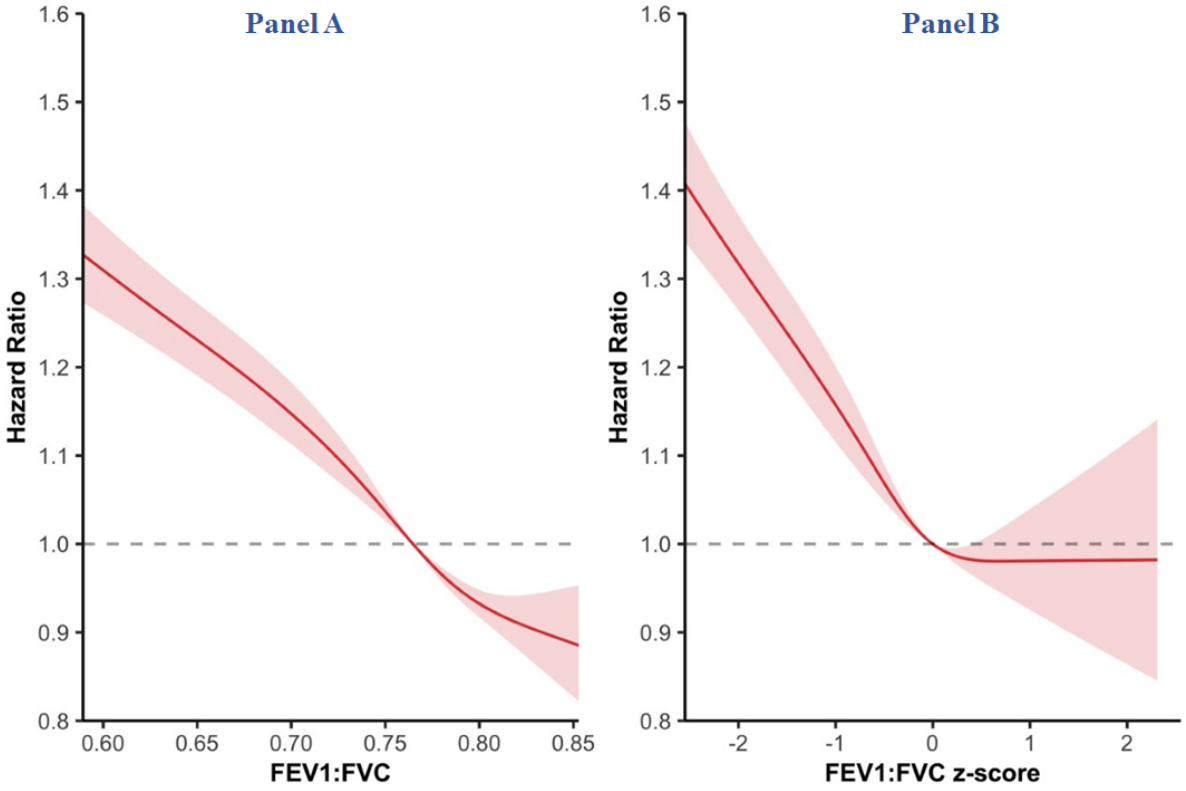
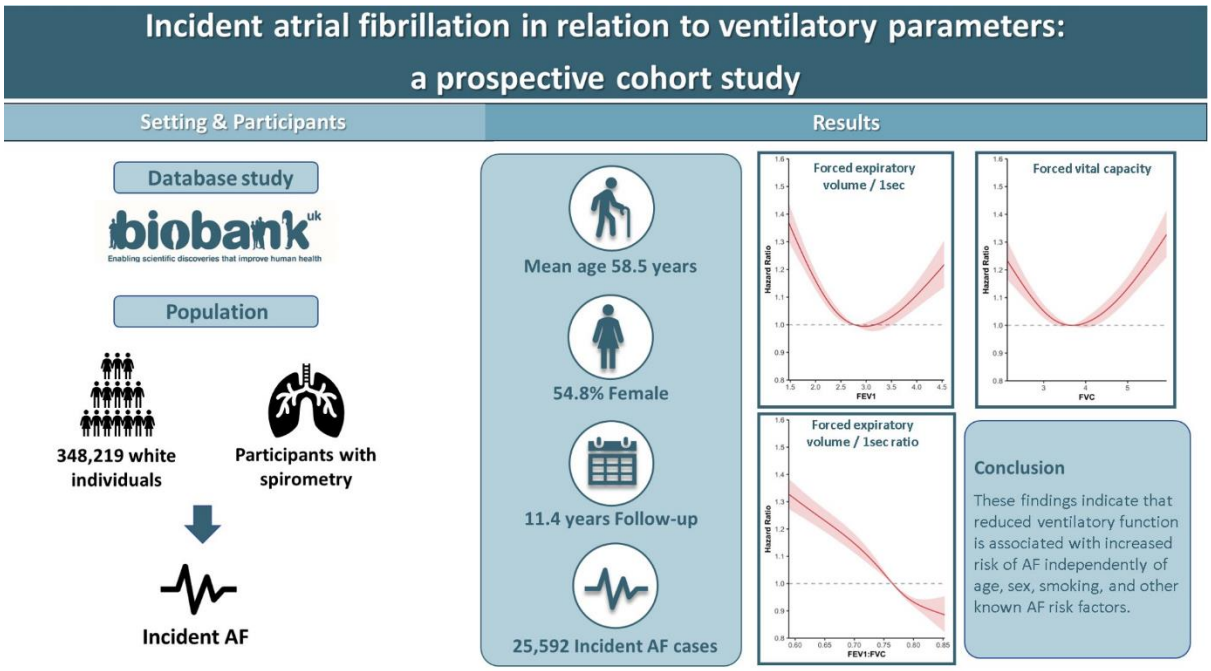


Figure 5. Graphical abstract



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2.7 Appendix

Supplementary Table 1. Akaike information criterion (AIC) of the regression model using different numbers of knots for each ventilatory parameter

	Numbers of knots			
	Three	**Four**	**Five**	**Six**
FEV1	287731.2	**287731.0**	287731.8	287733.9
FVC	**287767.7**	287768.7	287770.5	287771.8
FEV1:FVC ratio	287647.8	**287645.0**	287646.2	287646.1
FEV1 percentage predicted	287490.3	**287484.8**	287486.2	287486.4
FEV1 z-score	287481.7	**287478.0**	287479.7	287480.1
FVC z-score	287601.9	287595.3	**287594.8**	287595.7
FEV1:FVC z-score	287683.0	**287679.7**	287681.4	287682.6

The Akaike information criterion (AIC) is used to compare the quality of different models and is an estimator of out-of-sample prediction error. A lower AIC score is generally considered better, and a meaningful difference between two scores is generally considered >2.[377] The knots were placed at the following quantiles: for three knots, 0.1, 0.5, 0.9; for four knots, 0.05, 0.35, 0.65, 0.95; for five knots, 0.05, 0.275, 0.5, 0.725, 0.95; for six knots, 0.05, 0.23, 0.41, 0.59, 0.77, 0.95.

Supplementary Table 2. Characteristics of the participants excluded

				Standardised differences	
Variables	**UK Biobank (n = 502490)**	**Spirometry data available (n = 353000)**	**Spirometry data not available (n = 149190)**	**Cohen's *D***	**Cramer's *V***
Sociodemographic					
Age, years	58.3 (50.6, 63.7)	58.2 (50.7, 63.5)	58.4 (50.2, 64.0)	0.006	–
• Females	54.4	53.8	55.9	–	0.019
• White ethnicity	94.1	100	80.0	–	0.386
Lifestyles					
• Current smokers	10.5	10.2	11.4	–	0.018
• Current alcohol drinkers	91.6	93.7	86.6	–	0.117
• Physical activity (MET-min/week)	1770 (798, 3550)	1810 (832, 3600)	1650 (711, 3390)	0.059	–
Anthropomorphic parameters					
• BMI, kg/m^2	26.7 (24.1, 29.9)	26.7 (24.2, 29.8)	26.9 (24.1, 30.2)	0.036	–
Co-morbidities (in percentage)					
• Atrial fibrillation	1.5	1.4	1.8	–	0.012
• Hypertension	28.4	27.2	31.4	–	0.042
• Diabetes mellitus	5.5	4.7	7.5	–	0.057
• Hyperlipidemia	13.9	13.3	15.5	–	0.029
• Chronic kidney disease	0.4	0.3	0.5	–	0.018

• Heart failure	0.6	0.5	0.9	–	0.022
• Valvular heart disease	1.2	1.1	1.4	–	0.012
• Coronary artery disease	5.9	5.1	7.7	–	0.050
• Obstructive sleep apnoea	0.7	0.6	0.8	–	0.009
• COPD	2.2	1.8	3.2	–	0.044
• Asthma	12.1	12.2	12.0	–	0.002

Data are expressed as proportions (%) or as median (Q1, Q3). All comparisons between groups were $p<0.001$, except for asthma which was $p=0.10$. BMI: body mass index; COPD: chronic obstructive pulmonary disease; MET: metabolic equivalent of task

Supplementary Table 3. Baseline characteristics of study population by asthma and/or chronic obstructive pulmonary disease diagnosed at baseline

Variables	Total (n = 348219)	Neither (n = 302275)	Asthma (n = 39955)	COPD (n = 3552)	Both (n = 2437)
Sociodemographic					
• Age, years	58.1 (50.8, 63.5)	58.2 (50.7, 63.5)	56.6 (49.1, 62.8)	62.5 (57.4, 66.2)	61.8 (56.0, 65.8)
• Females	54.1	53.7	58.0	46.6	54.8
Lifestyles					
• Current smokers	10.2	10.2	8.3	25.0	22.3
• Current alcohol drinkers	93.8	94.0	92.8	89.9	87.9
• Physical activity (MET-min/week)	1820 (834, 3610)	1840 (852, 3630)	1720 (758, 3480)	1750 (693, 3870)	1440 (495, 3330)
Anthropomorphic parameters					
• BMI, kg/m^2	26.7 (24.1, 29.8)	26.6 (24.1, 29.6)	27.1 (24.4, 30.5)	27.3 (24.5, 30.6)	28.2 (25.0, 32.2)
Co-morbidities (in percentage)					
• Hypertension	26.8	26.4	27.7	39.2	44.0
• Diabetes mellitus	4.6	4.4	5.2	8.2	11.4
• Hyperlipidemia	13.0	12.9	12.3	22.4	23.2
• Chronic kidney disease	0.3	0.3	0.3	0.7	1.2
• Heart failure	0.3	0.3	0.4	1.6	1.9
• Valvular heart disease	0.9	0.9	0.9	1.6	1.8

• Coronary artery disease	4.8	4.5	4.8	14.7	18.8
• Obstructive sleep apnoea	0.6	0.6	0.8	1.6	2.5
Ventilatory function					
• FEV1 (L)	2.77 (2.30, 3.36)	2.81 (2.34, 3.39)	2.56 (2.10, 3.11)	2.25 (1.69, 2.83)	2.00 (1.51, 2.55)
• FEV1 percentage predicted (%)	94.0 (83.7, 104)	95.0 (85.1, 105)	87.8 (76.5, 98.3)	79.4 (63.1, 92.9)	72.6 (56.3, 88.0)
• FVC (L)	3.65 (3.06, 4.42)	3.68 (3.09, 4.45)	3.50 (2.92, 4.27)	3.23 (2.61, 3.96)	2.99 (2.46, 3.68)
• FEV1/FVC	0.765 (0.724, 0.798)	0.768 (0.730, 0.801)	0.738 (0.685, 0.780)	0.705 (0.621, 0.763)	0.677 (0.588, 0.747)

Data are expressed as proportions (%) or as median (Q1, Q3). All comparisons for a difference between groups were $p<0.001$ with the Kruskal-Wallis or chi-squared tests as appropriate.

BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MET: metabolic equivalent of task

CHAPTER 3:

Searching for atrial fibrillation after stroke

Publication 1

Statementof Authorship

Title of Paper	Atrial fibrillation detection using insertable cardiac monitor after stroke: a real-word cohort study
Publication Status	☒ Published ☐ Accepted for publication ☐ Submitted for publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Noubiap JJ**, Thomas G, Middeldorp ME, Fitzgerald JL, Harper C, Sanders P. Atrial fibrillation detection using insertable cardiac monitor after stroke: A real-world cohort study. J Cardiovasc Electrophysiol. 2022 Nov 9. doi: 10.1111/jce.15744. Epub ahead of print. PMID: 36349715.

Principal Author

Name of Principal Author (Candidate)	Jean Jacques Noubiap Nzeale		
Contribution to the Paper	Conception and design, access to data, data analysis, data interpretation, manuscript drafting, manuscript revision		
Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Publication 2

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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Overview

This chapter focuses on AF screening after stroke. It is divided in two sections. The first section reports AF diagnostic yield in a real-world cohort of patients receiving prolonged cardiac monitoring with implantable cardiac monitor (ICM) for stroke. The second section is a systematic review with meta-analysis that summarizes data on AF detection rates across different rhythm monitoring strategies (non-invasive and ICM) at precise time points (e.g. 1 month, 3 months, 6 months, 12 months, 24 months or 36 months) in patients with cryptogenic stroke or ESUS, and explores factors influencing these detection rates.

3.1 Atrial fibrillation detection using insertable cardiac monitor after stroke: a real-word cohort study

3.1.1 Introduction

Atrial fibrillation (AF) is a major cause of ischemic stroke [104]. AF-related cardioembolism accounts for up to one-third of all ischemic strokes [104], and AF increases the risk of recurrent ischemic stroke by 15% during the first year after stroke. Furthermore, the case fatality and disability are worse in ischemic strokes due to AF compared to those from other causes [106, 107]. There is also a substantial fraction of ischemic strokes for which the likely cause cannot be identified by routine investigations [106]. A proportion of these embolic strokes of undetermined source could be due to paroxysmal, asymptomatic AF [104]. Searching for AF poststroke is critical because recurrent AF-related stroke can largely be prevented by oral anticoagulation [104].

The rates of AF detection poststroke vary significantly depending on the population, the monitoring strategy, the length of monitoring, and the duration cut-off to define AF episodes [104]. Insertable cardiac monitors (ICM) have become an important tool for AF diagnosis after stroke [104]. The seminal Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial revealed significantly increased AF detection with prolonged continuous cardiac monitoring with ICM over standard-of-care monitoring in patients with cryptogenic stroke [148]. In this trial, the rate of AF detection was 12.4% at 12 months and 30.0% at 36 months of monitoring using ICM [148]. These detection rates in clinical trials might be different in real-word settings. In a real-world cohort of patients receiving prolonged cardiac monitoring with ICM, the current study aimed to report the AF diagnostic yield in patients undergoing monitoring after stroke, and to compare it to the yield in patients with ICM for unexplained syncope.

3.1.2 Methods

3.1.2.1 Study design and data source

This is an investigator-initiated retrospective multicenter observational cohort study including patients from device clinics across multiple states in the United States of America (Alabama, Colorado, Illinois, Kansas, Kentucky, Louisiana, Maine, New Jersey, Ohio, Oklahoma, South Carolina, Texas, Virginia), receiving remote monitoring using ICM via PaceMate™, a vendor-neutral digital technology software. Data were obtained from PaceMate LIVE™, a software system that automatically integrates all remote monitoring transmissions from multiple device vendor platforms and streamlines them into a single user interface.

3.1.2.2 Study population and diagnostic ascertainment

We included all patients receiving ICM for stroke or transient ischemic attack (TIA) (main group), and unexplained syncope (comparison group). Diagnoses were identified through the International Classification of Diseases, Tenth Revision (ICD-10) codes. Patients with known history of AF or atrial flutter were excluded. We collected data on age, sex, monitoring information including date of ICM implantation, date of AF detection, and duration of the AF episode.

The study outcome was AF defined as an episode of irregular rhythm without detectable P waves, lasting at least 2 minutes, detected by the ICM and adjudicated by a certified cardiac technician.

3.1.2.3 Statistical analysis

Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as mean with standard deviation (SD) or median with interquartile

range (IQR) as appropriate. AF detection rates were assessed using the Kaplan-Meier estimator. In addition to detection rates based on the cut-off duration of 2 minutes for an AF episode, rates were also determined for cut-offs of 6 minutes, 30 minutes and 60 minutes. Cox regression analysis was used to evaluate the impact of age and sex on AF detection rate. A p-value of < 0.05 was considered significant. All analyses were performed using IBM SPSS Statistics version 27.0 (Chicago, Illinois, USA) and STATA 16.1.

3.1.2.4 Ethical considerations

This study was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network, Adelaide, Australia (CALHN Reference Number: 14583).

3.1.3 Results

3.1.3.1 Sociodemographic and indications for ICM

We included a total of 2469 patients. The indication for ICM was stroke or TIA in 51.1% of them (n = 1262; 19.3% with TIA), and unexplained syncope in 48.9% (n = 1207). Those with ICM for stroke or TIA had a mean age of 69.7 (SD 12.2) years, with 41.1% being females; whereas those with ICM for unexplained syncope had a mean age of 67.0 (SD 17.1) years, with 59.4% being females.

3.1.3.2 AF detection rates

In this study with a median follow-up of 26.0 (IQR 13-29.3) months, AF ($\geq$ 2 min) was detected in 128 (10.1%) patients with stroke or TIA. The cumulative AF detection rate was 5.5% (95% CI: 4.3-7.0) at 12 months, 8.9% (95% CI: 7.2-10.9) at 24 months, and 14.0% (95% CI: 11.6-17.0) at 36 months (**Figure 1**). The median episode duration was 73 minutes

(IQR 10-456), ranging from 2 minutes to 40.9 days, with 52.3%, 28.6%, and 4.4% of episodes lasting at least 1 hour, 6 hours, and 24 hours, respectively. For comparison, the cumulative detection rate at 12, 24, and 36 months were respectively 2.4% (95% CI: 1.7-3.5), 5.2% (95% CI: 3.9-6.8), and 7.4% (95% CI: 5.7-9.6) in patients with unexplained syncope (**Figure 1**).

3.1.3.3 Impact of age and sex on AF detection

In patients with stroke or TIA, AF detection was increased by age (adjusted hazard ratio [for every 1-year increase] 1.02, 95% CI: 1.01-1.04; p = 0.003), but was not influenced by sex (p = 0.089) (**Table 1**).

3.1.3.4 Impact of AF duration cutoff on detection rates

Using different cutoff durations to define an AF episode resulted in different AF detection rates: 5.5% (≥ 2 min), 4.4% (≥6 min), 3.5% (≥30 min), and 3.0% (≥60 min) at 12 months; and 14.0% (≥ 2 min), 12.2% (≥6 min), 8.7% (≥30 min), and 7.5% (≥60 min) at 36 months (**Figure 2**).

3.1.4 Discussion

The main purpose of this study was to report the AF diagnostic yield of ICM in patients with stroke. In this large real-world cohort, we observed a cumulative AF detection rate of 14% at 36 months (**Figure 3**). The detection yield increased with age but did not differ between sexes. The AF diagnostic yield in patients with stroke in our study is lower than that reported in the landmark CRYSTAL AF trial, in which the rate of AF detection was 12.4% at 12 months, and 30.0% at 36 months of monitoring using ICM in patients with cryptogenic stroke [148]. The AF detection rate in our study is also lower than that of most previous studies using

ICM in patients with cryptogenic stroke or embolic stroke of undetermined source [378]. However, a similar detection rate to ours has been previously suggested. In a small sample of patients (n=145) who had ICM for cryptogenic stroke between 2014 and 2018 at New York University Langone Health [379], over a mean follow-up of 28 months, AF was diagnosed in 12% of patients, with detection rate being 7.6% at 12 months, 9% at 24 months, and 11.7% at 36 months [379].

There are a few plausible explanations for the lower detection rates in our study. We used a cut-off of 120 sec to define AF due to the reliability of detection documented by the Reveal Linq device. Although the CRYSTAL-AF study used the same device in terms of reliability, the study reports including AF episodes >30 seconds [148]. With a 30 sec cut-off definition, our AF detection yield might have been higher. In fact, we observed increasing AF detection rates with lower cut-offs (from 60 min to 2 min). Furthermore, the proportion of patients with TIA (19.3%), as the indication for monitoring in our study, was higher than what has been reported in several previous studies. For instance, this proportion was 9.5% in the CRYSTAL AF trial[148]. It has been shown that AF is more common in patients with ischemic stroke than in those with TIA [380]. In the absence of detailed clinical information, it was not possible for us to investigate the association between the clinical profile of patients and AF detection rates.

According to pooled data from previous studies, most cases of AF (about half) are detected in the first six months after ICM implantation following cryptogenic stroke [378]. We observed a different pattern in our study in which most cases of AF were detected more than 6 months after implantation. It is uncertain whether AF detected much later is responsible for the index stroke. These cases of AF might represent new onset AF resulting from increasing age and the impact of co-morbidities [104]. Indeed, in our study AF was also detected over time in patients with ICM for unexplained syncope, although the detection rate was almost half the

rate observed in patients with stroke or TIA. Further studies are needed to determine the clinical relevance of such cases of screen-detected AF, especially in view of the findings of the LOOP study in which ICM screening followed by anticoagulation initiation in cases with detected AF (duration ≥ 6 min) did not significantly reduce the risk of stroke or systemic embolism in individuals at high risk of stroke [381].

Our finding of higher AF detection with increasing age is consistent with what has been previously reported in patients with cryptogenic stroke or embolic stroke of undetermined source receiving prolonged continuous cardiac monitoring [378]. We found no association between sex and AF detection. A recent systematic review and meta-analysis showed an association of female sex with AF detection in patients with cryptogenic stroke [378]. However, this finding emerged from univariable pooled analysis that did not account for potential confounders, and the association between female sex and AF detection was driven by one study [378]. In general, most studies revealed that sex does not influence AF detection in this population [378].

Our study has some limitations. First, because this study was retrospective and based on data from a real-world remote monitoring registry using diagnosis codes, there is a potential of selection bias and ascertainment bias. Second, information on the time between stroke and ICM implantation, investigations done before ICM implantation, and clinical characteristics were not available. Such information would have helped understanding the AF detection rates observed in our study. Nevertheless, our study is one of the largest real-world cohorts of patients monitored with ICM after ischemic stroke [378].

3.1.5 Conclusion

This large real-world study shows lower AF detection rates in patients with ischemic stroke compared to what has been reported in most previous studies. The detection of AF increases with age but does not seem to be influenced by sex.

3.1.6 Table and figures

Table 1. Association of age and sex with atrial fibrillation detection in patients with stroke or transient ischemic attack

Figure 1. Cumulative atrial fibrillation detection rates in patients with stroke or transient ischemic attack and unexplained syncope

Figure 2. Cumulative atrial fibrillation detection rates in patients with stroke or transient ischemic attack according to different cutoff durations

Figure 3. AF detection yield in a real-word cohort of patients with ICM

Table 1. Association of age and sex with atrial fibrillation detection in patients with stroke or transient ischemic attack

	Univariable Cox regression		Multivariable Cox regression	
Factors	**Crude hazard ratio (95% CI)**	**P value**	**Adjusted hazard ratio (95% CI)**	**P value**
Age (years)	1.02 (1.01-1.04)	0.007	1.02 (1.01-1.04)	0.003
Male gender	1.64 (0.85-3.16)	0.143	1.78 (0.92-3.44)	0.089

CI: confidence interval

Figure 1. Cumulative atrial fibrillation detection rates in patients with stroke or transient ischemic attack and unexplained syncope

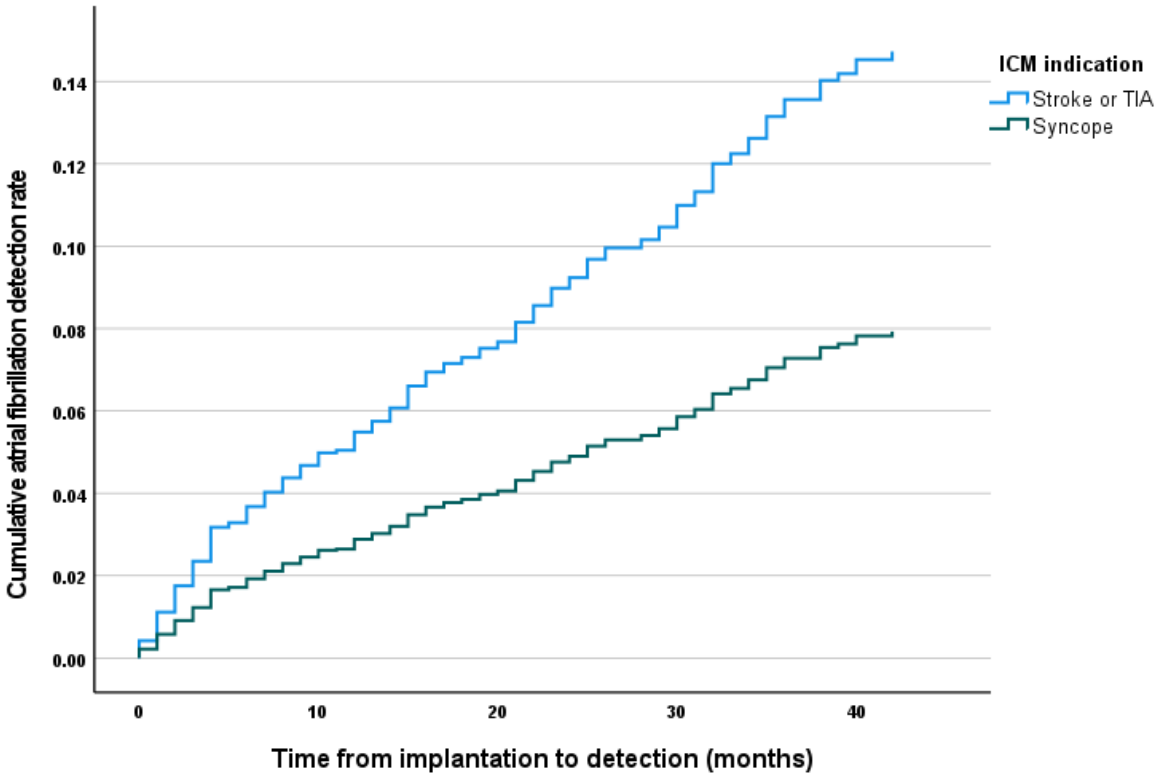


Figure 2. Cumulative atrial fibrillation detection rates in patients with stroke or transient ischemic attack according to different cut-off durations

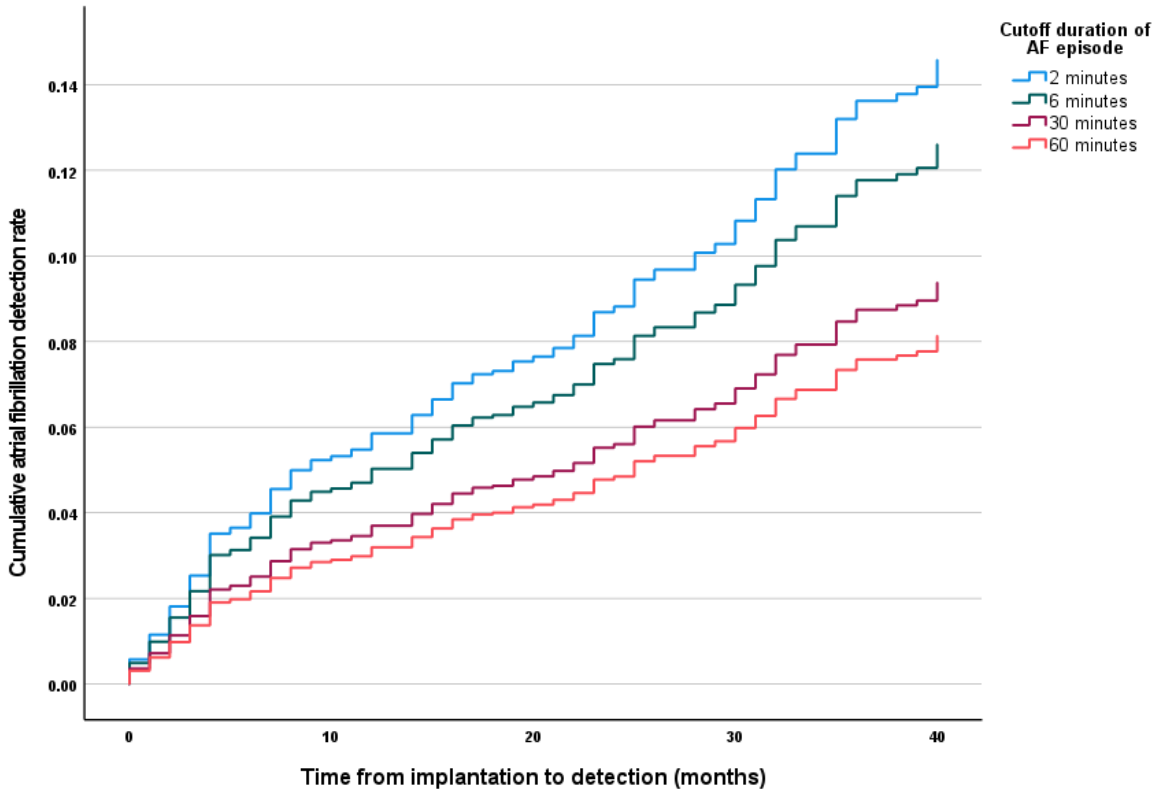
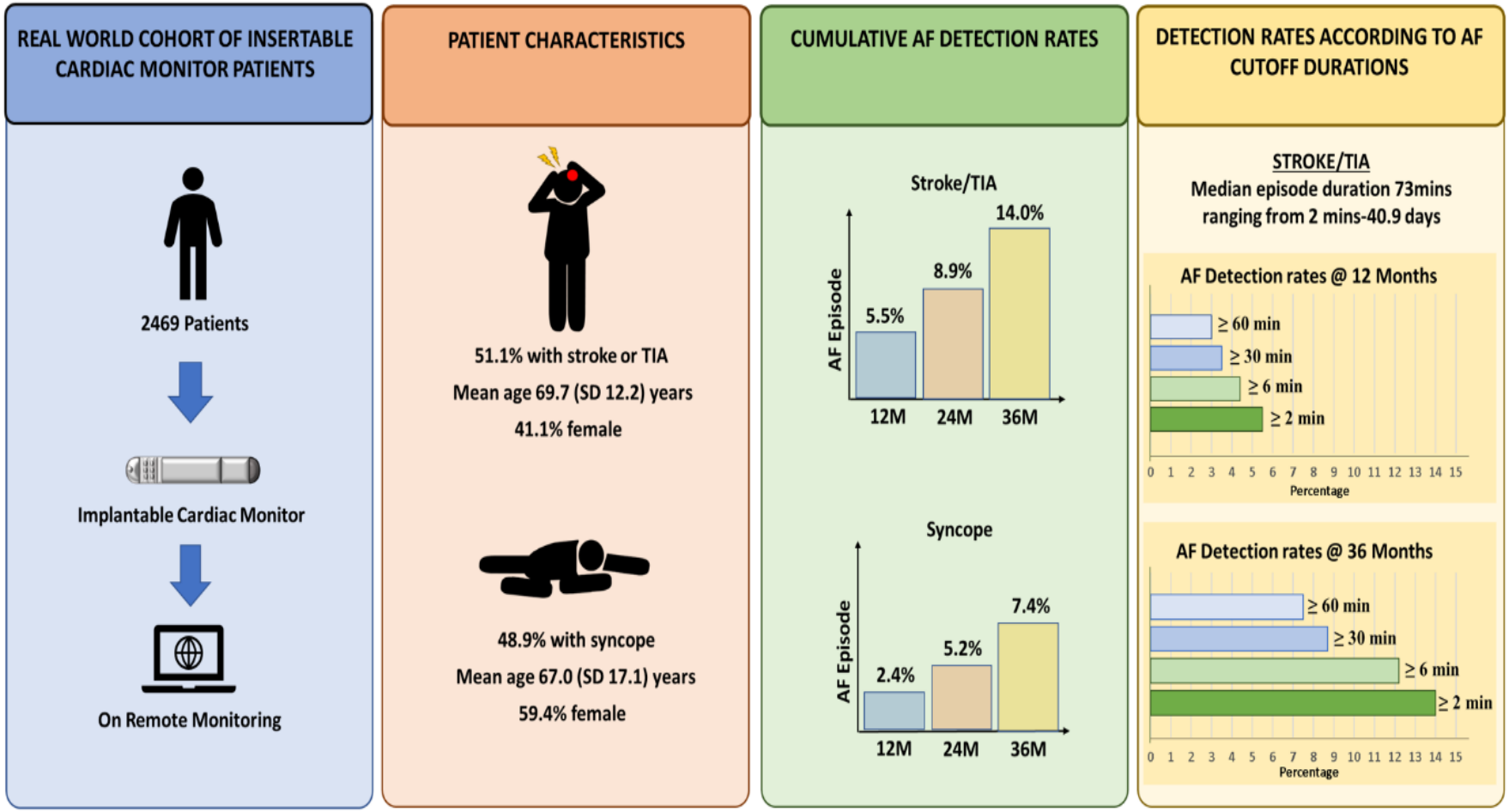


Figure 3. AF detection yield in a real-word cohort of patients with ICM



Legend. AF: atrial fibrillation; SD: standard deviation; TIA: transient ischemic attack

3.2 Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: A systematic review and meta-analysis

3.2.1 Introduction

Ischemic stroke is a leading cause of mortality and disability globally [382, 383]. Identifying stroke etiology is crucial for effective secondary prevention. However, in about one third of ischemic strokes, the likely cause cannot be identified despite extensive investigations according to current protocols [106]. AF-related cardioembolism is responsible for about one third of all ischemic strokes, and could be the underlying cause of a significant proportion of cryptogenic (CS) [104]. Ischemic stroke due to AF is associated with higher mortality and disability compared to stroke of other etiology [106, 107]. Because AF-related strokes can largely be prevented by oral anticoagulation, an active search for underlying AF is essential in patients with CS, including those with the more restrictive definition of embolic stroke of undetermined source (ESUS) [104].

According to the American Heart Association/American Stroke Association (AHA/ASA) guidelines the clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after acute ischemic stroke is uncertain (Class IIb; Level of Evidence C) and there is no consensus on the most appropriate modality and duration of monitoring [384]. The CRYSTAL AF trial was the first to evaluate the utility of prolonged continuous cardiac monitoring with implantable cardiac monitor (ICM) and demonstrated increased AF detection compared to standard-of-care monitoring in patients with CS (12.4% vs 2.0% at 12months) [148]. Several other studies have reported variable AF detection rates with ICM in patients with CS, depending on the length of monitoring or other potential factors such as the duration of qualifying AF episodes, or patient characteristics [104]. The current systematic review and meta-

analysis aimed to summarize data on AF detection rates across different rhythm monitoring strategies (non-invasive and ICM) at precise time points (e.g. 1 month, 12 months or 24 months) in patients with CS or ESUS, and to explore factors influencing these detection rates.

3.2.2 Methods

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines [385]. It was registered with PROSPERO (CRD42020204206).

3.2.2.1 Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science were searched to identify all cohort studies or randomized controlled trials (RCTs) reporting primary data on the rates and predictors of AF detection in patients with CS or ESUS, published by July 6, 2020 (date of the last search), without language restriction. The search strategy used a combination of the following terms or their synonyms "cryptogenic stroke", "embolic stroke of undetermined source", "atrial fibrillation", "implantable cardiac monitor", "holter" or "telemetry" (**Supplementary Table 1**). The reference lists of eligible articles were also scrutinized to identify potential additional data sources.

3.2.2.2 Study selection

We included: (1) cohort studies or RCTs, (2) with more than 30 participants, (3) reporting on rates and predictors of AF in patients with CS or ESUS, or studies with enough data to compute these estimates, (4) using either ICM or a non-invasive cardiac monitoring strategy. We excluded AF screening strategies such as 12-lead electrocardiography (ECG), 24-hour Holter or inpatient telemetry that are normally part of the minimum work-up for patients with acute ischemic stroke. For records/articles reporting data from the same group/cohort of

patients, we included the single most comprehensive report with the largest sample size. Two investigators (JJN and JKT) independently screened records for eligibility based on titles and abstracts. Full texts of articles deemed potentially eligible were retrieved and screened independently by the same investigators for final inclusion. Disagreements were resolved via discussion and consensus.

3.2.2.3 Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by second investigator (JKT). We collected data on study characteristics, study population (CS or ESUS), sample size, etiological work-up, definition criteria for CS or ESUS, mean or median time from event to initiation of monitoring, minimal duration of qualifying AF episodes (e.g. 30 sec, 2 min or more), monitoring device, mean or median age, sex proportion , frequency of/prevalence of/proportion of patients with co-morbidities such as hypertension, diabetes, heart failure or previous thromboembolism (stroke or transient ischemic attack [TIA]), number of participants with AF detected at various time points (3 weeks, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months and 36 months), and risk estimate (hazard ratio, odds ratio or relative risk) with the 95% confidence interval (95% CI) for each variable assessed as a potential predictor of AF. For each study, the risk of bias was assessed using an adapted version of the tool developed by Hoy et al. [386].

3.2.2.4 Statistical analysis

Analyses were conducted with R statistical software (version 3.6.2, The R Foundation for statistical computing, Vienna, Austria). We performed random-effects meta-analysis of detection rates using the inverse variance model. Clinical conditions potentially contributing to the variance of the estimates were evaluated by meta-regression, with the proportion of

categorical variables, such as diabetes, fitted on a continuous scale. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic [387], which was quantified by I^2 values, assuming that I^2 values of <25%, 50-75%, and >75% respectively represent low, medium, and high heterogeneity [388]. Heterogeneity across studies was further explored using the Leave-One-Out influencer analysis model, with the aim of detecting extreme effect sizes and assessing the influence of each study on the overall estimates. We assessed small-study effect by visual inspection of funnel plots and tests of funnel plot asymmetry (Egger's linear regression test). Next, we performed univariable random-effects meta-analyses to assess the association between clinical variables and AF detection rates, reporting this in odds ratio (OR) and 95% confidence interval (95% CI). For continuous variables, we converted the reported mean and standard deviations (SD) to standardized mean difference and rescaled to OR (95% CI) per SD change in the variable [389]. All statistical tests were two-tailed and statistical significance defined as p-value ≤0.05.

3.2.2.5 Ethical approval

This is a systematic review using published data. An ethic approval is not required.

3.2.3 Results

3.2.3.1 Study selection and characteristics

Database and bibliographic searches retrieved 1139 records and 47 articles were finally included (**Supplementary Figure 1**). The list of included studies and their characteristics are presented in the appendix (**Supplementary Table 2-4**). The included studies reported data from a pooled sample of 8,215 patients with CS or ESUS, were conducted between 2003 and 2019, and published between 2008 and 2020. Most studies were conducted in Europe (55.3%,

n = 26) and Northern America (36.2%, n = 17), with the most represented country being the U.S. (34.0%, n = 16). Most studies (59.6%, n = 28) had low risk of bias (**Supplementary Table 3**).

3.2.3.2 AF detection by implantable cardiac monitors

3.2.3.2.1 Rates of AF by duration of monitoring

The pooled rate of AF was 2.0% (95% CI 0.0-5.6, I^2 52%) at 1 week, 4.1% (95% CI 2.8-5.3, I^2 32%) at 1 month, 8.0% (95% CI 0.0-17.6, I^2 82%) at 2 months, 12.2% (95% CI 9.4-15.0, I^2 53%) at 3 months, 16.0% (95% CI 13.2-18.8, I^2 76%) at 6 months, 18.0% (95% CI 13.9-22.1, I^2 32%) at 9 months, 18.7% (95% CI 15.7-21.7, I^2 76%) at 12 months, 23.5% (95% CI 17.4-29.6, I^2 68%) at 18 months, 22.8% (95% CI 19.1-26.5, I^2 79%) at 24 months and 28.5% (95% CI 17.6-39.3, I^2 92%) at 36 months (**Table 1, Figure 1 [Panels A and B]**). Overall, AF detection rates significantly increased with duration of monitoring (p <0.001, **Figure 2**).

3.2.3.2.2 Rates of AF in ESUS versus CS

The pooled AF detection rate in ESUS vs CS was 16.4% (95% CI 11.0 – 21.9, I^2 41%) vs 10.7% (95% CI 7.8-13.6, I^2 43%) at 3 months (p = 0.067), 22.0% (95% CI 18.0 – 26.1, I^2 0%) vs 14.2% (95% CI 11.4-17.1, I^2 74%) at 6 months (p <0.001), 22.1% (95% CI 15.3-28.8, I^2 62%) vs 17.7% (95% CI 14.4 – 21.0, I^2 78%) at 12 months (p = 0.2579), 24.8% (95% CI 16.6 – 33.0, I^2 65%) vs 22.3% (95% CI 18.0 – 26.5, I^2 82%) at 24 months (p = 0.592) (**Table 1**).

3.2.3.2.3 Rates of AF by minimal duration of qualifying episodes

The rate of AF was lower in studies using a cut-off of 30 sec compared to those using a cut-off of 120 sec. The detection rate for the studies using a 30 sec cut-off vs studies using a 120

sec cut-off was 11.1% (95% CI 4.9-17.2, I^2 59%) vs 13.5% (95% CI 9.4-17.6, I^2 50%) at 3 months (p = 0.509), 9.9% (95% CI 6.1-13.7, I^2 59%) vs 19.2% (95% CI 15.5-22.9, I^2 71%) at 6 months (p = 0.001), 13.2% (95% CI 8.1-18.4, I^2 0%) vs 20.7% (95% CI 16.4 – 25.0, I^2 0%) at 9 months (p = 0.03), 12.9% (95% CI 9.8-15.9, I^2 0%) vs 22.2% (95% CI 18.6 – 25.9, I^2 69%) at 12 months (p < 0.001), 17.9% (95% CI 12.5-23.3, I^2 70%) vs 27.0% (95% CI 22.1-31.9, I^2 73%) at 24 months (p = 0.01) (**Table 1**).

3.2.3.2.4 Rates of AF by device type

The pooled AF detection rate was higher in studies using Reveal LINQ compared to those using Reveal XT, although the difference was not significant at all timepoints. The detection rate for Reveal LINQ vs Reveal XT was 15.1% (95% CI 11.8-18.4, I^2 0%) vs 9.7% (95% CI 5.4-14.0, I^2 47%) at 3 months (p = 0.052), 14.7% (95% CI 10.6-18.8, I^2 81%) vs 15.8% (95% CI 10.7-21.0, I^2 73%) at 6 months (p = 0.744), 19.1% (95% CI 14.9-23.3, I^2 82%) vs 13.0% (95% CI 9.7-16.3, I^2 0%) at 12 months (p = 0.001), 25.7% (95% CI 19.5-31.9, I^2 89%) vs 23.3% (95% CI 16.0-30.5, I^2 65%) at 24 months (p = 0.618) (**Table 1**).

3.2.3.2.5 Publication bias, meta-regression, and sensitivity analysis

There was evidence of publication bias by funnel plot analysis and by Egger's test (p < 0.01) only for studies reporting AF detection rates at 6 months (**Table 1, Supplementary Figures 2-5**). We performed meta-regression to assess the source of heterogeneity in the estimation of AF rates (**Supplementary Figures 6-9**). At 3 months of monitoring, history of hypertension accounted for most of the variation in AF detection rate (r^2=53.3%), though it was not significant (p = 0.07). At 6 months of monitoring, no variable significantly explained the variance in AF detection. At 12 months of monitoring, mean age and history of hypertension

explained 21.6% and 35.6% of the variation in AF detection rate, respectively, although it did not reach significance (p = 0.08 and 0.06, respectively). At 24 months of monitoring, history of dyslipidaemia explained most of the variance in the estimation (r^2 44.8%, p = 0.15).

Influencer analysis to ascertain the contribution of each study to the overall heterogeneity showed that no study markedly reduced the overall heterogeneity when its estimate was removed from the overall analysis (**Supplementary Figures 10-13**).

3.2.3.3 Predictors of AF detection

Data from 14 studies contributed to pooled univariable analysis of factors associated with AF detection (**Figure 3**). Age (OR 3.48, 95% CI 2.50 – 4.84), female sex (OR 1.35, 95% CI 1.04 – 1.74), left atrial size (OR 2.42, 95% CI 1.55 – 3.78), left atrial dilatation (>40 mm) (OR 1.55, 95% CI 1.08 – 2.23) and the CHA_2DS_2VASc score (includes age, sex, history of hypertension, diabetes, heart failure, vascular disease and stroke) (OR 1.84, 95% CI 1.00 – 3.38) were positively associated with AF detection.

Eleven studies reported multivariable estimates of potential predictors of AF detection (**Supplementary Table 5**). Due to high heterogeneity in these estimates, a meta-analysis was not performed. Age was consistently reported as a predictor of AF. In studies that used ICMs, other predictors included obesity, infarction in the posterior cerebral artery territory, total atrial conduction time assessed by tissue doppler imaging (PA-TDI Interval), left atrial enlargement, P wave maximal duration, prolonged PR interval and atrial runs (**Supplementary Table 5**).

3.2.3.4 Data on non-invasive cardiac monitoring strategies

Atrial fibrillation detection rates from studies that used non-invasive cardiac monitoring are reported in (**Supplementary Table 6**). A meta-analysis was only feasible for data on mobile cardiac outpatient telemetry (MCOT). The overall pooled AF detection rate (episode lasting at least 30 seconds) using MCOT was 9.5% (95% CI 5.6-13.4, I^2 64%) at 3 weeks and 13.7% (95% CI 10.2 – 17.2, I^2 64%) at 1 month (**Table 1, Figure 4**).

3.2.4 Discussion

This study aimed to summarize data on the rates and predictors of AF across different rhythm monitoring strategies at precise time points in patients with CS or ESUS. We found 1) a steady increase of AF rates with duration of monitoring using ICM; 2) higher rates of AF when the cut off of 120 seconds was used to define an episode of AF compared to 30 seconds; 3) higher rates of AF in patients with ESUS compared to those with CS; 4) association of older age, CHA_2DS_2-VASc score, PA-TDI Interval, left atrial enlargement, P wave maximal duration, prolonged PR interval and atrial runs with higher rates of AF detection.

Although there is still no specific recommendation on the optimal duration of prolonged cardiac monitoring [384], this study confirms that the longer the monitoring, the higher the AF detection rates in patients with CS. Therefore, it might be judicious to continue monitoring as long as possible until AF is detected. Most studies reported data on AF detection up to a maximum duration of ~ 36 months, probably because the current ICMs have about 3-year longevity. Although, as expected, the AF detection rate increases with the duration of monitoring, most of cases of AF (about half) are detected in the first six months (Figure 2). Moreover, it is uncertain whether AF detected much later, after two or three years of monitoring for instance, has any causative role in the index stroke. It is possible that AF detected long after the index stroke is of new onset, as a result of all the risk factors for AF

that patients with stroke usually have, including older age and cardio-metabolic co-morbidities [104]. Furthermore, few studies have shown similar yield of new AF on ICM in patients with no stroke history and those with CS [104]. Altogether, these findings highlight the need to rethink the implications of prolonged continuous ECG monitoring after a stroke. Moreover, studies are needed to determine the adequate cutoff for AF burden that is significant and requires anticoagulation prophylaxis, as the current expert consensus to treat as significant any episode of AF $\geq$ 30 seconds detected by continuous monitoring after a stroke is not evidence-based [104].

The duration of cardiac monitoring to detect AF after an ischemic stroke might be individualized, based on a risk stratification score. The HAVOC score (abbreviation for Hypertension, Age, Valvular heart disease, peripheral Vascular disease, Obesity, Congestive heart failure, and coronary artery disease) was developed based on seven clinical factors to stratify the risk of AF occurrence in patients with CS or TIA. The score showed good discrimination (c-statistic 0.77) of patients into three risk categories (low, medium, and high), with the potential of being used to select patients for prolonged monitoring [390]. Imaging parameters such as LA dimension and PA-TDI Interval, or electrocardiographic markers including PR interval and maximum P wave duration, could be combined with clinical risk factors to design efficient risk score to predict the development of AF in patients with CS. Blood biomarkers such as cardiac natriuretic peptides may also be useful to refine AF risk stratification [391, 392].

We found that female sex was a correlate of AF detection in patients with CS. This finding contrasts with evidence of lower AF incidence rates in women in the general population [303]. In fact, in a large multi-country patient-level meta-analysis including 141,220 individuals, the screened-detected AF rates were consistently lower in women across all age strata [393]. The finding of higher AF detection rates in female patients with CS emerged from

univariable analysis and is, therefore, not free from potential confounders. Furthermore, the sensitivity analysis revealed that this association between female sex and AF detection was driven by one study [394]. No association between female sex and AF detection was observed after excluding that study (**Supplementary Figure 27**).

Atrial fibrillation detection rates using ICM were somewhat higher in patients with ESUS compared to those with CS across all timepoints, with a marked difference at 6 months. An ischemic stroke is considered cryptogenic when no definite cause is identified during the baseline etiological workup, whereas an ESUS is a clinical construct that refers to non-lacunar non-atherosclerotic ischemic strokes of presumable cardioembolic origin. The relative lower rate of AF in patients with CS highlights the greater heterogeneity of stroke etiologies in this subgroup while ESUS are pre-selected based on their likelihood of being embolic and, therefore, related to covert AF. Moreover, it is known that patients with ESUS who have an ipsilateral mild carotid stenosis are 2 times less likely to develop AF during follow-up [395], and there are evidence to suggest that the mild carotid stenosis instead of AF might be the actual cause of the stroke [396]. This further emphasizes the fact that a more comprehensive work-up and classification of stroke cases at baseline is important to increase the yield of ICM and may help optimize the cost-benefit ratio. Because advanced carotid and intracranial vascular imaging was not required for the definition of ESUS in the NAVIGATE-ESUS trial [397], it is possible that the residual heterogeneity of stroke aetiologies contributed to the neutral results of the trial.

This review shows that higher rates of AF were reported by studies using a 2-minute cut off to define an episode of AF on ICM than in those using a 30-second cut off. This observation should not be considered as indicative that AF detection rates are higher with a cut-off of 2 minutes compared to 30-seconds. This is actually counterintuitive, as the lower the cut-off, the higher the yield. In fact, the two cut-offs were not compared in the same

patients using the same devices. This unexpected finding can be partly explained by devices' capabilities to detect AF. While the 30-seconds cut off was established by consensus, the 2-minute cut off is the duration needed for an accurate detection by recent ICM. In fact, the most recent AF detection algorithms have a better episode detection accuracy than the older ones. For instance, the P-wave enhanced AF detection algorithm of Reveal LINQ is based on both R-R interval and a P-wave evidence score. The P-wave evidence score limits inappropriate AF detections in the original R-R interval pattern–based algorithm and leverages the evidence of a single P wave between two R waves using morphologic processing of the ECG signal [131]. The algorithm requires a 2-minute detection window. As a result, Reveal LINQ has better AF detection capabilities compared to the previous generation device Reveal XT [131]. Indeed, the detection rates in our study were higher with Reveal LINQ compared to the Reveal XT, although the difference was significant only at 6 months.

There was a relative high detection rate with 1-month MCOT, highlighting the importance of prolonged non-invasive cardiac monitoring before ICM. This is in keeping with AHA/ASA guidelines for secondary prevention of stroke which considers that cardiac rhythm monitoring for about a month is reasonable in the first six months following CS [384]. Although it is striking to see that the detection rate with 1-month MCOT (14.4%) was higher than the detection rate with ICM at the same timepoint (4.1%), these rates are unlikely comparable due to difference in populations' characteristics. In fact, patients who had an ICM were likely a more selected population who had extensive non-invasive monitoring before implantation and therefore, with a lower likelihood of AF detection compared to patients undergoing MCOT.

This study has some limitations. There were differences across studies, in terms of participants' clinical characteristics and extent of etiologic investigations done before reaching the diagnosis of cryptogenic stroke. Even within the same study, the etiologic work-up was not always standardized. For instance, not all stroke units have inpatient telemetry and

when available, only a small proportion of patients receives it [398]. The time between the index stroke and the start of monitoring, ICM for instance, was not always reported or when reported, it was done very differently across studies (Supplementary Table 3), making its contribution in interpreting the AF detection rates very limited. Moreover, many studies did not provide the criteria used to define ESUS. Therefore, it was not possible for us to make sure that appropriate criteria were applied. Furthermore, we could not appropriately investigate the predictors of AF detection. A multivariable meta-analysis was not possible due to insufficient data and inconsistent reporting across studies. Nevertheless, our review has important strengths. It has added value compared to previous systematic reviews on AF detection in the broader population of patients with ischemic stroke [399, 400]. Our study provides the most up-to-date estimates of AF detection rates and predictors from various rhythm monitoring strategies, specifically in patients with CS. We included only fully published peer-reviewed articles, not conference abstracts, to ensure that we have data with the highest possible quality and avoid including duplicates. All analyses were performed at precise timepoints (e.g. 3 months, 6 months, 12 months, 24 months), providing a better appreciation of the trends of AF rates over time.

3.2.5 Conclusion

This study shows that more than one quarter of patients with CS or ESUS will be diagnosed with AF during follow-up and that the yield of ICM increases with the duration of monitoring. About one in seven patients had AF detected within a month of MCOT, suggesting that a non-invasive monitoring strategy should be considered before invasive monitoring. Predictors of AF detection during monitoring include older age, CHA_2DS_2-VASc score, PA-TDI Interval, left atrial enlargement, P wave maximal duration, prolonged PR interval and atrial runs. Such

factors combined in a score might help in risk stratification and selection of patients for extended ICM monitoring.

3.2.6 Tables and Figures

Table 1. Pooled estimates of atrial fibrillation detection using invasive and non-invasive cardiac monitoring strategies

Figure 1. Panel A. Overall pooled atrial fibrillation detection rates on implantable cardiac monitor in patients with cryptogenic stroke (one week to 9 months)

Figure 1. Panel B. Overall pooled atrial fibrillation detection rates on implantable cardiac monitor in patients with cryptogenic stroke (12 months to 36 months)

Figure 2. Relationship of atrial fibrillation detection with duration of monitoring in patients with cryptogenic stroke. ***Legend****: the black bold line and dot lines represent the curves of atrial fibrillation detection and the upper and lower limits of the 95% confidence interval.*

Figure 3. Univariable correlates of atrial fibrillation detection on implantable cardiac monitors in patients with cryptogenic stroke

Figure 4. Overall pooled atrial fibrillation detection rates on mobile cardiac outpatient telemetry in patients with cryptogenic stroke

Table 1. Pooled estimates of atrial fibrillation detection using invasive and non-invasive cardiac monitoring strategies

Subgroup	Number of Studies	No. of patients		Detection rate (95% CI)	Heterogeneity		*Egger's* test (*P* value)
		Total	Cases		I^2	*P* value	
ICM monitoring							
3 months							
• Overall	11	1 098	143	12.19 (9.36 – 15.01)	52.8%	0.0199	0.0692
• Type of stroke							
- ESUS	3	307	51	16.44 (10.99 – 21.90)	41.2%	0.1827	0.0297
- CS	8	791	92	10.68 (7.77 – 13.58)	43.2%	0.0905	0.3490
• Cut off							
- 30 second	3	521	74	11.06 (4.94 – 17.18)	59.3%	0.0857	0.3150
- 120 second	6	255	29	13.54 (9.43 – 17.66)	49.5%	0.0779	0.0651
• Type of device							
- Reveal LINQ	4	447	69	15.07 (11.76 – 18.38)	0.0%	0.4718	0.6839
- Reveal XT	4	340	35	9.69 (5.39 – 14.00)	46.7%	0.1311	0.1187
6 months							
• Overall	18	3 223	476	16.00 (13.21 – 18.79)	76.3%	<.0001	0.0085
• Type of stroke							
- ESUS	4	408	91	22.05 (18.04 – 26.06)	0.0%	0.6027	0.2102
- CS	14	2 815	385	14.25 (11.41 – 17.09)	73.8%	<.0001	0.0864
• Cut off							
- 30 second	5	613	61	9.89 (6.12 – 13.66)	59.1%	0.0444	0.0555
- 120 second	11	2 288	360	19.22 (15.54 – 22.89)	71.1%	0.0001	0.0002
• Type of device							
- Reveal LINQ	7	2 132	293	14.72 (10.64 – 18.80)	80.8%	<.0001	0.2880
- Reveal XT	7	705	106	15.82 (10.67 – 20.96)	72.8%	0.0012	0.0098
- Reveal LINQ or XT	2	175	45	25.62 (19.16 – 32.08)	0.0%	0.5515	NE
12 months							

• Overall	16	3 310	603	18.71 (15.71 – 21.70)	76.3%	<.0001	0.1229
• Type of stroke							
- ESUS	4	372	86	22.08 (15.32 – 28.88)	61.8%	0.0492	0.5716
- CS	12	2 938	517	17.74% (14.45 – 21.03)	77.9%	<.0001	0.3224
• Cut off							
- 30 second	4	464	60	12.88 (9.84 – 15.93)	0.0%	0.9598	0.3096
- 120 second	9	2 379	461	22.21 (18.55 – 25.87)	69.0%	0.0011	0.0022
• Type of device							
- Reveal LINQ	8	2 460	448	19.14 (14.95 – 23.34)	82.0%	<.0001	0.2757
- Reveal XT	4	470	63	13.32 (10.25 – 16.39)	0.0%	0.9024	0.0333
- Reveal LINQ or XT	3	240	60	23.86 (11.47 – 36.26)	82.2%	0.0036	0.3252
24 months							
• Overall	13	2 901	661	22.78 (19.90 – 26.47)	78.6%	<.0001	0.4384
• Type of stroke							
- ESUS	3	312	79	24.79 (16.60 – 32.98)	64.7%	0.0586	0.8340
- CS	10	2 589	582	22.27 (18.02 – 26.52)	81.6%	<.0001	0.6144
• Cut off							
- 30 second	7	880	174	19.13 (13.84 – 24.42)	75.3%	0.0005	0.3194
- 120 second	5	1 926	459	26.98 (22.11 – 31.85)	72.5%	0.0057	0.0027
• Type of device							
- Reveal LINQ	7	2 262	530	25.70 (19.53 – 31.87)	89.2%	<.0001	0.2727
- Reveal XT	4	398	93	23.27 (16.00 – 30.54)	65.2%	0.0347	0.5355
MCOT monitoring							
• Overall	13	1745	218	11.76 (9.12 – 14.40)	65.4%	0.0005	0.1203
• Duration							
- 3 weeks	6	643	70	9.49 (5.55 – 13.43)	64.0%	0.0164	0.6172
- 1 month	7	1 102	148	13.67 (10.16 – 17.18)	63.8%	0.0110	0.0659

ICM: implantable cardiac monitor; MCOT: mobile cardiac outpatient telemetry

Figure 1. Panel A. Overall pooled atrial fibrillation detection rates on implantable cardiac monitor in patients with cryptogenic stroke (one week to 9 months)

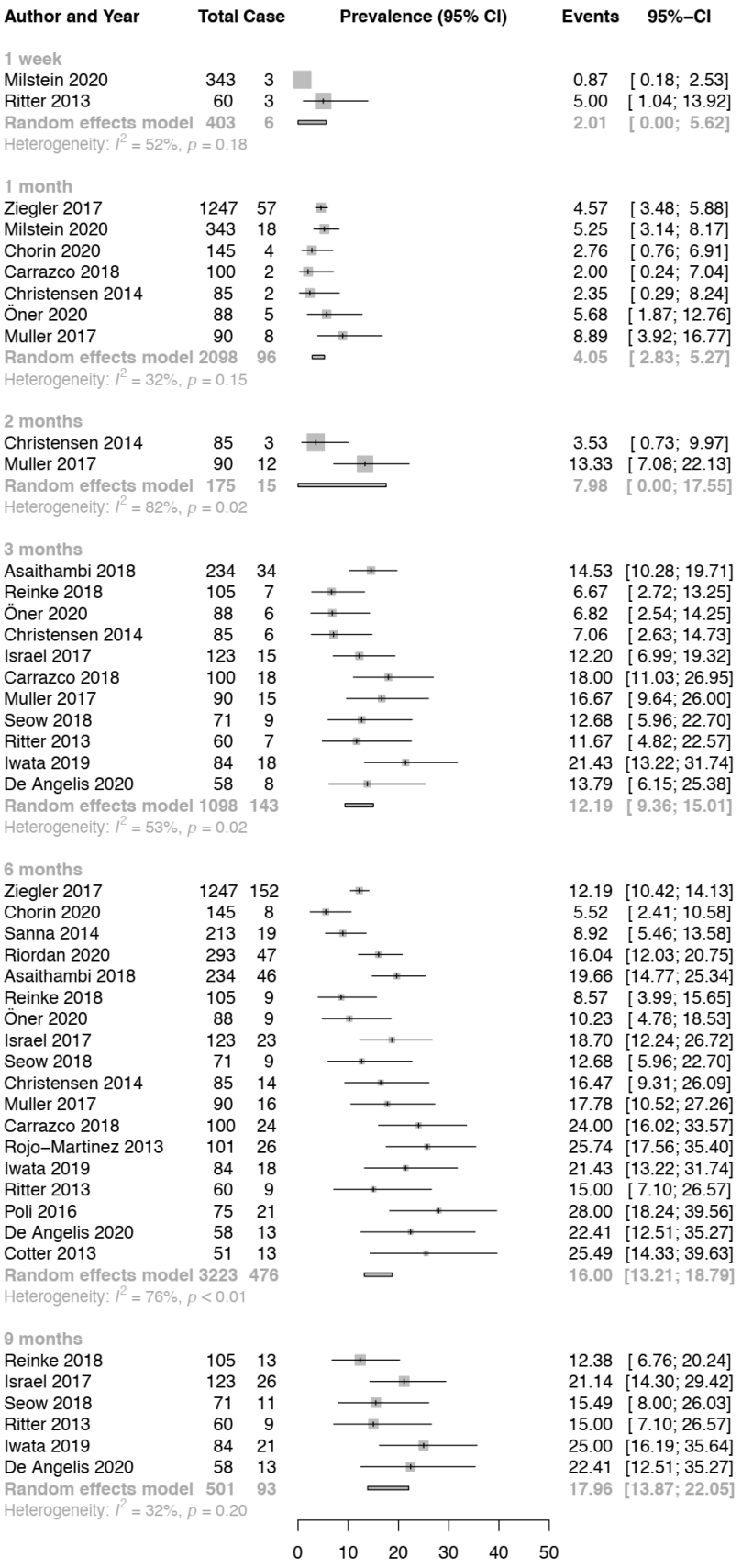


Figure 1. Panel B. Overall pooled atrial fibrillation detection rates on implantable cardiac monitor in patients with cryptogenic stroke (12 months to 36 months)

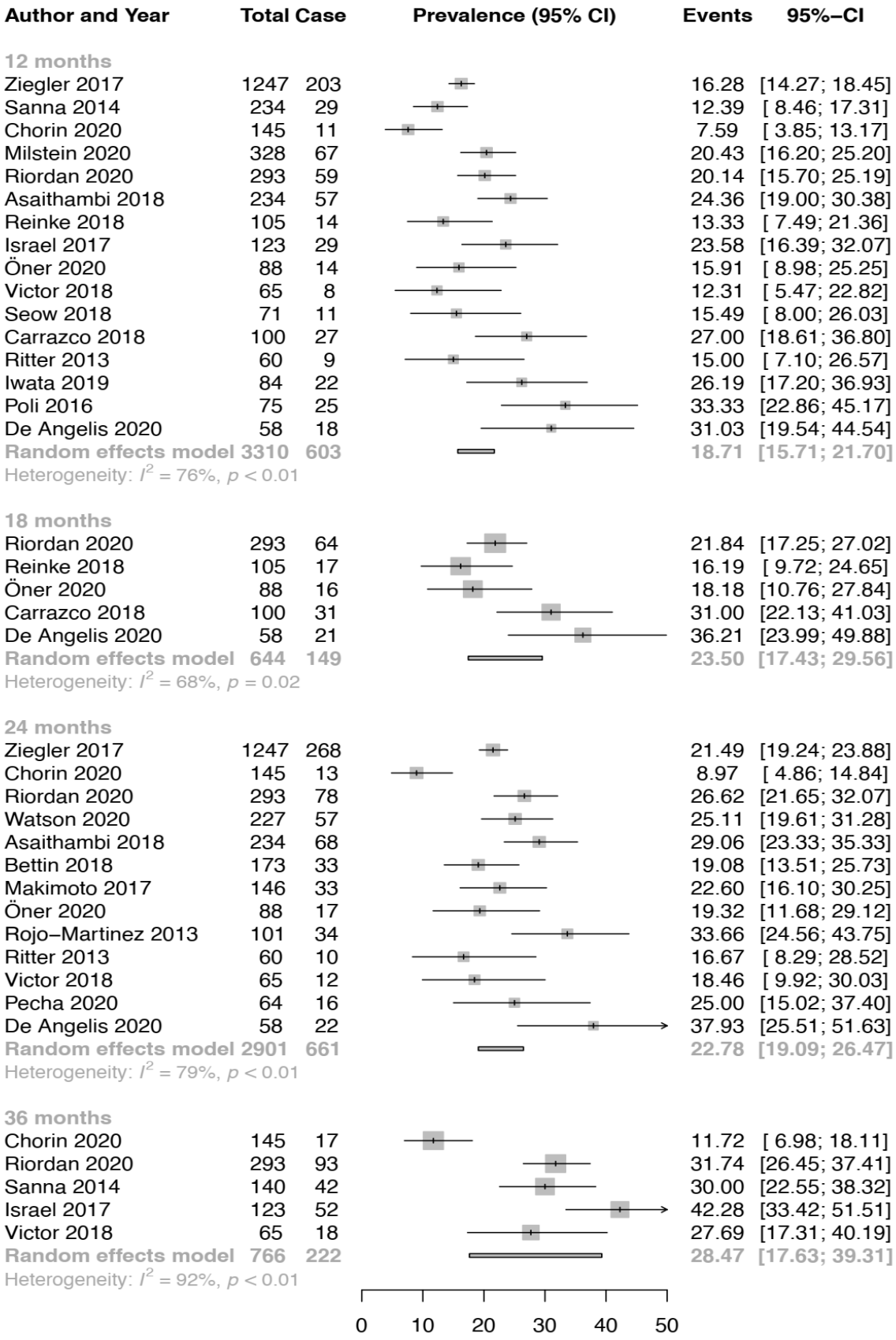
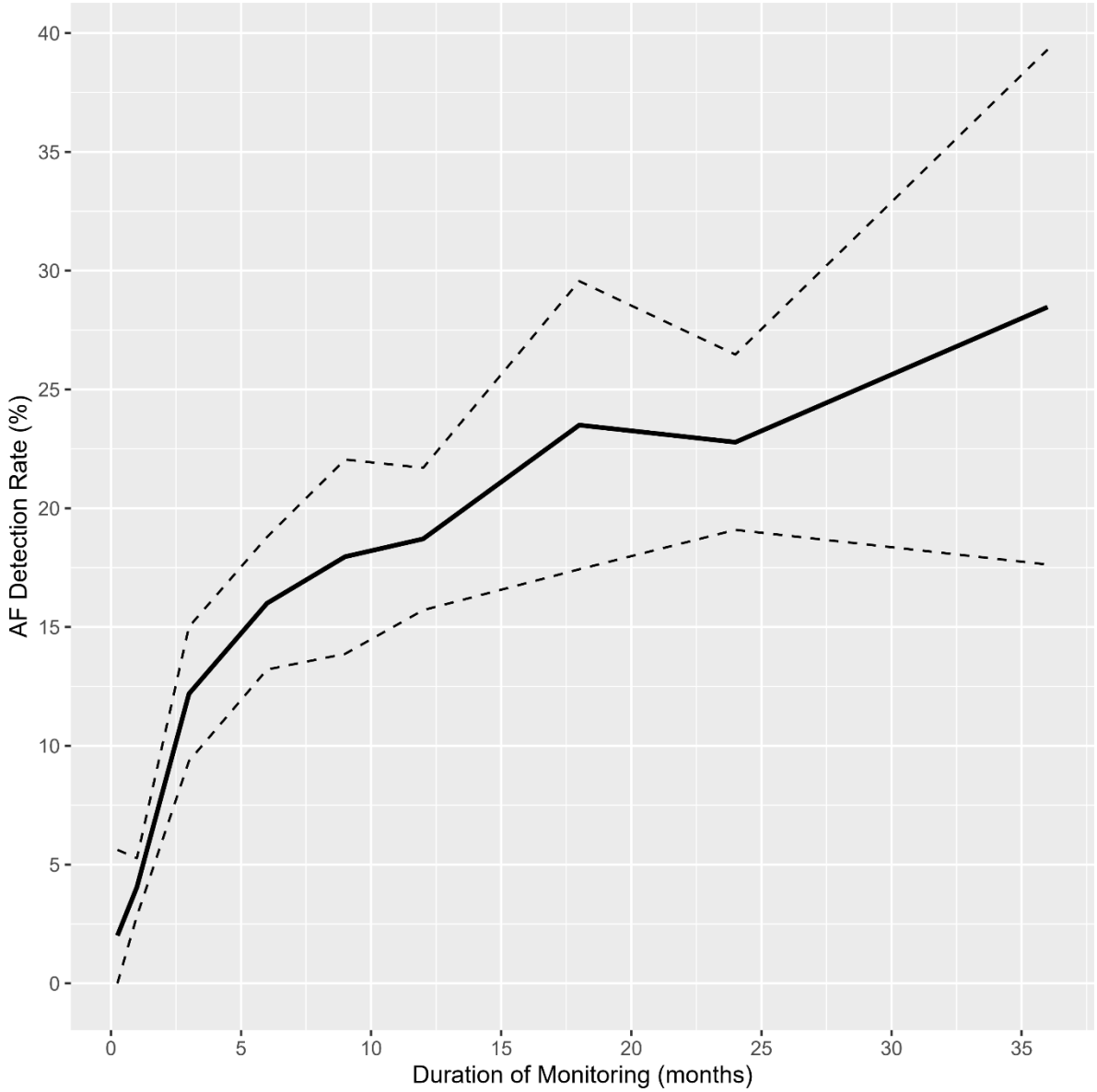
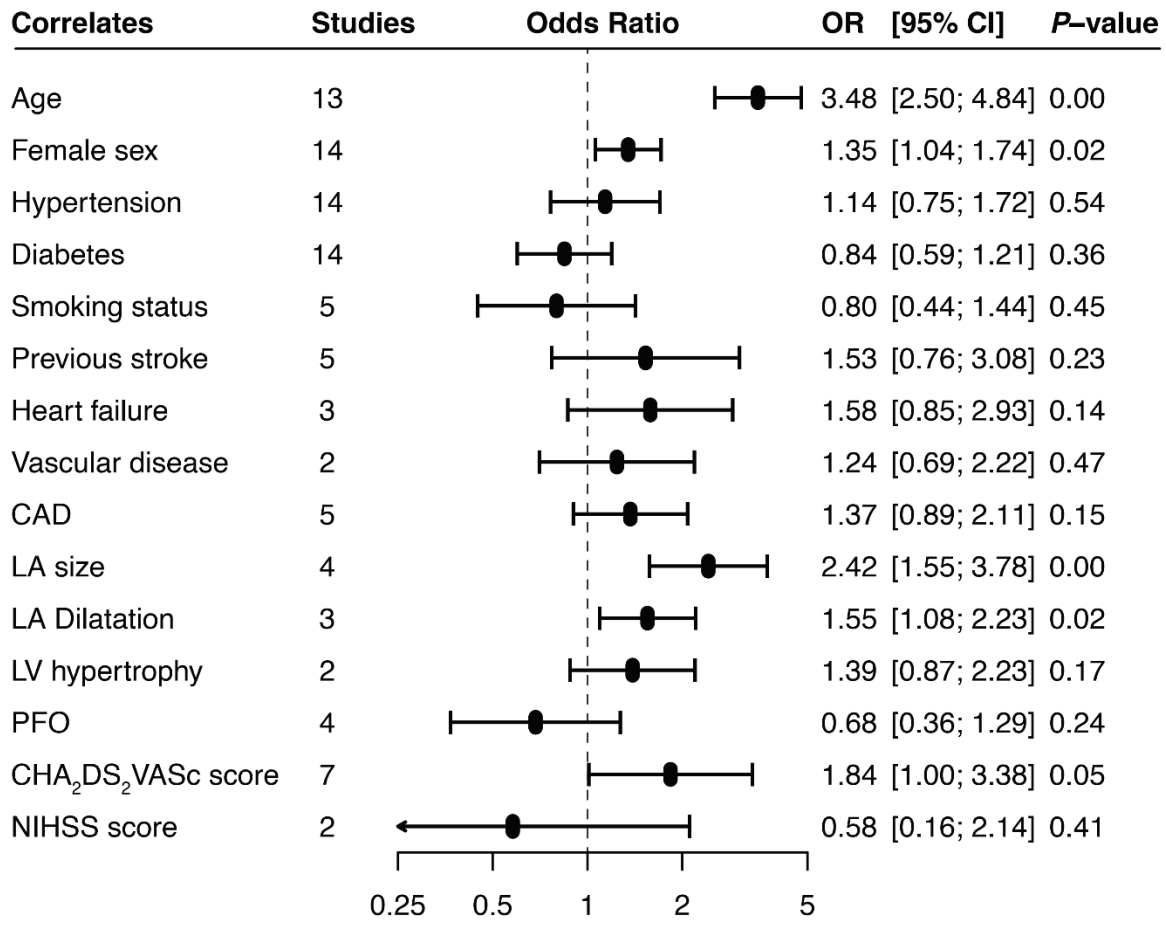


Figure 2. Relationship of atrial fibrillation detection with duration of monitoring in patients with cryptogenic stroke.



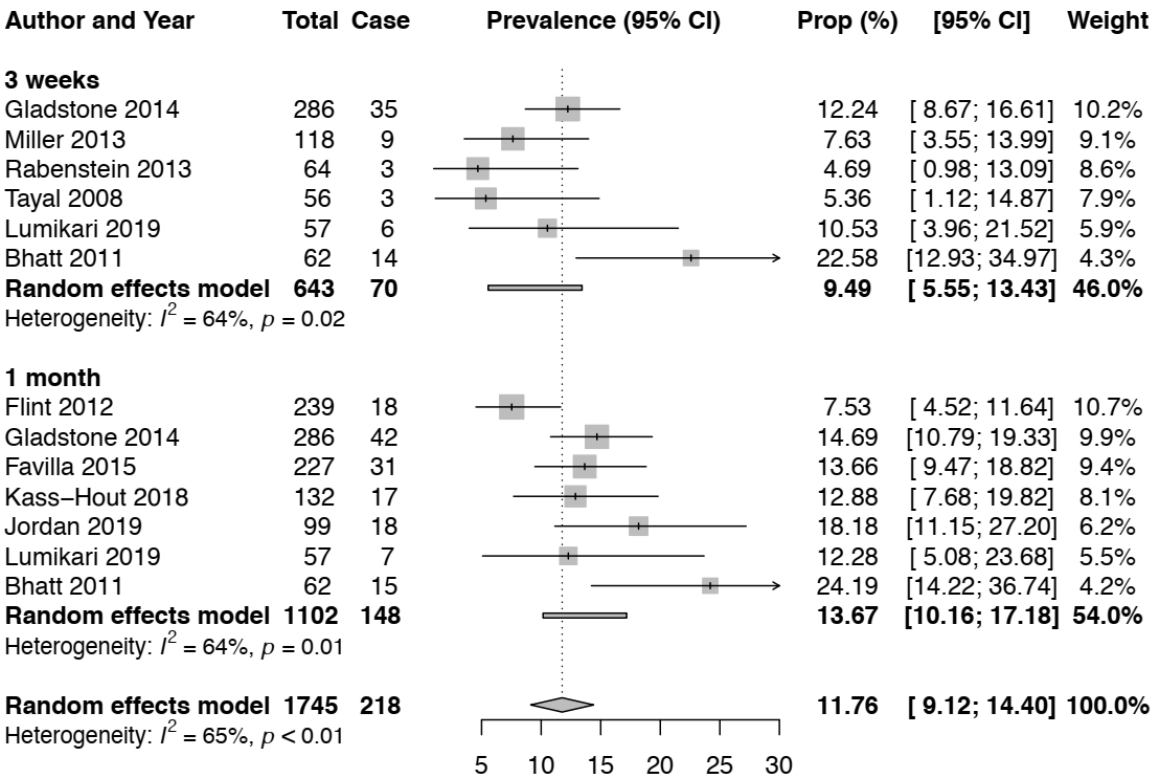
Legend: the black bold line and dot lines represent the curves of atrial fibrillation detection and the upper and lower limits of the 95% confidence interval.

Figure 3. Univariable correlates of atrial fibrillation detection on implantable cardiac monitors in patients with cryptogenic stroke



CAD: coronary artery disease; LA: left atrial; LV: left ventricular; PFO: persistent foramen ovale; NIHSS: National Institutes of Health Stroke Scale

Figure 4. Overall pooled atrial fibrillation detection rates on mobile cardiac outpatient telemetry in patients with cryptogenic stroke



3.2.7 Appendix

Supplementary Table 1. Search strategies

	Search strategy for PubMed
#P1	Holter OR electrocardiography OR electrocardiogram OR electrocardiographic OR ECG OR EKG OR telemetry OR telemetric OR “loop recorder” OR “loop recording” OR “cardiac monitor”
#P2	“cryptogenic stroke” OR “embolic stroke of undetermined source” OR ESUS OR “cryptogenic transient ischemic attack” OR “cryptogenic transient ischaemic attack” OR “cryptogenic TIA” OR “cryptogenic cerebrovascular event” OR “cryptogenic CVA” OR “cryptogenic cerebral infarct” OR “cryptogenic brain infarct” OR “stroke of undetermined etiology” OR “stroke of undetermined aetiology” OR “stroke of undetermined cause”
#P3	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib” OR “atrial flutter” OR tachyarrhythmia OR arrhythmia
#P4	#P1 AND #P2 AND #P3
	Search strategy for EMBASE
#E1	holter:ab,ti OR electrocardiography:ab,ti OR electrocardiogram:ab,ti OR electrocardiographic:ab,ti OR ecg:ab,ti OR ekg:ab,ti OR telemetry:ab,ti OR telemetric:ab,ti OR 'loop recorder':ab,ti OR 'loop recording':ab,ti OR 'cardiac monitor':ab,ti
#E2	'cryptogenic stroke':ab,ti OR 'embolic stroke of undetermined source':ab,ti OR esus:ab,ti OR 'cryptogenic transient ischemic attack':ab,ti OR 'cryptogenic transient ischaemic attack':ab,ti OR 'cryptogenic tia':ab,ti OR 'cryptogenic cerebrovascular event':ab,ti OR 'cryptogenic cva':ab,ti OR 'cryptogenic cerebral infarct':ab,ti OR 'cryptogenic brain infarct':ab,ti OR 'stroke of undetermined etiology':ab,ti OR 'stroke of undetermined aetiology':ab,ti OR 'stroke of undetermined cause':ab,ti
#E3	'atrial fibrillation':ab,ti OR 'auricular fibrillation':ab,ti OR af:ab,ti OR afib:ab,ti OR 'atrial flutter':ab,ti OR tachyarrhythmia:ab,ti OR arrhythmia:ab,ti
#E4	holter:ab,ti OR electrocardiography:ab,ti OR electrocardiogram:ab,ti OR electrocardiographic:ab,ti OR ecg:ab,ti OR ekg:ab,ti OR telemetry:ab,ti OR telemetric:ab,ti OR 'loop recorder':ab,ti OR 'loop recording':ab,ti OR 'cardiac monitor':ab,ti
#E5	#E1 AND #E2 AND #E3 AND #E4
	Search strategy for Web of Science
#W1	Holter OR electrocardiography OR electrocardiogram OR electrocardiographic OR ECG OR EKG OR telemetry OR telemetric OR “loop recorder” OR “loop recording” OR “cardiac monitor”
#W2	“cryptogenic stroke” OR “embolic stroke of undetermined source” OR ESUS OR “cryptogenic transient ischemic attack” OR “cryptogenic transient ischaemic attack” OR “cryptogenic TIA” OR “cryptogenic

	cerebrovascular event" OR "cryptogenic CVA" OR "cryptogenic cerebral infarct" OR "cryptogenic brain infarct" OR "stroke of undetermined etiology" OR "stroke of undetermined aetiology" OR "stroke of undetermined cause"
#W3	"atrial fibrillation" OR "auricular fibrillation" OR "AF" OR "Afib" OR "atrial flutter" OR tachyarrhythmia OR arrhythmia
#W4	#W1 AND #W2 AND #W3

Supplementary Table 2. Summarized study characteristics

Characteristics	**N = 47**
Total population	**8 215**
Year of publication, range	2008-2020
Period of inclusion of participants, range	2003-2019
Design	
- Cohort	42
- Randomized controlled trial	5
Data collection	
- Prospective	35
- Retrospective	12
Regions	
- Europe	26
- Northern America	17
- Asia	2
- Multiregional	2
Countries	
- United States	16
- Germany	9
- Spain	5
- Italy	4
- France	3
- Multinational	2
- Japan	1
- Canada	1
- Finland	1
- United Kingdom	1
- Portugal	1
- Denmark	1
- Singapore	1
Sampling	
- Consecutive	42
- Random	5
Risk of bias	
- Low	28
- Moderate	18
- High	1

Supplementary Table 3. General characteristics of included studies

Part A

Author, year	Country	Design	Population	Etiological investigations	Definition CS	Diagnostic modality (AF)	Device
Chorin, 2020	USA	Cohort	Cryptogenic stroke/TIA	NR	NR	ICM	Reveal LINQ and TruRhythm LINQ
Jordan, 2019	USA	Cohort	ESUS	Neuroimaging, 12-lead EKG, transthoracic echocardiography (TTE), and cardiac telemetry monitoring for at least 24 hours, laboratory testing	NR	MCOT	NR
Riordan, 2020	USA	Cohort	Cryptogenic stroke	Electrocardiographic and telemetry monitoring, transesophageal echocardiography, laboratory testing for thrombophilia, and imaging studies of the head and neck vasculature often including magnetic resonance imaging	NR	ICM	Reveal LINQ
Tayal, 2008	USA	Cohort	Cryptogenic stroke/TIA	Brain imaging, admission ECG, inpatient cardiac telemetry monitoring or 24-hour Holter, MRA or CTA head and neck, transthoracic or transesophageal echocardiography	TOAST criteria	MCOT	CardioNet
Flint, 2012	USA	Cohort	Cryptogenic stroke	NR	NR	MCOT	CardioPAL SAVI
Gaillard, 2010	France	Cohort	Cryptogenic stroke	Brain imaging, 24-hour Holter ECG, cervical artery duplex ultrasound, transthoracic or transesophageal echocardiography	NR	Transtelephonic ECG (at least daily ECG)	Cardiomemo
Miller, 2013	USA	Cohort	Cryptogenic stroke	Brain imaging, transthoracic or transesophageal echocardiography	TOAST criteria	MCOT	CardioNet
Ziegler, 2017	USA	Cohort	Cryptogenic stroke	NR	NR	ICM	Reveal LINQ
Yayehd, 2015	France	Cohort	Cryptogenic stroke	Brain imaging, 24-hour ECG recording, biological tests, transthoracic echocardiography and carotid Doppler assessment; transoesophageal echocardiography and limb venous Doppler assessment if required.	NR	MCOT	SpiderFlash

Watson, 2020	USA	Cohort	Cryptogenic stroke	Brain imaging, CTA or MRA of the head and neck by computed, transthoracic/transesophageal echocardiography cardiac telemetry, electrocardiography, and basic lab testing	NR	ICM	Reveal LINQ
Seow, 2018	Singapore	Cohort	Cryptogenic stroke	Brain imaging, 12-lead ECG, 24-hour in-hospital ECG monitoring, 24-hour outpatient ECG Holter, transthoracic echocardiography, ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels	NR	ICM	Reveal LINQ
Sanna, 2014	Europe, USA, Canada	Cohort	Cryptogenic stroke/TIA	Brain imaging, 12-lead ECG, 24 hours or more of ECG monitoring, screening for thrombophilic states (in patients <55 years of age), transesophageal echocardiography, ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels or MRA/CTA of head and neck	NR	ICM	Reveal XT
Rojo-Martinez, 2013	Spain	Cohort	ESUS	24-hours ECG monitoring, transthoracic echocardiography, screening for thrombophilic states (under 55 years of age), transcranial and neck Doppler ultrasound, magnetic resonance angiography, computed tomography angiography of the head and neck	NR	ICM	Reveal XT
Ritter, 2013	Germany	Cohort	Cryptogenic stroke	Brain imaging, Duplex ultrasound, and computed tomography angiography or magnetic resonance angiography of brain-supplying arteries, routine ECG, 72-hour continuous rhythm monitoring on the stroke unit and manual re-evaluation of the signal, and additional 24-h Holter ECG	TOAST criteria	ICM	Reveal XT
Rabenstein, 2013	USA	Cohort	Cryptogenic stroke	NR	The Causative Classification of Stroke system	MCOT	CardioNet
Pecha, 2020	Germany	Cohort	Cryptogenic stroke	Brain imaging, vascular ultrasound of carotid arteries, echo and 24 h-Holter ECG	NR	ICM	Reveal XT

Öner, 2020	Germany	Cohort	Cryptogenic stroke	Brain imaging, CT angiography of the head and neck, duplex ultrasonography of extra- and intracranial brain supplying arteries, resting electrocardiogram (ECG), 24-h Holter-ECG, and 72-h ECG-monitoring on the stroke unit, transthoracic or transesophageal echocardiography, screening for thrombophilic states or vasculitis	NR	ICM	Biomonitor2-AF, Reveal LINQ, Reveal XT, SJM confirm
Milstein, 2020	USA	Cohort	Cryptogenic stroke	Brain imaging, MRA, transthoracic echocardiogram, and/or transesophageal echocardiogram, in-hospital telemetry	NR	ICM	Reveal LINQ
Manina, 2014	Italy	Cohort	Cryptogenic stroke/TIA	Brain imaging, 12-lead ECG, 24-hour ECG monitoring	NR	96-hour Holter	Spider View recorder
Lumikari, 2019	Finland	Cohort	ESUS	Brain imaging, CT- or MR-angiography, transthoracic/transoesophageal echocardiography, electrocardiography, 24- or 48-hr ECG monitoring	NR	MCOT	Bittium Faros
Kass-Hout, 2018	USA	Cohort	Cryptogenic stroke/TIA	Brain imaging, non-invasive angiography, echocardiography, electrocardiography, inpatient telemetry, hematologic, and inflammatory tests	TOAST criteria	MCOT	NR
Kalani, 2015	USA	Cohort	Cryptogenic stroke	Brain imaging, 12-lead ECG, MR angiography or computed tomography angiography of head and neck vessels, transthoracic/transoesophageal echocardiography	TOAST criteria	MCOT	Lifestar ACT, Lifestar AF Express or Cardiomedix
Jorfida, 2014	Italy	Cohort	ESUS	12-lead ECG, 48 h of inhospital continuous telemetry, 24 h Holter monitoring, transthoracic echocardiography, cerebral computed tomography (CT) or MRI scans, carotid and vertebro-basilar systems ultrasound or angio-MRI, haematological and inflammatory tests	A-S-C-O and TOAST criteria	ICM	Reveal Plus XT 9526
Iwata, 2019	Japan	Cohort	ESUS	Brain imaging, 12-lead ECG, 7 days cardiac monitoring, ambulatory ECG monitoring using a monitor for at least 24 hours, angiography of carotid/intracranial arteries and echocardiography	A-S-C-O classification of stroke	ICM	Reveal LINQ
Israel, 2017	Germany	Cohort	ESUS	Brain imaging, 12-lead electrocardiography,	TOAST	ICM	BioMonitor

				ultrasound of brain-supplying arteries, and transthoracic and transoesophageal echocardiographic, 24-72 hour Holter	criteria		or Reveal XT
Gladstone, 2014	Canada	RCT	Cryptogenic stroke/TIA	12-lead ECG, ambulatory ECG monitoring with the use of a Holter monitor for a minimum of 24 hours, brain and neurovascular imaging, and echocardiography	TOAST criteria	MCOT	ER910AF Cardiac Event Monitor, Braemar
Fonseca, 2013	Portugal	Cohort	Cryptogenic stroke	Brain imaging, 12-lead electrocardiography, transcranial Doppler, carotid and vertebral duplex scanning, and transthoracic echocardiographic, 24-hour Holter	TOAST criteria	Post-stroke F/U with 24-h Holter at 3 and 6 months	NR
De Angelis, 2020	Italy	Cohort	Cryptogenic stroke	24-hours ECG monitoring, transthoracic echocardiography, screening for thrombophilic states (under 55 years of age), transcranial and neck Doppler ultrasound, magnetic resonance angiography, computed tomography angiography of the head and neck	NR	ICM	Reveal LINQ
Cotter, 2013	UK	Cohort	Cryptogenic stroke	Brain imaging, 12-lead electrocardiography, transthoracic or transesophageal echocardiography, and cardiac monitoring at least for 24 hours	TOAST criteria	ICM	Reveal XT
Christensen, 2014	Denmark	Cohort	Cryptogenic stroke/TIA	NR	NR	ICM	Reveal XT
Asaithambi, 2018	USA	Cohort	Cryptogenic stroke	NR	NR	ICM	Reveal LINQ
Victor, 2018	Spain	Cohort	ESUS	Blood tests, chest X-ray, supra-aortic vessels echo-Doppler, transcranial Doppler, and CT angiography or angio-MRI, if needed. A 12 lead Electrocardiogram (ECG) was also performed, 24-hour Holter monitoring, transthoracic or transesophageal echocardiogram or thrombophilia screening (in subjects under 55 years)	NR	ICM	Reveal XT or Reveal LINQ
Thijs, 2016	Multinational	RCT	Cryptogenic stroke/TIA	12-lead ECG, 24-hour ECG monitoring (Holter or telemetry), transesophageal echocardiography, screening for thrombophilic states (in patients younger than 55 years), and	NR	ICM	Reveal XT

				detailed vascular imaging			
Poli, 2016	Germany	Cohort	Cryptogenic stroke/TIA	computed tomography, including CT angiography, or magnetic resonance imaging, including MR angiography, neurosonology, transesophageal echocardiography, ECG monitoring for 72 h plus at least one 24 h Holter ECG recording, and screening for thrombophilia (in patients <55 years)	TOAST criteria	ICM	Reveal XT or Reveal LINQ
Pagola, 2020	Spain	Cohort	Cryptogenic stroke	Brain imaging, 12-lead electrocardiography, CT angiography, transthoracic echocardiography	NR	MCOT	wearable Holter (Nuubo System®)
Mendieta, 2020	Spain	Cohort	ESUS	Brain imaging (CT and MRI), CT/MR angiography or ultrasonography, twelve-lead electrocardiography, transthoracic or transesophageal echocardiography, and cardiac monitoring at least for 72 hours	TOAST criteria	Post-stroke F/U (1, 6, 12 by neurologist and every 6 months by GP) with ECG or MCOT	NR
Bugnicourt, 2013	France	Cohort	Cryptogenic stroke	Computed tomography, electrocardiogram, Doppler ultrasonography of neck vessels, transthoracic echocardiography, and standard laboratory tests in all patients; Holter ECG monitoring, magnetic resonance imaging , and/or angiography were performed in selected patients	A-S-C-O classification of stroke	Post-stroke F/U (6, 12 then yearly) with ECG or MCOT	NR
Ntaios, 2020	Greece, Switzerland, UK	Cohort	ESUS	NR	Cryptogenic Stroke/ESUS International Working Group	Post-stroke F/U (6, 12 then yearly) with ECG or MCOT	NR
Muller, 2017	Germany	RCT	Cryptogenic stroke	Brain imaging, 12-lead electrocardiography, transthoracic or transesophageal echocardiography, and cardiac monitoring at least for 24 hours	TOAST criteria	ICM	Reveal XT
Makimoto, 2017	Germany	Cohort	ESUS	Brain imaging, twelve-lead electrocardiography, transthoracic or transesophageal echocardiography, and cardiac monitoring at least for 24 hours	Cryptogenic Stroke/ESUS International Working	ICM	NR

					Group		
Favilla, 2015	USA	Cohort	Cryptogenic stroke/TIA	Brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]), echocardiography	TOAST criteria	MCOT	CardioNet MCOT
Carrazco, 2018	USA	Cohort	Cryptogenic stroke	Brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]), cervical and cerebral vascular imaging (magnetic resonance angiography or computed tomography angiography), echocardiography (transthoracic and/or transesophageal), a minimum of 24 hours of cardiac telemetry monitoring, ECG, and standard poststroke blood work	Patients with non-lacunar strokes and no identifiable stroke source	ICM	Reveal LINQ ICM (90%) and Reveal XT (10%)
Campal, 2020	Spain	Cohort	ESUS	12-lead ECG, brain and neurovascular imaging (magnetic resonance imaging or plain computed tomography scan, angio computed tomography scan when needed, transcranial and supra-aortic vessel Doppler ultrasound), routine transthoracic and transesophageal echocardiography and basic biochemical and hematologic determinations	TOAST criteria	21-days Holter	Textile wearable Holter (Nuubo, Valencia, Spain)
Bhatt, 2011	USA	Cohort	Cryptogenic stroke/TIA	MRI scan with DWI imaging, transesophageal echocardiogram, transthoracic echocardiogram, a CT angiogram, EKG on admission and at least 24 hours of cardiac telemetry	NR	MCOT	CardioNet MCOT
Bettin, 2018	Germany	RCT	Cryptogenic stroke	cerebral imaging (MRI or CT), a 12-lead ECG recording upon admission, a 24-h-Holter ECG, a duplex and Doppler ultrasound of the carotid and vertebral arteries and a transesophageal echocardiography	TOAST criteria	ICM	Reveal XT
Acampa, 2019	Italy	Cohort	Cryptogenic stroke	neuroimaging examination (brain computed tomography [CT] with angio-CT scan including the aortic arch and intra-extracranial arteries; and/or brain magnetic resonance imaging), extracranial and transcranial arterial ultrasound examination, transthoracic echocardiography, 12-lead resting ECG at admission	TOAST criteria	7-day in-hospital telemetry	NR
Reinke,	Germany	RCT	Cryptogenic	cerebral imaging (MRI or CT), a 12-lead ECG	TOAST	ICM	Reveal XT

2018			stroke	recording upon admission, a 24-h-Holter ECG, a duplex and Doppler ultrasound of the carotid and vertebral arteries and a transesophageal echocardiography	criteria		

NR: not reported; AF: atrial fibrillation; CT: computed tomography; ECG: electrocardiographic; ESUS: embolic stroke of undetermined source; ICM: implantable cardiac monitor; IQR: interquartile range; MCOT: mobile outpatient telemetry; MRI: magnetic resonance imaging; RCT: randomized controlled trial; SD: standard deviation; TIA: transient ischemic attack;

Part B

Author, year	**Diagnostic modality (AF)**	**Device**	**AF Diagnostic Criteria**	**Mean/Median time from stroke to monitoring initiation**	**Mean/Median Recording Duration**	**Mean/Median Time to AF diagnosis (days)**	**Sample Size**	**Risk of bias**
Chorin, 2020	ICM	Reveal LINQ and TruRhythm LINQ	AF duration > 30 s	NR	28 (SD 12) months	7.4 (12.3) months	145	Moderate
Jordan, 2019	MCOT	NR	AF duration > 30 s	NR	28 days	NR	99	Moderate
Riordan, 2020	ICM	Reveal LINQ	AF duration > 120 s	Within 30 days	22 (SD 12) months	NR	293	Low
Tayal, 2008	MCOT	CardioNet	AF duration > 30 s	NR	21 (range 5-21) days	NR	56	Moderate
Flint, 2012	MCOT	CardioPAL SAVI	AF duration > 30 s	NR	28 (IQR 20-30) days	NR	239	Low
Gaillard, 2010	Transtelephonic ECG (at least daily ECG)	Cardiomemo	AF duration > 30 s	NR	1 month	NR	82	Moderate
Miller, 2013	MCOT	CardioNet	AF duration > 30 s	32.7 (SD 36) days	21 (range 1-20) days	8.8 days	118	Moderate
Ziegler, 2017	ICM	Reveal LINQ	AF duration > 120 s	NR	579 (SD 222) days	NR	1247	Low
Yayehd, 2015	MCOT	SpiderFlash	AF duration > 30 s	34 (range 22-57) days	20 (SD 3) days	NR	39	Moderate
Watson, 2020	ICM	Reveal LINQ	AF duration > 120 s	21 days	NR	NR	227	Low

Seow, 2018	ICM	Reveal LINQ	AF duration > 120 s	66 days	345 (SD 229) days	50 days	71	Low
Sanna, 2014	ICM	Reveal XT	AF duration > 30 s	Within 10 days after randomization which occurred at a mean of 38.1 (SD 27.6) days	NR	NR	221	Low
Rojo-Martinez, 2013	ICM	Reveal XT	AF duration > 120 s	NR	281 (212) days	102 (range 26-240)	101	Low
Ritter, 2013	ICM	Reveal XT	AF duration > 30 s	13 (IQR 10-67) days	382 (IQR 89-670) days	64 (range 1-556) days	60	Low
Rabenstein, 2013	MCOT	CardioNet	AF duration > 30 s	Within about 3 months	21 days	3 (range 0-20) days	64	Moderate
Pecha, 2020	ICM	Reveal XT	AF duration > 30 s	NR	419 (309) days	NR	64	Moderate
Öner, 2020	ICM	Biomonitor2-AF, Reveal LINQ, Reveal XT, SJM confirm	NR	NR	21.5 (range: 1–33) months	NR	88	Low
Milstein, 2020	ICM	Reveal LINQ	AF duration > 120 s	3.7 (SD 1.7) days	30 days	121 (101) days	343	Low
Manina, 2014	96-hour Holter	Spider View recorder	AF of any duration	Within the first 30 days	4 days	NR	114	Low
Lumikari, 2019	MCOT	Bittium Faros	AF duration > 30 s	8 (IQR 4-44) days	4 weeks	NR	57	Moderate
Kass-Hout, 2018	MCOT	NR	AF duration > 30 s	NR	25 days	NR	132	Moderate
Kalani, 2015	MCOT	Lifestar ACT, Lifestar AF Express or Cardiomedix	AF duration > 30 s	10 days	30 days	NR	85	High
Jorfida, 2014	ICM	Reveal Plus XT 9526	AF duration > 300 s	NR	14.5 (IQR 8.7–22.5) months	NR	54	Low

Iwata, 2019	ICM	Reveal LINQ	AF duration > 120 s	31.5 (range: 1-318) days	221.5 (range: 93-365) days	NR	84	Low
Israel, 2017	ICM	BioMonitor or Reveal XT	AF duration > 120 s	20 days	12.7 (SD5.5) months	NR	123	Low
Gladstone, 2014	MCOT	ER910AF Cardiac Event Monitor, Braemar	AF duration > 30 s	NR	90 days	NR	571	Low
Fonseca, 2013	Post-stroke F/U with 24-h Holter at 3 and 6 months	NR	AF duration > 30 s	NR	NR	NR	80	Moderate
De Angelis, 2020	ICM	Reveal LINQ	AF duration > 120 s	83 (SD 64) days	NR	6 months	58	Low
Cotter, 2013	ICM	Reveal XT	AF duration > 120 s	174 (134) days	NR	48 (34-118) days	51	Low
Christensen, 2014	ICM	Reveal XT	AF duration > 120 s	107 (SD 117) days	569 (310) days	NR	87	Low
Asaithambi, 2018	ICM	Reveal LINQ	NR	4 days	536 (282-848) days	94.5 (16-239) days	234	Low
Victor, 2018	ICM	Reveal XT or Reveal LINQ	AF duration > 30 s (Reveal XT) or 120 s (Reveal LINQ)	56 days	17.1 (SD10.7) months	31 days	65	Low
Thijs, 2016	ICM	Reveal XT	NR	NR	NR	NR	221	Low
Poli, 2016	ICM	Reveal XT or Reveal LINQ	AF duration > 120 s	27 (SD 24) days	311 (SD 251) days	105 (SD 135) days	75	Low
Pagola, 2020	MCOT	wearable Holter (Nuubo System®)	No cut off	2 to 3 days	28 days	NR	264	Moderate
Mendieta, 2020	Post-stroke F/U (1, 6, 12 by neurologist and every 6 months by GP) with ECG or MCOT	NR	AF duration > 30 s	NR	521 (SD306) days	NR	75	Moderate

Bugnicourt, 2013	Post-stroke F/U (6, 12 then yearly) with ECG or MCOT	NR	AF duration > 30 s	NR	352 (SD105) days	806 (SD172) days	164	Moderate
Ntaios, 2020	Post-stroke F/U (6, 12 then yearly) with ECG or MCOT	NR	No cutoff	NR	24.3 months	NR	839	Low
Muller, 2017	ICM	Reveal XT	AF duration > 30 s	NR	331 (SD186) days	30 days	90	Low
Makimoto, 2017	ICM	NR	AF duration > 30 s	NR	387 days	NR	146	Low
Favilla, 2015	MCOT	CardioNet MCOT	AF duration > 30 s	NR	28 days	NR	227	Moderate
Carrazco, 2018	ICM	Reveal LINQ ICM (90%) and Reveal XT (10%)	AF duration > 120 s	4.2 (SD 2.6) days	NR	108 days	100	Moderate
Campal, 2020	21-days Holter	Textile wearable Holter (Nuubo, Valencia, Spain)	AF duration > 30 s	NR	21 days	NR	100	Moderate
Bhatt, 2011	MCOT	CardioNet MCOT	AF duration > 30 s	NR	28 days	NR	62	Moderate
Bettin, 2018	ICM	Reveal XT	AF duration > 30 s	35.5 (SD 47.5) days	24.8(SD11.5) months	10.7 (SD11.4) months	173	Low
Acampa, 2019	7-day in-hospital telemetry	NR	irregular tachycardia lasting >5 minutes with no visible P wave or with unorganised F wavelets	NR	7 days	NR	222	Low
Reinke, 2018	ICM	Reveal XT	AF duration > 30 s	Within the first 4 weeks	NR	31 (IQR 72.5-338) days	105	Low

Supplementary Table 4. Clinical characteristics of participants in the included studies

Author	Year	Mean Age	Male (%)	Index Stroke (%)	Index TIA (%)	Recurrent Stroke/TIA (%)	Hypertension (%)	Diabetes (%)	Dyslipidaemia (%)	Smokers (%)	CAD (%)	Heart Failure (%)
Chorin	2020	67	57	83	17	NR	73	27	NR	NR	26	6
Jordan	2019	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Riordan	2020	68.7	57.3	NR	NR	20.5	75	32.8	NR	NR	23.2	6.5
Tayal	2008	66	51	86	14	NR	77	16	75	36	14	2
Flint	2012	64.6	60.5	NR	NR	18.8	66	14.7	90.8	NR	NR	4.6
Gaillard	2010	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miller	2013	68.5	50	NR	NR	NR	87	42	63	21	24	8
Ziegler	2017	NR	53	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yayehd	2015	47	62	NR	NR	8	20.5	3	23	31	3	NR
Watson	2020	64.7	51.5	NR	NR	NR	66.8	NR	54.3	NR	NR	NR
Seow	2018	61.9	77.5	NR	NR	NR	74.7	39.4	NR	NR	NR	NR
Sanna	2014	61.6	64.3	90.5	9.5	16.7	65.2	15.4	56.6	19.5	7.2	NR
Rojo-Martinez	2013	67	46.5	90.1	9.9	NR	55.4	19.8	52.5	23.8	NR	NR
Ritter	2013	63	56.7	NR	NR	NR	70	11.7	NR	NR	NR	NR
Rabenstein	2013	67.9	65.6	NR	NR	31.3	65.6	7.8	81.2	6.3	18.8	6.3
Pecha	2020	65.4	50	NR	NR	NR	75	25	29	NR	14	NR
Öner	2020	66.5	61.4	90.9	9.1	NR	67	22.7	NR	28.4	NR	3.4
Milstein	2020	68.1	55	NR	NR	30	85	38	NR	NR	NR	4
Manina	2014	63.1	NR	91.2	8.8	NR	52.6	9.6	27.2	13.1	NR	NR
Lumikari	2019	64.5	52.6	NR	NR	21.1	61.4	NR	NR	10.5	NR	NR
Kass-Hout	2018	70	50	72	28	NR	75.8	32.6	64.4	NR	NR	NR
Kalani	2015	65.6	50.6	83.5	16.5	18.8	58.8	15.3	50.6	30.6	15.3	2.4
Jorfida	2014	67.8	57.4	NR	NR	27.8	88.7	18.5	NR	NR	NR	NR
Iwata	2019	70	76.2	NR	NR	NR	NR	NR	NR	NR	NR	NR

Israel	2017	65	60.2	NR	NR	NR	82.9	24.4	NR	NR	33.3	NR
Gladstone	2014	72.7	55	63	37	14.2	69.2	19.3	64.4	NR	NR	2.1
Fonseca	2013	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Angelis	2020	68.1	67	NR	NR	14	67	26	62	16	12	NR
Cotter	2013	51.5	54.9	NR	NR	NR	NR	NR	NR	NR	NR	NR
Christensen	2014	56.7	55.2	72.4	NR	NR	44.8	6.9	NR	NR	NR	NR
Asaithambi	2018	72	55	NR	NR	NR	85	28	NR	44	NR	11
Victor	2018	65.4	55.4	NR	NR	NR	56.9	15.4	26.2	28.2	6.2	NR
Thijs	2016	61.6	64.3	90.5	9.5	16.5	65.2	15.4	56.6	NR	7.2	3.2
Poli	2016	66.4	47	89	11	NR	79	15	NR	NR	NR	NR
Pagola	2020	74.5	50.2	NR	NR	NR	76.7	26.2	NR	NR	NR	NR
Mendieta	2020	73	48	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bugnicourt	2013	65.4	52	NR	NR	15	60	23	35	NR	16	NR
Ntaios	2020	56.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Muller	2017	57.7	52	NR	NR	NR	70	18	NR	NR	7	NR
Makimoto	2017	62.0	57.5	NR	NR	NR	73.3	NR	NR	NR	11.6	NR
Favilla	2015	62.9	41.9	78.9	21.1	NR	NR	NR	NR	NR	NR	NR
Carrazco	2018	65.8	47.5	NR	NR	15	78	27	78	27	NR	4
Campal	2020	69	56	100	0	NR	72	21	NR	21	NR	NR
Bhatt	2011	61	51.6	80.6	19.4	NR	25.8	4.8	41.9	NR	12.9	NR
Bettin	2018	61.5	57.8	100	0	NR	71.1	17.9	NR	NR	NR	4.1
Acampa	2019	NR	48.6	100	0	6.8	58.1	19.8	37.8	32.9	8.6	NR
Reinke	2018	64.4	46.2	100	0	NR	71.1	17.9	NR	NR	NR	4.1

NR: not reported; TIA: transient ischemic attack; OSA: obstructive sleep apnea; CAD: coronary artery disease

Supplementary Table 5. Potential predictors of atrial fibrillation detection in patients with cryptogenic stroke or ESUS

Study	Monitoring strategy	Study population	Sample size	AF cases	Mean duration of follow up	Device used	Adjustment for	Potential predictors of AF	Adjusted risk estimate
Acampa, 2019	7-day in-hospital telemetry	Cryptogenic stroke	222	44	7 days	NR	age, atrial size, all ECG parameters (PWD, P max, P min, P-wave index, PR interval, P-wave axis)	Age (5 years)	OR 1.41 (95% CI 1.15-1.72)
								Abnormal P wave axis	OR 3.31 (95% CI 1.49-7.35)
								P wave dispersion	OR 1.92 (95% CI 1.45-2.55)
								P wave max	OR 1.01 (95% CI 0.99-1.03)
								PR interval	OR 1.00 (95% CI 0.99-1-01)
								Atrial size	OR 1.00 (95% CI 0.93-1.07)
								Smoking	OR 1.52 (95% CI 0.54-4.14)
								C reactive protein	OR 1.06 (95% CI 0.92-1.22)
Ntaios, 2020	Post-stroke F/U (6, 12 then yearly) with ECG or MCOT	ESUS	839	125	24.3 months	NR	Age, hypertension, LVH, LA diameter, LVEF, SVE, subcortical infarct	Age 60-70 years	OR 1.71 (95% CI 0.96-2.47)
								Age > 70-80 years	OR 1.60 (95% CI 0.85-2.35)
								Age > 80 years	OR 1.66 (95% CI 0.82-2.50)
								Hypertension	OR 0.90 (95% CI 0.33-1.47)
								LVH	OR -0.65 (95% CI -1.16 to -0.14)
								LA diameter > 40 mm	OR 0.95 (95% CI 0.46-1.43)
								LVEF < 35%	OR -1.34 (95% CI -2.33 to -0.34)
								Any SVE	OR 0.64 (95% CI 0.16-1.11)
								Subcortical infarct	OR -0.81 (95% CI -1.30 to -0.33)
								Non-stenotic CP	OR -1.42 (95% CI -1.93 to -0.91)

Campal, 2020	21-day Holter	ESUS	100	22	21 days	Textile wearable Holter (Nuubo, Valencia, Spain)	Age, LA enlargement, renal impairement, CHA_2DS_2-VASc score	Sinus heart rate ≤ 60	OR 104.9 (95% CI 9.7-1127)
Pagola, 2020	MCOT	Cryptogenic stroke	264	61	28 days	wearable Holter (Nuubo System ®)	Age, large vessel occlusion, hemorrhagic transformation, LAVI, BNP	Age	OR 1.06 (95% CI 1.00-1.16)
								Large vessel occlusion	OR 4.58 (95% CI 2.27-21.38)
								Hemorrhagic transformation	OR 2.11 (95% CI 0.62-10.84)
								LAVI	OR 1.01 (95% CI 0.97-1.05)
								BNP	OR 1.00 (95% CI 0.994-1004)
Favilla, 2015	MCOT	Cryptogenic stroke	227	31	28 days	CardioNet MCOT	Age, sex, race, previous stroke	Age > 60 years	OR 8.9 (95% CI 1.07-74)
								Previous stroke	OR 5.6 (95% CI 1.4-22)
Carrazco, 2018	Implantable cardiac monitor	Cryptogenic stroke	100	31	NR	Reveal LINQ ICM (90%) and Reveal XT (10%)	Age	Obesity (BMI ≥ 30)	OR 1.24 (95% CI 1.12-1.36)
Bettin, 2018	Implantable cardiac monitor	Cryptogenic stroke	173	33	24.8 (SD11.5) months	Reveal XT	Age, sex, hypertension, diabetes, CAD	Age	OR 1.06 (95% CI 1.02-1.11)
								Male	OR 1.31 (95% CI 0.59-2.94)
								Hypertension	OR 0.96 (95% CI 0.33-2.75)
								Diabetes	OR 1.55 (95% CI 0.53-4.52)
								CAD	OR 2.23 (95% CI 0.58-8.53)

Makimoto, 2017	Implantable cardiac monitor	ESUS	146	33	387 days	NR	Age, sex, hypertension, diabetes, CAD, PFO, Infarct location,	Posterior cerebral artery territory	OR 2.27 (95% CI 1.09-4.57)
								Age (1 year increase)	OR 1.02 (95% CI 1.00-1.06)
Muller, 2017	Implantable cardiac monitor	Cryptogenic stroke	90	16	331 (SD 186) days	Reveal XT	PA-TDI interval, P wave max, LA diameter, CHA_2DS_2-VASc score	PA-TDI interval (10 ms increase)	HR 3.51 (95% CI 2.05-6.71)
								P wave max (10 ms increase)	HR 1.64 (95% CI 1.00-2.80)
								CHA_2DS_2-VASc score (1 point increase)	HR 1.86 (95% CI 1.21-294)
Poli, 2016	Implantable cardiac monitor	Cryptogenic stroke	75	25	311 (SD 251) days	Reveal XT or Reveal LINQ	CHA_2DS_2-VASc score, LA size, SEC in LAA, atrial runs at baseline	CHA_2DS_2-VASc score (1 point increase)	HR 1 (95% CI 0.8-1.4)
								Atrial runs	HR 2.7 (95% CI 1.2-6.7)
								LA size > 45 mm	HR 3.6 (95% CI 1.6-8.4)
								SEC in LAA	HR 1.4 (95% CI 0.5-3.8)
Thijs, 2016	Implantable cardiac monitor	Cryptogenic stroke	221		36	Reveal XT	Age, diabetes, $CHADS_2$ score, PAC, PR interval	Age (10 years)	HR 1.84 (95% CI 1.33-2.52)
								PR interval (10 ms)	HR 1.41 (95% CI 1.21-1.64)

95% CI: 95% confidence interval; HR: hazard ratio; OR: odds ratio; SD: standard deviation: ESUS: embolic stroke of undetermined source; F/U: follow-up; MCOT: mobile cardiac outpatient telemetry; SVE: supraventricular extrasystole; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LA: left atrium; LAA: left atrial appendage; SEC: spontaneous echo-contrast; CP: carotid plaque; LAVI: left atrial volume index; BNP: brain natriuretic peptide; PAC: premature atrial contractions.

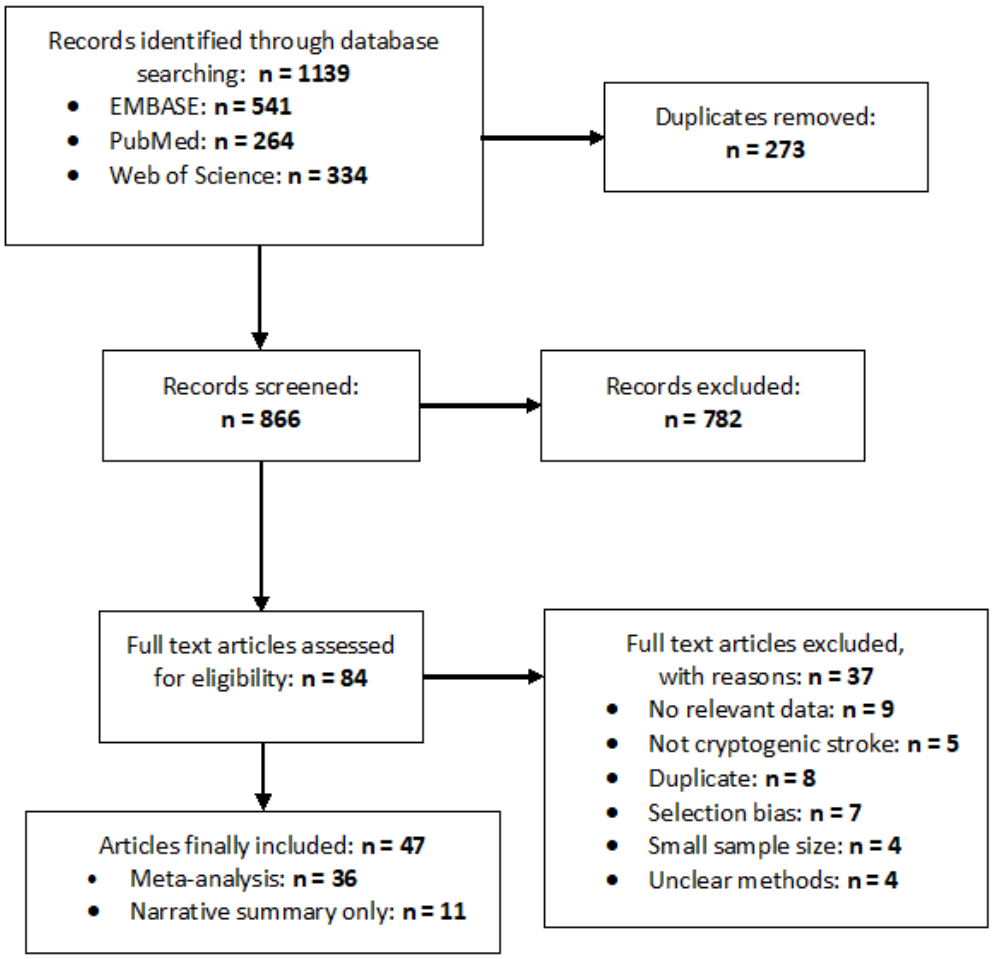
Supplementary Table 6. Atrial fibrillation detection rates with non-invasive cardiac monitoring in patients with cryptogenic stroke

Author	Country	Monitoring strategies	Population	Time point (ILR)	AF duration cut-off	Total population	AF cases	AF detection rate (%)
Manina, 2014	Italy	Holter	Cryptogenic stroke/TIA	4 days	No cut-off	85	29	34.1
Campal, 2020	Spain	Holter	ESUS	3 weeks	> 30 sec	100	14	14.0
Acampa, 2019	Italy	MCOT	Cryptogenic stroke	1 week	> 300 sec	222	44	19.8
Ritter, 2013	Germany	MCOT	Cryptogenic stroke	1 week	> 30 sec	60	1	1.7
Tayal, 2008	USA	MCOT	Cryptogenic stroke	3 weeks	> 30 sec	56	3	5.4
Miller, 2013	USA	MCOT	Cryptogenic stroke	3 weeks	> 30 sec	118	9	7.6
Lumikari, 2019	Finland	MCOT	ESUS	3 weeks	> 30 sec	57	6	10.5
Rabenstein	USA	MCOT	Cryptogenic stroke	3 weeks	> 30 sec	64	3	4.7
Bhatt, 2011	USA	MCOT	Cryptogenic stroke/TIA	3 weeks	> 30 sec	62	14	22.6
Flint, 2012	USA	MCOT	Cryptogenic stroke	1 month	> 30 sec	239	18	7.5
Lumikari, 2019	Finland	MCOT	ESUS	1 month	> 30 sec	57	7	12.3
Kass-Hout, 2018	USA	MCOT	Cryptogenic stroke/TIA	1 month	> 30 sec	132	17	12.9
Kalani, 2015*	USA	MCOT	Cryptogenic stroke/TIA	1 month	> 30 sec	85	4	4.7
Pagola, 2020	Spain	MCOT	Cryptogenic stroke	1 month	No cut-off	264	61	23.1
Favilla, 2015	USA	MCOT	Cryptogenic stroke/TIA	1 month	> 30 sec	227	31	13.7
Jordan, 2019	USA	MCOT	ESUS	1 month	> 30 sec	99	18	18.1
Bhatt, 2011	USA	MCOT	Cryptogenic stroke/TIA	1 month	> 30 sec	62	15	24.2

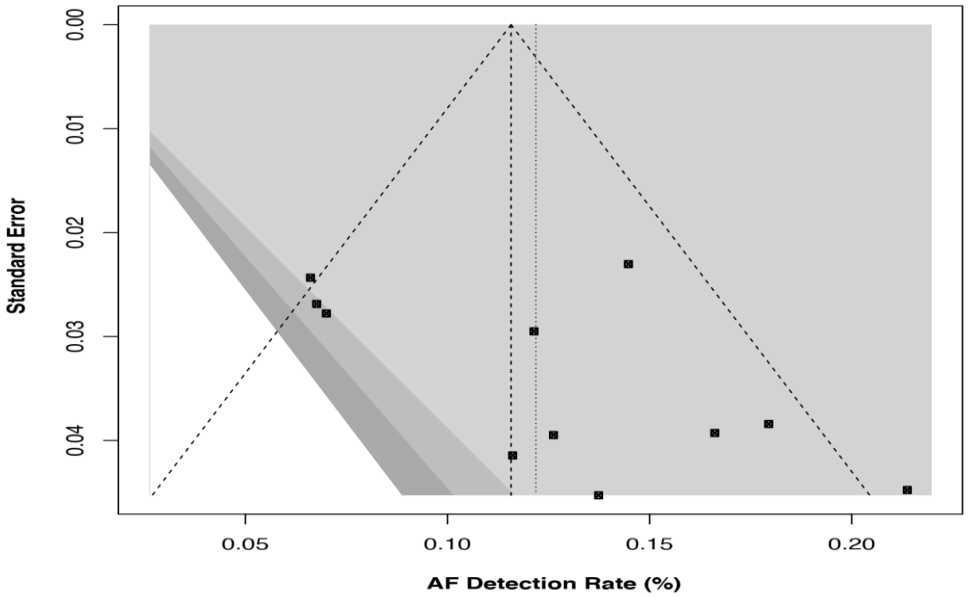
Gladstone, 2014	Canada	MCOT	Cryptogenic stroke/TIA	3 months	> 30 sec	286	45	15.7
Gladstone, 2014	Canada	Post-stroke F/U with an additional 24-h Holter	Cryptogenic stroke/TIA	3 months	> 30 sec	285	9	3.2
Sanna, 2014	Europe, USA, Canada	Post-stroke F/U with ECG at visit	Cryptogenic stroke/TIA	6 months	> 30 sec	214	3	1.4
Fonseca, 2013	Portugal	Post-stroke F/U with 24-h Holter at 3 and 6 months	Cryptogenic stroke	6 months	> 30 sec	80	14	17.5
Bugnicourt, 2013	France	Post-stroke F/U	Cryptogenic stroke	12 months	> 30 sec	164	6	3.7
Sanna, 2014	Europe, USA, Canada	Post-stroke F/U with ECG at visit	Cryptogenic stroke/TIA	12 months	> 30 sec	200	4	2.0
Bugnicourt, 2013	France	Post-stroke F/U	Cryptogenic stroke	24 months	> 30 sec	164	11	6.7
Sanna, 2013	Europe, USA, Canada	Post-stroke F/U with ECG at visit	Cryptogenic stroke/TIA	36 months	> 30 sec	167	5	3.0
Bugnicourt, 2013	France	Post-stroke F/U	Cryptogenic stroke	36 months	> 30 sec	164	22	13.4
Mendieta, 2020	Spain	Post-stroke F/U	ESUS	NR	> 30 sec	75	14	18.7
Ntaios, 2020	Greece, Switzerland, UK	Post-stroke F/U	ESUS	NR	No cut-off	839	125	14.9

ESUS: embolic stroke of undetermined source; TIA: transient ischemic attack; F/U: follow-up; ECG: electrocardiographic; NR: not reported
MCOT = mobile cardiac output telemetry
*Some patients discontinued monitoring before 1 month of MCOT, for a reason other than AF detection

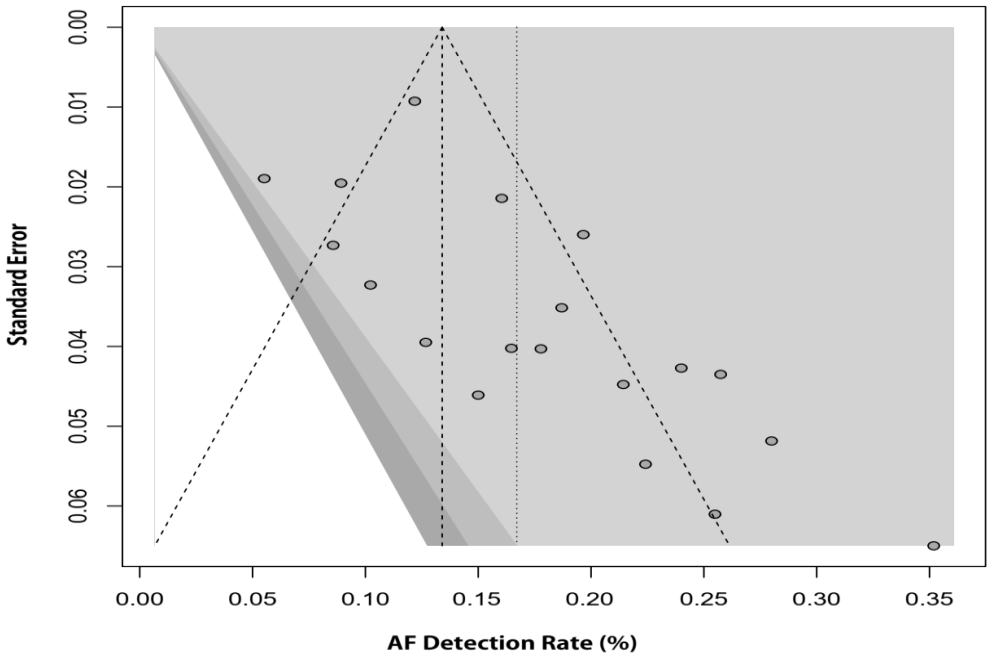
Supplementary Figure 1. Study selection



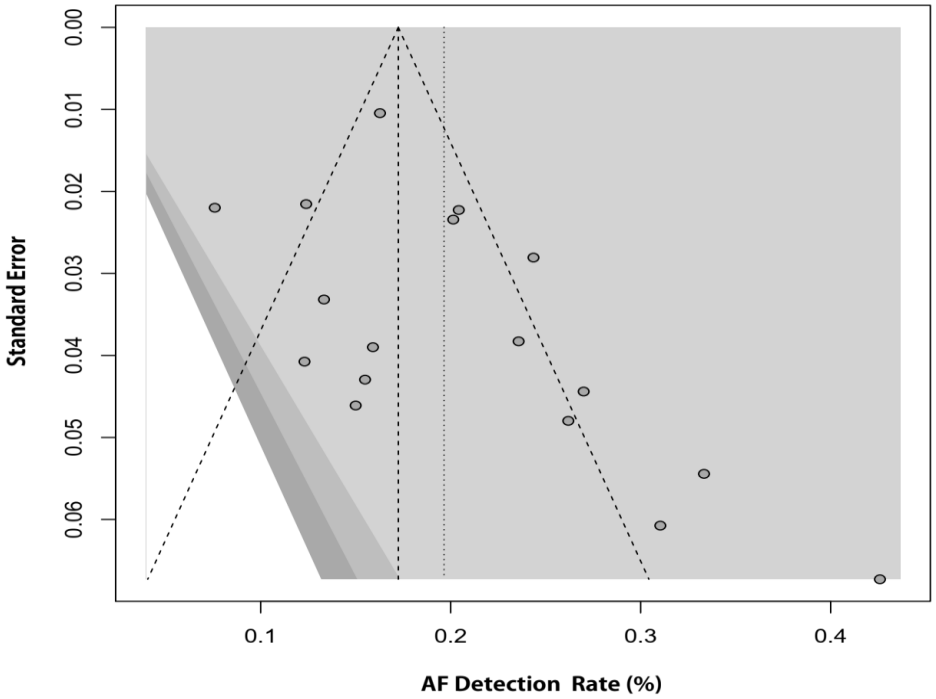
Supplementary Figure 2. Funnel plot for the meta-analysis of rates of atrial fibrillation detected by implantable cardiac monitor at 3 months in patients with cryptogenic stroke



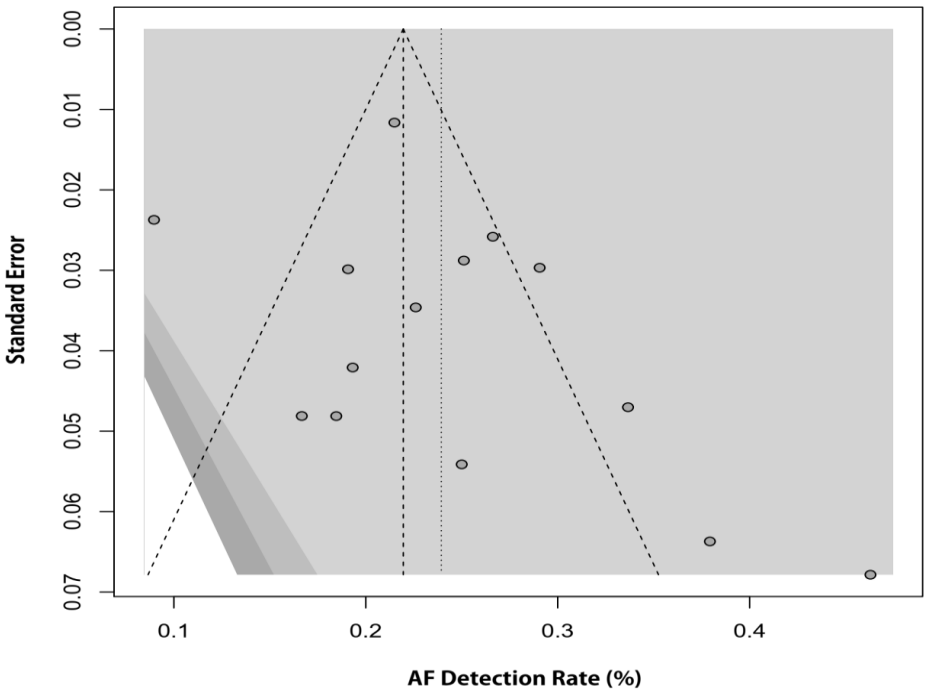
Supplementary Figure 3. Funnel plot for the meta-analysis of rates of atrial fibrillation detected by implantable cardiac monitor at 6 months in patients with cryptogenic stroke



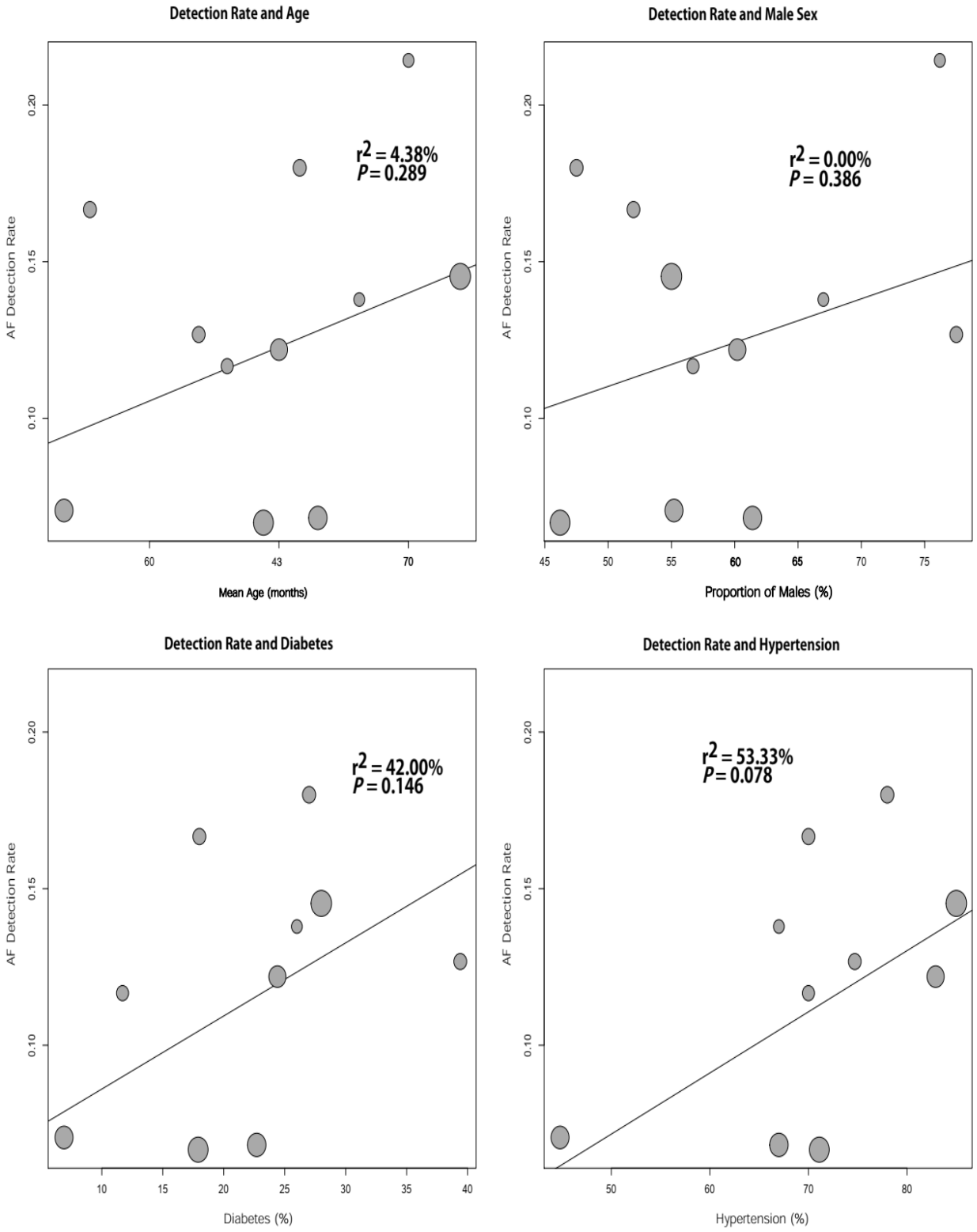
Supplementary Figure 4. Funnel plot for studies reporting atrial fibrillation detection rates by implantable cardiac monitor at 12 months in patients with cryptogenic stroke



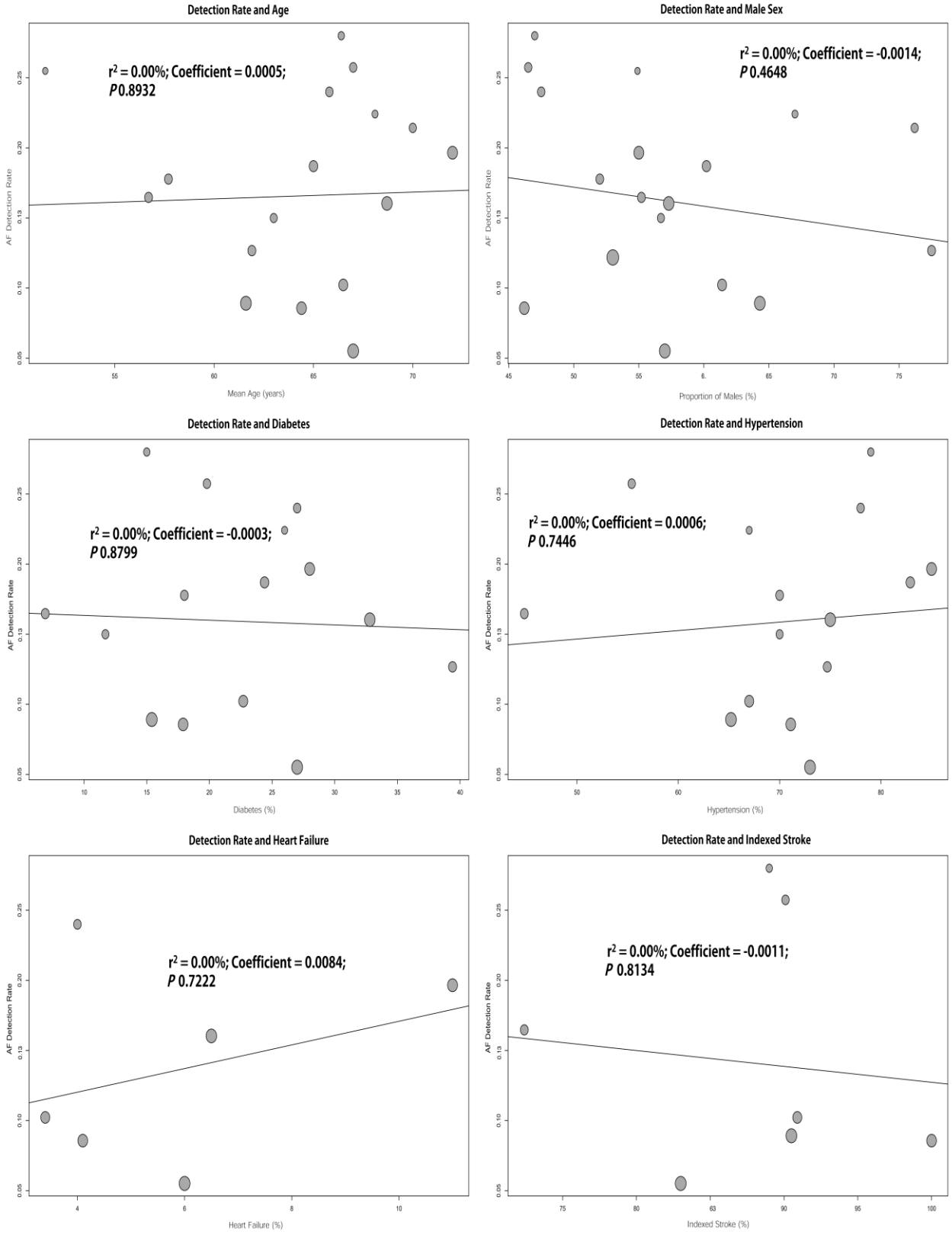
Supplementary Figure 5. Funnel plot for studies reporting atrial fibrillation detection rates at 24 months on implantable cardiac monitor in patients with cryptogenic stroke



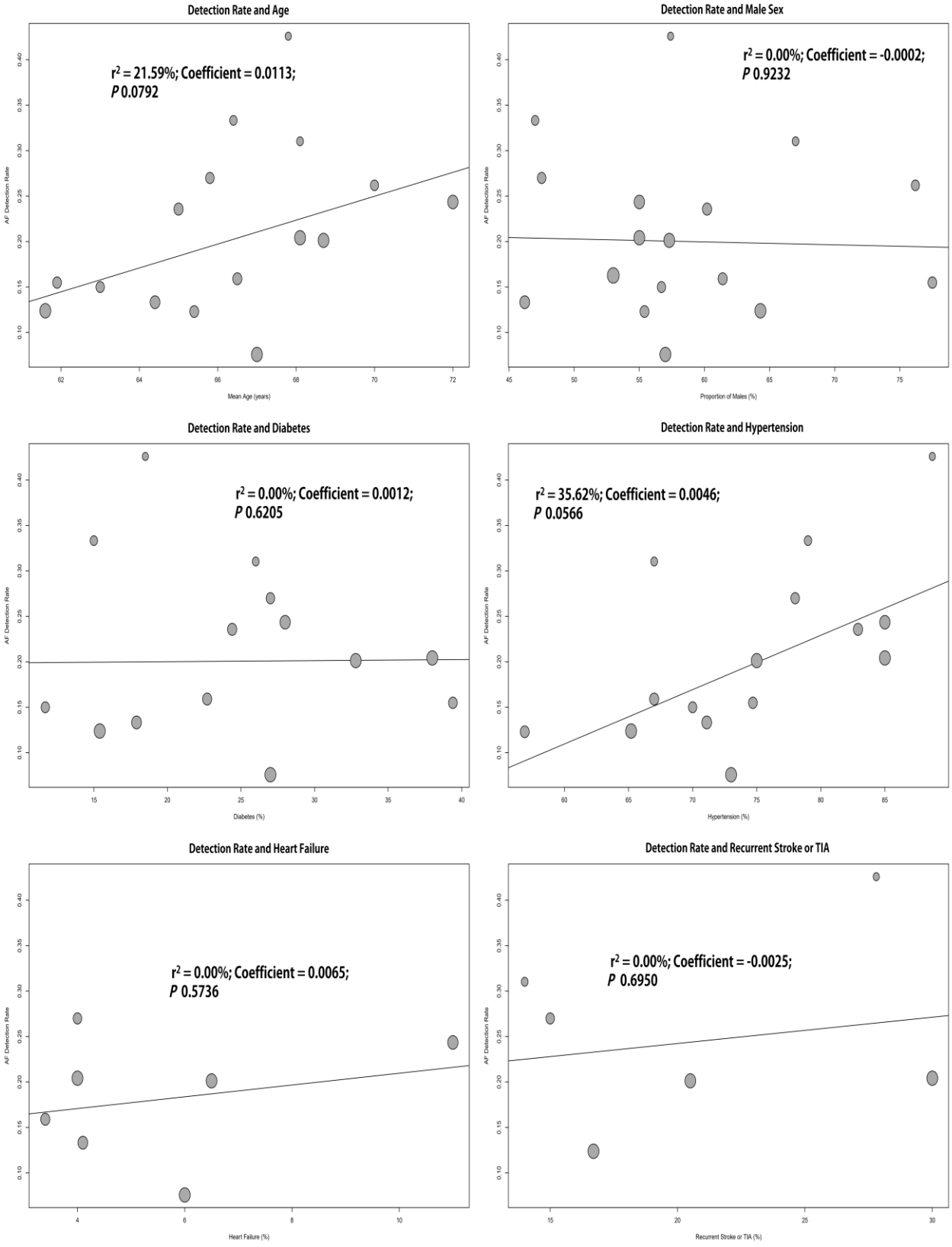
Supplementary Figure 6. Meta-regression of atrial fibrillation detection rates at 3 months on implantable cardiac monitor in patients with cryptogenic stroke



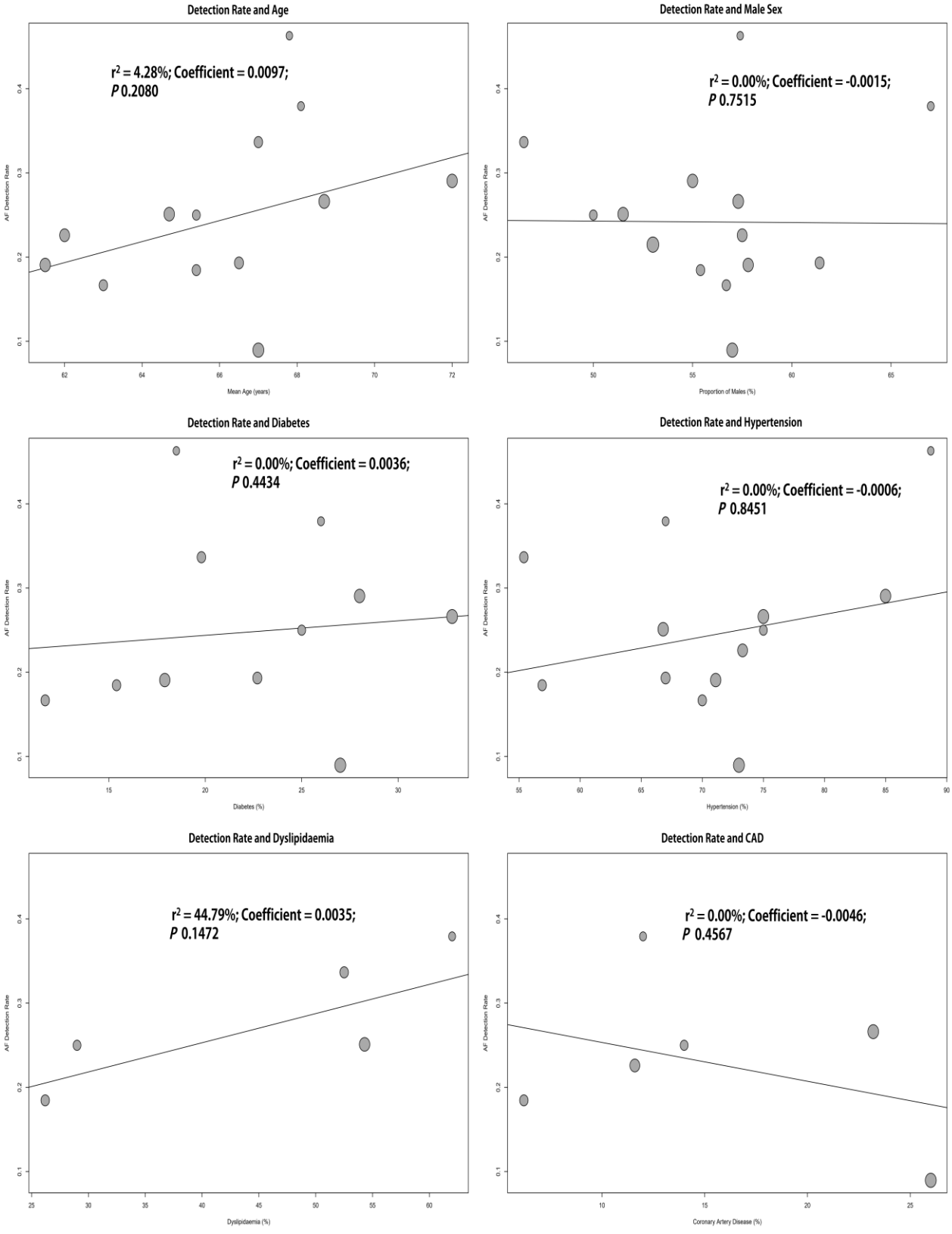
Supplementary Figure 7. Metaregression of atrial fibrillation detection rates at 6 months on implantable cardiac monitor in patients with cryptogenic stroke



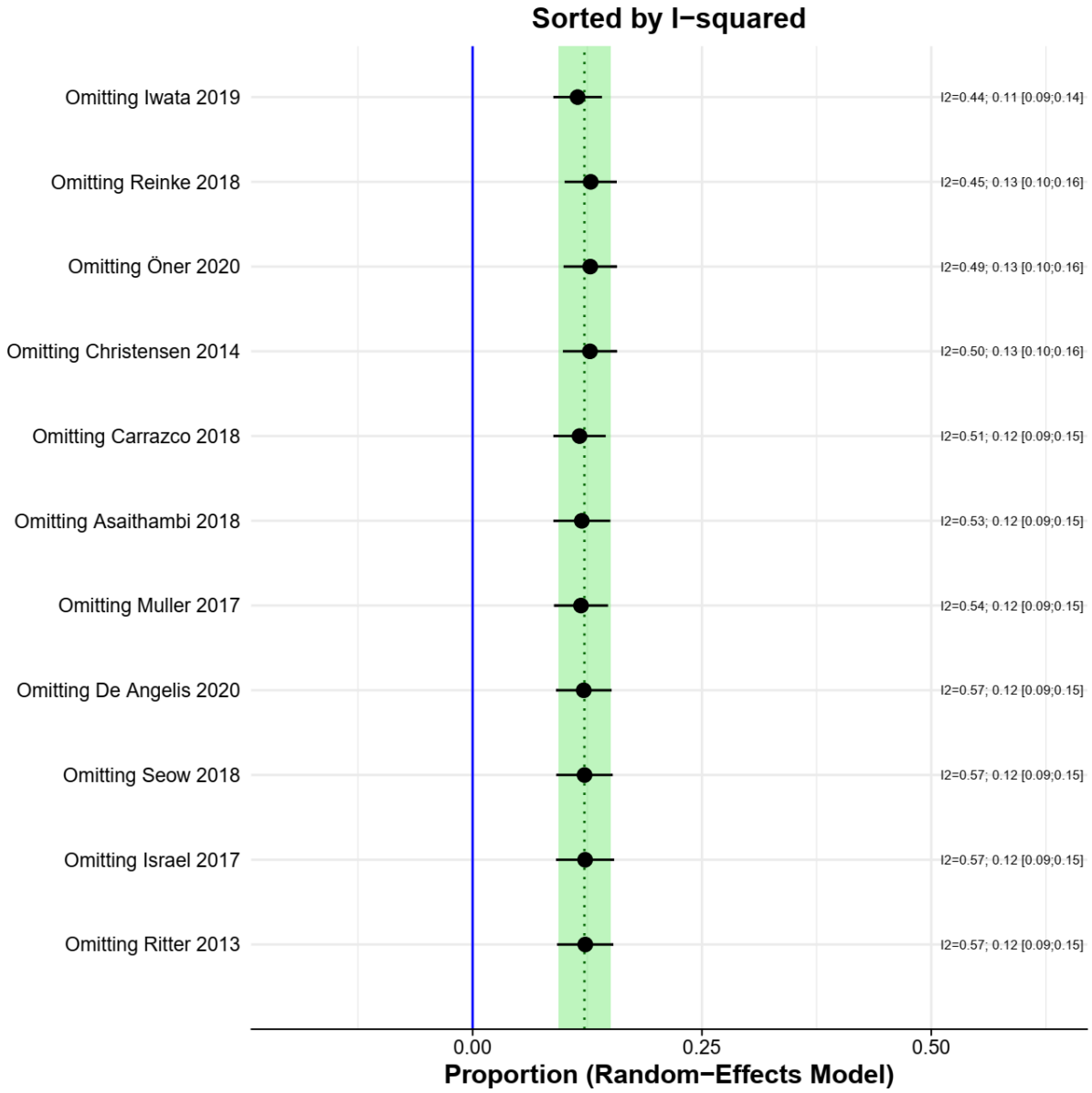
Supplementary Figure 8. Metaregression of atrial fibrillation detection rates at 12 months on implantable cardiac monitor in patients with cryptogenic stroke



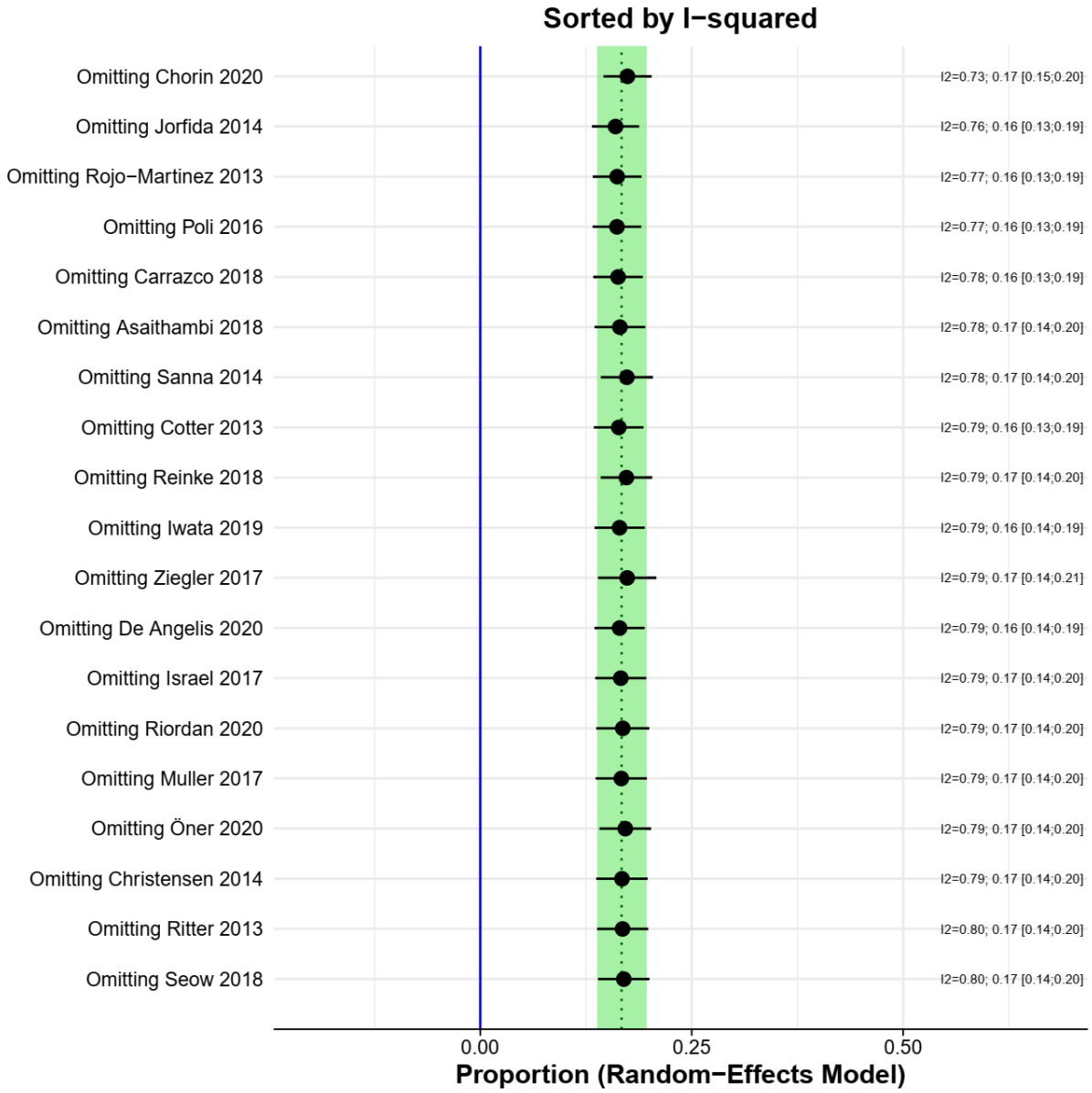
Supplementary Figure 9. Metaregression of atrial fibrillation detection rates at 24 months on implantable cardiac monitor in patients with cryptogenic stroke



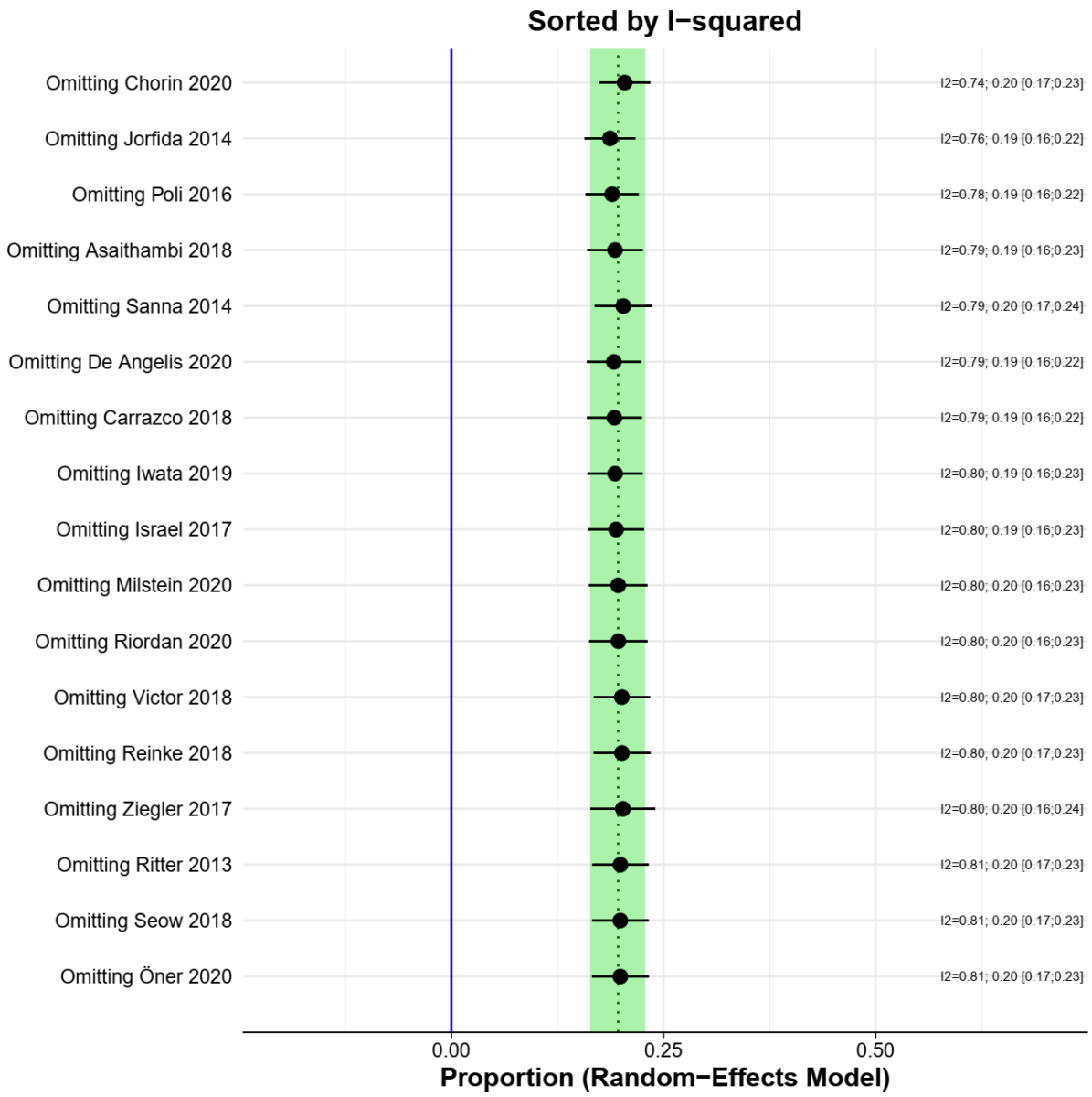
Supplementary Figure 10. Influencer analysis of AF detection rates at 3 months on implantable cardiac monitor in patients with cryptogenic stroke



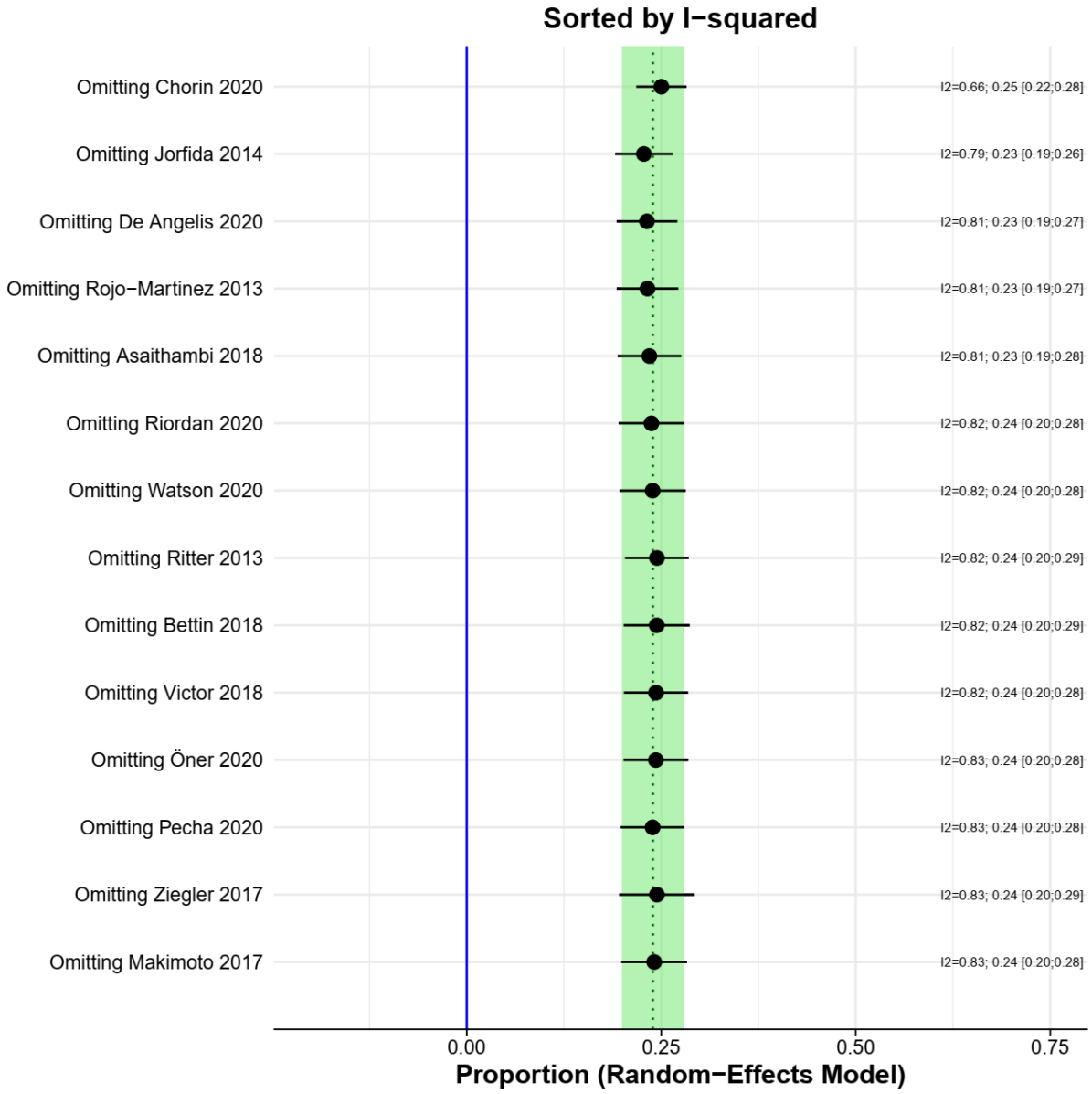
Supplementary Figure 11. Influencer analysis of AF detection rates at 6 months on implantable cardiac monitor in patients with cryptogenic stroke



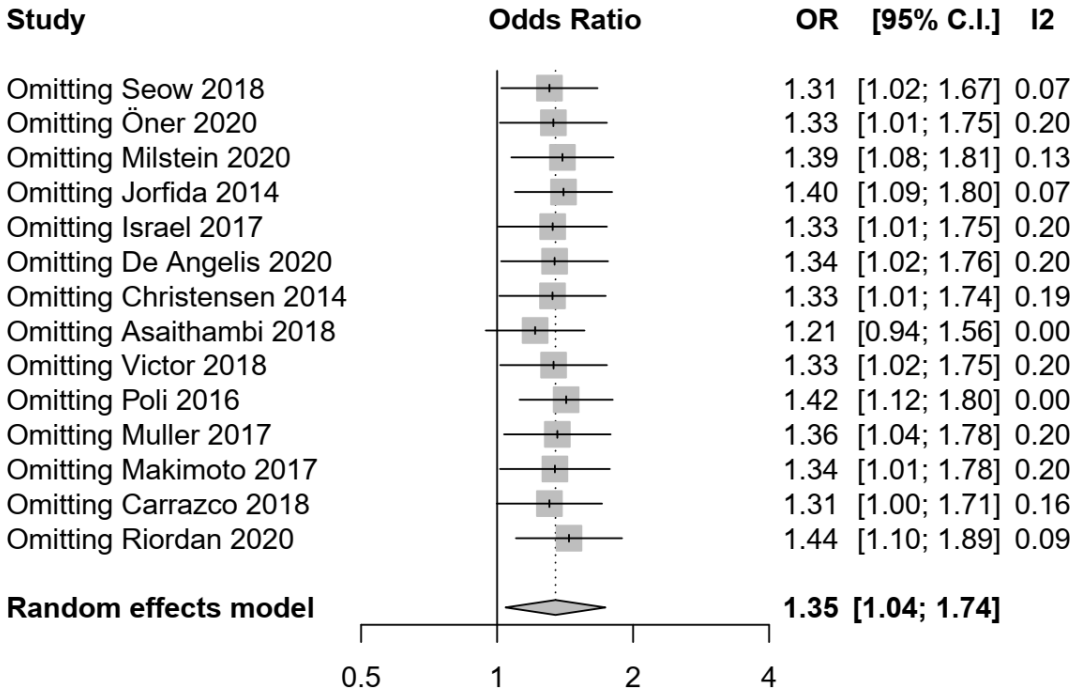
Supplementary Figure 12. Influencer analysis of AF detection rates at 12 months on implantable cardiac monitor in patients with cryptogenic stroke



Supplementary Figure 13. Influencer analysis of AF detection rates at 24 months on implantable cardiac monitor in patients with cryptogenic stroke



Supplementary Figure 14. Influencer analysis of the univariable association between female sex and AF detection in patients with cryptogenic stroke



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CHAPTER 4:

Clinical and cardiac predictors of stroke in patients with atrial fibrillation

Publication 1

Statement of Authorship

Title of Paper	A meta-analysis of clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation.
Publication Status	☒ Published ☐ Accepted for publication ☐ Submitted for publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Jean Jacques Noubiap Nzeale		
Contribution to the Paper	Conception and design, literature search, data collection, manuscript drafting, manuscript revision		
Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Overall percentage (%)	65%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Overview

This chapter covers clinical and cardiac predictors of stroke in patients with AF. It is divided in two sections. The first section is a systematic review and meta-analysis that comprehensively summarizes data from prospective cohort studies on clinical predictors of stroke and systemic embolism in anticoagulant-naïve AF patients. The ultimate goal of this study is to provide pooled risk estimates that may serve as reference values for the development of future stroke risk prediction schemes combining clinical and non-clinical factors. The second section is a systematic review and meta-analysis that comprehensively summarizes data on potential cardiac imaging correlates and predictors of stroke or systemic embolism in patients with AF. on AF screening after stroke.

4.1 Clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation

4.1.1 Introduction

According to the data from the Global Burden of Disease 2016, stroke is the second leading cause of death and disability globally, accounting for almost 5% of all disability-adjusted life-years and 10% of all deaths.[382, 383] Ischemic strokes represent about two-third of all strokes, and atrial fibrillation (AF)-related cardioembolism accounts for up to a third of these ischemic strokes.[261, 401] Stroke prevention is considered the cornerstone of AF management; the main strategies including oral anticoagulation with either vitamin K antagonists or direct oral anticoagulants, dedicated anticoagulation clinics and percutaneous left atrial appendage occlusion.[261]

Several clinical stroke risk scores have been developed over time to guide pharmacological and interventional stroke prevention strategies in AF patients. The most popular include the $CHADS_2$ score, the CHA_2DS_2-VASc score and the ATRIA stroke risk score, released in 2001, 2010 and 2013, respectively.[252, 264, 265] The predictors of stroke included in these scores comprise older age, female gender, history of hypertension, diabetes, congestive heart failure, previous stroke or transient ischemic attack (TIA), vascular disease and renal disease (reduced glomerular filtration or proteinuria).[252, 264, 265] More recently, the GARFIELD-AF risk calculator was released. It is a computer-based risk calculator that simultaneously provides risk estimates for mortality, ischemic stroke or systemic embolism and major bleeding for up to 24 months.[255] The CHA_2DS_2-VASc score which remains the most commonly used risk stratification tool for AF patients has shown modest performance in predicting stroke and systemic embolic events in real-world cohorts.[261] This has urged the call

for new risk predictor tools incorporating both clinical factors and non-clinical factors such as left atrial imaging features, electrocardiographic markers and biomarkers.[261]

Stroke risk assessment is required for anticoagulant-naïve patients to guide anticoagulation stroke prevention treatment. Therefore, there is a need for investigation of new stroke prediction tools to be evaluated in anticoagulant-naïve AF populations. Due to greater prevalence of oral anticoagulation in AF patients, it has become challenging to perform further large homogeneous cohort studies of anticoagulant-naïve AF patients with unselected risk profiles. In this context, this systematic review and meta-analysis aimed to comprehensively summarize data from prospective cohort studies on clinical predictors of stroke and systemic embolism in anticoagulant-naïve AF patients. The pooled risk estimates from this study may serve as reference values for the development of future stroke risk prediction schemes combining clinical and non-clinical factors.

4.1.2 Methods

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines (MOOSE) and was registered with PROSPERO (CRD42020160572).

4.1.2.1 Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), Global Index Medicus and Web of Science were searched to identify all cohort studies reporting primary data on the incidence and predictors of stroke in patients with non-valvular AF, published and included in these bibliographic databases by November 28, 2019 (date of the last search), irrespective of the language. The search strategy was built based on the combination of relevant terms including "atrial fibrillation", "stroke" and "cohort" and their bibliographic synonyms (**Supplementary**

Table 1). Furthermore, the reference list of eligible articles and relevant reviews were examined to identify potential additional data sources.

4.1.2.2 Selection of studies to include in the review

We included cohort studies reporting on the incidence and predictors of stroke in patients with non-valvular AF who were not on anticoagulation, or studies with enough data to compute these estimates. Because estimates from interventional studies are not always reproducible in real-world settings, we excluded randomized-controlled trials and focused on observational cohort studies. We also excluded articles without primary data. For studies reporting data from the same primary study or registry (duplicates), we included the single most comprehensive reporting the largest sample size, or articles presenting complementary data. Two investigators (JJN and VFF) independently screened records for eligibility based on titles and abstracts, and then full texts for final inclusion. Selection discrepancies were resolved via discussion and consensus.

4.1.2.3 Data extraction and management

Two investigators (JJN and JF) independently extracted data on the general characteristics of each study, the distribution of various co-morbidities, the total sample size, the mean or median follow-up time, the total number of person-years of follow-up, the total number of thromboembolic events (stroke, TIA, systemic embolism) during follow-up, the risk estimate (hazard ratio, odds ratio or relative risk) with the 95% confidence interval (95% CI) for each variable assessed as a potential predictor of stroke. A predefined list of potential predictors of stroke in AF patients was established based on the available literature and included diabetes, hypertension, dyslipidemia, heart failure, chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2), proteinuria, previous stroke/TIA/systemic

embolism, vascular disease, peripheral artery disease, prior myocardial infarction, previous pulmonary embolism, chronic obstructive pulmonary disease (COPD), female sex, race (Black or Hispanic) and age (≥65, 65-74, ≥75, ≥85 years). Although vascular disease and peripheral artery disease may be considered as the same entity, in the CHA_2DS_2-VASc score, vascular disease is defined as prior myocardial infarction, peripheral artery disease, or aortic plaque.[264] Therefore, risk estimates for vascular disease, peripheral artery disease, and prior myocardial infarction were collected separately according to how they were reported in original studies. However, when risk estimates for vascular disease were not provided, we attributed estimates for peripheral artery disease and prior myocardial infarction to vascular disease. Two investigators (JJN and JF) independently assessed the risk of bias in included studies using the Newcastle-Ottawa Quality Assessment Scale.[402] Discrepancies were resolved through discussion and consensus.

4.1.2.4 Statistical analysis

Meta-analyses were conducted using the *meta* packages of the R statistical software (version 3.6.0, The R Foundation for statistical computing, Vienna, Austria). To describe the overall population, we pooled prevalence estimates of main characteristics related to age, gender and co-morbidities, using a random-effects meta-analysis model with single arcsine transformation. Incidence data were pooled using the inverse variance method. All incidence and prevalence data were reported with their 95% CI. The generic inverse variance method was also used to pool adjusted risk estimates (hazard ratio [HR], odds ratio [OR] and risk ratio [RR]) and their standard errors with the random-effects meta-analysis model using the *metagen* function. Hazard ratio, OR and RR were treated as equivalent measures of risk, as they were all derived from cohort studies. For both incidence and risk estimate analyses, heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic, which was quantified by I^2

values, assuming I^2 values of 25, 50 and 75% respectively representing low, medium and high heterogeneity.[388] We calculated R^2 through meta-regression analysis (with *metareg* function) to identify covariates that explained the heterogeneity in risk estimate analyses, and therefore quantify the heterogeneity accounted for. The Egger test was used to assess the presence of publication bias.[403] Because the predictive value of gender for stroke in AF patients has been reported to differ according to race, especially in Asians,[404] we performed subgroup analysis comparing studies done in Asia to those done outside Asia.

4.1.3 Results

4.1.3.1 Study selection and characteristics

In total, we identified 17,617 records from bibliographic searches, among which 47 eligible studies were finally included **(Figure 1**). The list of included studies is presented at the end of the appendix, and their characteristics are summarized in the **Supplementary Tables 2 and 3**. Forty-four (93.6%) and three (6.4%) studies had a low and moderate risk of bias, respectively (**Supplementary Table 3**). These studies reported data from 1,756,984 participants in 15 countries.

4.1.3.2 Incidence of stroke, TIA, or systemic embolism

The pooled incidence of stroke in anticoagulant-naïve AF patients was 23.8 per 1000 person-years (95% CI: 19.7-28.2) and varied across regions from 20.3 per 1000 person-years (95% CI: 12.9-29.4) in studies done in Asia to 31.7 per 1000 person-years (95% CI: 29.8-33.7) in one study from Middle East (**Supplementary Figure 1**). There was high heterogeneity (I^2 = 99.8%). There was no evidence of publication bias (Egger test, p value = 0.4675). The pooled incidence was 28.7 per 1000 person-years (95% CI: 21.3-37.2) for the composite of stroke and TIA (**Supplementary Figure 2**), and 34.2 per 1000 person-years (95% CI: 12.5-66.7) for

the composite of stroke, TIA and systemic embolism (**Supplementary Figure 3**). Additional incidence data are presented in the **Supplementary Table 4**.

4.1.3.3 Potential risk factors for stroke or systemic embolism

4.1.3.3.1 Age

In all studies, most patients were aged ≥ 65 years, with proportions ranging from 55.7% to 87.5%, pooled proportion of 75.6% (15 studies, N = 901,697) (**Supplementary Table 5**). The proportions of patients aged ≥ 75 years ranged from 12.1% to 64.7% with a pooled proportion of 45.1% (15 studies, N = 612,853) (**Supplementary Table 5**). Pooled analyses showed that older age categories were predictors of stroke or systemic embolism with a pooled HR of 2.14 (95% CI 1.85-2.47) for age 65-75 years, 2.83 (95% CI 2.27-3.51) for age ≥ 75 years and 6.87 (95% CI 6.33-7.44) for age ≥ 85 years (**Table 1 and Figure 2**).

4.1.3.3.2 Female sex

Females represented 47% (34 studies, N = 1,639,026) of the pooled population, ranging from 25.6% to 67.5% (**Supplementary Table 5**). In overall studies, female sex was associated with incident stroke or systemic embolism (pooled HR 1.18, 95% CI 1.02-1.36) (Table 1). In sub-group analysis, there was an association for studies done outside Asia (pooled HR 1.33 (95% CI 1.15-1.55), but not in those from Asia (pooled HR 0.95, 95% CI 0.81-1.10) (**Figure 3**).

4.1.3.3.3 Hypertension

Hypertension was the most common cardiovascular risk factors, reported in 59.5% (33 studies, N = 1,413,175; range: 22.8%-85%) of participants (**Supplementary Table 5**). Hypertension was a predictor of stroke or systemic embolism (pooled HR 1.60, 95% CI 1.37-1.86) (**Table 1 and Figure 4**).

4.1.3.3.4 Diabetes mellitus

Diabetes was reported in 18.9% (34 studies, N = 1,415,173), ranging from 8.8% to 38.8% (**Supplementary Table 5**). Diabetes was significantly associated with incident stroke or systemic embolism (pooled HR 1.28, 95% CI 1.20-1.37) (**Table 1 and Figure 4**).

4.1.3.3.5 Heart failure

Heart failure was reported in 25.2% (range: 3.8%-92.5%) of patients (29 studies, N = 1,384,665) (**Supplementary Table 5**). These patients with heart failure had a higher risk of incident stroke or systemic embolism (pooled HR 1.25, 95% CI 1.11-1.40) compared to those without heart failure (**Table 1 and Figure 5**).

4.1.3.3.6 Previous stroke or transient ischemic attack

History of stroke or TIA was reported in 14.0% (range: 1.8%-43.1%) of the pooled population (20 studies, N = 962,533) (**Supplementary Table 5**) and it was a strong predictor of stroke or systemic embolism (pooled HR 2.84, 95% CI 2.19-3.67) (**Table 1 and Figure 6**).

4.1.3.3.7 Vascular disease, peripheral artery disease, and prior myocardial infarction

The pooled prevalence was 21.3% (12 studies, N = 1,110,724; range: 12.0%-49.7%) for vascular disease, 18.6% (10 studies, N = 53,202; range: 5.1%-63.1%) for coronary artery disease, 8.1% (9 studies; N = 61,985; range 1.3%-28.9%) for peripheral artery disease (**Supplementary Table 5**). Vascular disease (pooled HR 1.21, 95% CI 1.06-1.39), prior myocardial infarction (pooled HR 1.08, 95% CI 1.03-1.14) and peripheral artery disease

(pooled HR 1.35, 95% CI 1.04-1.75) were significantly associated with incident stroke or systemic embolism (**Table 1** and **Figure 5**).

4.1.3.3.8 Other co-morbidities

The pooled prevalence of co-morbidities was 16.6% (range: 3.8%-34.9%) for chronic kidney disease, 16.6% (range: 4.0%-28.2%) for chronic obstructive pulmonary disease, 14.9% (9 studies, N = 157,008; range: 1.2%-34.9%) for smoking and 33.9% (6 studies, N = 183,760; range 13.0%-55.4%) for dyslipidemia (**Supplementary Table 5**). Chronic kidney disease (pooled HR 1.06, 95% CI 0.88-1.28), proteinuria (pooled HR 1.22, 95% CI 0.79-1.90), smoking (pooled HR 0.99, 95% CI 0.85-1.15), chronic obstructive pulmonary disease (pooled HR 1.02, 95% CI 0.89-1.18) and pulmonary embolism (pooled HR 0.89, 95% CI 0.74-1.06) were not predictors of stroke or systemic embolism (Table 1).

4.1.3.4 Heterogeneity and publication bias

All pooled analyses of prevalence showed high heterogeneity, in keeping with significant variation in the distribution of cardiovascular risk factors across studies from different countries and regions. Exploration of source of heterogeneity was not deemed necessary.

Regarding meta-analyses of risk estimates, according to the Egger test, there was evidence of publication bias for age ≥ 75 years, hypertension, diabetes and vascular disease (**Table 1**). High heterogeneity was found in meta-analyses for age 65-74, age ≥ 75 years, female sex, hypertension, heart failure, previous stroke or systemic embolism and proteinuria. Meta-regression analyses exploring the factors accounting for this heterogeneity are reported in the Appendix (**Supplementary Table 6**).

4.1.4 Discussion

The evidence base that has contributed to the development of stroke risk predictors in AF has been varied. To the best of our knowledge, this is the first meta-analysis of potential clinical predictors of stroke in anticoagulant-naïve AF patients. It shows that increasing age (from ≥ 65 years), hypertension, diabetes, heart failure, vascular and previous stroke or TIA are predictors of stroke in anticoagulant-naïve AF patients. In contrast, some factors that are currently utilized for predicting risk such as chronic kidney disease and proteinuria were not shown to predict stroke in this meta-analysis. Although female sex is associated with thromboembolism in general, subgroup analysis shows that there is no association in studies done in Asia, as opposed to those conducted elsewhere.

Our findings confirm older age as the strongest clinical risk factor for stroke in AF patients. The older AF patients are, the higher their stroke risk. While $CHADS_2$ score only included age ≥ 75 years, the relationship between age and risk of stroke in AF as a continuum was recognized in the CHA_2DS_2-VASc score (age 65-74 years and ≥ 75 years) and the ATRIA stroke risk score (age 65-74, 75-84 and ≥ 85 years).[252, 264, 265] The markedly higher risk attributed to age ≥ 85 years compared to the categories ≥ 75 years and 65-74 years (pooled HR of 6.87, 2.83 and 2.14, respectively) should be better reflected in age risk-weighting than in the ATRIA stroke risk score (65–74 years = 3 points, 75-84 years = 5 points, ≥ 85 years = 6 points). Furthermore, it has been suggested that stroke risk in AF patients rises from age 55 years upwards. A modified CHA_2DS_2-VASc score which assigns one point for patients aged 50 to 74 years was shown to perform better than the CHA_2DS_2-VASc in an Asian cohort, and would further identify AF patients who may derive a positive net clinical benefit from oral anticoagulation.[405]

There is some controversy regarding whether female sex should be considered as a risk factor for thromboembolism in AF patients, due to inconsistent findings across studies.

For instance, in the Euro Heart Survey on Atrial Fibrillation and the ATRIA study, female sex increased the risk of thromboembolism.[320, 330] For this reason, female sex was included in the CHA_2DS_2-VASc score and the ATRIA risk score, whereas it is not a component of the older $CHADS_2$ score [252, 264, 265]. However, the absent significant association of female sex with thromboembolism in other individual studies motivated the revision of several AF management guidelines, including those of the Japanese Circulation Society, the Canadian Cardiovascular Society, and the National Heart Foundation of Australia Consensus Statement which excluded female sex as a risk factor.[267-269] Our subgroup analysis showed that female sex was not associated with thromboembolism in AF patients in studies done in Asia. Indeed, an analysis of data from the Japanese J-RHYTM registry showed that a CHA_2DS_2-VA score, excluding the female sex criterion, had a better performance than the CHA_2DS_2-VASc score, especially in identifying truly low-risk patients.[404] A study based on data from three nationwide Swedish AF registries showed similar findings. Furthermore, the study found that the prognostic power of female sex varied across different CHA_2DS_2-VASc score levels, with the excess risk for women being significant among those with two or more risk factors other than sex.[406] Overall, although there is an association between female sex and incident thromboembolism in anticoagulant-naïve AF patients in general (mostly from studies in Caucasian populations), the current body of knowledge suggests that female sex alone is not enough to initiate antithrombotic therapy in contradistinction to current American guidelines.[266] According to the 2020 ESC guidelines for the diagnosis and management of AF, the simplified CHA_2DS_2-VA score (without the sex component) could guide the initial decision about oral anticoagulation in AF patients, but not considering the sex component would underestimate stroke risk in women with AF, because their risk of stroke is consistently higher in the presence of more than one non-sex stroke risk factor, compared to men.[407]

This meta-analysis confirms hypertension, diabetes, vascular disease and congestive heart failure as prognostic factors for stroke and systemic embolism in patients with AF but suggests differential risk factor potency. Although all three are given 1 point in the $CHADS_2$, CHA_2DS_2-VASc and ATRIA stroke risk scores,[252, 264, 265] the risk attributed to hypertension (HR 1.60) is higher than that of diabetes (HR 1.28), vascular disease (HR 1.21) and heart failure (HR 1.19). Although a narrow-scale score (0 to 9 for the CHA_2DS_2-VASc) is simpler, it underestimates the weight of some score components. Furthermore, one of the major limitations of the abovementioned risk scores is that they only considered history of these factors and do not consider whether they are controlled or not and their severity. For instance, among patients with hypertension, up to 90% of strokes occur in those with uncontrolled blood pressure,[408] and blood pressure lowering post-stroke lowers cardioembolism risk.[251] Therefore, as the risk of stroke is certainly much higher in patients with uncontrolled hypertension, poor blood pressure control should be given more weight in risk stratification schemes than just history of hypertension. Furthermore, the dynamic changes in risk profile in AF patients is now well established, with the 2020 ESC guidelines for the diagnosis and management of AF recommending that in AF patients initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation (Class IIa; Level of Evidence B).[407]

Besides older age, previous stroke or TIA is the most important predictor of thromboembolism in AF patients, conferring almost a two and half fold increased risk. Data from the ATRIA and ATRIA-CVRN cohorts have shown that there is a strong interaction between increased age and prior history of stroke[265]. As such, the ATRIA stroke risk score confers points to age strata according to history of prior stroke. Besides, including history of TIA as a risk factor for future thromboembolism might lead to significant inaccuracy in risk assessment. Indeed, TIA mimics are common,[409] and high rates of TIA misdiagnosis, up to

~50%, have been reported in emergency departments.[410] Therefore, a substantial proportion of patients reporting prior TIA potentially did not have it, leading to the inappropriate commencement of oral anticoagulation. It is worth noting that while the $CHADS_2$ and CHA_2DS_2-VASc scores consider history of stroke or TIA, the more recent ATRIA stroke score only considers prior stroke.[252, 264, 265]

Proteinuria and chronic kidney disease (eGFR < 45) or end-stage renal disease are included in the ATRIA stroke risk score, based on findings from the ATRIA cohort [265, 411]. Only two studies, including the ATRIA cohort study, were included in our meta-analysis for proteinuria, with conflicting results.[411, 412] Therefore, a definite conclusion cannot be made regarding the risk of stroke attributable to proteinuria. On the other hand, the absence of association between chronic kidney disease (eGFR < 60) and incident stroke in our study is likely due to cut-off differences, with most of studies included in our meta-analysis using a cutoff eGFR of < 60, which is higher than the one used in the ATRIA cohort study and the resultant ATRIA stroke risk score.

The current study focuses on clinical risk factors for thromboembolism in patients with AF. The limited performance of exclusively clinical risk stratification tool in predicting thromboembolism in real-world settings highlights the need for hybrid risk predictor tools incorporating clinical and non-clinical factors such as atrial fibrosis and function, left atrial appendage morphology, electrocardiographic markers and biomarkers.[261, 392] The ABC (Age, Biomarkers [high-sensitivity troponin and N-terminal fragment B-type natriuretic peptide], and Clinical history of prior stroke/transient ischemic attack)-stroke risk score was shown to outperform the CHA_2DS_2-VASc score.[392] However, studies comparing the ABC (Age, Biomarkers [growth differentiation factor-15, hsTnT, and haemoglobin], and clinical history [previous bleeding])-bleeding risk score and the HAS-BLED score (exclusively clinical) have shown inconsistent results,[251] suggesting that the addition of biomarkers to clinical factors

does not always lead to better accuracy. Studies that provide a holistic assessment of clinical factors, imaging and biomarkers for stroke risk prediction in patients with AF are highly needed. Such studies should incorporate feasibility and cost-effectiveness data to justify the need for additional testing and more complex tools, especially in primary care settings.[392] The main limitation of this study is the moderate to high level of heterogeneity in most analyses. Although this heterogeneity is reflective of the reality in routine clinical practice, as risk stratification schemes are used in real-world patients with various risk profiles and from diverse clinical settings, it is also due to differences and weaknesses in the assessment, definition and reporting of some clinical factors across studies. Indeed, in most studies there was no information about whether patients remained or not anticoagulant-free during follow-up. The absence of censoring for oral anticoagulation initiation in some studies may have biased the estimation of stroke risk.[413] One study was restricted to patients who did not use anticoagulant therapy, excluding high risk patients initiated on anticoagulation during the follow-up period and therefore, biasing events rates towards lower values.[414] Differences in duration of follow-up across studies are also potential source of bias. Finally, although we included only estimates from multivariable regression analyses, the level of adjustment for confounders was not the same in the included studies.

4.1.5 Conclusion

This study confirms older age and prior stroke as the strongest predictors of stroke or systemic embolism in anticoagulant-naïve AF patients. Although weighted similarly in most risk stratification schemes, the absolute risk of stroke attributable to hypertension, diabetes, vascular, and heart failure may not be the same in individual patients. Female sex seems not to be universally associated with stroke or systemic embolism, suggesting that the decision to initiate anticoagulation should not be made on the sole basis of female sex. Chronic kidney

disease, prior pulmonary embolism, chronic obstructive pulmonary disease and smoking were not predictors of stroke or systemic embolism in anticoagulant-naïve AF patients.

4.1.6 Tables and figures

Table 1. Meta-analysis of the potential predictors of stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

Figure 1. Study selection

Figure 2. Association between older age and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation **Panel A.** 65-74 years; **Panel B.** Age ≥ 74 years; **Panel C.** Age ≥ 85 years

Figure 3. Association between female sex and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation: **Panel A.** From studies done outside Asia; **Panel B.** From studies done in Asia

Figure 4. Association between hypertension and diabetes, and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation **Panel A.** Hypertension; **Panel B.** Diabetes

Figure 5. Association between heart failure and vascular disease, and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation **Panel A.** Heart failure; **Panel B.** Vascular disease

Figure 6. Association between previous thromboembolism and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

Table 1. Meta-analysis of the potential predictors of stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

Potential predictors	HR	95% confidence interval	N studies	Heterogeneity		Egger test, p value
				I^2 (%)	P value	
Age 65-74 years	2.14	1.85-2.47	11	75.3	< 0.0001	0.267
Age ≥ 75 years	2.83	2.27-3.51	15	90.5	< 0.0001	0.006
Age ≥ 85 years	6.87	6.33-7.44	3	0.0	0.5033	0.614
Female	1.18	1.02-1.36	17	88.4	< 0.0001	0.941
Diabetes	1.28	1.20-1.37	18	62.4	0.0002	0.008
Hypertension	1.60	1.37-1.86	16	87.7	< 0.0001	0.006
Heart failure	1.25	1.11-1.40	17	88.3	< 0.0001	0.077
Previous stroke or TIA	2.84	2.19-3.67	15	95.3	< 0.0001	0.656
Vascular disease	1.21	1.06-1.39	15	71.0	< 0.0001	0.011
Peripheral artery disease	1.35	1.04-1.75	5	69.8	0.0101	0.423
Prior myocardial infarction	1.08	1.03-1.14	3	29.0	0.2447	0.928
Pulmonary embolism	0.89	0.74-1.06	2	0.0	0.4940	NA
Chronic kidney disease	1.06	0.88-1.28	5	63.1	0.0284	0.999
Proteinuria	1.22	0.79-1.90	2	93.3	0.0001	NA
Smoking	0.99	0.85-1.15	4	27.6	0.2465	0.463
Chronic obstructive pulmonary disease	1.02	0.89-1.18	2	48.7	0.1628	NA

TIA: transient ischemic attack; HR: hazard ratio

Figure 1. Study selection

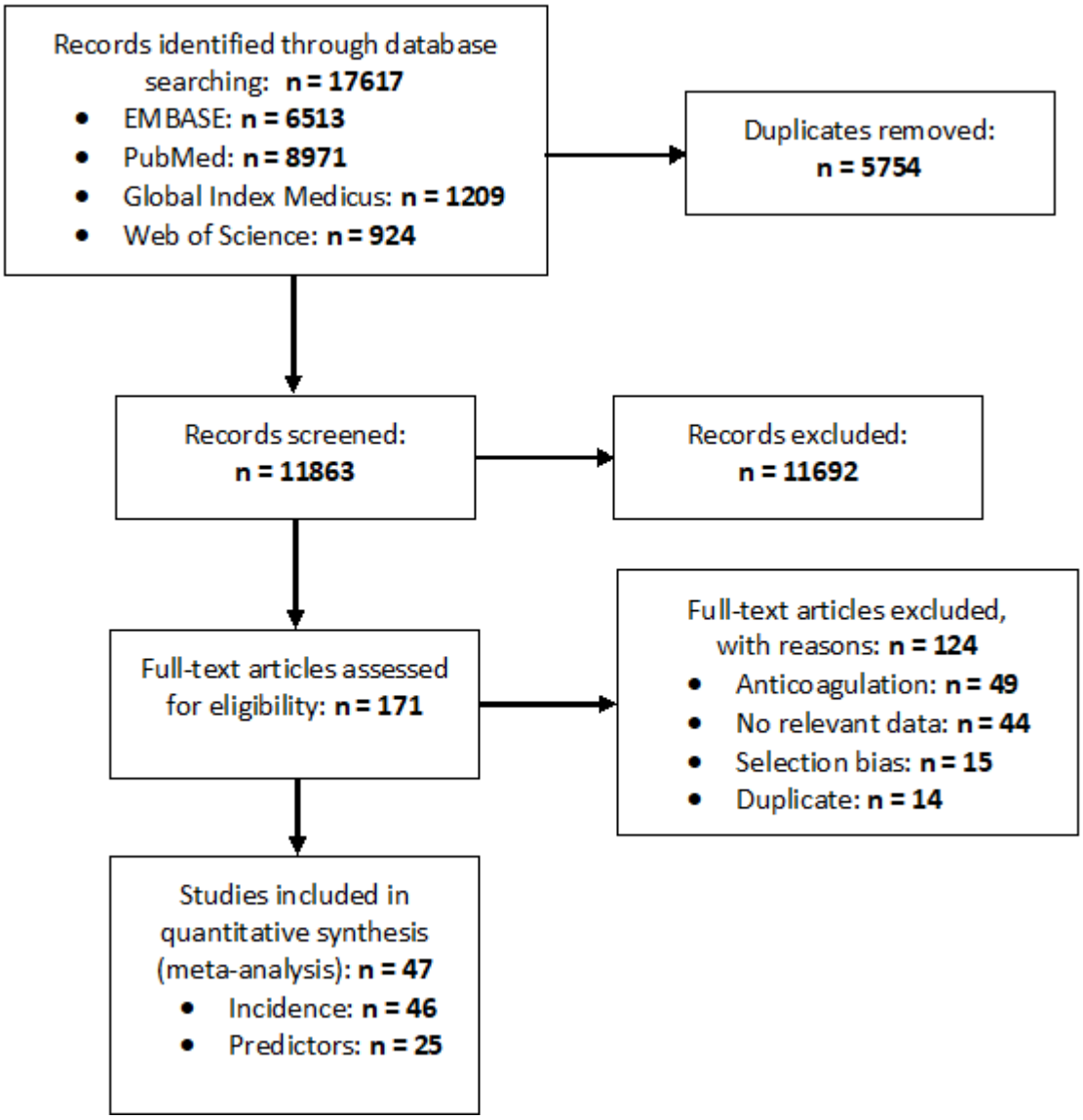


Figure 2. Association between older age and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

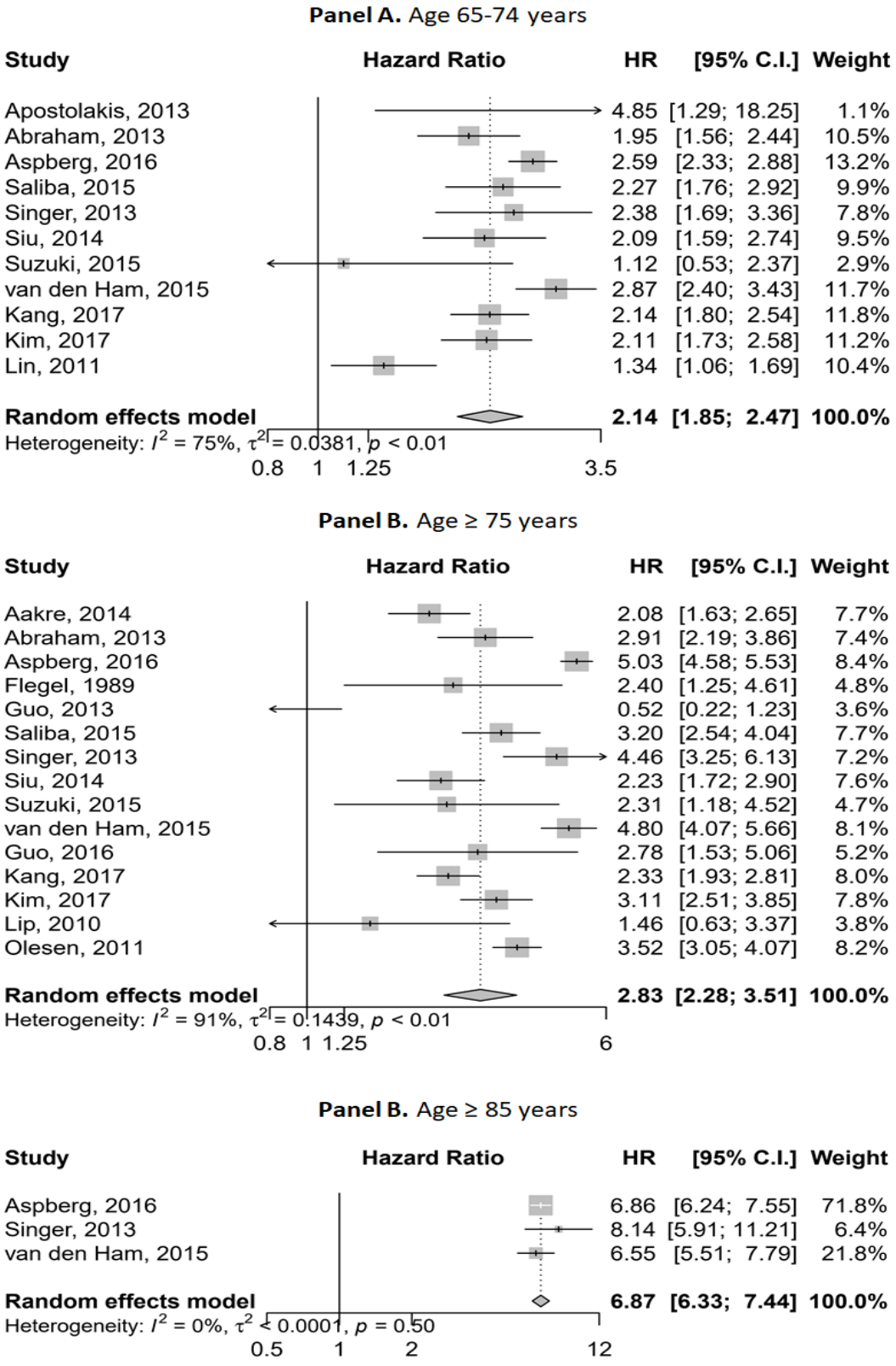


Figure 3. Association between female sex and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

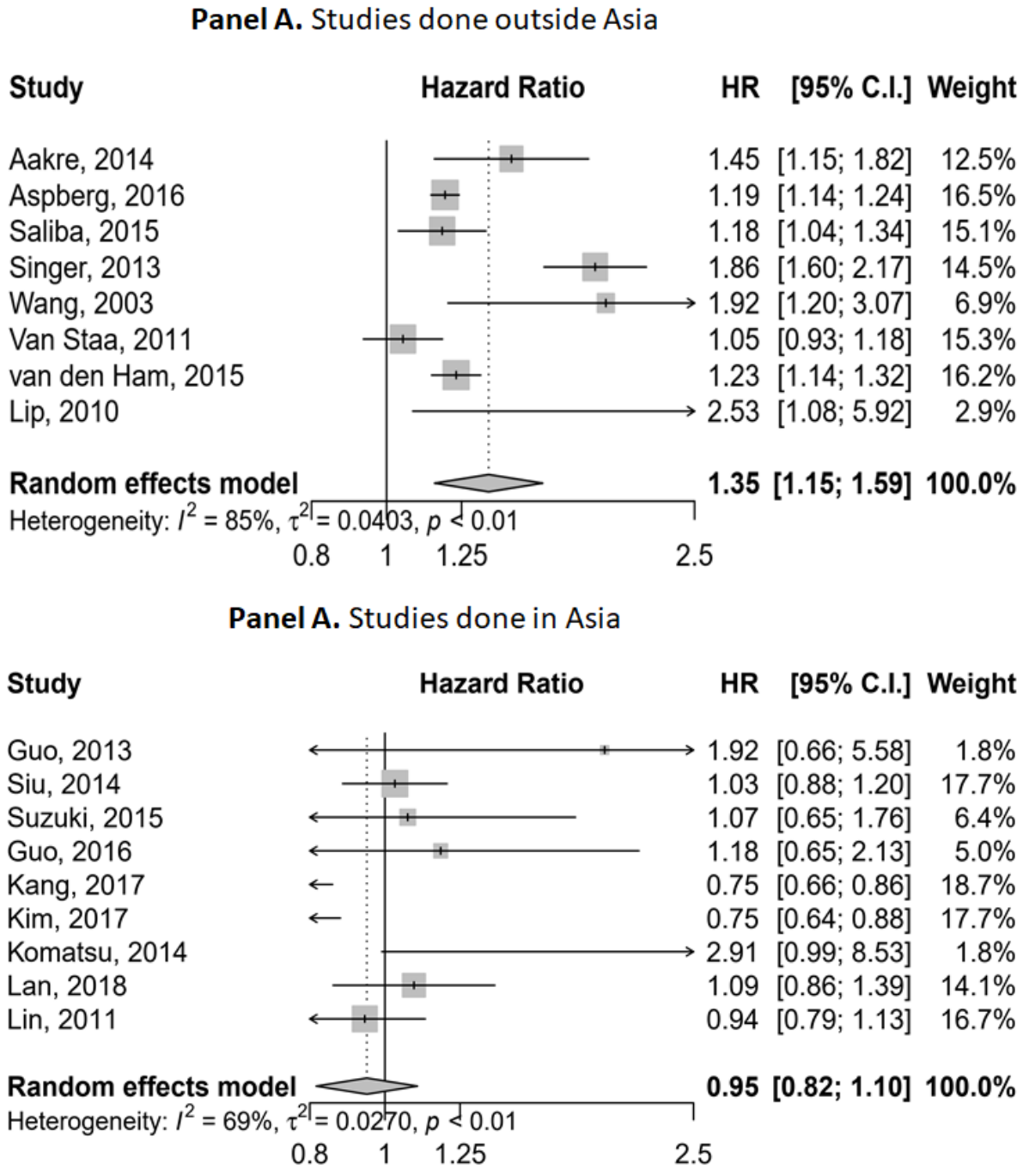


Figure 4. Association between hypertension and diabetes, and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

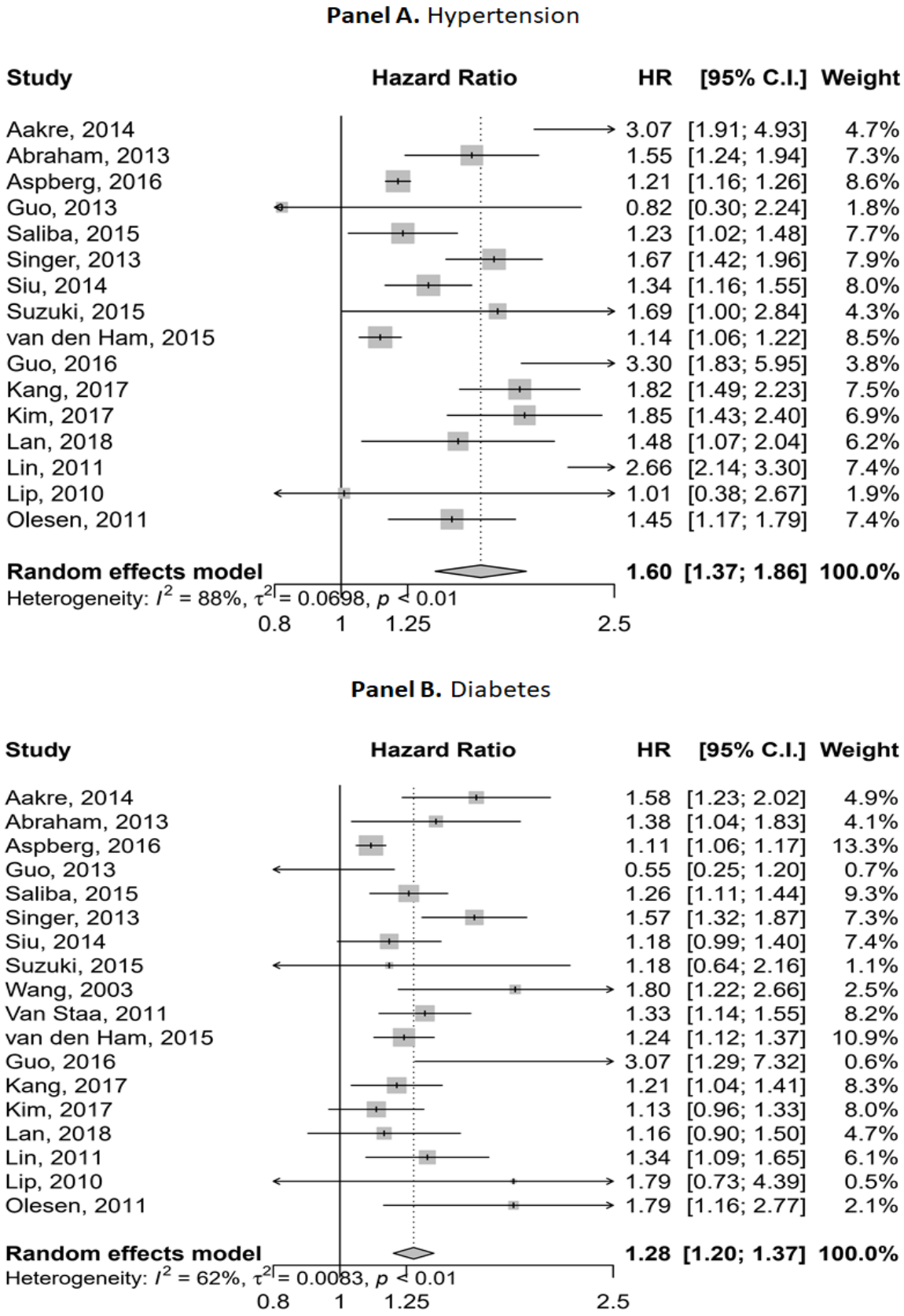


Figure 5. Association between heart failure and vascular disease, and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

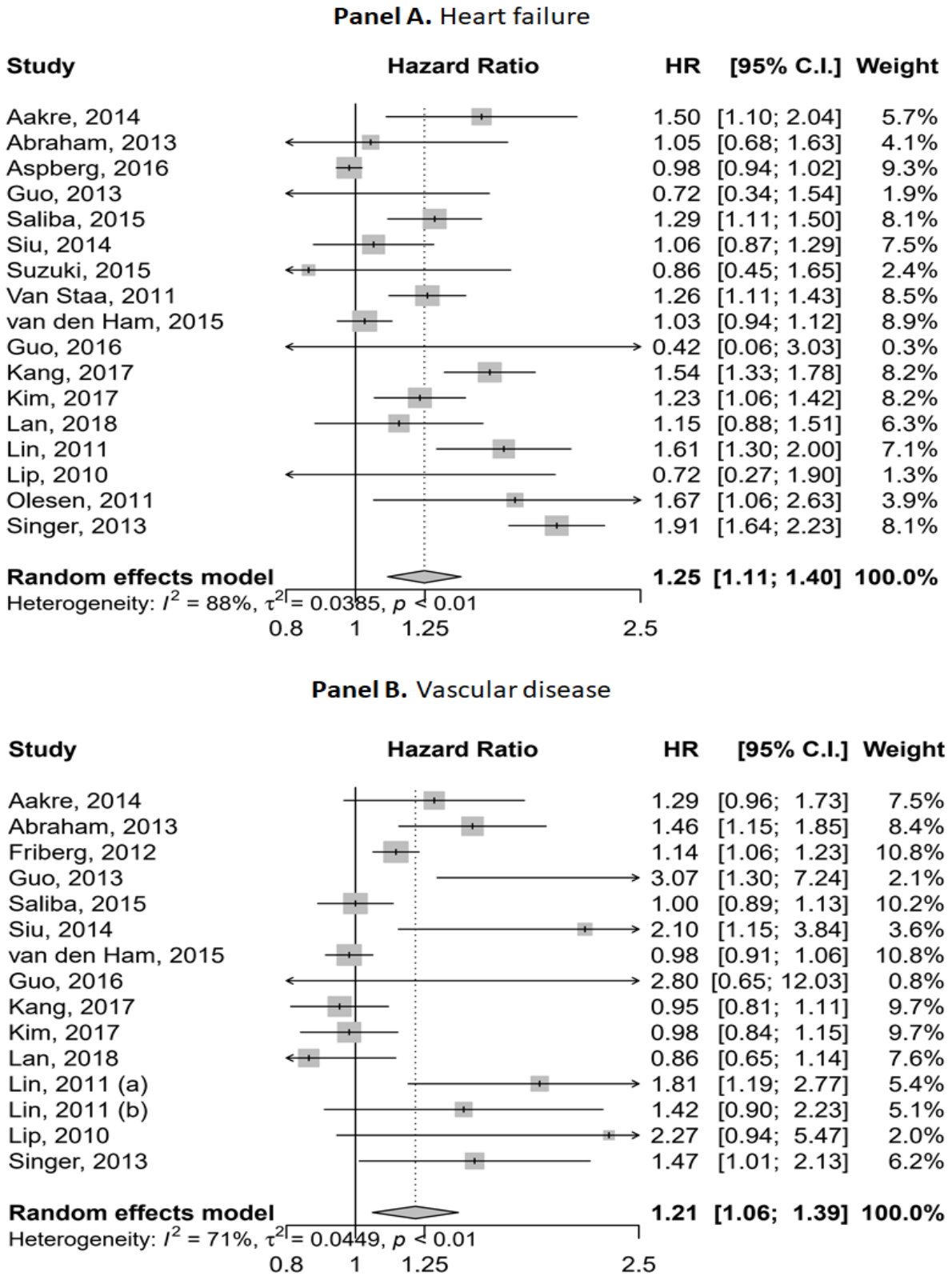
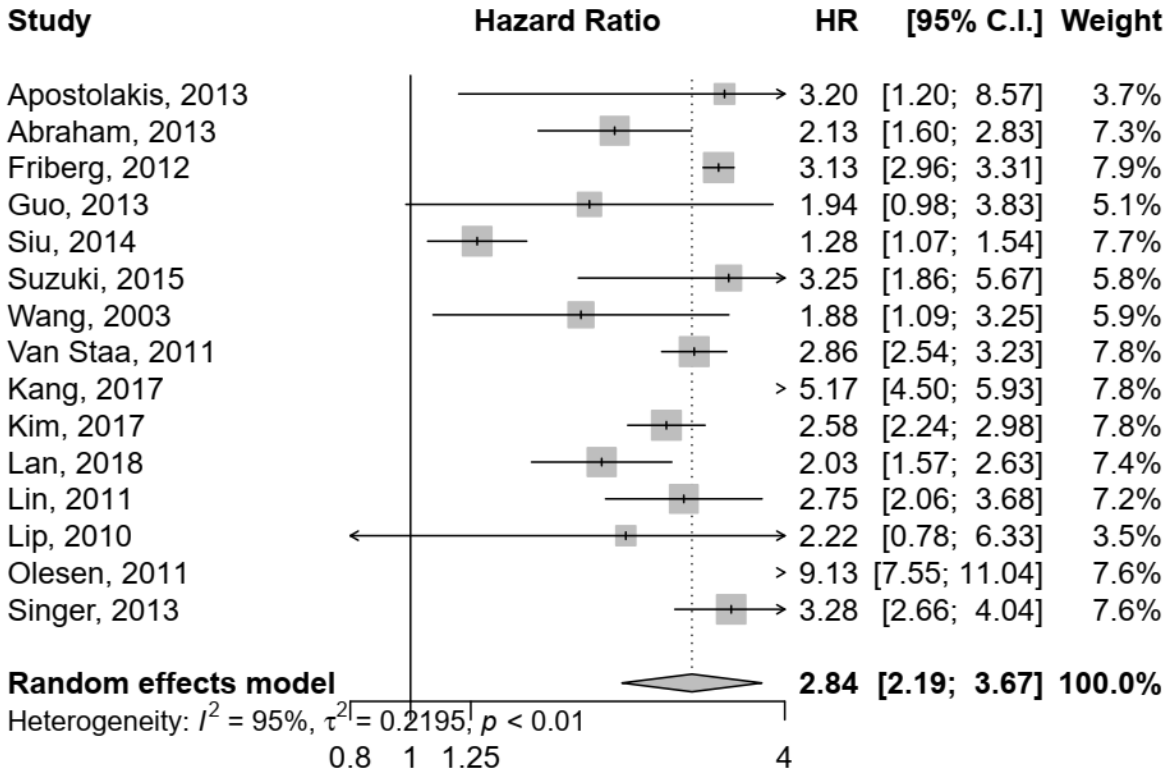


Figure 6. Association between previous thromboembolism and incident stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation



4.1.7 Appendix

Supplementary Table 1. Search strategies

	Search strategy for PubMed
#P1	“stroke” [tiab] OR “cerebrovascular accident” [tiab] OR “CVA” [tiab] OR “cerebral infarct” [tiab] OR “brain infarct” [tiab] OR “subcortical infarct” [tiab] OR “transient ischaemic attack” [tiab] OR “transient ischemic attack” [tiab] OR “TIA” [tiab] OR “apoplexy” [tiab] OR “thromboembol*” [tiab] OR “cardioembol*” [tiab] OR “embol*” [tiab]
#P2	“cohort” [tiab] OR “longitudinal” [tiab] OR “prospective” [tiab] OR “incidence” [tiab] OR “follow up” [tiab] OR “follow-up” [tiab] OR “relative risk” [tiab] OR “risk ratio” [tiab]
#P3	“atrial fibrillation” [tiab] OR “auricular fibrillation” [tiab]
#P4	#P1 AND #P2 AND #P3
	Search strategy for EMBASE
#E1	stroke:ab,ti OR 'cerebrovascular accident*':ab,ti OR 'cva':ab,ti OR 'cerebrovascular apoplexy':ab,ti OR 'brain vascular accident':ab,ti OR 'cerebrovascular stroke':ab,ti OR 'cerebral stroke*':ab,ti OR 'acute stroke*':ab,ti OR 'acute cerebrovascular accident*':ab,ti OR 'subcortical infarct*':ab,ti OR 'posterior choroidal artery infarct*':ab,ti OR 'anterior choroidal artery infarct*':ab,ti OR 'transient ischaemic attack':ab,ti OR 'transient ischemic attack':ab,ti OR 'tia':ab,ti OR 'brain tia':ab,ti OR 'carotid circulation transient ischemic attack':ab,ti OR 'vertebrobasilar circulation transient ischemic attack':ab,ti OR 'crescendo transient ischemic attacks':ab,ti OR 'posterior circulation transient ischemic attack':ab,ti OR 'anterior circulation transient ischemic attack':ab,ti OR 'transient brainstem ischemia':ab,ti OR 'brainstem transient ischemic attack':ab,ti OR 'brain stem transient ischemic attack':ab,ti OR 'transient cerebral ischemia':ab,ti OR 'cerebral infarct*':ab,ti OR 'thromboembolic':ab,ti OR 'thromboembolism':ab,ti OR 'cardioembolic':ab,ti OR 'cardioembolism':ab,ti OR 'embolism':ab,ti OR 'embolic':ab,ti OR 'emboli':ab,ti
#E2	'atrial fibrillation':ab,ti OR 'auricular fibrillation':ab,ti OR 'familial atrial fibrillation':ab,ti
#E3	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'follow-up'/exp OR cohort*
#E4	'article'/it OR 'article in press'/it OR 'letter'/it OR 'short survey'/it
#E5	#E1 AND #E2 AND #E3 AND #E4
	Search strategy for Global Index Medicus
#G1	“stroke” OR “cerebrovascular accident” OR “CVA” OR “cerebral infarct” OR “brain infarct” OR “subcortical infarct” OR “transient ischaemic attack” OR “transient ischemic attack” OR “TIA” OR “apoplexy” OR “thromboembolic”

#G2	“cohort” OR “longitudinal” OR “prospective” OR “incidence” OR “follow up” OR “follow-up” OR “relative risk” OR “risk ratio”
#G3	“atrial fibrillation” OR “auricular fibrillation”
#G4	#G1 AND #G2 AND #G3
	Search strategy for Web of Science
#W1	“stroke” OR “cerebrovascular accident” OR “CVA” OR “cerebral infarct” OR “brain infarct” OR “subcortical infarct” OR “transient ischaemic attack” OR “transient ischemic attack” OR “TIA” OR “apoplexy” OR “thromboembolic”)
#W2	“atrial fibrillation” OR “auricular fibrillation”
#W3	Refined by: [excluding] Databases: (MEDLINE) AND [excluding] DOCUMENT TYPES: (ABSTRACT OR LETTER OR CASE REPORT OR OTHER OR MEETING OR EDITORIAL OR BOOK OR RETRACTION OR CORRECTION OR UNSPECIFIED OR REPORT OR REVIEW OR NEWS) Databases= WOS, CCC, KJD, MEDLINE, RSCI, SCIELO Timespan=All years Search language=Auto
#W4	#W1 AND #W2 AND #W3

Supplementary Table 2. Summarized study characteristics

Characteristics	**N = 47**
Total population	1756984
Year of publication, range	1989-2019
Period of inclusion of participants, range	1974-2016
Design	
- Hospital-based	38
- Community-based	9
Data source	
- Registry	39
- Directly from patients	8
Regions	
- Asia	15
- Northern America	17
- Europe	14
- Middle East	2
Countries	
- United States	13
- Japan	7
- China	4
- Sweden	3
- Canada	4
- Denmark	2
- Multinational Europe	2
- Taiwan	2
- United Kingdom	2
- Korea	2
- Germany	1
- Israel	1
- The Netherland	1
- Spain	2
- France	1
- Multinational Middle-East	1
Representativeness	
- Local	25
- National	19
- Multinational	3
Risk of bias	
- Low	44
- Moderate	3

Supplementary Table 3. Individual characteristics of included studies

Author, year of publication	Country	Study setting	Study level	Timing of data collection	Sample size	Quality*
Aakre, 2014	US	Community	Local	Retrospective	2720	Good
Abraham, 2013	US	Community	National	Retrospective	5981	Good
Aronow, 1996	USA	Hospital	Local	Prospective	283	Fair
Aspberg, 2016	Sweden	Hospital	National	Retrospective	152153	Good
Chao, 2016	Taiwan	Hospital	National	Retrospective	186570	Good
Chen, 2019	US	Hospital	National	Retrospective	267419	Good
Flegel, 1989	Canada	Hospital	Local	Retrospective	91	Good
Friberg, 2012	Sweden	Hospital	National	Retrospective	90490	Good
Gage, 2001	US	Hospital	National	Retrospective	1733	Good
Go, 2008	US	Hospital	Local	Retrospective	13535	Good
Guo, 2013	China	Hospital	Local	Retrospective	885	Good
Guo, 2016	China	Both	Local	Retrospective	880	Good
Hamatani, 2015	Japan	Both	Local	Retrospective	1541	Good
Heeringa, 2006	Netherlands	Community	Local	Retrospective	162	Good
Inoue, 2000	Japan	Both	Local	Retrospective	421	Fair
Kang, 2017	Korea	Both	National	Retrospective	10846	Good
Kim, 2017	Korea	Both	National	Retrospective	5855	Good
Komatsu, 2014	Japan	Community	Local	Retrospective	332	Fair
Kwon, 2016	US	Community	National	Retrospective	1978	Good
Lan, 2018	China	Both	Local	Retrospective	6239	Good
Lin, 2011	Taiwan	Both	National	Retrospective	7920	Good
Lip, 2010	Europe	Both	Multinational	Retrospective	1084	Good
Nielsen, 2018	Denmark	Both	National	Retrospective	239671	Good
Olesen, 2011	Denmark	Both	National	Retrospective	73538	Good
O'Neal, 2016	US	Both	National	Retrospective	1321	Good
Patti, 2017	Europe	Both	Multinational	Retrospective	738	Good
Redfors, 2017	US	Both	National	Retrospective	43248	Good
Renoux, 2017	Canada	Hospital	Local	Retrospective	147622	Good
Ruiz Ortiz, 2008	Spain	Hospital	Local	Prospective	296	Good
Saliba, 2015	Israel	Hospital	National	Retrospective	32912	Good
Singer, 2013	US	Hospital	Local	Retrospective	25 306	Good
Singer, 2013	US	Hospital	Local	Retrospective	10 927	Good
Siu, 2014	China	Hospital	Local	Retrospective	3881	Good
Suzuki, 2015	Japan	Hospital	National	Retrospective	3588	Good
Tohgi, 1991	Japan	Community	Local	Retrospective	3642	Good
Tomasdottir, 2019	Sweden	Hospital	National	Retrospective	231 077	Good

Tomita, 2020	Japan	Hospital	Local	Prospective	1998	Good
van den Ham, 2015	UK	Hospital	National	Retrospective	60594	Good
Van Staa, 2011	UK	Hospital	National	Retrospective	79844	Good
Wang, 2003	US	Community	National	Prospective	705	Good
Wicke, 2019	Germany	Hospital	Local	Retrospective	30229	Good
Yamaji, 2019	Japan	Hospital	Local	Prospective	80	Good
Yu, 2016	Canada	Community	Local	Retrospective	3387	Good
Banerjee, 2013	France	Hospital	Local	Retrospective	2886	Good
Abu-Assi, 2013	Spain	Hospital	Local	Retrospective	181	Good
Boulanger, 2006	US	Hospital	Local	Retrospective	1787	Good
Apostolakis, 2013	Middle-East	Hospital	Multinational	Prospective	876	Good
Parkash, 2007	Canada	Community	Local	Prospective	130	Good

*Methodological quality assessed using the the Newcastle-Ottawa Quality Assessment Scale
NR: not reported

Supplementary Table 4. Data on incidence of stroke, transient ischemic attack and systemic embolism

Author	Year of publication	Country	Sample size	Mean follow-up (years)	Number of incident stroke	Number of incident TIA	Number of incident systemic embolism	Number of incident stroke or TIA	Number of incident stroke or TIA or systemic embolism
Aakre	2014	United States	2720	4.37	346		6		350
Banerjee	2013	France	2886		154				
Abu-Assi	2013	Spain	186	2.8					10
Parkash	2007	Canada	130	2.0	13				
Boulanger	2006	United States	2658		208				
Tomita	2000	Japan	1998	2	64	14	10	78	88
Tomasdottir	2019	Sweden	231 077	2.5	17540				
Abraham	2013	United States	5981	11.8	420	137		457	
Aspberg	2016	Sweden	152153	2.23	11053				
Aronow	1996	United States	283	3	38				
Aronow	1996	United States	283	5	72				
Chao	2016	Taiwan	186570	3.4	23723				
Chen	2019	United States	267419	1.8	4217				
Chen	2019	United States	267419	1.8				5168	
Flegel	1989	Canada	91	2.2	28				
Guo	2013	China	885	1.9	55				
Gage	2001	United States	1733	1.2	71	23		94	
Yamaji	2019	Japan	80	3	4				
Wang	2003	United States	705	4	83				
Van Staa	2011	United Kingdom	79844	2.4	1233				
van den	2015	United Kingdom	60594	2.81	3751				

Ham									
Guo	2016	China	880	1.75	52				
Hamatani	2015	Japan	1541	2.03	42		3		61
Heeringa	2006	Netherlands	162	6	24				
Inoue	2000	Japan	421	3.4					35
Kang	2017	Korea	10846	1.17	888				
Kim	2017	Korea	5855	4.22	819				
Komatsu	2014	Japan	332	4.42	35				
Kwon	2016	United States	1978	5.14	205				
Lan	2018	China	6239	2.81	291		33		324
Lin	2011	Taiwan	7920	4.48					
Lip	2010	Europe	1084	1					25
Nielsen	2018	Denmark	239671	5					12278
Nielsen	2018	Denmark	239671	1					7 642
O'Neal	2016	United States	1321	11	633				
Olesen	2011	Denmark	73538	10					
Patti	2017	Europe	738	1					26
Redfors	2017	United States	43248	1	2908		335		3243
Renoux	2017	Canada	147622	3.06	11 326				
Ruiz Ortiz	2008	Spain	296	1.75	15	12	2	27	29

Supplementary Table 5. Pooled prevalence of clinical factors in anticoagulant-naïve patients with atrial fibrillation

Potential predictors	Prevalence	95% confidence interval	N studies	Pooled population	Heterogeneity	
					I^2 (%)	P value
Paroxysmal AF	65.1	53.0-76.2	7	13554	99.4	< 0.0001
Chronic AF	31.4	17.9-46.8	5	5774	99.5	< 0.0001
Patients aged ≥ 65 years	75.6	71.1-79.9	15	901697	99.8	< 0.0001
Patients aged ≥ 75 years	45.1	37.2-53.1	15	612853	99.9	< 0.0001
Females	47.0	44.5-49.5	34	1639026	99.1	< 0.0001
Diabetes	18.9	16.6-21.4	34	1415173	100	< 0.0001
Hypertension	59.5	54.0-64.9	33	1413175	100	< 0.0001
Heart failure	25.2	19.4-31.5	29	1384665	100	< 0.0001
Dyslipidemia	33.9	22.5-46.4	6	183760	100	< 0.0001
Previous stroke or TIA	14.0	10.3-18.2	20	962533	100	< 0.0001
Vascular disease	21.3	16.5-26.5	13	1110724	100	< 0.0001
Peripheral artery disease	8.1	3.7-13.9	9	61985	99.9	< 0.0001
Coronary artery disease	16.8	8.4-27.2	10	53202	99.7	< 0.0001
Chronic kidney disease	16.6	10.7-23.6	12	481656	100	< 0.0001
Smoking	14.9	9.3-21.6	9	157008	99.9	< 0.0001
COPD	16.6	9.7-24.9	6	191535	99.9	< 0.0001

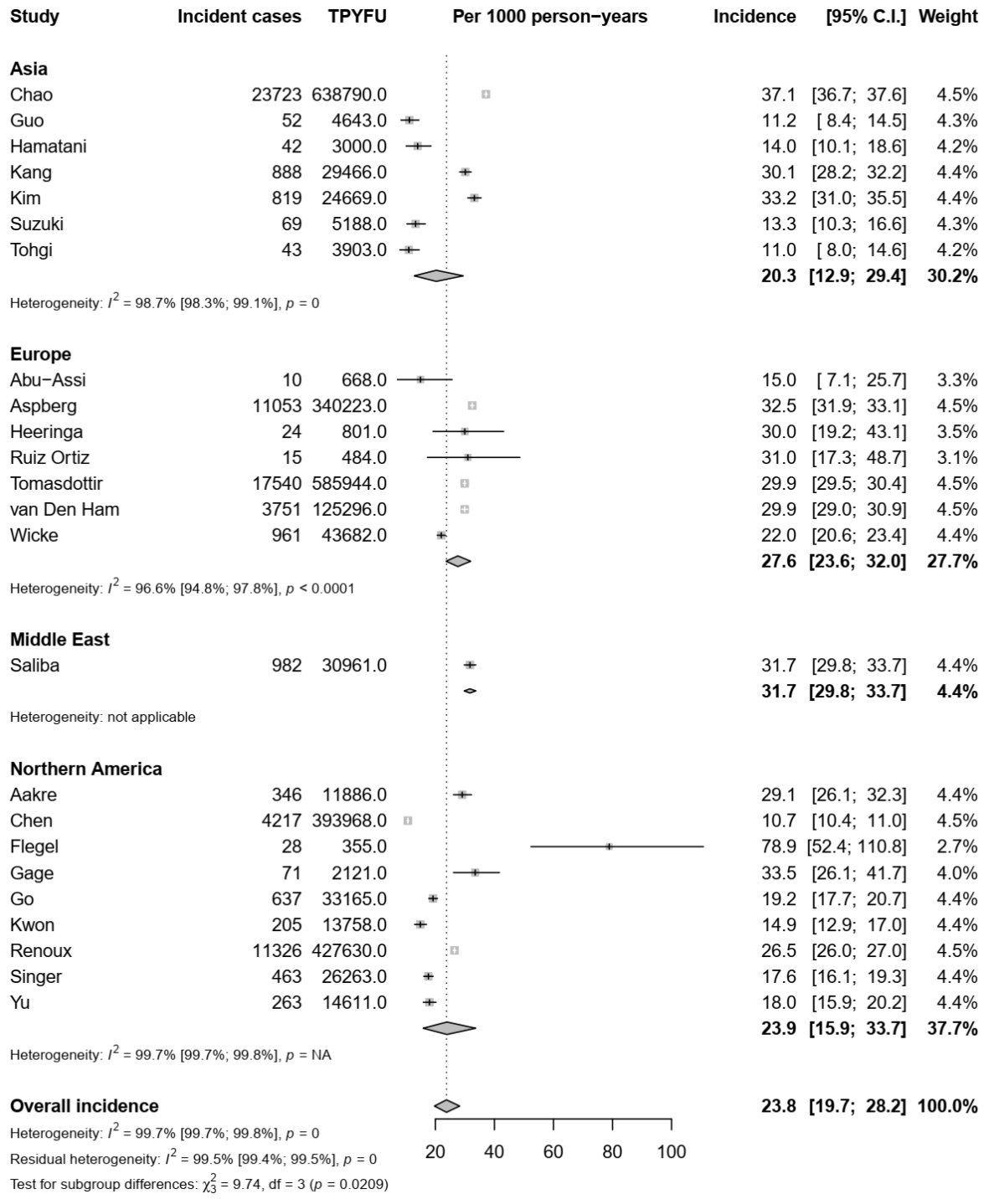
AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack

Supplementary Table 6. Regression analyses of risk estimates for stroke or systemic embolism in anticoagulant-naïve patients with atrial fibrillation

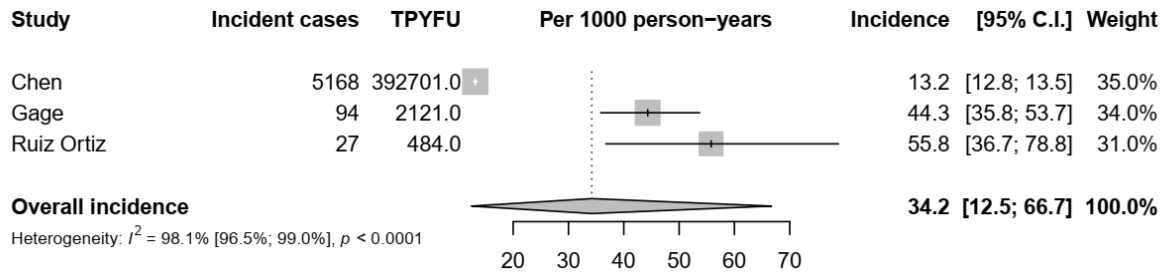
Potential predictors	Overall heterogeneity I^2 (%)	Heterogeneity accounted for (R^2)	Residual heterogeneity	
			I^2 (%)	P value
Age 65-74 years	75.3			
• Region		44.2	60.9	0.006
• Setting		0.0	76.6	< 0.0001
• Representativeness		0.0	79.5	< 0.0001
Age ≥ 75 years	90.5			
• Region		32.7	86.0	< 0.0001
• Setting		9.6	89.6	< 0.0001
• Representativeness		22.4	88.8	< 0.0001
Age ≥ 85 years	0.0			
• Region		NA	NA	NA
• Setting		NA	NA	NA
• Representativeness		0.0	0.0	0.647
Female	88.4			
• Region		47.4	79.0	0.002
• Setting		3.9	88.4	< 0.0001
• Representativeness		4.9	88.3	< 0.0001
Diabetes	62.4			
• Region		0.0	64.7	0.0001
• Setting		26.0	55.7	0.0028
• Representativeness		11.4	60.3	0.0010
Hypertension	87.7			
• Region		35.2	81.3	< 0.0001
• Setting		4.2	87.5	< 0.0001
• Representativeness		2.1	87.7	< 0.0001
Heart failure	88.4			
• Region		6.2	86.8	< 0.0001
• Setting		0.4	88.8	< 0.0001
• Representativeness		4.7	88.3	< 0.0001
Previous stroke or TIA	95.7			
• Region		0.0	95.9	< 0.0001
• Setting		6.9	95.6	< 0.0001
• Representativeness		20.0	95.9	< 0.0001
Vascular disease	65.6			
• Region		0.0	68.4	0.001
• Setting		63.0	42.0	0.088
• Representativeness		7.6	67.6	0.003
Peripheral vascular disease	69.6			
• Region		0.0	76.7	0.005
• Setting		NA	NA	NA
• Representativeness		20.0	66.8	0.029

Pulmonary embolism	0.0			
• Region		NA	NA	NA
• Setting		NA	NA	NA
• Representativeness		NA	NA	NA
Chronic kidney disease	63.1			
• Region		25.5	62.2	0.048
• Setting		NA	NA	NA
• Representativeness		16.3	61.4	0.051
Proteinuria	93.3			
• Region		NA	NA	NA
• Setting		NA	NA	NA
• Representativeness		NA	NA	NA
Smoking	27.6			
• Region		100.0	0.0	0.658
• Setting		0.0	46.9	0.152
• Representativeness		100.0	0.0	0.684
Chronic obstructive pulmonary disease	48.7			
• Region		NA	NA	NA
• Setting		NA	NA	NA
• Representativeness		NA	NA	NA

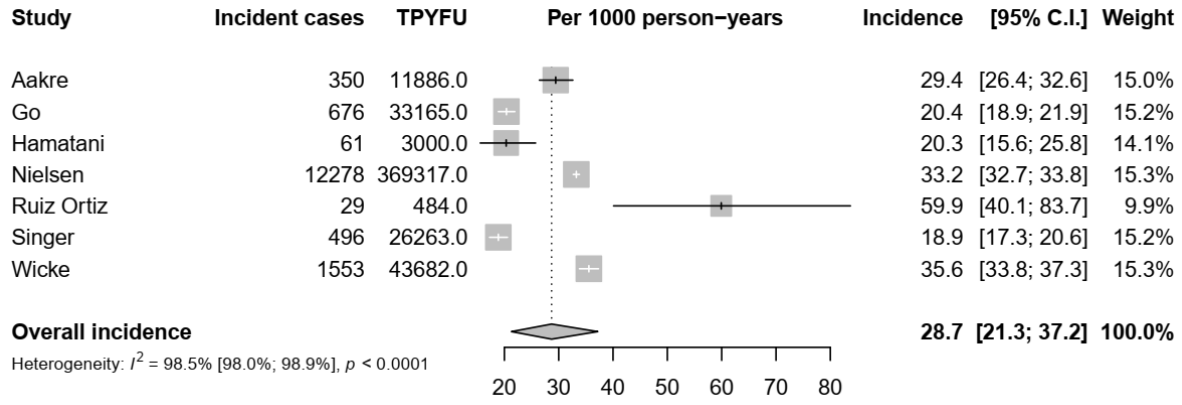
Supplementary Figure 1. Pooled incidence of stroke in anticoagulant-naive patients with atrial fibrillation



Supplementary Figure 2. Pooled incidence of stroke and transient ischemic attack in anticoagulant-naive patients with atrial fibrillation



Supplementary Figure 3. Pooled incidence of stroke, transient ischemic attack and systemic embolism in anticoagulant-naive patients with atrial fibrillation



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4.2 Cardiac imaging correlates and predictors of stroke in patients with atrial fibrillation: A systematic review and meta-analysis

4.2.1 Introduction

Atrial fibrillation (AF) is a major global health problem owing to its increasing incidence and prevalence, and to its complications including impaired quality of life, heart failure, dementia, thromboembolism, and death [1, 70, 167]. Stroke is the most common and devastating complication of AF [167]. People with AF have a five-fold increased risk of stroke [167], and AF-related cardioembolism accounts for up to a third of all ischemic strokes [143]. Anticoagulation can reduce stroke rate by up to two-third [262], with direct oral anticoagulants slightly more effective and much safer pertaining to the bleeding risk, than the vitamin K antagonist warfarin [263].

The decision to start anticoagulation in AF patients is guided by risk stratification schemes that help balancing the benefit of anticoagulation for preventing stroke against the risk of bleeding. Several clinical stroke risk scores have been developed over time including the $CHADS_2$ score, the CHA_2DS_2-VASc score, the ATRIA stroke risk score and recently, the GARFIELD-AF risk calculator [252, 255, 264, 265]. Unfortunately, these stroke risk stratification scores have shown modest performance in predicting thromboembolism in routine clinical practice, especially in identifying truly low-risk individuals [261, 263]. Indeed, most stroke risk scores have a C-statistic of approximately 0.6 to 0.65, with the most commonly used CHA_2DS_2-VASc score having a c-statistic of only 0.6 [263, 264].

The modest performance of the abovementioned stroke risk stratification scores is partially attributed to their lack of specificity for predicting AF-associated versus non-AF-associated ischemic stroke [261]. For instance, the CHA_2DS_2-VASc score has been shown to have similar predictive value for thromboembolism in patients with and without AF [261, 415]. In

fact, these scores are only based on clinical risk factors such as age, hypertension, diabetes or heart failure that increase the risk of stroke irrespective of the presence of AF [261]. Therefore, it is clinically desirable to identify AF-specific risk factors for stroke including cardiac structural, functional, and electrophysiological parameters, that might substantially improve the performance of the current clinical stroke risk stratification schemes. Hence, this systematic review and meta-analysis aimed to comprehensively summarize data on potential cardiac imaging correlates and predictors of stroke or systemic embolism in AF patients.

4.2.2 Methods

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines [385]. It was registered with PROSPERO (CRD42020203059).

4.2.2.1 Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE) and Web of Science were searched to identify all studies reporting primary data on the association between cardiac imaging features and stroke or systemic embolism in patients with non-valvular AF, published and included in these bibliographic databases by November 16, 2022 (date of the last search). No language restriction was applied. We were interested in all cardiac imaging parameters related to the left atrium (LA), left ventricle (LV) and the left atrial appendage (LAA), assessed transthoracic, transoesophageal or speckle tracking echocardiography, computed tomography or magnetic resonance imaging. The search strategy was built based on the combination of relevant terms and bibliographic synonyms of atrial fibrillation, stroke, left atrium, left atrial appendage, left ventricle, thrombus, and echo contrast (**Supplementary Table 1**). Potential additional data sources were searched from the reference list of eligible articles and relevant reviews.

4.2.2.2 Selection of studies to include in the review

We included comparative cross-sectional studies, cohort studies and randomized controlled trials reporting on 1) the association between any cardiac imaging features of interest as outlined above, and incident stroke or systemic embolism in patients with non-valvular AF; or 2) the comparison of these cardiac imaging features between patients with and without previous stroke, transient ischemic attack (TIA) or systemic embolism. We excluded letters, editorials, reviews and studies without primary data or clear description of methods, as well as primary studies on patients who underwent rhythm control procedures such as AF catheter ablation. For studies reporting data from the same primary source (duplicates), we included the single most comprehensive reporting the largest sample size, or articles presenting complementary data (each article having original information not included in the others). Because this is specifically a meta-analysis, we excluded studies reporting only parameters that could not be meta-analyzed due to limited or highly heterogeneous data. Two reviewers (JJN and UFN) independently screened the titles and abstracts of identified citations and then performed a detailed review of all selected full texts to ascertain eligibility. Disagreements were resolved through discussion and consensus.

4.2.2.3 Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by another investigator (UFN). We collected data on the general characteristics of studies, including first author's surname, year of publication, period and country of recruitment, design (clinical trial, cross-sectional or cohort), timing of data collection (retrospective or prospective), general description of participants, proportion of participants on anticoagulation, mean or median age, proportion of males, median or mean follow-up

period for longitudinal studies. We also gathered data on each imaging parameter and its definition, imaging modality, clinical endpoint (stroke, ischemic stroke, TIA, systemic embolism), total sample size, number of participants with the clinical endpoint (either past history or incident), mean or median value of the imaging parameter in the participants with and without the endpoint, numbers of participants with a cardiac imaging abnormality who developed the endpoint and of those who did not, any risk estimate (hazard ratio or odds ratio or relative risk) reported, with the 95% confidence interval (95% CI). Furthermore, The risk of bias was assessed in cross-sectional studies using an adapted version of the tool developed by Hoy et al. [386], whereas it as assessed in randomized controlled trials and cohort studies using the tools developed by the CLARITY group at McMaster University [416, 417].

4.2.2.4 Statistical analysis

Meta-analyses were conducted using the *meta* packages of the R statistical software (version 3.6.0, The R Foundation for statistical computing, Vienna, Austria). To investigate cardiac imaging features associated with stroke or systemic embolism, a meta-analysis using the random-effects method of DerSimonian and Laird was performed to pool weighted odds ratios (OR) and weighted mean differences (MD) with *metabin* and *metacont* functions respectively [418]. For studies reporting median and interquartile range (Q1-Q3), the median was considered as an equivalent of the mean, and the standard deviation was derived by dividing the difference between Q3 and Q1 by 1.35 [419]. For studies reporting on risk estimates, the generic inverse variance method was also used to pool unadjusted and adjusted risk estimates (hazard ratio [HR] and OR) and their standard errors with the random-effects meta-analysis model using the *metagen* function. HR and OR are reported as either unadjusted (uHR and uOR) and adjusted (aHR and aOR). The between-study variance was estimated using the restricted maximum-likelihood estimator [420]. All strengths of association

were reported with their 95% CI. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic [387], which was quantified by I^2 values, assuming I^2 values of 25, 50 and 75% respectively representing low, medium and high heterogeneity [388]. For analyses including more than 2 studies, the influence of each study on the overall heterogeneity was assessed through *Leave-One-Out* influencer analysis model.The Egger test was used to assess the presence of publication bias [403]. A *p* value < 0.10 was considered indicative of a statistically significant publication bias [421].

4.2.3 Results

4.2.3.1 Study selection and characteristics

In total, we identified 31,575 records among which 64 studies [422-485] were finally included (**Figure 1**). Studies characteristics are summarized in the **Supplementary Tables 2 and 3**. These studies reported data from 56,639 participants in 13 individual countries or in multinational registries. The most represented countries were Japan (15 studies, 23.4%) and South Korea (12 studies, 18.8%). Most studies were cross-sectional (42 studies, 65.6%), with most data collected prospectively (48 studies, 75%). Transthoracic echocardiography was the most used imaging modality (37 studies, 57.8%) followed by cardiac computed tomography (15 studies, 23.4%), transoesophageal echocardiography (9 studies, 14.1%), cardiac magnetic resonance (5 studies, 7.8%), and speckle tracking echocardiography (4 studies; 6.3%). The risk of bias assessment is reported in **Supplementary Tables 4-6**.

4.2.3.2 Left atrial imaging parameters

4.2.3.2.1 Structure

Compared to patients with AF and without stroke, those with previous stroke had higher LA diameter (MD 1.8 mm, 95% CI 0.8-2.9) (**Figure 2**), LA diameter index (MD 1.2 mm/m^2, 95% CI 0.6-1.8), LA volume (MD 15.0 ml, 95% CI 7.4-22.7), LA volume index (MD 6.3 ml/m^2, 95% CI 0.8-11.9), and LA sphericity (MD 3.5%, 95% CI 1.2-5.9) (**Table 1, Supplementary Figures 1-4**).

In the meta-analysis of adjusted risk estimates, higher LA diameter (aOR 1.10, 95% CI 1.05-1.15, I^2 74%; 11 studies) (**Figure 3. Panel A**), LA enlargement (aOR 2.12, 95% CI 1.45-3.08, I^2 85%; 6 studies) (**Figure 3. Panel B**), higher LA volume (aOR 1.03, 95% CI 1.01-1.04, I^2 53%; 3 studies) (**Figure 4. Panel A**), higher LA volume index (aOR 1.014, 95% CI 1.004-1.023, I^2 19%; 2 studies) (**Supplementary Figure 5**), and higher LA sphericity (aOR 1.14, 95% CI 1.01-1.29, I^2 50%; 2 studies) (**Supplementary Figure 6**) were associated with an increased risk of stroke (**Table 2**). Left atrial diameter index was a predictor of incident stroke (aHR 1.08, 95% CI 1.05-1.10, I^2 70%; 3 studies) (**Figure 4. Panel B**). Considering the high heterogeneity in these analyses (except for LA volume index), we performed influencer analysis when more than 2 studies were included. The omission of none of the studies significantly reduced the level of heterogeneity in the pooled analyses for LA diameter and LA enlargement (**Supplementary Figures 7 and 8**). For LA diameter index, the omission of the study by Ogata et al. reduced the heterogeneity from 70% to 23%. (**Supplementary Figure 9**), whereas for LA volume, the omission of the study by Ogata et al. reduced the heterogeneity from 53% to 34%. (**Supplementary Figure 10**).

4.2.3.2.2 Function

There was no difference in LA ejection fraction between AF patients with previous stroke and those without (MD -7.6%, 95% CI -16 to 0.8), whereas LA reservoir strain was lower in AF patients with previous stroke (MD -3.9%, 95% CI -6.0 to -1.8) (**Table 1 and Supplementary Figures 11 and 12**).

In a pooled analysis of adjusted risk estimates, lower LA reservoir strain was associated with an increased risk of stroke (aHR 0.86, 95% CI 0.76–0.98, I^2 73%; 4 studies) (**Figure 4. Panel C**). In the influencer analysis to explore the source of heterogeneity, the omission of the study by Liai et al. reduced the heterogeneity from 73% to 0% (**Supplementary Figure 13**).

4.2.3.3 Left atrial appendage imaging parameters

4.2.3.3.1 Structure

Compared to AF patients without stroke, those with stroke had higher LAA depth (MD 3.0 mm, 95% CI 1.9-4.1), higher LAA orifice area (MD 1.0 cm^2, 95% CI 0.7-1.2, I^2 0%), higher LAA volume (MD 1.9 ml, 95% CI 0.1-3.6), but there was no difference regarding LAA length (MD -3.3 mm, 95% CI -7.6-1.1) and LAA orifice diameter (MD 0.7 mm, 95% CI -2.4-3.7) (Table 1, **Supplementary Figures 14-18**).

Left atrial appendage orifice diameter was associated with an increased risk of stroke (aOR 1.56, 95% CI 1.18-2.05, I^2 74%; 4 studies) whereas LAA volume was not (aOR 1.37, 95% CI 0.85-2.21, I^2 79%; 2 studies) (**Figure 5. Panels A and B**). The study by Huang et al. partly explained the high heterogeneity in the meta-analysis of risk estimates for LAA orifice diameter, as its exclusion reduced the heterogeneity from 74% to 57% (**Supplementary Figure 19**). Furthermore, compared to chicken wing morphology, non-chicken wing morphology of the LAA was associated with an increased risk of stroke (aOR 2.15, 95% CI

1.11-4.18, I^2 84%; 6 studies) (**Figure 5. Panel C**). In influencer analysis, the omission of none of the studies reduced the level of heterogeneity (**Supplementary Figure 20**).

4.2.3.3.2 Function

Left atrial appendage ejection fraction (MD -12%, 95% CI -22.0 to -1.9), LAA filling velocity (MD -6.8 cm/sec, 95% CI -10.0 to -3.6), LAA emptying velocity (MD -8.7 cm/sec, 95% CI -11.8 to -5.5), and LAA average flow velocity (MD -5.3 cm/sec, 95% CI -8.0 to -2.6) were significantly lower in patients with stroke compared to those without (**Table 1, Supplementary Figures 21-25**). There was not enough data on these parameters to perform a pooled analysis of risk estimates.

4.2.3.4 Left ventricular imaging parameters

4.2.3.4.1 structure

Atrial fibrillation patients with stroke, compared to those without, had significantly higher interventricular wall thickness (MD 1.0 mm, 95% CI 0.7-1.3) and LV mass index (MD 6.0 g/m^2, 95% CI 1.8-10.2), and lower LV end-diastolic volume (MD -9.9 ml, 95% CI -17.8 to -2.0) (**Table 1, Supplementary Figures 26-28**). There was no difference for LV end-diastolic diameter (MD 0.2 mm, 95% CI -0.6-1.0), LV end-systolic diameter (MD 0.4 mm, 95% CI -1.4-2.2), LV end-diastolic volume index (MD 2.8 ml/m^2, 95% CI -1.4-6.9), LV end-systolic volume index (MD 2.3 ml/m^2, 95% CI -1.0-5.7) and LV end-systolic volume (MD -3.5 mm, 95% CI -12.3-5.3) (**Table 1, Supplementary Figures 29-33**).

In a pooled analysis of risk estimates, LV mass index was associated with an increased risk of stroke (aOR 1.010, 95% CI 1.005-1.015, I^2 0%; 2 studies) (**Table 2, Supplementary Figure 34**).

4.2.3.4.2 Function

Left ventricular ejection fraction was significantly lower (MD -8%, 95% CI -1.4 to -0.2) and the E/e' ratio higher (MD 2.2%, 95% CI 1.5 to 2.9) in AF patients with stroke compared to those without (**Table 1, Supplementary Figures 35 and 36**). The E/e' ratio was associated with an increased risk of stroke (aOR 1.12, 95% CI 1.07-1.16, I^2 0%; 6 studies) (**Figure 6. Panel A**).

4.2.3.5 Spontaneous echo-contrast

Meta-analysis of adjusted risk estimates showed that patients with LA or LAA spontaneous echo-contrast had increased risk of stroke (aOR 3.32, 95% CI 1.98-5.49, I^2 0%; 5 studies) (**Table 2, Figure 6. Panel B**).

4.2.4 Discussion

This systematic review with meta-analysis aimed to summarize available data on potential cardiac imaging correlates and predictors of stroke or systemic embolism in AF patients. We observed significant mean differences in several imaging parameters related to LA, LAA, and LV structure and function between AF patients with and without stroke. A pooled analysis of adjusted risk estimates identified several parameters associated with stroke or systemic embolism, including LA diameter, LA diameter index, LA enlargement, LA volume, LA volume index, LA sphericity, LA reservoir strain, LAA orifice diameter, non-chicken wing LAA morphology, LV mass index, E/e' ration and LA spontaneous echo-contrast (**Figure 7**).

Most of left ventricular imaging features on echocardiography have not shown significant association with thromboembolism in AF patients. The pooled mean difference in

LV end-diastolic volume, LV mass index and interventricular wall thickness between AF patients with and without prior stroke was statistically significant. However, the clinical significance of this difference is uncertain, in the absence of proper association studies. Although heart failure is a well-recognized predictor of stroke in this population [252, 264], there is marked inconsistency in findings from various studies regarding the association of reduced LV ejection fraction and thromboembolism [479]. We could not obtain enough data to pool adjusted estimates on the association of reduced LV ejection fraction with thromboembolism because in most studies, there was no significant association in multivariable regression analysis and hence, risk estimates were not reported. However, this review shows that the E/e' ratio, a ratio between early mitral inflow velocity and mitral annular early diastolic velocity that is a surrogate of LV filling pressure, is associated with thromboembolism. This suggests that among LV anatomic and functional parameters, E/e' ratio can have an added value in risk stratification in AF patients.

There was a significant difference between AF patients with and without prior stroke pertaining to echocardiographic LA anatomical parameters including LA diameter, diameter index, volume, volume index, sphericity, and LA functional parameters such as LA ejection fraction and reservoir strain. Pooled analyses adjusted risk estimates confirmed the association between most of these parameters and stroke. In fact, there are convincing evidence demonstrating that echocardiographic LA dimensions are predictors of major adverse cardiovascular events in both patients with and without AF [486]. Importantly, two studies showed that LA reservoir strain assessed by speckle-tracking echocardiography is independently associated with prior stroke or predictor of incident stroke [436, 464], with a higher predictive value than the CHA_2DS_2VASc score [436], stressing its potential benefit in improving current stroke risk stratification schemes. However, speckle tracking analysis is challenging, especially during AF because of irregular cardiac cycles [483]. In fact, most studies using

speckle tracking echocardiography in patients with AF reported an association between LA strain and incident stroke during sinus rhythm, with only few studies that were performed exclusively during AF [483].

We found an association between non-chicken wing LAA morphology (windsock, cactus, or cauliflower) and stroke. Although this finding suggests that LAA morphology might improve stroke risk stratification in patients with AF, there is a controversy regarding its reproducibility between different observers [432]. There is a need for a clear and rigorous classification of LAA morphology to reduce the subjectivity in its assessment. LAA function in terms of LAA spontaneous echo-contrast and LAA emptying velocity have been correlated with stroke risk following cardioversion [487]. Importantly, these have been demonstrated to be impaired at the time of cardioversion, to be functionally improved and improve with time [488-490]. LAA function parameters such as ejection fraction, filling, emptying and average flow velocities demonstrated marked difference between AF patients with and without stroke are also potential prognostic factors that need further investigation. Unsurprisingly, the presence of spontaneous echo-contrast or thrombus in the LAA or LA was associated with previous or future stroke. Although LA/LAA thrombus is a contraindication for immediate cardioversion or catheter ablation and should be first treated to achieve thrombus resolution [491], there is no clear recommendation on long-term oral anticoagulation in AF patients with LA/LAA thrombus or spontaneous echo-contrast and not eligible based on the CHA_2DS_2VASc score for instance [491].

The findings from this review have important implications. The need for improved stroke risk stratification tools to determine eligibility for stroke prevention strategies in AF patients is of utmost importance. This review suggests some promising structural and functional cardiac factors that might improve this risk stratification. Large prospective studies assessing concurrent clinical, cardiac imaging and biomarkers (serum brain natriuretic

peptides, cardiac troponins, etc.) are highly needed to derive and validate new holistic risk stratification tools. From a cardiac imaging perspective, priority should be placed on more accessible and affordable modalities such as speckle-tracking and measurements obtained on transthoracic echocardiography. Although transesophageal echocardiography is more accurate for some cardiac parameters compared to transthoracic echocardiography, it is less readily accessible and is not tolerable by many patients. The scaling up of the use of handheld echocardiography can be capitalized for this purpose, and the use of artificial intelligence for interpretation may ease the use of this technology and be cost-saving [261]. Although cardiac CT and MRI can provide very useful information, they have a high cost and limited accessibility. An alternative approach may be the selective use of cardiac CT and cardiac MRI only in a subset of patients who have a low embolic score and in whom additional information might improve risk discrimination and confirmation of truly low risk profile.

This review has some limitations. Firstly, most data came from comparative cross-sectional studies or retrospective cohort studies, leading to selection bias and an inability to establish causality for most associations shown in our analyses. Only few studies provided adjusted risk estimates from prospective cohort studies. Therefore, instead of drawing definitive conclusions, this review highlights imaging parameters that might potentially predict thromboembolism in AF patients, and accordingly, warrant further investigation. Secondly, there was significant heterogeneity and due to the limited number of available studies for several analyses, it was not possible to adequately explore sources of heterogeneity. However, this heterogeneity is likely attributed to differences across studies in terms of the overall risk profile of the study populations. For instance, the proportion of AF patients on anticoagulation varied significantly across studies. Furthermore, there was ineluctably some difference in the assessment of the various reported imaging parameters within and across studies, due to interobserver variability and the use of different imaging

modalities and devices. Thirdly, in the absence of established cutoff values for many imaging parameters, only a meta-analysis of standardized mean differences between patients with and without stroke was possible for those parameters. Fourthly, we only included parameters for which we had enough data to perform meta-analysis. As a result, parameters related to epicardial adipose tissue and left atrial fibrosis were not covered. Finally, although we did a careful screening of bibliographic databases and supplementary manual searches, due to the broad scope of this review, there is a chance that few studies might have been missed. Despite these limitations, this review is the first to compile evidence in patients with AF on the association of thromboembolism with a broad spectrum of cardiac imaging parameters using robust statistical methods.

4.2.5 Conclusion

This study suggests an association between stroke or systemic embolism and several structural and functional cardiac imaging parameters including LA diameter, LA diameter index, LA enlargement, LA volume, LA volume index, LA sphericity, LA reservoir strain, LAA orifice diameter, non-chicken wing LAA morphology, LV mass index, E/e' ration, LA spontaneous echo-contrast. These imaging factors should be tested with established clinical risk factors and biomarkers in large prospective cohort studies, to develop and validate holistic stroke risk stratification schemes with better prognosis performance compared to the existing clinical scores.

4.2.6 Figures and tables

Figure 1. Study selection

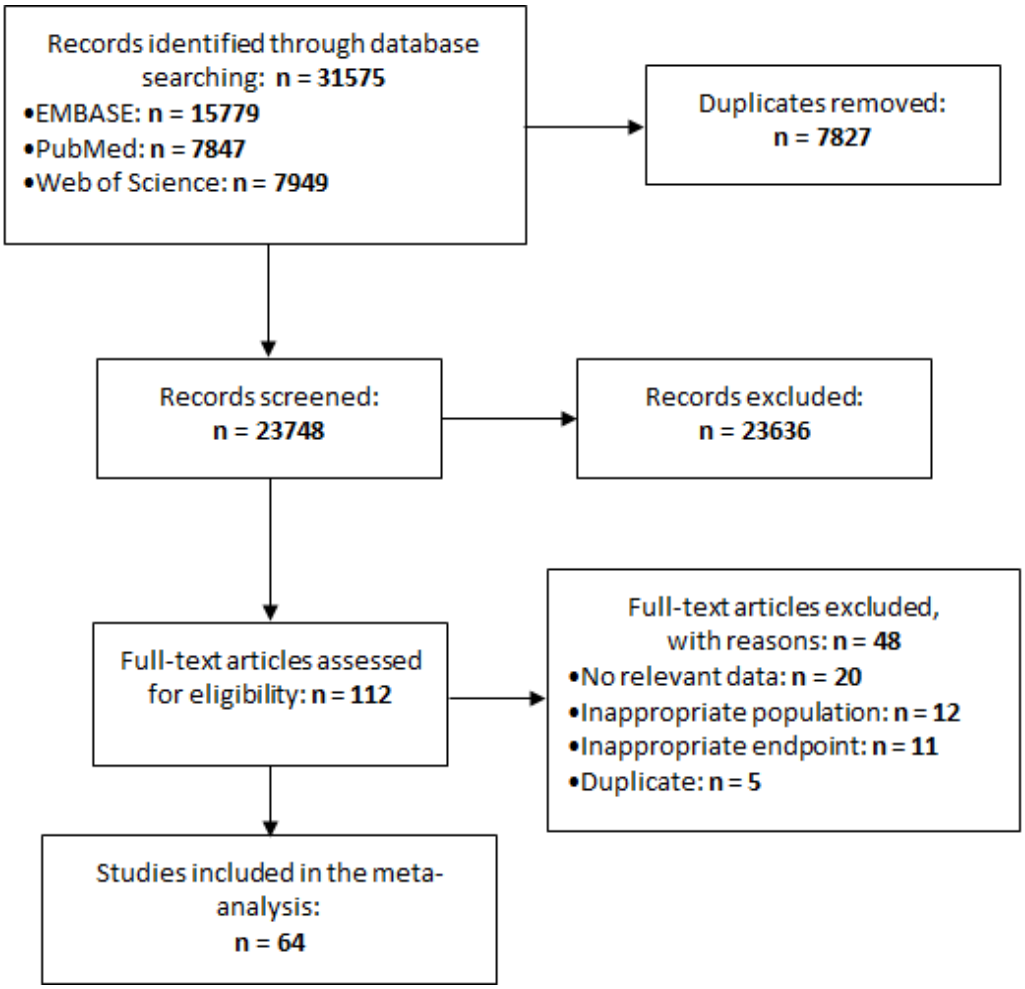


Figure 2. Meta-analysis of mean differences in left atrial diameter between AF patients with and without stroke

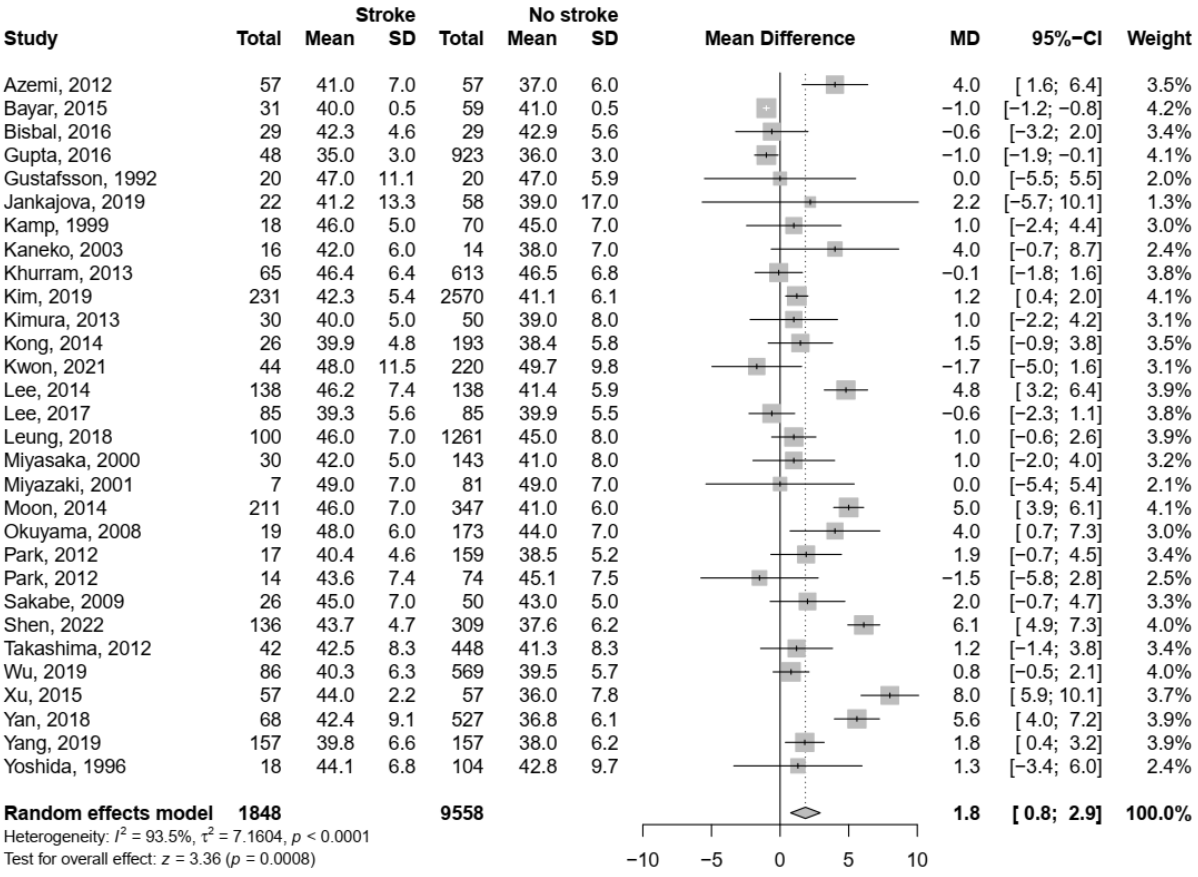


Figure 3. Association of left atrial diameter and left atrial enlargement with stroke

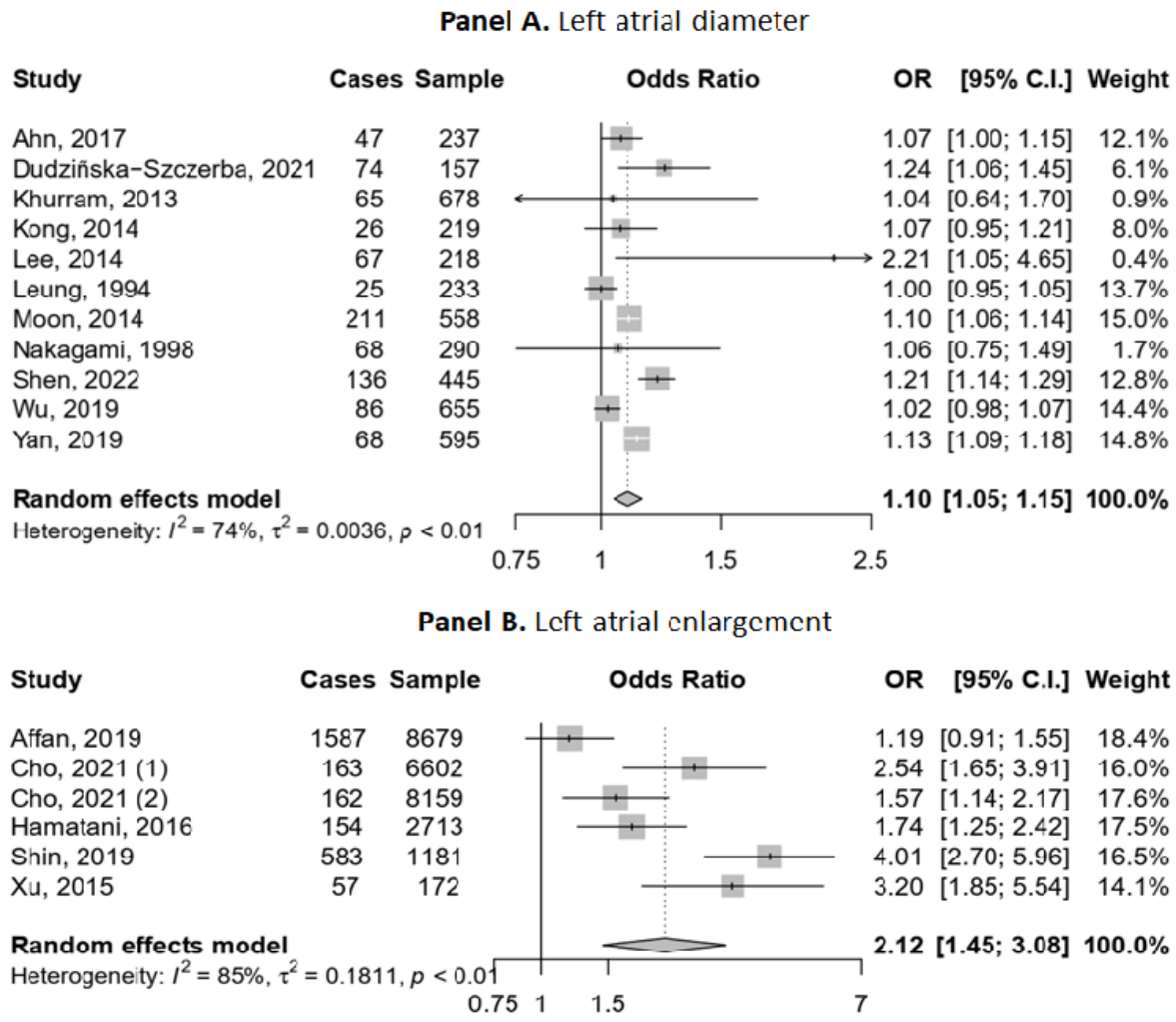


Figure 4. Association of left atrial volume, diameter index, and reservoir strain with stroke

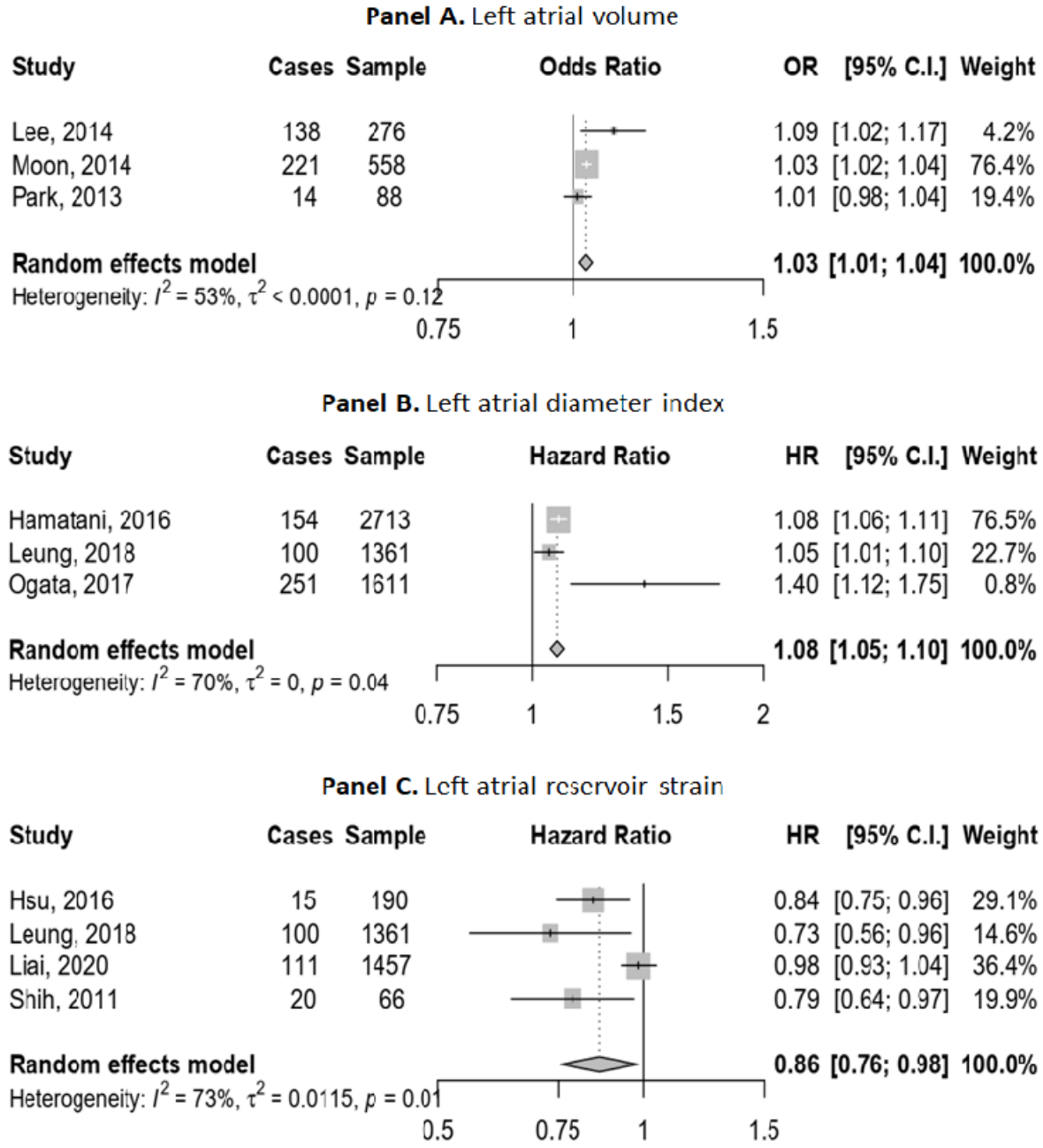


Figure 5. Association of left atrial appendage parameters with stroke

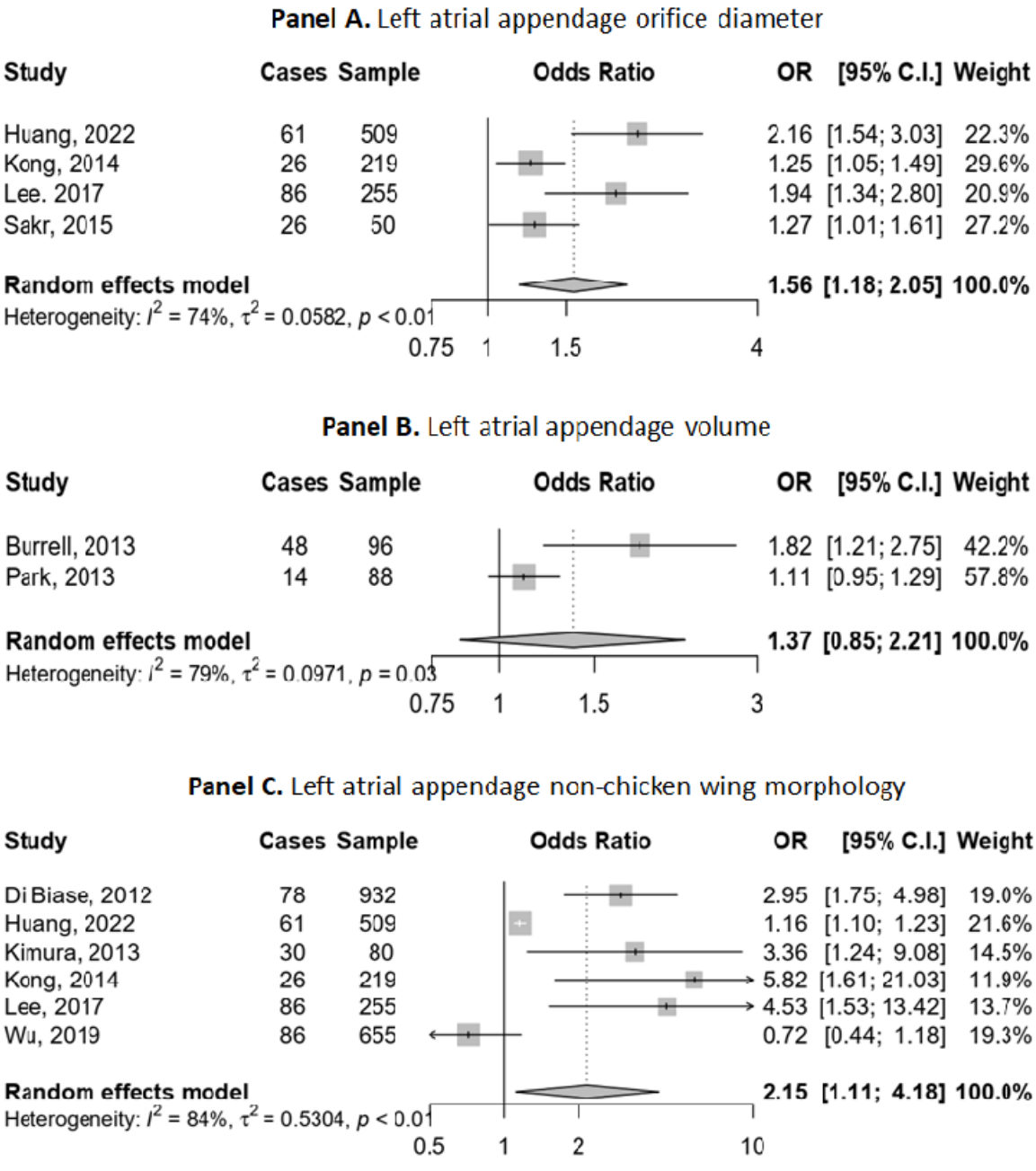


Figure 6. Association of E/e' ratio and spontaneous echo-contrast with stroke

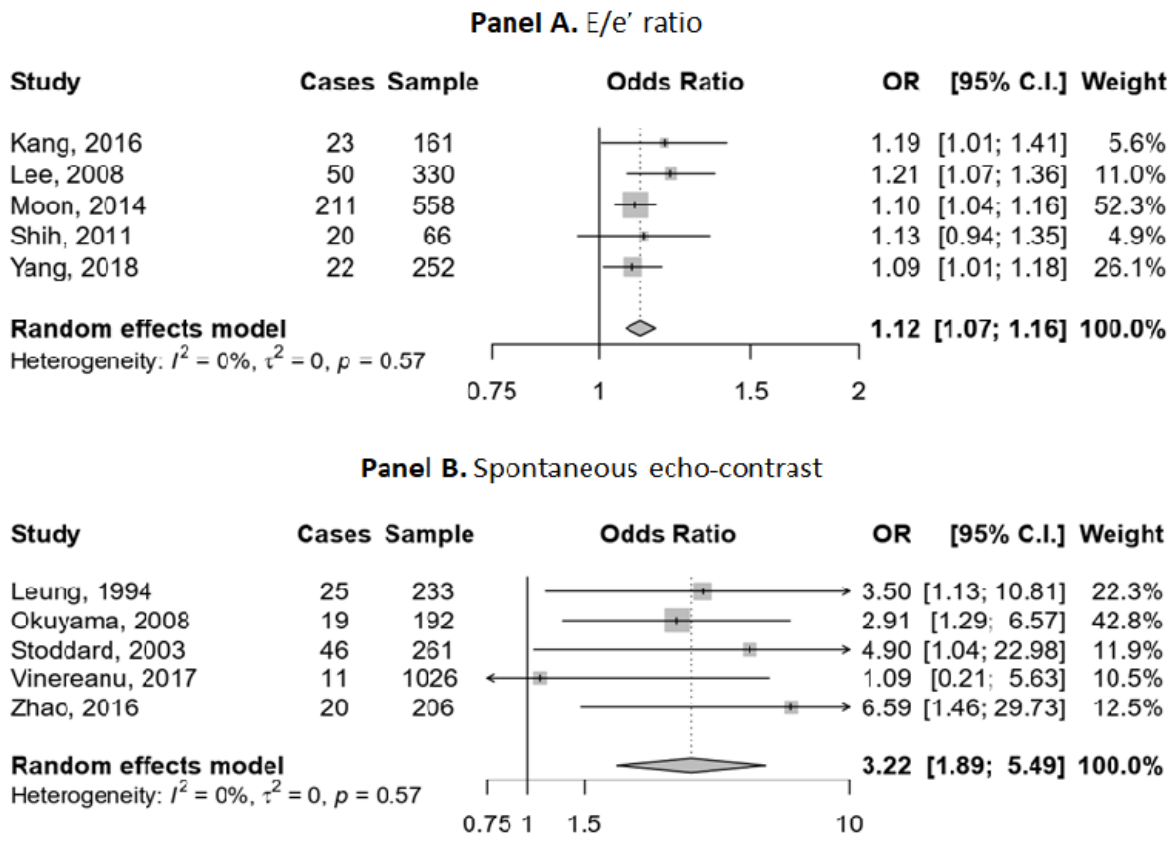


Figure 7. Graphical abstract

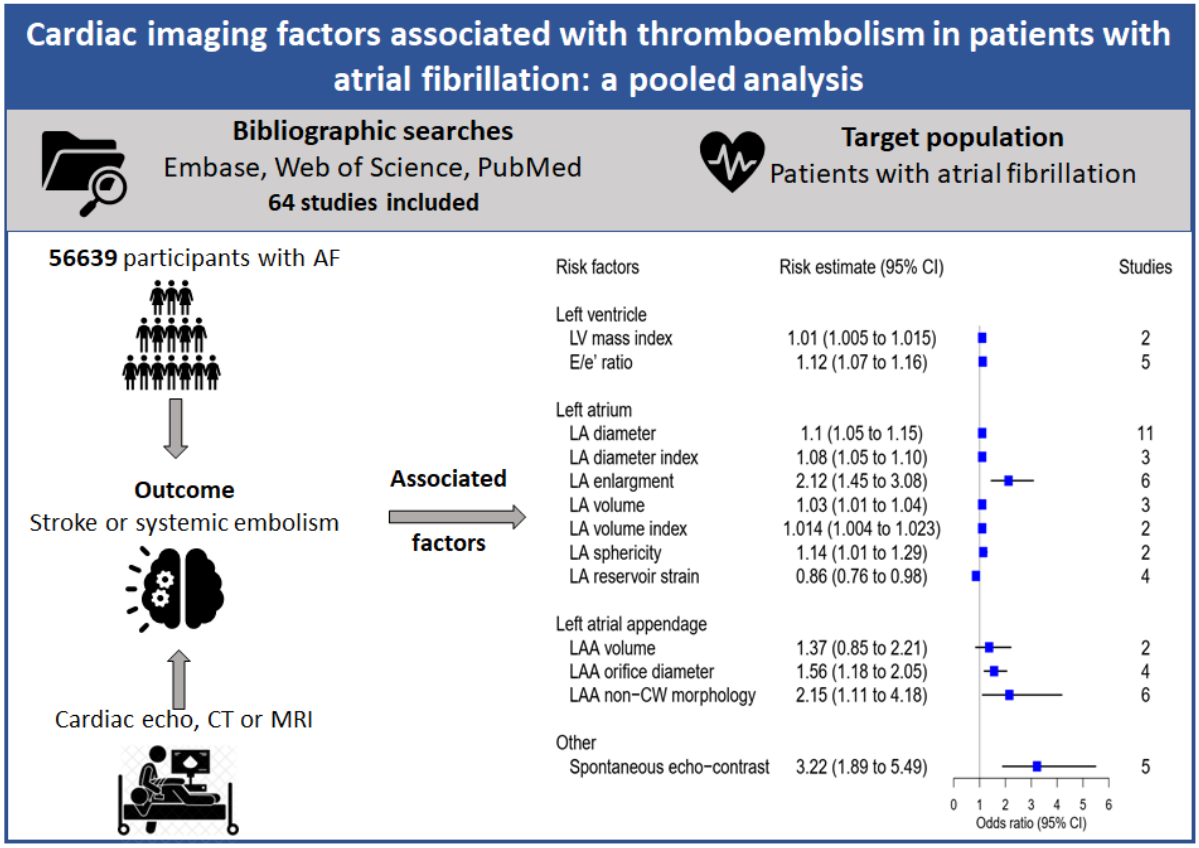


Table 1. Meta-analysis of mean difference in cardiac imaging features between atrial fibrillation patients with and without stroke

Cardiac imaging features (measurement unit)	Mean difference	95% confidence interval	P value	Number of studies	Number of cases	Number of controls	Heterogeneity		Egger test, p value
							I^2 (%)	P value	
LV anatomy									
• LV end-diastolic diameter (mm)	0.2	-0.6 to 1.0	0.621	10	586	3150	44.4	0.061	0.807
• LV end-systolic diameter (mm)	0.4	-1.4 to 2.0	0.660	4	172	1562	52.8	0.096	0.151
• LV end-diastolic volume (ml)	-9.9	-17.8 to -2.0	0.014	4	258	1794	70.2	0.018	0.636
• LV end-systolic volume (ml)	-3.5	-12.3 to 5.3	0.439	2	150	1541	83.8	0.013	NA
• LV end-diastolic volume index (ml/m^2)	2.8	-1.4 to 6.9	0.196	2	42	276	0.0	0.870	NA
• LV end-systolic volume index (ml/m^2)	2.3	-1.0 to 5.7	0.175	2	42	276	0.0	0.603	NA
• LV mass index (g/m^2)	6.0	1.8 to 10.2	0.005	5	260	1601	44.6	0.125	0.310
• Interventricular wall thickness (mm)	1.0	0.7 to 1.3	< 0.0001	3	200	1568	0.0	1.000	0.976
LV function									
• LV ejection fraction (%)	-0.8	-1.4 to -0.2	0.014	32	2489	10999	57.6	< 0.0001	0.129
• E/e' ratio	2.2	1.5 to 2.9	< 0.0001	10	838	4240	75.8	< 0.0001	0.459
LA anatomy									
• LA volume (ml)	15.0	7.4 to 22.7	0.0001	10	795	2426	81.5	< 0.0001	0.542
• LA volume index (ml/m^2)	6.3	0.8 to 11.9	0.026	6	329	908	78.2	0.0004	0.435
• LA sphericity (%)	3.5	1.2 to 5.9	0.003	2	186	186	77.5	0.035	NA
• LA diameter(mm)	1.8	0.8 to 2.9	0.0008	30	1848	9558	93.5	< 0.0001	0.0016
• LA diameter index (mm/m^2)	1.2	0.6 to 1.8	0.0001	2	257	1418	0.0	0.515	NA
LA function									
• LA ejection fraction (%)	-7.6	-16.0 to 0.8	0.074	5	132	1480	92.3	< 0.0001	0.164
• LA reservoir strain (%)	-3.9	-6.0 to -1.8	0.003	3	142	1537	41.0	0.184	0.101
LAA anatomy									
• LAA depth (mm)	3.0	1.9 to 4.1	< 0.0001	4	209	559	0.0	0.464	0.962
• LAA length (mm)	-3.3	-7.6 to 1.1	0.140	2	91	806	77.4	0.035	NA
• LAA orifice area (cm^2)	1.0	0.7 to 1.2	< 0.0001	4	274	453	0.0	0.622	0.255
• LAA orifice diameter (mm)	0.7	-2.4 to 3.7	0.664	6	307	1025	95.3	< 0.0001	0.269
• LAA volume (ml)	1.9	0.1 to 3.6	0.034	9	457	1563	83.2	< 0.0001	0.394

LAA function									
• LAA ejection fraction (%)	-12.0	-22.0 to -1.9	0.020	4	84	385	87.1	< 0.0001	0.902
• LAA filling velocity (cm/sec)	-6.8	-10.0 to -3.6	< 0.0001	2	257	2594	16.9	0.273	NA
• LAA emptying velocity (cm/sec)	-8.7	-11.8 to -5.5	< 0.0001	4	349	2760	61.5	0.051	0.747
• LAA average flow velocity (cm/sec)	-5.3	-8.0 to -2.6	0.0001	2	261	2620	0.0	0.388	NA

LV: left ventricular; LA: left atrial; LAA: left atrial appendage; NA: not applicable (when only 2 studies included)

Table 2. Meta-analysis of the association between cardiac imaging parameters and stroke in patients with atrial fibrillation

Cardiac imaging features (measurement unit)	Type of RE	RE	95% confidence interval	P value	Number of studies	Heterogeneity		Egger test, p value
						I^2 (%)	P value	
• LV mass index (g/m^2)	aOR	1.010	1.005 to 1.015	0. 0001	2	0.0	0.480	NA
• E/e' ratio	aOR	1.12	1.07 to 1.16	< 0.0001	5	0.0	0.57	0.185
• LA diameter (mm)	aOR	1.10	1.05 to 1.15	0.010	11	74.0	< 0.01	0.535
• LA diameter index (mm/m^2)	aHR	1.08	1.05 to 1.10	< 0.0001	3	70.0	0.035	0.563
• LA enlargement	aOR	2.12	1.45 to 3.08	< 0.01	6	85.0	< 0.01	0.035
• LA volume (ml)	aOR	1.03	1.01 to 1.04	0.0001	3	53.0	0.120	0.827
• LA volume index (ml/m^2)	aOR	1.014	1.004 to 1.023	0.004	2	19.0	0.27	NA
• LA sphericity (%)	aOR	1.14	1.01 to 1.29	0.028	2	50.0	0.16	NA
• LA reservoir strain (%)	aOR	0.86	0.76 to 0.98	0.026	4	73.0	0.01	0.029
• LAA volume (ml)	aOR	1.37	0.85 to 2.21	0.199	2	79.0	0.03	NA
• LAA orifice diameter (mm)	aOR	1.56	1.18 to 2.05	0.0016	4	74.0	< 0.01	0.068
• LAA non-CW morphology	aOR	2.15	1.11 to 4.18	0.0234	6	84.0	< 0.01	0.132
• Spontaneous echo-contrast	aOR	3.22	1.89 to 5.49	< 0.0001	5	0.0	0.570	0.919

LV: left ventricular; LA: left atrial; LAA: left atrial appendage; NA: not applicable (when only 2 studies included); RE: risk estimate; aOR: adjusted odds ratio; aHR: adjusted hazard ratio

Non-chicken wing morphology: cactus, cauliflower, windsock

4.2.7 Appendix

Supplementary Table 4. Search strategy

		Search strategy
#1	Cardiac imaging parameters	(((((((("Left ventricular" OR "left ventricle") OR ("E/e")) OR (((“left atrium” OR “left atrial”) AND (“echo contrast” OR “echo dense” OR “echo density” OR “thrombus”)))) OR (“left atrium appendage” OR “left atrial appendage”)) OR (((“left atrium” OR “left atrial”) AND (“function” OR “ejection fraction” OR emptying OR strain)))) OR (((“left atrium” OR “left atrial”) AND (fibrosis OR stiffness)))) OR (((“left atrium” OR “left atrial”) AND (enlargement OR dilatation OR dilated OR hypertrophy OR size OR volume OR dimension OR volume OR diameter OR sphericity OR width OR length OR area))))
#2	Atrial fibrillation	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#3	Stroke	“stroke” OR “cerebrovascular accident” OR “CVA” OR “cerebral infarct” OR “brain infarct” OR “subcortical infarct” OR “transient ischaemic attack” OR “transient ischemic attack” OR “TIA” OR “apoplexy” OR “thromboembolism” OR “cardioembolism” OR “emboli” OR “thrombus”
#4	Final search	#1 AND #2 AND #3

Supplementary Table 5. Summarized study characteristics

Characteristics	**N = 64**
Total population	**56639**
Year of publication, range	1992-2022
Period of inclusion of participants, range	1987-2022
Design	
- Cohort	18
- Randomized controlled trial	4
- Cross-sectional	42
Timing of data collection	
- Prospective	48
- Retrospective	16
Cardiac imaging modality	
- Transthoracic echocardiography	37
- Transoesophageal echocardiography	9
- Speckle tracking echocardiography	4
- Cardiac computed tomography	15
- Cardiac magnetic resonance	5
Regions	
- Asia	41
- Northern America	8
- Interregional	5
- Europe	5
- Oceania	1
- Africa	1
Countries	
- Japan	15
- South Korea	12
- US	7
- China	10
- Multinational	5
- Taiwan	7
- The Netherland	2
- Australia	1
- Egypt	1
- Poland	1
- Slovakia	1
- Sweden	1
- Turkey	1
Methodological quality	
- Good	30
- Fair	33
- Poor	1

Supplementary Table 6. Individual characteristics of included studies

First author, year of publ	Period of recruitment	Country	Study design	Data collection	Characteristics of study population	OAC (%)	Mean or median age	Proportion of male (%)	Cardiac imaging modality	Endpoint	Sample size
Affan, 2019	2016	USA	Cross-sectional comparative	Prospective	Patients with NVAF	17.7	65	46	TTE	Stroke	1920
Ahn, 2019	2000-2016	Korea	Cohort	Prospective	Patients with NVAF post-ablation	~ 30	67.2 for the stroke group and 66.7 for the non-stroke group	68.1 for the stroke group and 61.6 for the non-stroke group	CT	Cardio-embolic stroke	237
Al-Issa, 2016	2005-2007	USA	Cross-sectional comparative	Retrospective	Patients with NVAF referred for catheter ablation	86.1	Cases: 67.4; controls: 67.7	66.7	TOE	Stroke or transient ischemic attack	36
Azemi, 2012	NR	USA	Cross-sectional comparative	Prospective	Patients with NVAF, and CHADS2 score ≤ 1 before their thromboembolic events	0	65	53	TTE	Stroke or transient ischemic attack	114
Bayar, 2015	2012-2014	Turkey	Cross-sectional comparative	Prospective	Patients with NVAF with and without prior stroke/TIA	NR	Cases: 67.3; controls: 63.4	48.9	TTE	Stroke or transient ischemic attack	90
Beinart, 2011	2002-2008	USA	Cross-sectional comparative	Prospective	Patients with NVAF referred for catheter ablation	0	54.5	75	CMR	Stroke or transient ischemic attack	144

Bisbal, 2016	2000-2009	USA & Spain	Cross-sectional comparative	Prospective	Patients with NVAF with and without prior stroke/TIA	NR	Cases: 61; controls: 61	Cases: 79; controls: 79	CMR or CT	Ischemic stroke	58
Burrell, 2013	2003-2011	USA	Cross-sectional comparative	Retrospective	Patients with NVAF	NR	Cases: 70.0; controls: 64.8	71.9	CMR	Stroke or transient ischemic attack	96
Cho, 2021	2006-2016	Korea	Cohort	Retrospective	Patients with NVAF and low thromboembolic risk	16.5	55.9	70	TTE	Ischemic stroke and systemic embolism	6602
Cho, 2021	2016-2020	Korea	Cohort	Prospective	Patients with NVAF and low thromboembolic risk	71.5	67	64.5	TTE	Stroke and systemic embolism	8159
Chu, 2016	2010-2012	Taiwan	Cohort	Prospective	Patients with NVAF	29	70	67.4	TTE	Composite of stroke, myocardial infarction, hospitalization for heart failure and cardiovascular mortality	190
Di Biase, 2012	NR	Italy, USA	Cross-sectional comparative	Prospective	Patients with NVAF undergoing catheter ablation	NR	Cases: 62; controls: 58	78.6	CMR or CT	Stroke or transient ischemic attack	932
Dudziñska-Szczerba, 2021	2014-2016	Poland	Cross-sectional comparative	Prospective	Patients with NVAF	63.1	66.1	56.7	CT	Stroke	157
Fukushima, 2016	2010-2014	Japan	Cross-sectional comparative	Prospective	Patients with atrial fibrillation undergoing catheter ablation	100	59	75	CT	Stroke or transient ischemic attack	96

Gupta, 2016	2008-2013	Multinational	RCT	Prospective	Patients with NVAF and a CHADS2 index score of at least 2	100	71	62.7	TTE	Ischemic stroke, transient ischemic attack or systemic embolic event	971
Gustafsson, 1992	NR	Sweden	Cross-sectional comparative	Prospective	Patients with NVAF	0	77	Not reported	TTE	Stroke	40
Hamatani, 2016	2011-2012	Japan	Cohort	Prospective	Patients with NVAF	54.5	73	60.2	TTE	Stroke or systemic embolism	2713
Huang, 2022	2014-2018	China	Cohort	Prospective	Patients with NVAF and CHA2DS2-VASc score of 0 or 1	0.0	48.9	65.2	CT	Ischemic stroke	509
Hsu, 2016	2010-2012	Taiwan	Cohort	Prospective	Patients with persistent NVAF	13.6	70	67	TTE	Stroke	190
Inoue, 2019	NR	Japan	Cross-sectional comparative	Prospective	Patients with NVAF undergoing catheter ablation or cardiac surgery	40.1	69.9	82	CT	Stroke	147
Jankajova, 2019	2017	Slovakia	Cross-sectional comparative	Prospective	Patients with NVAF	81.3	65	76.3	TTE	Ischemic stroke or systemic embolism	80
Kamp, 1999	1989-1994	Netherlands	Cohort	Prospective	Patients with NVAF	15.9	Cases: 71; controls: 67	65.9	TTE	Stroke or systemic embolism	88
Kaneko, 2003	2000-2001	Japan	Cross-sectional comparative	Prospective	Patients with NVAF	NR	72	67.7	TTE	Cardioembolic stroke	31

Kang, 2016	2010-2016	Japan	Cross-sectional comparative	Prospective	Patients with NVAF with or without prior stroke	3.7	Cases: 62; controls: 59	Cases: 82; controls: 68	TTE	Stroke	161
Khurram, 2013	2001-2012	USA	Cross-sectional comparative	Prospective	Patients with NVAF undergoing catheter ablation	NR	59.5	74.8	CT	Stroke or transient ischemic attack	678
Kim, 2019	1998-2018	Korea	Cross-sectional comparative	Retrospective	Patients with NVAF with or without prior stroke underdoing catheter ablation	NR	55.6	79.2	CMR, TTE and TOE	Ischemic stroke, transient ischemic attack or systemic embolic event	2801
Kimura, 2013	2008-2011	Japan	Cross-sectional comparative	Prospective	Patients with NVAF underdoing catheter ablation	NR	58.6	82.5	CT	Stroke	80
Kong, 2014	2012-2013	China	Cross-sectional comparative	Prospective	Patients with NVAF underdoing catheter ablation	NR	Cases: 62.04; controls: 58.24	64.8	CT	Stroke	219
Kwon, 2021	2004-2016	Korea	Cross-sectional comparative	Retrospective	Patients with NVAF	0	54.2	34.1	TTE	Stroke	264
Lee, 2014	2008-2011	South Korea	Cross-sectional comparative	Prospective	Patients with NVAF	0	Stroke: 66; Non-stroke: 65	68.8	TTE	Stroke	276
Lee, 2014	2008-2011	South Korea	Cross-sectional comparative	Prospective	Patients with NVAF	0	64	68.3	TTE	Stroke	360

Lee, 2017	2011-2015	South Korea	Cross-sectional comparative	Prospective	Patients with NVAF	12.9	Cases: 68.3; controls: 62.1	57.6	TOE	Cardioembolic stroke	170
Lee, 2008	2005-2006	South Korea	Cross-sectional comparative	Prospective	Patients with persistent NVAF	37.9	66	65.5	TTE	Ischemic stroke	330
Leung, 1994	1989-1993	Australia	Cohort	Prospective	Patients with NVAF	16.5	68	68.0	TOE	Ischemic stroke, transient ischemic attack or systemic embolic event	233
Leung, 2018	1995-2015	Netherlands	Cohort	Prospective	Patients with NVAF	71.7	65	74	TTE	Stroke or transient ischemic attack	1361
Liai, 2020	2009-2015	Taiwan	Cohort	Retrospective	Patients with NVAF	36.0	71.6	55.5	STE	Ischemic stroke	1457
Mao, 2020	2019	China	Cross-sectional comparative	Prospective	Patients with NVAF	91	63	62.9	STE	Stroke and systemic embolism	116
McMurray, 2013	2006-2011	Multinational (44 countries)	RCT	Prospective	Patients with NVAF and at least one CHADS2 risk factor	100	70	64.4	TTE	Stroke and systemic embolism	14671
Miyasaka, 2000	1996-1997	Japan	Cross-sectional comparative	Retrospective	Patients with chronic NVAF	33.2	Cases: 66; controls: 64	67	TTE	Stroke, transient ischemic attack and systemic embolism	173

Miyazaki, 2001	1996-1999	Japan	Cohort	Prospective	Patients with NVAF	75	66.9	67.0	TOE	Stroke, transient ischemic attack and systemic embolism	264
Moon, 2014	NR	South Korea	Cross-sectional comparative	Prospective	Patients with NVAF	15	60	75	TTE	Stroke	558
Nakagami, 1998	1987-1995	Japan	Cohort	Retrospective	Patients with NVAF	0	68	60.3	TTE	Stroke	290
Obokota, 2014	2011-2013	Japan	Cross-sectional comparative	Prospective	Patients with NVAF	58.1	Cases: 79; controls: 72	62.8	STE	Stroke or systemic embolism	285
Ogata, 2017	2007-2014	Japan	Cohort	Prospective	Patients with NVAF and previous stroke	62	77.8	55.6	TTE	Recurrent stroke	1611
Okuyama, 2008	2003-2006	Japan	Cohort	Prospective	Patients with NVAF and acute stroke	92	70	74	TTE	Recurrent stroke	192
Park, 2012	2007-2010	South Korea	Cross-sectional comparative	Retrospective	Patients with NVAF who underwent catheter ablation	55.7	56.9	84	CT	Stroke or transient ischemic attack	88
Sakabe, 2009	NR	Japan	Cross-sectional comparative	Prospective	Patients with paroxysmal NVAF	40	72	52	TTE	Stroke	76
Sakr, 2015	2012-2014	Egypt	Cross-sectional comparative	Prospective	Patients with NVAF	50	63.7	44	TOE	Ischemic stroke	50
Shen, 2022	2020-2022	China	Cross-sectional comparative	Retrospective	Patients with NVAF	27.6	71.3	55.5	TTE	Stroke	445

Shih, 2011	2009	Taiwan	Cross-sectional comparative	Retrospective	Patients with NVAF	29	Stroke: 78; Non-stroke: 75	57.6	STE	Stroke	66
Shin, 2019	2013-2016	South Korea	Cross-sectional comparative	Retrospective	Patients with NVAF and CHA2DS2-VA score of 0 or 1, with or without previous stroke	0	Cases: 59.8; controls: 51.3	87.8	TTE	Stroke	970
Stoddard, 2003	NR	USA	Cohort	Prospective	Patients with NVAF	54.8	66	84.3	TTE	Stroke, transient ischemic attack and systemic embolism	261
Stollberger, 1998	1990-1994	Austria & Slovakia	RCT	Prospective	Patients with NVAF	NR	62	64	TTE	Stroke or systemic embolism	409
Takashima, 2012	1994-2007	Japan	Cohort	Prospective	Patients with NVAF	70.7	67.0	72.9	TOE	Ischemic stroke	490
Tsao, 2016	2012-2013	Taiwan	Comparative cross-sectional	Prospective	Patients with NVAF with or without previous cardioembolic stroke	~64	70.1 for the stroke group and 76.5 for the non-stroke group	NR	CT	cardioembolic stroke	95
Tsao, 2017	NR	Taiwan	Cross-sectional comparative	Prospective	Patients with NVAF	8.2	Cases: 69.6; controls: 57.1	Cases: 60.7; controls: 68.1	CT	Ischemic stroke	97
Vinereanu, 2017	2006-2011	Multinational (44 countries)	RCT	Prospective	Patients with NVAF and at least one CHADS2 risk factor for stroke	100	70	64.4	TTE or TOE	Ischemic stroke	1005

					or systemic embolism						
Wang, 2020	2014-2017	China	Cross-sectional comparative	Retrospective	Patients with NVAF	10.6	63.9	57	CT	Cardioembolic stroke	179
Wu, 2019	2011-2017	China	Cross-sectional comparative	Prospective	Patients with NVAF	NR	Cases: 58.8; controls: 56.6	63.3	CT	Stroke	655
Xu, 2015	2012-2014	China	Cross-sectional comparative	Prospective	Patients with NVAF	~ 17	67.0	51.2	TOE	Stroke or transient ischemic attack	114
Yan, 2018	2009-2016	China	Cross-sectional comparative	Retrospective	Patients with NVAF and CHA2DS2-VASc score of 0 (male) or 1 (female)	0	55.1	69.6	TTE	Ischemic stroke and systemic embolism	595
Yang, 2019	2011-2018	China	Cross-sectional comparative	Retrospective	Patients with NVAF	NR	65	58.6	TTE	Stroke	314
Yang, 2018	2010-2014	Taiwan	Cross-sectional comparative	Retrospective	Patients with permanent NVAF	25	67.8	68	TTE	Ischemic stroke	252
Yoshida, 1996	NR	Japan	Cohort	Prospective	Patients with NVAF and no previous stroke	NR	61.7	76.2	TTE	Stroke	122
Zhao, 2016	2008-2014	China	Cohort	Prospective	Patients with NVAF	NR	54	68	TTE or TOE	Stroke	206

CMR: cardiac magnetic resonance; CT: cardiac computed tomography; NR: not reported; NVAF: non-valvular atrial fibrillation; OAC: anticoagulation; TTE: transthoracic echocardiography; TOE: transoesophageal echocardiography

Supplementary Table 4. Risk of bias assessment in cross-sectional studies

Author	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Outcome 1	Outcome 2	Outcome 3	Final assessment
Affan	1	1	1	1	2	1	1	1	Good quality
Al-Issa	1	0	0	1	2	1	1	1	Fair quality
Azemi	1	1	0	1	2	1	1	1	Good quality
Bayar	1	0	0	1	0	1	1	1	Poor quality
Beinart	1	0	0	1	2	1	1	1	Fair quality
Bisbal	1	0	0	1	1	1	1	1	Fair quality
Burrell	1	0	0	1	2	1	1	1	Fair quality
Di Biase	1	0	0	1	2	1	1	1	Fair quality
Dudziñska-Szczerba	0	0	0	1	2	1	1	1	Poor quality
Fukushima	1	0	0	1	2	1	1	1	Fair quality
Gustafsson	1	0	0	1	0	1	1	0	Poor quality
Inoue	1	0	0	1	2	1	1	1	Fair quality
Jankajova	1	0	0	1	2	1	1	1	Fair quality
Kaneko	1	0	0	1	1	1	1	1	Fair quality
Kang	0	1	1	1	2	1	1	1	Good quality
Kang	0	1	1	1	2	1	1	1	Good quality
Khurram	1	1	0	1	2	1	1	1	Good quality
Kim	1	1	0	1	2	1	1	1	Good quality
Kimura	1	0	0	1	2	1	1	1	Fair quality
Kong	1	0	0	1	2	1	1	1	Fair quality
Kwon	0	0	1	1	2	1	1	1	Fair quality
Lee	1	0	0	1	2	1	1	1	Fair quality
Lee	1	0	0	1	2	1	1	1	Fair quality
Lee	1	0	0	1	2	0	1	1	Fair quality
Lee	1	0	0	1	2	1	1	1	Fair quality

Mao	1	0	0	1	2	1	1	1	Fair quality
Miyasaka	1	0	0	1	2	1	1	1	Fair quality
Moon	1	0	0	1	2	1	1	1	Fair quality
Nakagami	0	1	1	1	2	1	1	1	Good quality
Okuyama	0	1	1	1	2	1	1	1	Good quality
Park	1	0	0	1	2	1	1	1	Fair quality
Sakabe	1	0	0	1	2	1	1	1	Fair quality
Sakr	1	0	0	1	2	1	1	1	Fair quality
Shen	0	1	1	1	2	1	1	1	Good quality
Shih	1	0	0	1	2	1	1	1	Fair quality
Shin	1	1	0	1	2	1	1	1	Good quality
Tezuka	1	1	1	1	2	1	1	1	Good quality
Tsao	0	0	1	1	2	1	1	1	Fair quality
Tsao	1	0	0	1	2	1	1	1	Fair quality
Wang	1	0	0	1	2	1	2	1	Fair quality
Wu	1	0	0	1	2	1	1	1	Fair quality
Xu	1	0	0	1	2	1	1	1	Fair quality
Yan	1	0	0	1	2	1	1	1	Fair quality
Yang	1	0	0	1	2	1	1	1	Fair quality
Yang	1	0	0	1	2	1	1	1	Fair quality

Assessment done using the Newcastle-Ottawa Quality Assessment Scale
The SPAFI: The Stroke Prevention in Atrial Fibrillation Investigators

Supplementary Table 5. Risk of bias assessment in cohort studies

Author, year of publication	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8
Ahn, 2019	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Cho, 2021	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Chu, 2016	Probably yes	Probably yes	Definitively yes	Definitively yes	Probably yes	Probably yes	Probably yes	Probably yes
Hamatani, 2016	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Hsu, 2016	Definitively yes	Probably yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes
Huang, 2022	Probably yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Probably yes
Kamp, 1999	Probably yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Probably yes
Leung, 1994	Probably yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Probably yes
Leung, 2018	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Liao, 2020	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Miyazaki, 2001	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes
Obokata, 2014	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Probably yes	Probably yes
Ogata, 2017	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes
Stoddard, 2003	Probably yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Definitively yes	Probably yes
Takashima, 2012	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Definitively yes	Probably yes	Probably yes
Yoshida, 1996	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes
Zhao, 2016	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Definitively yes	Probably yes

Question 1: Was selection of exposed and non-exposed cohorts drawn from the same population?
Question 2: Can we be confident in the assessment of exposure?
Question 3: Can we be confident that the outcome of interest was not present at start of study?
Question 4: Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?
Question 5: Can we be confident in the assessment of the presence or absence of prognostic factors?
Question 6: Can we be confident in the assessment of outcome?
Question 7: Was the follow up of cohorts adequate?
Question 8: Were co-interventions similar between groups?

Potential answers: Definitely yes (low risk of bias); Probably yes; Probably no; Definitely no (high risk of bias)
CLARITY group. Tool to Assess Risk of Bias in cohort Studies [Accessed 2022 December 14]. Available from: https://www.distillersr.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-cohort-studies-distillersr

Supplementary Table 6. Risk of bias assessment in randomized control trials

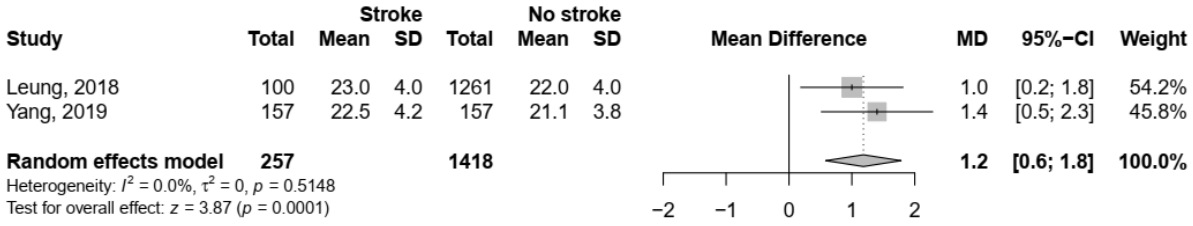
Author, year of publication	Question 1	Question 2	Question 3	Question 3a	Question 3b	Question 3c	Question 3d	Question 3e
Gupta, 2016	Not applicable	Probably yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Probably yes	Probably yes
McMurray, 2013	Not applicable	Probably yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Probably yes	Probably yes
Stollberger, 1998	Not applicable	Probably yes	Probably yes	Definitively yes	Definitively no	Definitively no	Probably no	Probably no
Vinereanu, 2017	Not applicable	Probably yes	Definitively yes	Definitively yes	Definitively yes	Probably yes	Probably yes	Probably yes

Author, year of publication	Question 4	Question 5	Question 6
Gupta, 2016	Definitively yes	Definitively yes	Definitively yes
McMurray, 2013	Definitively yes	Definitively yes	Definitively yes
Stollberger, 1998	Probably yes	Probably yes	Probably yes
Vinereanu, 2017	Definitively yes	Definitively yes	Definitively yes

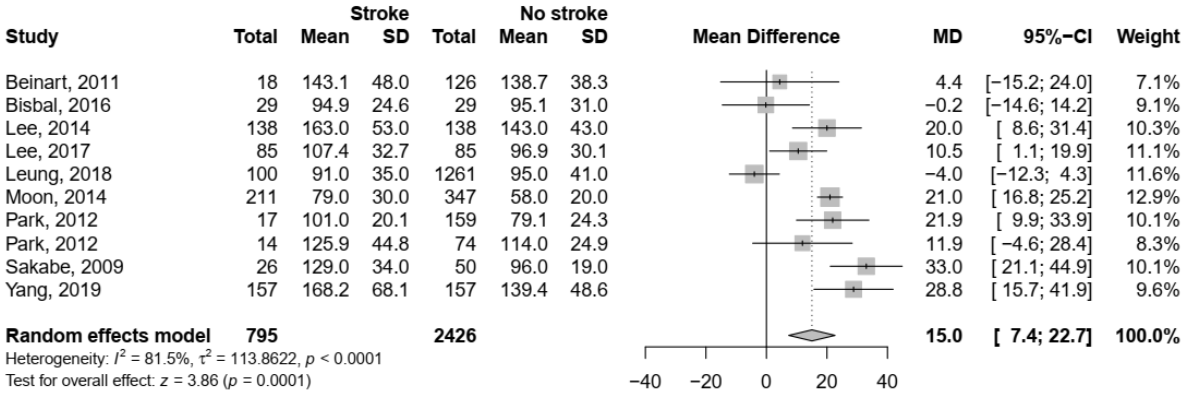
Question 1: Was the allocation sequence adequately generated?*
Question 2: Was the allocation adequately concealed?
Question 3: Blinding: Was knowledge of the allocated interventions adequately prevented? *
Question 3a: Were patients blinded?
Question 3b: Were healthcare providers blinded?
Question 3c: Were data collectors blinded?
Question 3d: Were outcome assessors blinded?
Question 3e: Were data analysts blinded?
Question 4: Was loss to follow-up (missing outcome data) infrequent?
Question 5: Are reports of the study free of selective outcome reporting?*
Question 6: Was the study apparently free of other problems that could put it at a risk of bias?*
*Option to omit this item

Potential answers: Definitely yes (low risk of bias); Probably yes; Probably no; Definitely no (high risk of bias)
CLARITY group. Tool to Assess Risk of Bias in randomized controlled trials [Accessed 2022 December 14]. Available from: https://www.distillersr.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-randomized-controlled-trials-distillers

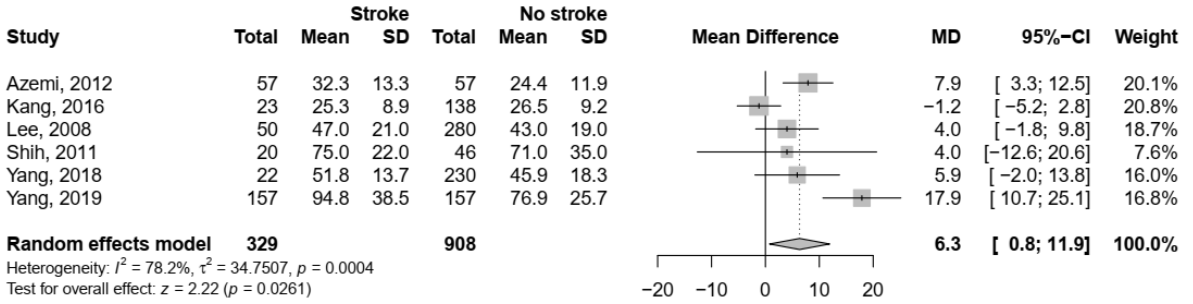
Supplementary Figure 1. Mean differences in left atrial diameter index between AF patients with and without stroke



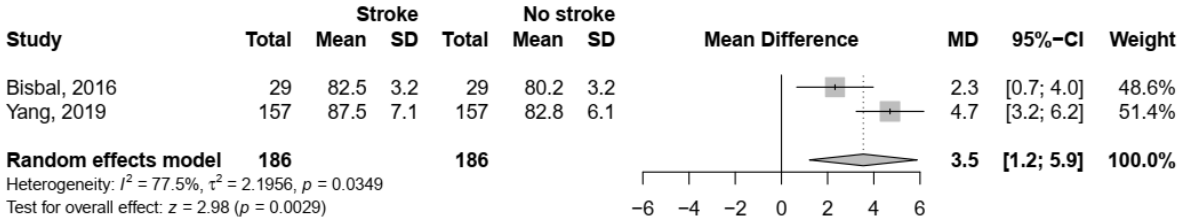
Supplementary Figure 2. Mean differences in left atrial volume between AF patients with and without stroke



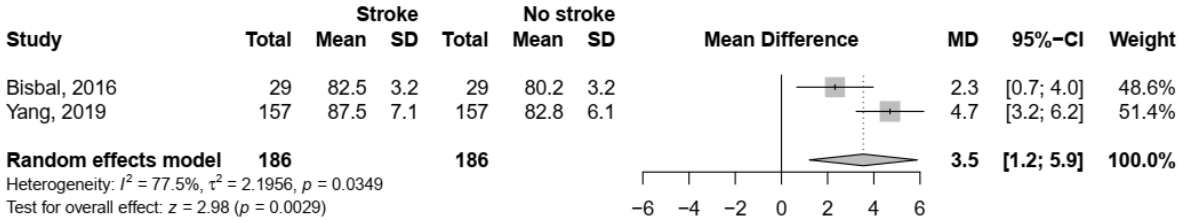
Supplementary Figure 3. Mean differences in left atrial volume index between AF patients with and without stroke



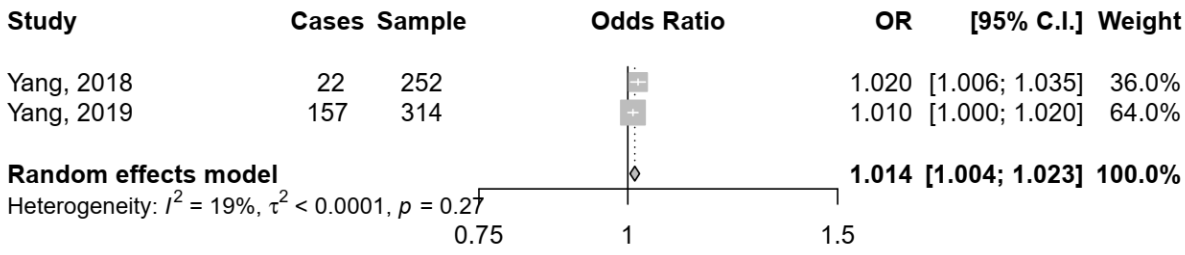
Supplementary Figure 4. Mean differences in left atrial sphericity between AF patients with and without stroke



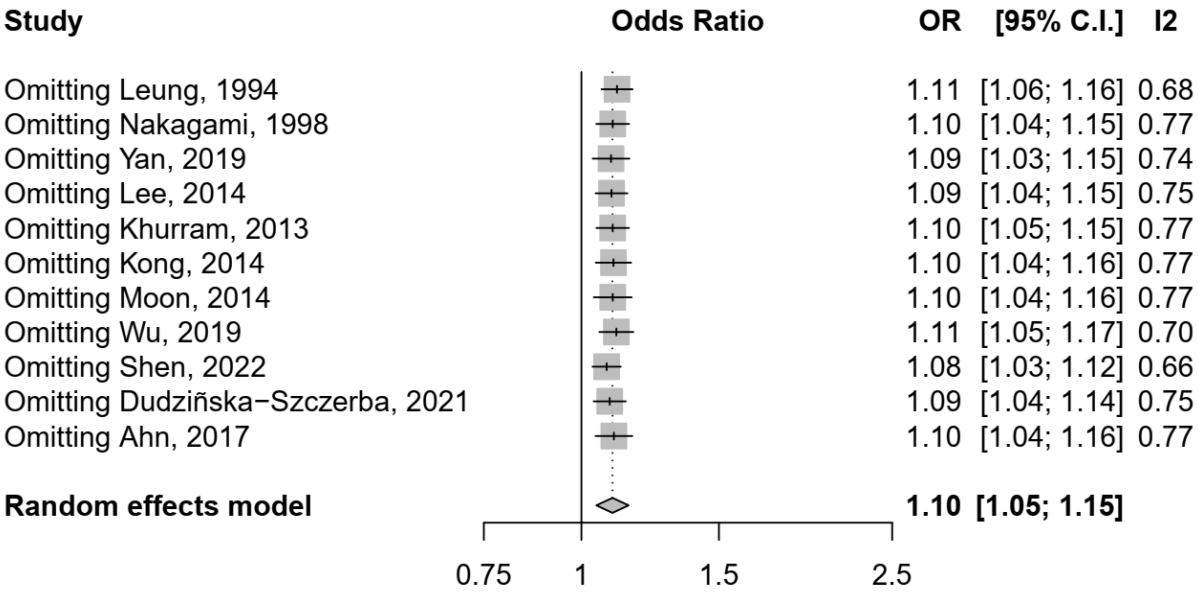
Supplementary Figure 5. Association of left atrial volume index with stroke



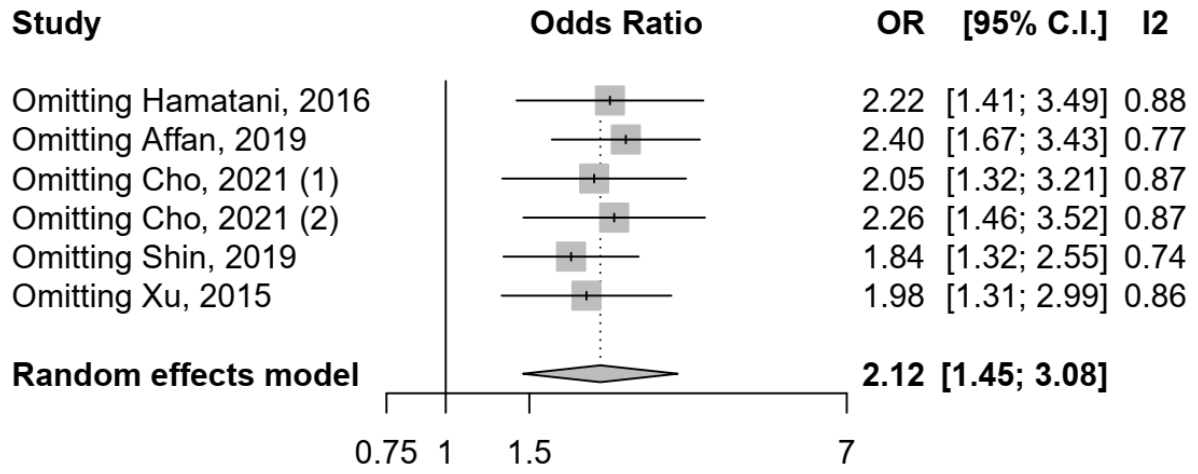
Supplementary Figure 6. Association of left atrial sphericity with stroke



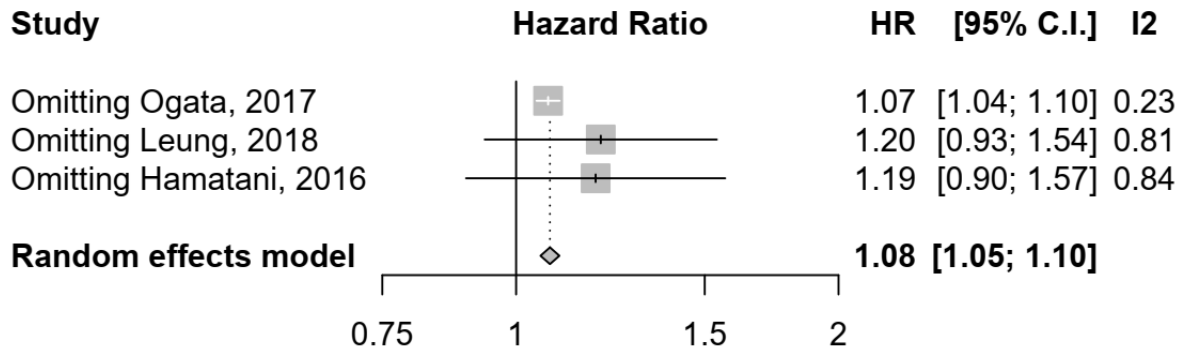
Supplementary Figure 7. Influencer analysis for the association between left atrial diameter and stroke



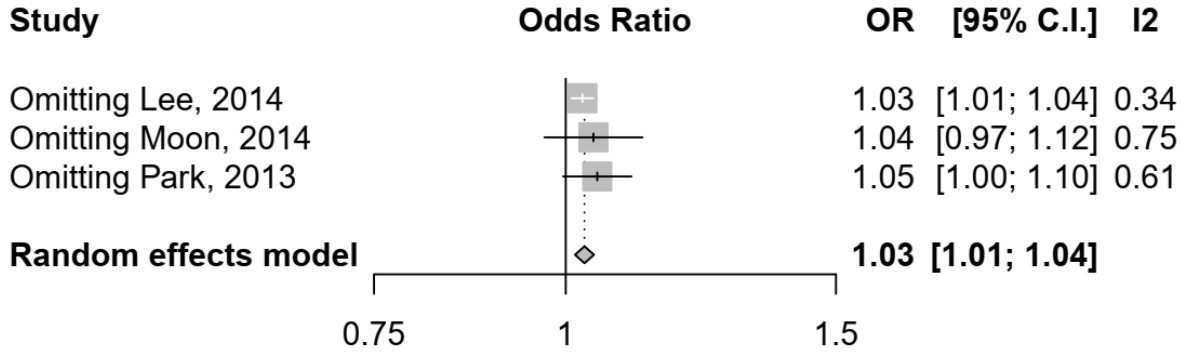
Supplementary Figure 8. Influencer analysis for the association between left atrial enlargement and stroke



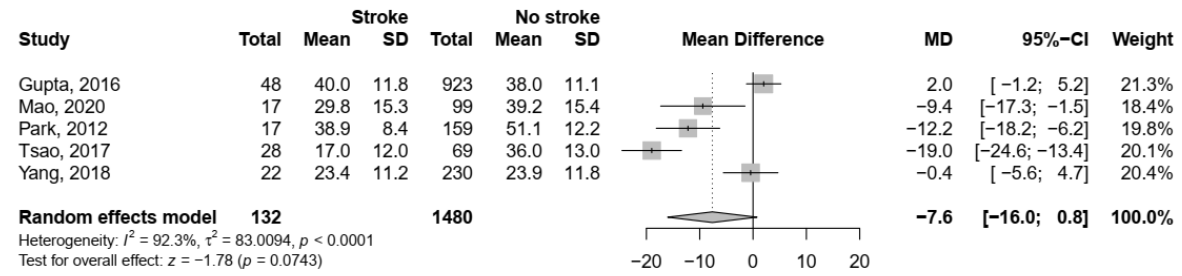
Supplementary Figure 9. Influencer analysis for the association between left atrial diameter index and stroke



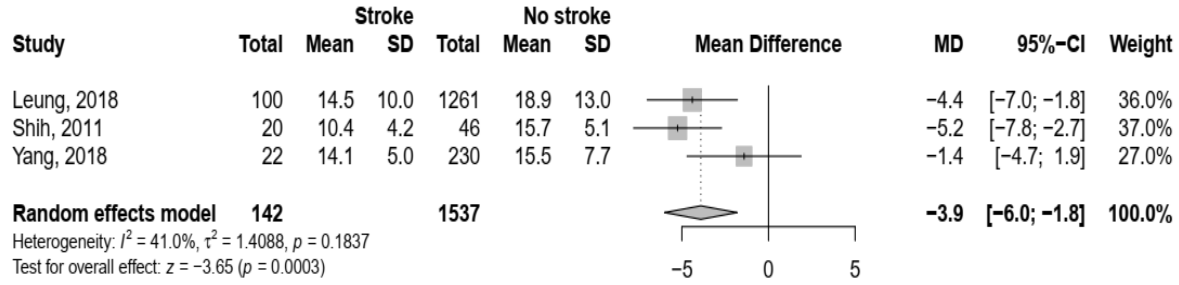
Supplementary Figure 10. Influencer analysis for the association between left atrial volume and stroke



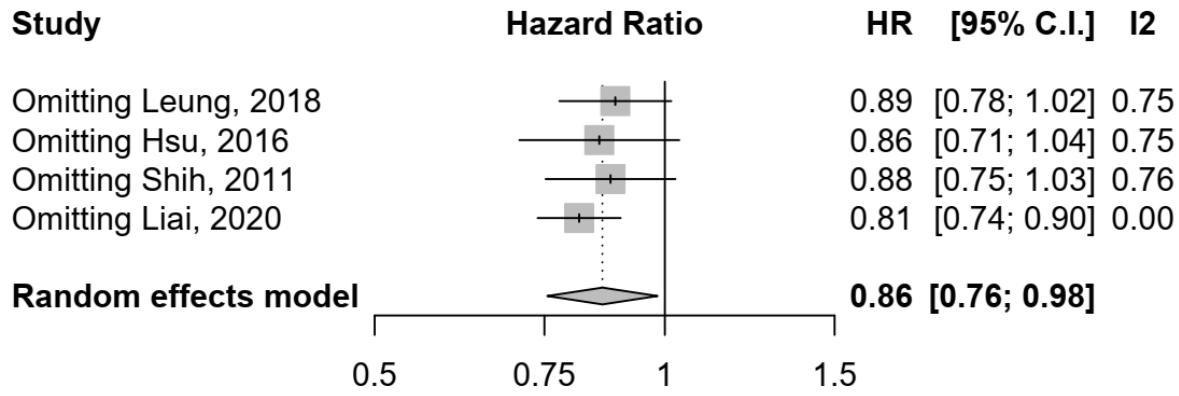
Supplementary Figure 11. Mean differences in left atrial ejection fraction between AF patients with and without stroke



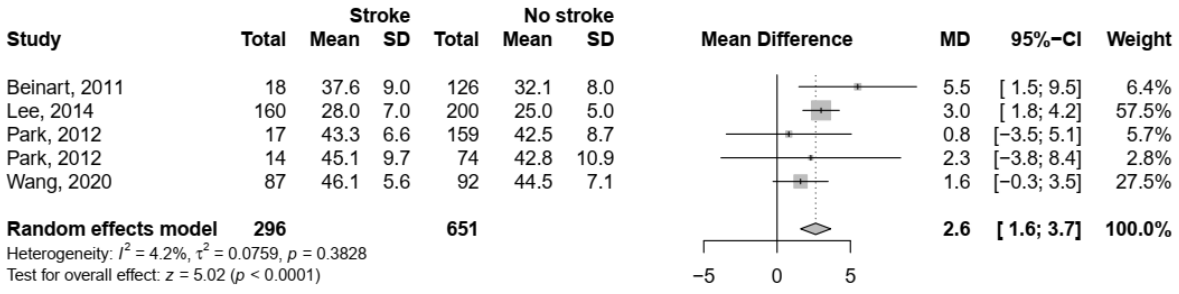
Supplementary Figure 12. Mean differences in left atrial reservoir strain between AF patients with and without stroke



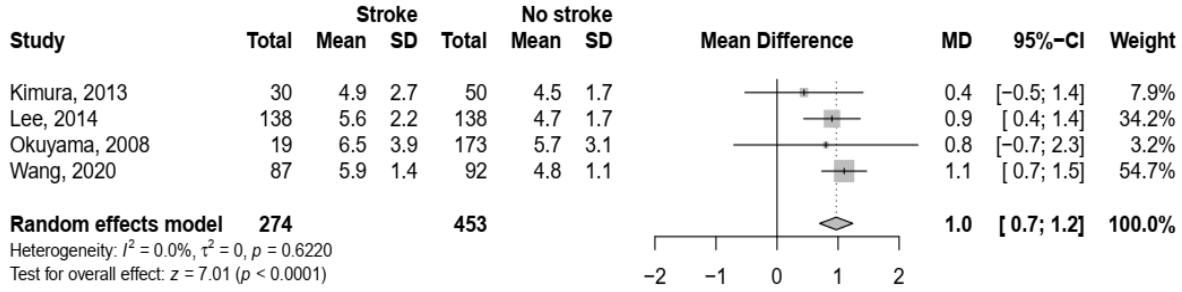
Supplementary Figure 13. Influencer analysis for the association between left atrial reservoir strain and stroke



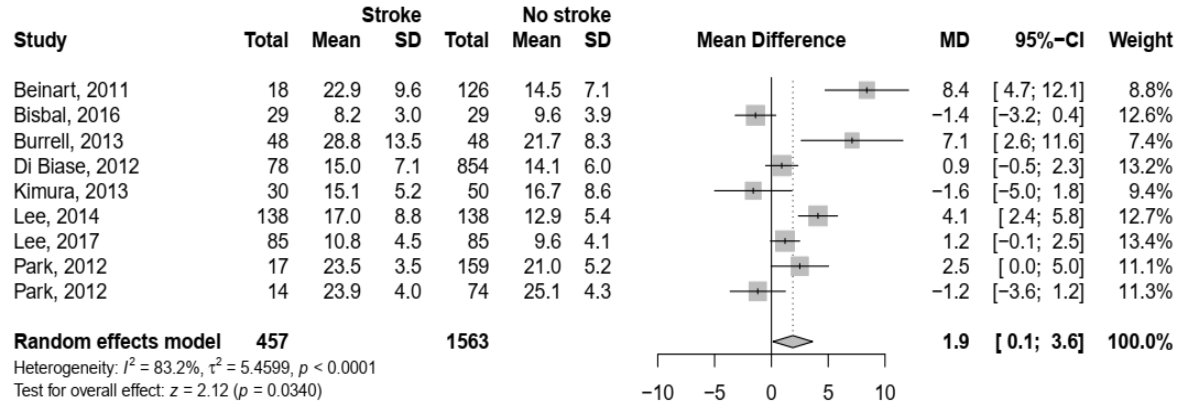
Supplementary Figure 14. Mean differences in left atrial appendage depth between AF patients with and without stroke



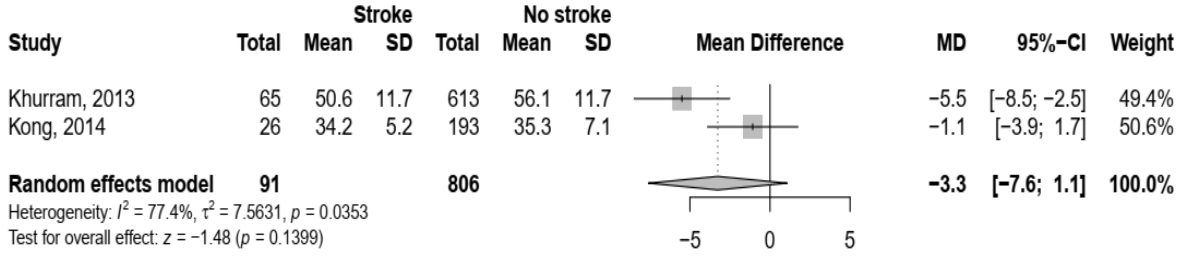
Supplementary Figure 15. Mean differences in left atrial appendage orifice area between AF patients with and without stroke



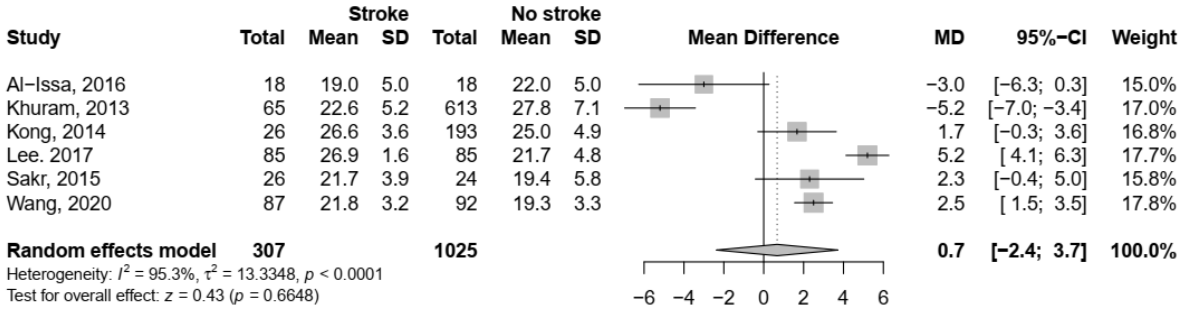
Supplementary Figure 16. Mean differences in left atrial appendage volume between AF patients with and without stroke



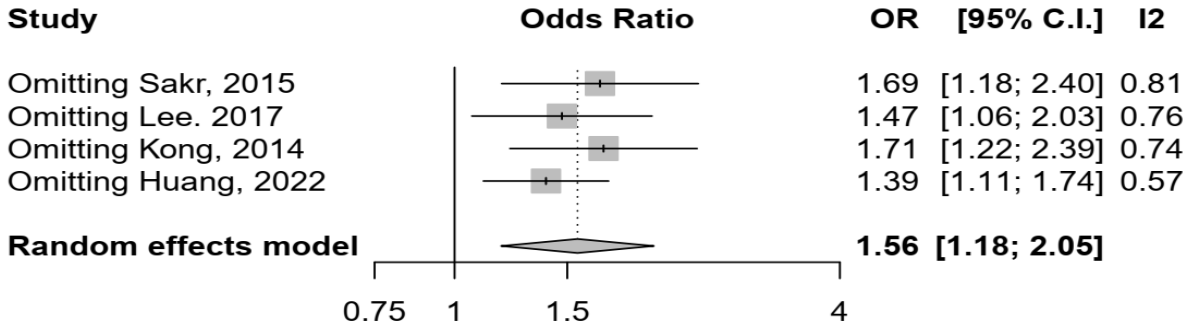
Supplementary Figure 17. Mean differences in left atrial appendage length between AF patients with and without stroke



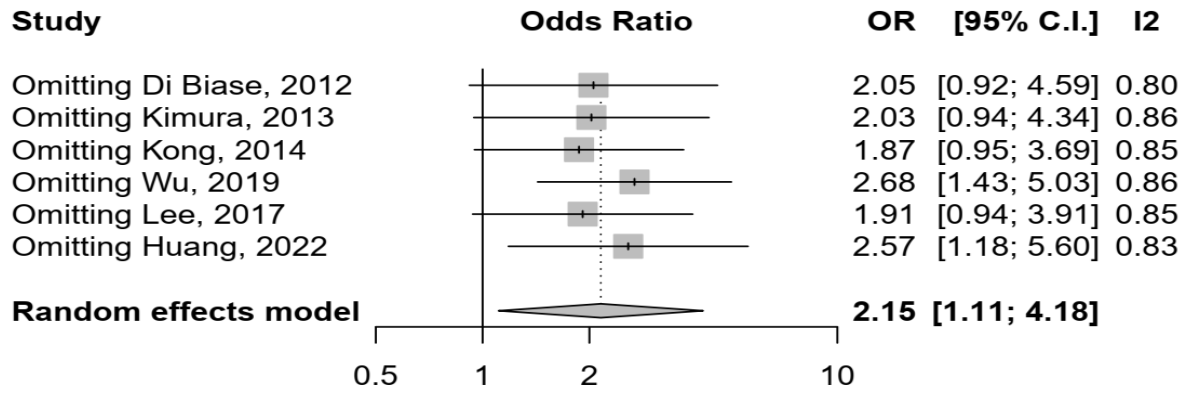
Supplementary Figure 18. Mean differences in left atrial appendage orifice diameter between AF patients with and without stroke



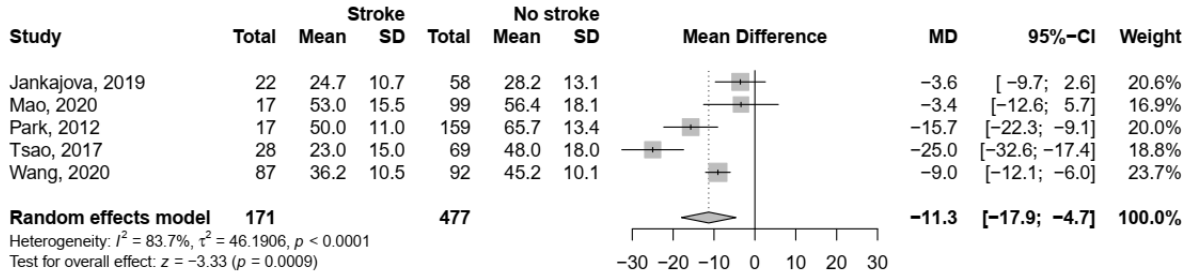
Supplementary Figure 19. Influencer analysis for the association between left atrial appendage orifice diameter and stroke



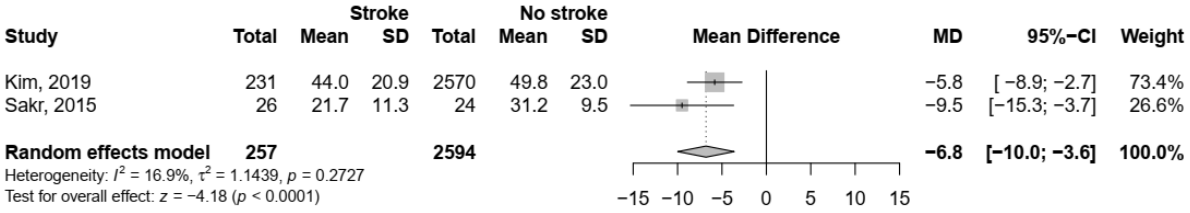
Supplementary Figure 20. Influencer analysis for the association between non-chicken wing left atrial appendage morphology and stroke



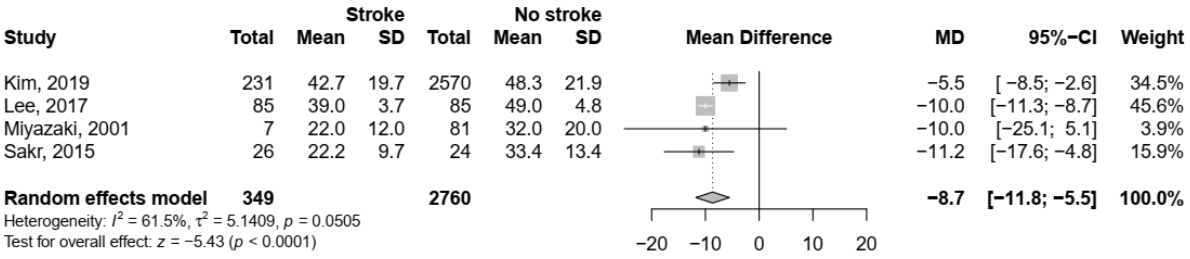
Supplementary Figure 21. Mean differences in left atrial appendage ejection fraction between AF patients with and without stroke



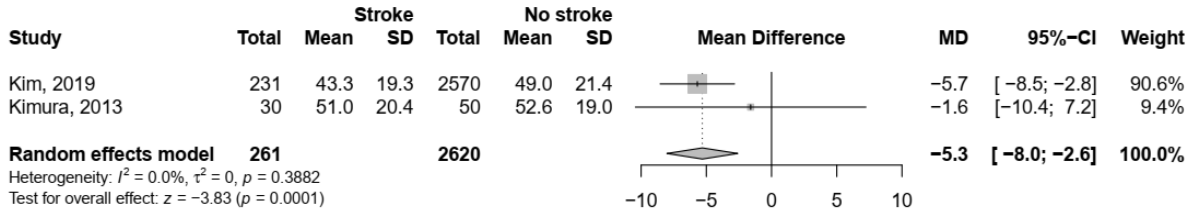
Supplementary Figure 22. Mean differences in left atrial appendage filling velocity between AF patients with and without stroke



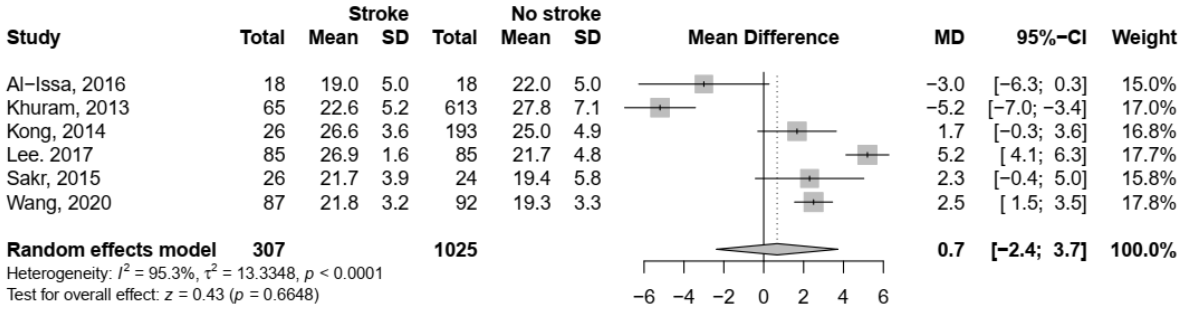
Supplementary Figure 23. Mean differences in left atrial appendage emptying velocity between AF patients with and without stroke



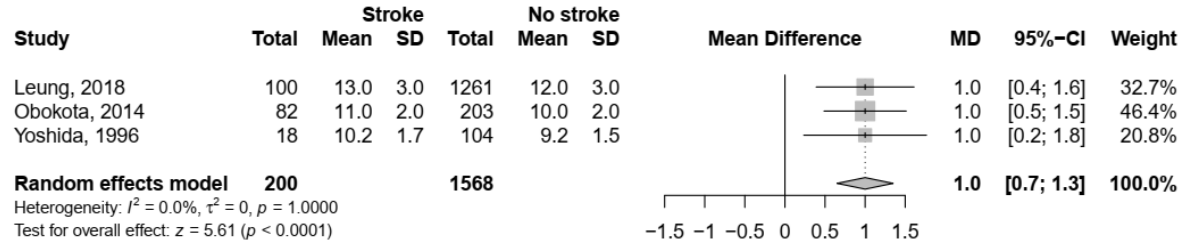
Supplementary Figure 24. Mean differences in left atrial appendage average flow velocity between AF patients with and without stroke



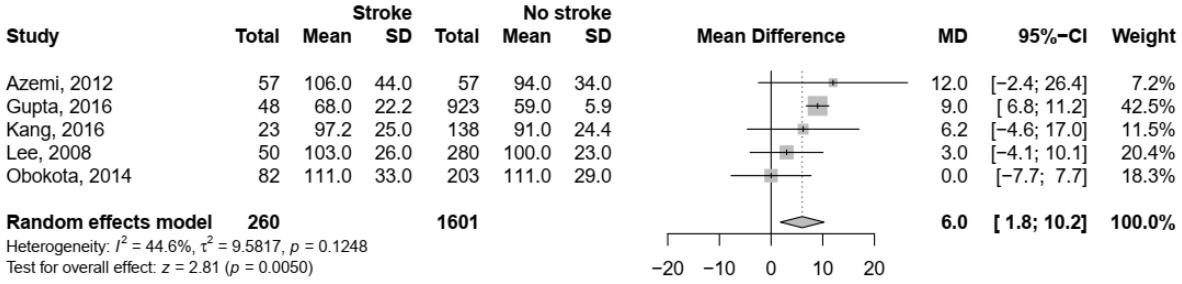
Supplementary Figure 25. Mean differences in left atrial appendage orifice diameter between AF patients with and without stroke



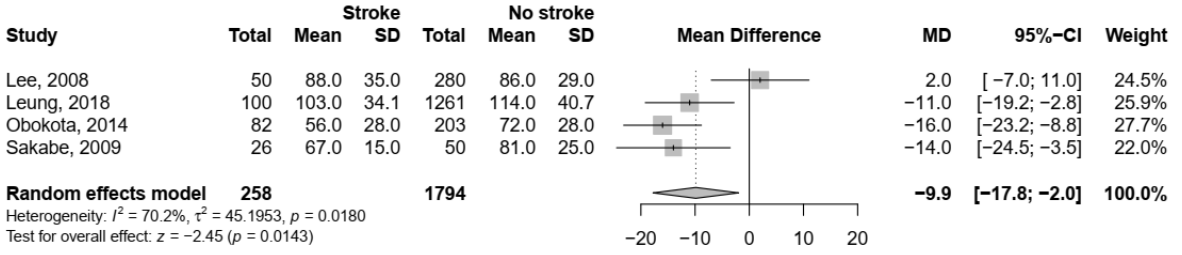
Supplementary Figure 26. Mean differences in interventricular wall tickness between AF patients with and without stroke



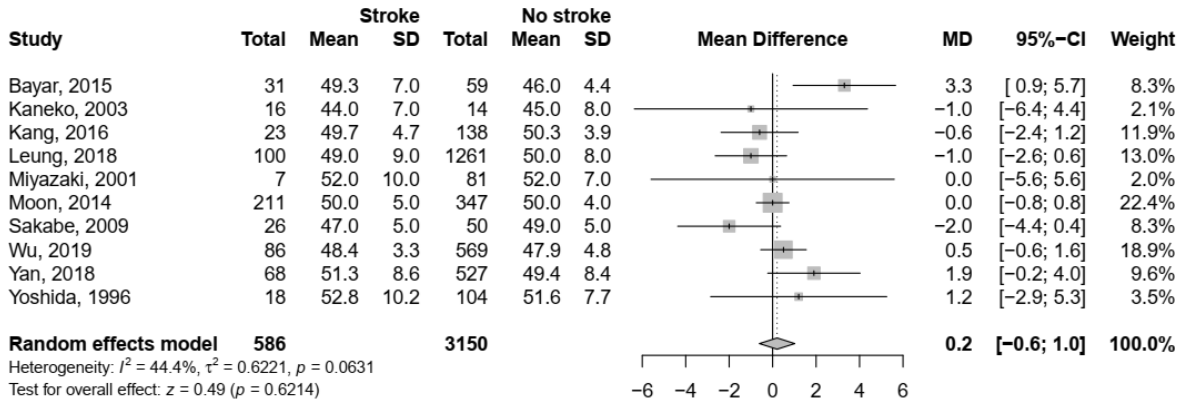
Supplementary Figure 27. Mean differences in left ventricular mass index between AF patients with and without stroke



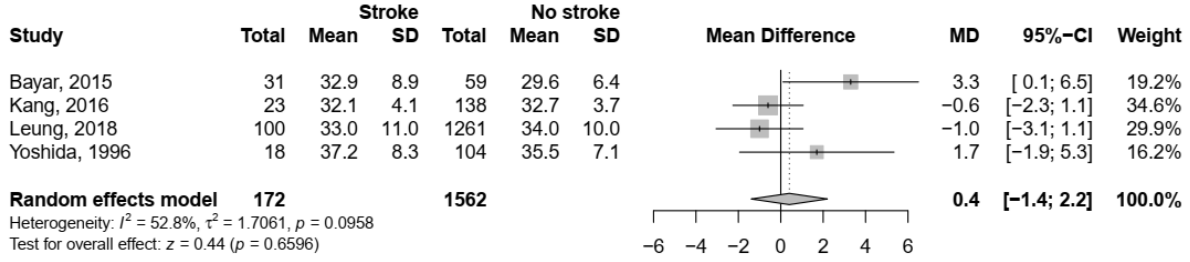
Supplementary Figure 28. Mean differences in left ventricular end-diastolic volume between AF patients with and without stroke



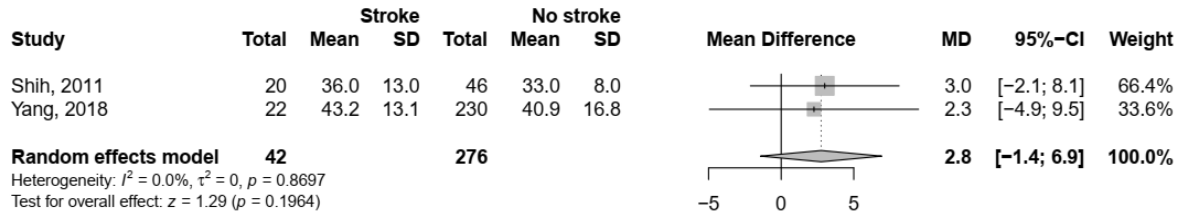
Supplementary Figure 29. Mean differences in left ventricular end-diastolic diameter between AF patients with and without stroke



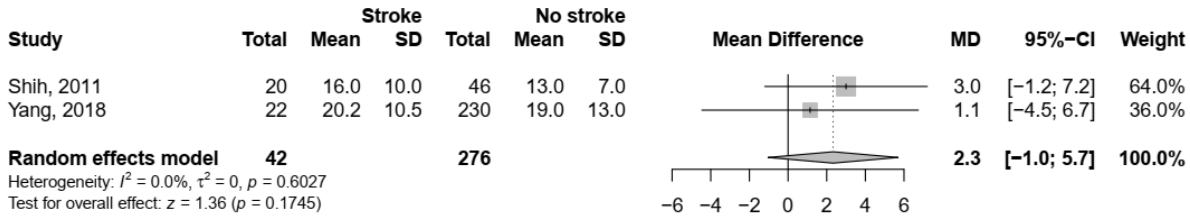
Supplementary Figure 30. Mean differences in left ventricular end-systolic diameter between AF patients with and without stroke



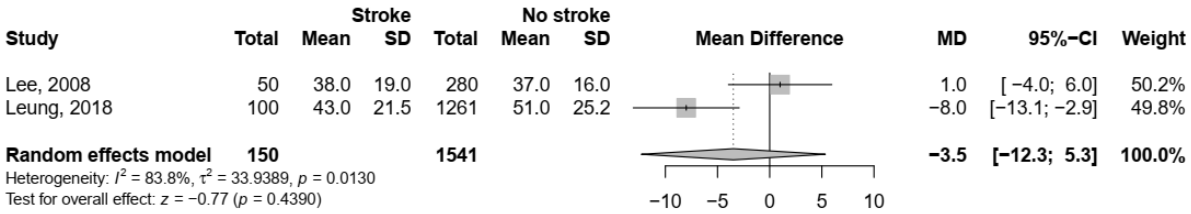
Supplementary Figure 31. Mean differences in left ventricular end-diastolic volume index between AF patients with and without stroke



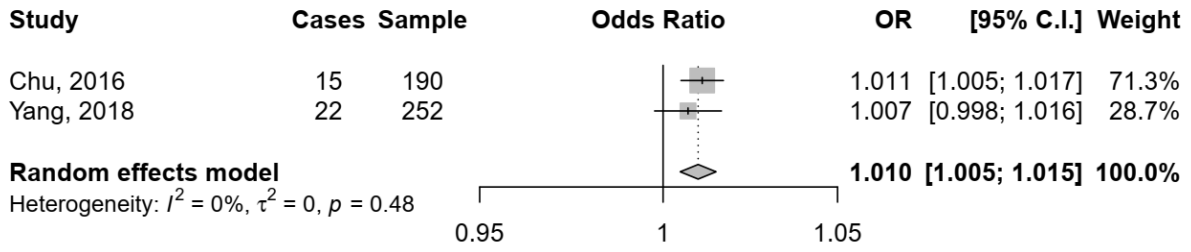
Supplementary Figure 32. Mean differences in left ventricular end-systolic volume index between AF patients with and without stroke



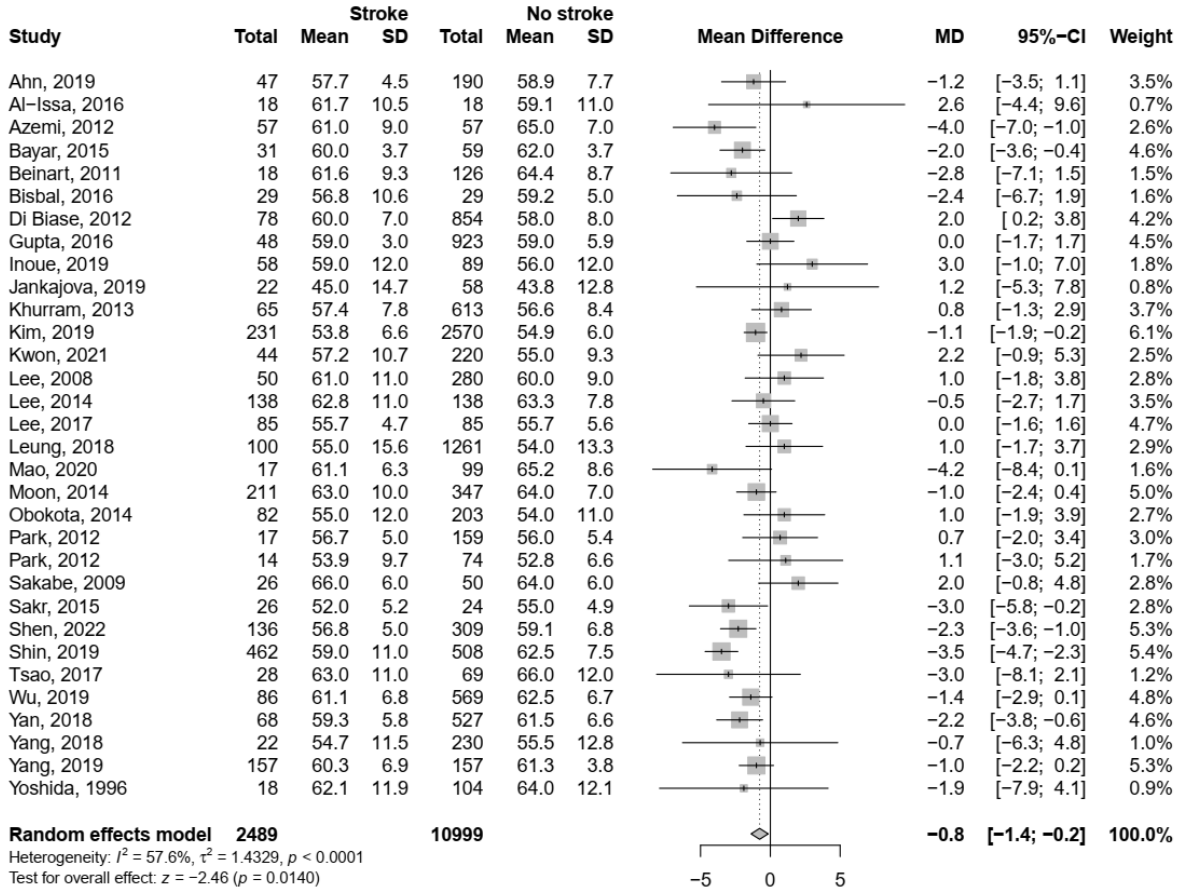
Supplementary Figure 33. Mean differences in left ventricular end-systolic volume between AF patients with and without stroke



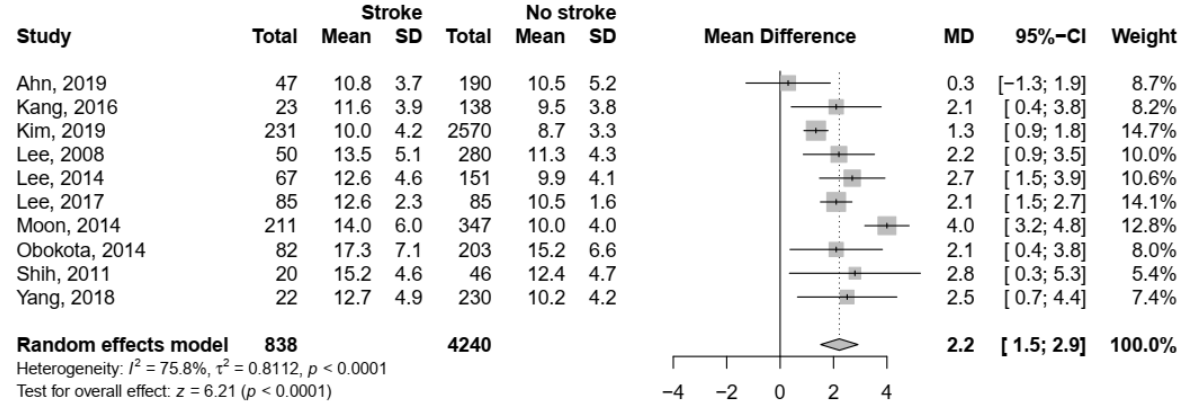
Supplementary Figure 34. Association of left ventricular mass index with stroke



Supplementary Figure 35. Mean differences in left ventricular ejection fraction between AF patients with and without stroke



Supplementary Figure 36. Mean differences in E/e' ratio between AF patients with and without stroke



CHAPTER 5:

Carotid and aortic atherosclerotic disease and stroke risk stratification in patients with atrial fibrillation

Publication 1

Statement of Authorship

Title of Paper	Meta-Analysis Comparing the Frequency of Carotid Artery Stenosis in Patients With Atrial Fibrillation and Vice Versa
Publication Status	☒ Published ☐ Accepted for publication ☐ Submitted for publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Noubiap JJ**, Agbaedeng TA, Tochie JN, Nkeck JR, Ndoadoumgue AL, Fitzgerald JL, Kleinig T, Thomas G, Middeldorp ME, Sanders P. Meta-Analysis Comparing the Frequency of Carotid Artery Stenosis in Patients With Atrial Fibrillation and Vice Versa. *Am J Cardiol*. 2021 Jan 1;138:72-79.

Principal Author

Name of Principal Author (Candidate)	Jean Jacques Noubiap Nzeale		
Contribution to the Paper	Conception and design, literature search, data collection, manuscript drafting, manuscript revision		
Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Publication Details	**Noubiap JJ**, Kamtchum-Tatuene J, Fitzgerald JL, Sanders P. Stroke risk associated with carotid and aortic atherosclerosis in patients with atrial fibrillation: A systematic review. *J Neurol Sci*. 2021 Jun 15;425:117444.

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Contribution to the Paper	Conception and design, bibliographic searches, data collection, data analysis, data interpretation, manuscript drafting, manuscript revision		
Overall percentage (%)	65%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Manuscript revision (5%)		
Signature		**Date**	3/13/2022

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Conception and design, manuscript revision (10%)		
Signature		**Date**	3/12/2022

Publication 3

Statement of Authorship

Title of Paper	High-risk carotid plaques and incident stroke in patients with atrial fibrillation in the Cardiovascular Health Study
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Publication Details	**Noubiap JJ**, Thomas G, Kamtchum-Tatuene J, Middeldorp ME, Sanders P. High-risk carotid plaques and incident stroke in patients with atrial fibrillation in the Cardiovascular Health Study

Principal Author

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Contribution to the Paper	Conception and design, access to data, data analysis, data interpretation, manuscript drafting, manuscript revision		
Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

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ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Name of Co-Author	Joseph Kamtchum-Tatuene		
Contribution to the Paper	Conception and design, access to data, data analysis, data interpretation, manuscript revision (15%)		
Signature		**Date**	3/12/2022

Name of Co-Author	Melissa E. Middeldorp		
Contribution to the Paper	Manuscript revision (5%)		
Signature		**Date**	3/22/2022

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Access to data, manuscript revision (10%)		
Signature		**Date**	3/12/2022

Overview

This chapter explores the contributions of carotid and aortic atherosclerotic disease to stroke risk stratification in patients with AF. It is divided into three sections. The first section is a systematic review and meta-analysis aimed to summarize data on the prevalence of carotid stenosis in patients with AF, and of AF in patients with carotid stenosis or carotid plaques. The second section the evidence on the risk of thromboembolism associated with carotid and aortic atherosclerosis in patients with AF, and the impact of their inclusion in current stroke risk stratification scores. The third section is a prospective cohort study that investigates 1) the prevalence of occlusive and non-occlusive carotid disease in patients with AF; 2) the distribution of non-occlusive carotid disease and high-risk features (plaque irregularity, ulceration, and echolucency) in patients with AF; 3) the risk of stroke associated with occlusive and non-occlusive carotid disease in patients with AF; 4) and the potential added value of high-risk carotid plaques on stroke risk stratification compared to the classical CHA_2DS_2-VASc score.

5.1 Meta-analysis comparing the frequency of carotid artery stenosis in patients with atrial fibrillation and vice versa

5.1.1 Introduction

Ischemic stroke is the fourth leading cause of death globally, accounting for about 5% of all deaths in 2017.[383] Atrial fibrillation (AF) and carotid stenosis (CS) are major causes of ischemic stroke. Atrial fibrillation is associated with up to a third of all ischemic strokes.[167, 401] Carotid stenosis accounted for 11.5% of ischemic stroke in one study in the US.[492] The co-existence of AF and CS is associated with a much higher risk of stroke than what is attributed by each condition alone. For instance, CS doubles the risk of stroke recurrence and is also a predictor of death in AF patients despite anticoagulation.[493] It was shown that ischemic stroke in AF patients is not always cardioembolic.[494] Indeed, severe CS was reported to account for a fourth of ischemic strokes in AF patients, and to be associated with larger cortical infarction, hemorrhagic transformation and worse clinical outcome.[494] This systematic review and meta-analysis aimed to summarize data on the prevalence of CS in AF patients, and of AF in patients with CS or carotid plaques (CP).

5.1.2 Methods

PubMed/MEDLINE, Excerpta Medica Database (EMBASE) and Web of Science were searched to identify all studies reporting primary data of the prevalence of CS in AF patients, and of AF in patients with CS or CP, published until February 27, 2020, irrespective of the language. The search strategy was built based on the combination of relevant terms including "carotid artery stenosis", "atrial fibrillation" and their bibliographic synonyms (**Supplementary Table 1**). Furthermore, the reference list of eligible articles and relevant reviews were examined to identify potential additional data sources.

We included cohort or cross-sectional studies, reporting on the prevalence of CS in AF patients, and of AF in patients with CS or CP, or enough data to compute these estimates. We excluded articles that did not include primary data, such as editorials, case reports, and reviews. For studies reporting data from the same primary study or registry (duplicates), we included the single most comprehensive reporting the largest sample size

Two investigators (JJN and TAA) independently screened records for eligibility based on titles and abstracts. Full texts of articles deemed potentially eligible were retrieved and screened by the same investigators for final inclusion. Selection discrepancies were solved through discussion and consensus.

Data were extracted using a standardized data abstraction form. Three investigators (JRN, ALN, and JNT) independently extracted data including: name of the first author, year of publication, study design, period of recruitments of participants, country of recruitment, proportion of participants with various cardiovascular risk factors including hypertension, diabetes, dyslipidemia, obesity, smoking, proportion of males, mean or median age, type of carotid disease (CS, carotid occlusive disease, CP), diagnostic cut-offs (≥ 50% or ≥70% stenosis for instance), method used to diagnosed carotid artery disease, any carotid procedure done (carotid artery stenting [CAS] or endarterectomy [CEA]) in case participants were included on this basis, presence or absence of symptomatic disease, total sample size of either participants with AF or CS, number of cases of AF or CS/CP. CP was defined as non-stenotic carotid atherosclerosis; details on diagnostic criteria are reported in the appendix (**Supplementary Table 2**). Data were collected to compute subgroup analysis according to geographic region (Europe, Asia, Northern America), carotid procedure (carotid artery stenting or carotid artery endarterectomy), presence of symptoms or not and diagnostic cut-off. One investigator (JJN) crosschecked all the data.

We used an adapted version of the tool developed by Hoy et al. to assess the risk of bias in included studies [386]. Three investigators (JRN, ALN, and JNT) independently ran and then crosschecked the assessment. Discrepancies were discussed and resolved through consensus.

All analyses were conducted using the R statistical software (version 3.5.03, The R Foundation for statistical computing, Vienna, Austria). We performed random-effects meta-analysis of proportion using the inverse variance model. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic, which was quantified by I^2 values, assuming I^2 values of 25, 50 and 75% respectively representing low, medium and high heterogeneity [388]. Heterogeneity across studies was further explored using the mixed-effects multiple meta-regression model. Publication year, recruitment period (1990-1999, 2000-2009, and 2010-2019), region, and study design were fitted as moderators in the meta-regression model. The influence of each study on the overall estimates and heterogeneity was assessed through *Leave-One-Out* influencer analysis model. We assessed small-study effect by funnel plots and tests of funnel plot asymmetry. We identified statistical significance using a two-tailed p-value of ≤ 0.05.

5.1.3 Results

In total, we identified 6202 records among which 46 articles were finally included,[493-538] providing data for 48 studies (**Figure 1**). Of the included studies, 20 reported on the prevalence of carotid disease from a pooled population of 49,070 AF patients.[493, 494, 523-538] Studies were conducted between 1990 and 2017, most of them being cross-sectional (45%) and cohort (45%), hospital-based (85%); and predominantly came from the U.S. (30%). Six (30%) and 11 (55%) had a low and moderate risk of bias, respectively. General and individual characteristics of included studies are presented in **Supplementary Tables 3-6**.

A total of 11 studies reported on the prevalence of CS in a pooled sample of 3919 AF patients. The pooled prevalence of CS was 12.4%, ranging from 4.4% to 24.3% (**Figure 2**). In AF patients with a previous cerebrovascular event (transient ischemic stroke or ischemic stroke), the pooled prevalence of CS was 13.5%, ranging from 5.5% to 24.3%, compared to a pooled prevalence of 10.5%, ranging from 4.4% to 20.9%, in AF patients with no history of cerebrovascular event (**Table 1**). However, the difference was not significant ($p = 0.411$). Most studies (9 out 10) used a diagnostic cut-off of ≥ 50% stenosis, and in those studies the pooled prevalence of CS was 13.9%. In the sole study using a diagnosis cut-off of ≥ 70% stenosis, the prevalence was 5.8% (**Table 1**).

Ten studies reported on the prevalence of CP in AF patients, with rates ranging from 16.6% to 71.0% (**Figure 3**). The pooled prevalence was 48.4%.

We performed funnel plot analysis to assess whether there was any selective publication of large studies. We found no statistical evidence of publication bias in the CS analysis ($p = 0.150$, **Supplementary Figure 1**) nor in the analysis of CP ($p = 0.304$, Supplementary Figure 2). Given the high level of heterogeneity in the pooled prevalence rates, we next investigated the contribution of each study to the overall heterogeneity. No study markedly reduced the overall heterogeneity when its estimate was removed from the overall analysis (**Supplementary Figures 3 and 4**).

Four studies reported on the prevalence of either carotid occlusion or carotid occlusive disease in AF patients, and were not eligible for the meta-analysis.[494, 524, 537, 538] Following an acute ischemic stroke in AF patients, a complete carotid occlusion (100% stenosis) was found in 11 (8 ipsilateral and 3 contralateral to the infarct) out of 103 AF patients, giving a frequency of 10.7%.[494] In another study, 37 out of 221 (16.7%) AF patients had an occluded internal carotid artery. [524] Two studies reported carotid occlusion in AF, with 221 and 103 patients evaluated. In the GARFIELD-AF and ROCKET-AF registries, the prevalence of

carotid occlusive disease (no specific threshold of stenosis) was 2.4% (95% CI 2.2-2.6; n = 24,436) and 4.2% (95% CI 3.8-4.5; n = 14,263), respectively.[537, 538]

Of the included studies, 28 reported on the prevalence of AF from a pooled population of 2,288,265 patients with carotid disease. [495-522] Studies were conducted between 1990 and 2018, most of them being cohort (64.3%), hospital-based (96.4%); and predominantly came from the U.S. (35.7%). Nine (32.1%) and 18 (64.3%) had a low and moderate risk of bias, respectively. General and individual characteristics of included studies are presented in **Supplementary Tables 3-6**.

A total of 25 studies reported on the prevalence of AF in a pooled population of 2,286,518 patients with CS. The pooled prevalence of AF was 9.3%, ranging from 3.6% to 10.0% (**Figure 4**). There was no difference (p = 0.137) between patients with CS and a previous cerebrovascular event (pooled prevalence 11.7%) and those without prior history of cerebrovascular event (pooled prevalence 12.2%) (**Table 2**). The pooled prevalence of AF in patients with CS undergoing CAS was almost double that in those undergoing CEA (p < 0.001, Table 2). The pooled prevalence of AF was almost 3% higher, but not significantly (p = 0.277), in studies with a diagnostic cutoff of ≥ 50% for CS compared to those in which a cutoff of ≥ 70% was used (**Table 2**).

We performed funnel plot analysis to assess publication bias in AF prevalence rate analyses. There was no evidence of publication bias in the analysis (p >0.05, **Supplementary Figure 5**). Investigation of potential source of heterogeneity did not reveal any study that markedly reduced the overall heterogeneity when its estimate was removed (**Supplementary Figure 6**). Additionally, meta-regression was performed to assess the effects of publication year, recruitment period, study region, and study design on AF prevalence in patients with CS. The meta-regression model explained 56.2% AF prevalence rates estimation (p <.001). More recent publication years and recruitment periods significantly predicted higher AF

prevalence (p <.001 for both). On the other hand, the region that the primary study was conducted and study design were not significantly associated with AF prevalence rates (p >.05).

Three studies reporting on the prevalence of AF in various populations with carotid disease were not eligible for meta-analysis due to non-reconcilable diagnostic cut-offs [510, 514, 516]. One of them reported an AF prevalence of 35.3% (95% CI 27.7-43.4; n = 153) in patients who had a stroke due to internal carotid occlusion [510]. In the Bruneck study in Italy, the prevalence of AF was 3.5% (95% CI 2.4-4.9; n = 923) in patients with CP [516], compared to 13.1% (95% CI 10.6-15.9, n = 671) in a similar population in Israel [514].

5.1.4 Discussion

According to recent data, carotid stenosis doubles the risk of stroke in AF patients, after adjustment for classical clinical risk factors and antithrombotic therapy (8.1 vs. 3.6 events/100 follow-up years; p = 0.005).[493] Our study suggests that about 12% of patients with AF have significant CS (≥50%), with prevalence rates reaching about 25% in some settings. This means that, considering the significant prevalence of CS in AF patients, along with its high attributed stroke risk, CS should be a major component of stroke risk stratification in the AF population. In fact, most stroke risk stratification schemes have shown modest performance in predicting thromboembolism in real-world settings, with C-statistics between 0.60 and 0.65.[253] One of the reasons for this limited performance is that these stroke risk stratification tools do not appropriately take into account competing causes of stroke such as carotid or intracranial arterial stenosis. [261] For instance, the CHA_2DS_2-VASc score, which is the most commonly used stroke risk stratification tool, allocates one point (over a total of nine points) to vascular disease, an umbrella risk component including prior myocardial infarction, peripheral artery disease, and aortic plaque.[253] Indeed, this score, which was released about

ten years ago, does not take into account carotid disease. Future stroke risk stratification scores in AF patients should integrate carotid disease.

Atrial fibrillation and atherosclerosis have similar risk factors including obesity, hypertension, dyslipidemia, diabetes and age, amongst others. This explains why carotid atherosclerosis is very common in AF patients. While significant CS (≥50%) is a well-recognized risk factor for stroke, plaques that do not significantly occlude the carotid lumen have been long neglected. [492, 539] We found that about half of AF patients had CP. None of the studies included in this subgroup analysis reported on high-risk CP. High-risk imaging features of CP such as echolucency, lipid-rich necrotic core, intraplaque hemorrhage, or ulcerations are associated with an increased risk of ipsilateral embolic stroke in non-stenotic carotid disease. In a recent study we have shown that high-risk plaques are common in asymptomatic CS and are associated with a significant risk of cerebrovascular events.[540] Similarly, in the Athens Stroke Registry, non-stenotic atherosclerotic plaques with ulceration represent ~15% of potential causes of embolic stroke of undetermined source.[541] These findings together with the high frequency of CP in AF patients call for an investigation of the risk of stroke conferred by high-risk CP in the AF population. Such information might be very useful in refining risk stratification for predicting thromboembolism in AF.

From a therapeutic perspective, it is uncertain whether AF patients with concomitant CS should receive additional treatment such as antiplatelet therapy, besides anticoagulation. No clinical trials have addressed this question. In fact, CS doubles the risk of stroke recurrence and increases the risk of death in AF patients despite anticoagulation.[493] This suggests that additional therapies might be needed to address the residual atherosclerotic risk of stroke associated with CS in AF patients. For instance, in the context of coronary artery disease, antiplatelet therapy may be combined with oral anticoagulant following percutaneous coronary intervention, to prevent stent thrombosis, or after acute coronary syndromes.[165]

Considering the significant frequency of CS in AF patients, it is important to conduct clinical trials in order to determine whether antiplatelet therapy in combination with oral anticoagulants can provide an additional benefit for stroke prevention, when balancing the risk of bleeding in patients with concomitant AF and CS. Other crucial questions include whether dual antiplatelet and anticoagulant therapy should be considered in AF patients after CEA; and following CES, for how long should this combination therapy be given? Importantly, the commonness of concomitant AF and CS highlights the need to intervene on common risk factors to reduce the development and progression of other conditions.

Carotid atherosclerosis is a strong predictor of AF. In the Bruneck Study, individuals with carotid atherosclerosis, compared to those without, had an almost two-fold increased risk of incident AF after adjusting for common cardiovascular risk factors [516]. We found that one in ten patients with CS had AF. Interestingly, AF was much more frequent in patients undergoing CAS (12.7%) compared to CEA (6.9%). Although real-world data have shown that the cardiovascular risk profile of patients undergoing CAS and CEA are usually similar, the higher prevalence of AF in patients undergoing CAS can be explained by a possible tendency of vascular surgeons to do CAS in patients who have a higher perioperative risk of stroke, such as patients with AF. This hypothesis is supported by the results of a representative nationwide observational study in the U.S. that explored the impact of AF on outcomes in patients undergoing CAS or CEA in general practice [505]. The study revealed that AF was associated with a 57% increased risk of postoperative stroke in patients undergoing CEA, but not in patients undergoing CAS. Furthermore, the risk of a composite of postoperative stroke, cardiac complications, and mortality in AF patients was 31% higher following CEA than CAS. An opposite relationship was seen in patients without AF, in whom the composite endpoint was significantly lower in patients undergoing CEA.[505] This suggests

that CEA might be a better option for the treatment of CS in the ~ 10% of AF patients who have this condition as shown by our study.

The findings of this review should be interpreted with caution. There was marked heterogeneity across studies; we found recruitment period and publication year explained a significant amount of this heterogeneity, possibly because the recent studies had better reporting. Besides, this high heterogeneity is also explained by significant variations of baseline characteristics of participants across these studies done in various clinical settings. Furthermore, ineluctably there was a difference in the diagnosis of both AF and carotid disease between studies. As most patients did not have enhanced long-term electrocardiographic monitoring for the detection of AF, with implantable loop recorder or prolonged Holter for example, the prevalence of AF reported is likely underestimated in most studies, hence in our meta-analysis.

5.1.5 Conclusion

This systematic review shows that AF and CS frequently co-exist. About one in ten patients with AF has CS, and vice versa; and non-stenotic carotid disease is much more frequent. The commonness of concomitant AF and CS calls for investigations to appropriately address the important residual risk of thromboembolism in patients with both conditions, despite anticoagulation. The benefit of aggressive lipid-lowering therapy and antiplatelets in this specific population needs to be clarified. Furthermore, considering that half of AF patients were found to have CP, the prevalence and prognostic value of high-risk CP in AF should be studied. Finally, these findings have important implications for AF screening in patients with CS, stroke prevention and the opportunities to intervene on common risk factors to reduce the development and progression of other conditions.

5.1.6 Tables and figures

Table 1. Summary prevalence rates of carotid stenosis in atrial fibrillation by subgroups

Table 2. Summary prevalence rates of atrial fibrillation in carotid stenosis by subgroups

Figure 1. Study selection

Figure 2. The prevalence of carotid stenosis in patients with atrial fibrillation

The prevalence of any carotid disease has been presented as a proportion (prop, %) of the overall AF population. The shaded squares indicate the prevalence rates for each study, with the 95% confidence interval (95% CI) shown as horizontal lines traversing each square. The pooled estimate is presented as a shaded diamond, with horizontal line indicating the 95% CI. The plot has been ordered by the weight of each study.

Figure 3. The prevalence of carotid plaque in patients with atrial fibrillation

The summary forest plot, with similar notes as in Figure 1.

Figure 4. The prevalence of AF in patients with carotid stenosis

Summary forest plot of AF prevalence in patients diagnosed with carotid stenosis, with similar notes as in Figure 1.

Table 1. Summary prevalence rates of carotid stenosis in atrial fibrillation by subgroups

Subgroup	Studies (N)	Participants (N)	Prevalence			Heterogeneity		*Egger's* test (*P*-value)
			Rate	95% CI (LL)	95% CI (UL)	I^2	*P*-value	
By Region								
Asia	5	1357	14.22%	7.4	21.04	93.3%	<0.001	0.1898
Europe	4	1893	12.85%	6.03	19.67	95.3%	<0.001	0.6179
North America	2	669	8.24%	0.79	15.69	91.8%	<0.001	ND
By Presence of Stroke								
Yes	7	1402	13.53%	8.12	18.93	94.4%	<0.001	0.3572
No	4	2517	10.5%	5.73	15.27	88.7%	<0.001	0.3855
By Cut-off								
≥50%	9	3457	13.89%	9.59	18.2	93.4%	<0.001	0.1393
≥70%	1	259	5.79%	3.28	9.37	NA	NA	NA

95% CI: 95 percent confidence interval; NA: not applicable; LL: lower limit of 95% CI; UL: upper limit of 95% CI

Table 2. Summary prevalence rates of atrial fibrillation in carotid stenosis by subgroups

Subgroup	Studies (N)	Participants (N)	Prevalence			Heterogeneity		*Egger's* test (*P*-value)
			Rate	95% CI (LL)	95% CI (UL)	I^2	*P*-value	
By Region								
Asia	3	734	11.11%	2.9	19.32	90.8%	<0.001	0.7412
Europe	10	4 561	10.69%	7.38	14.0	93.4%	<0.001	0.0468
North America	12	2 281 223	9.14%	8.33	9.96	99.6%	<0.001	0.3190
By Procedure								
CAS and CEA	7	2 255 771	9.34%	8.29	10.39	99.7%	<0.001	0.3397
CEA	10	17 113	6.85%	5.31	8.39	94.1%	<0.001	0.1259
CAS	4	11 700	12.67%	11.32	14.02	38.3%	0.1823	0.2600
Symptomatic								
Asymptomatic	3	25 366	12.23%	9.99	14.46	89.7%	<0.001	0.0965
Symptomatic	5	2 164	11.68%	6.04	17.32	93.7%	<0.001	0.2836
Asymptomatic or Symptomatic	13	697 639	9.41%	7.66	11.15	97.9%	<0.001	0.8399
By cut-off								
≥50%	6	5 524	12.65%	9.12	16.18	93.7%	<0.001	0.3079
≥70%	7	2 286 518	9.75%	5.89	13.61	90.4%	<0.001	0.0566

Symptomatic: patients with prior cerebrovascular event; Asymptomatic: patients without prior cerebrovascular event; LL: lower limit of 95% CI; UL: upper limit of 95% CI

Figure 1. Study selection

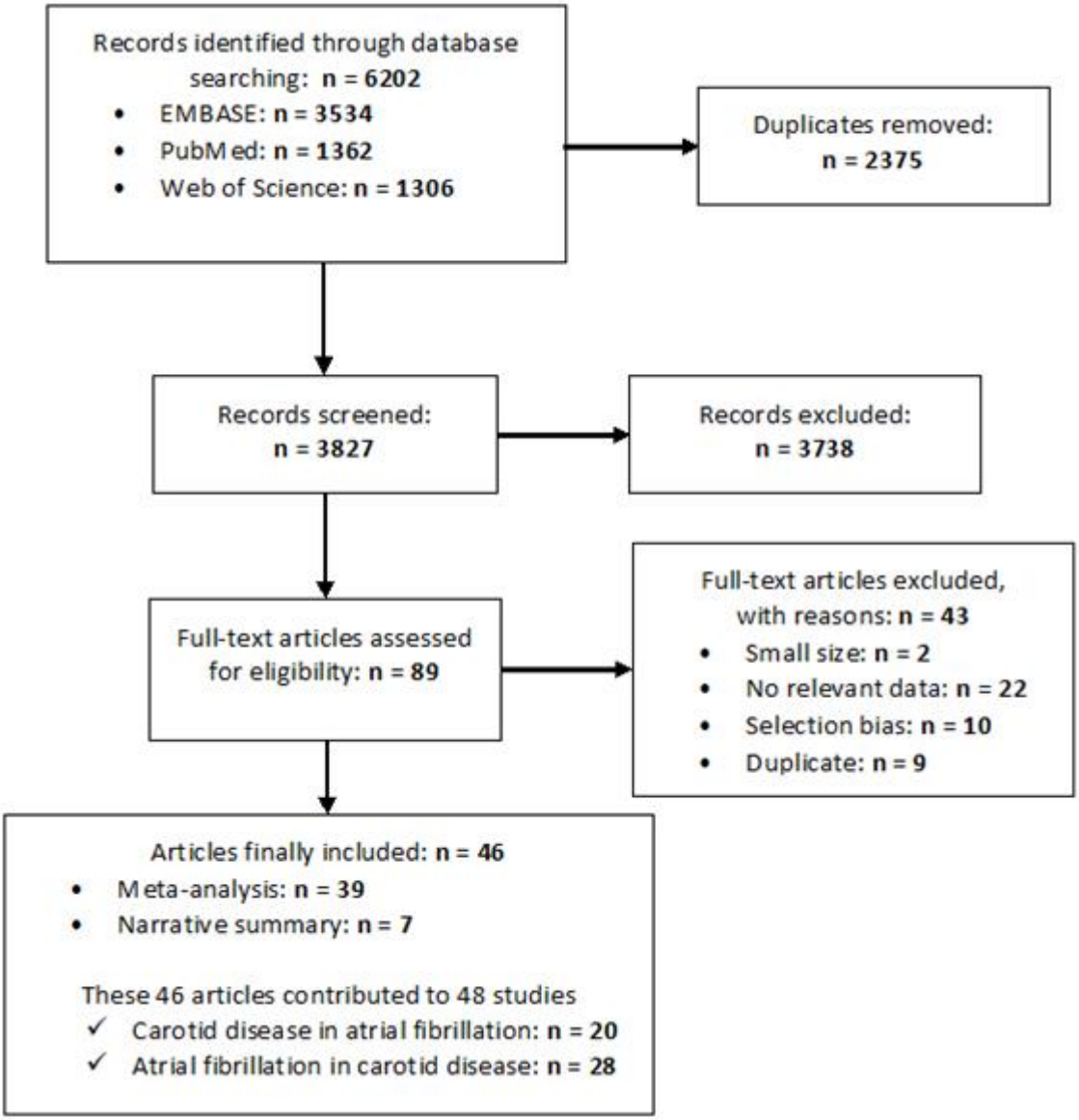
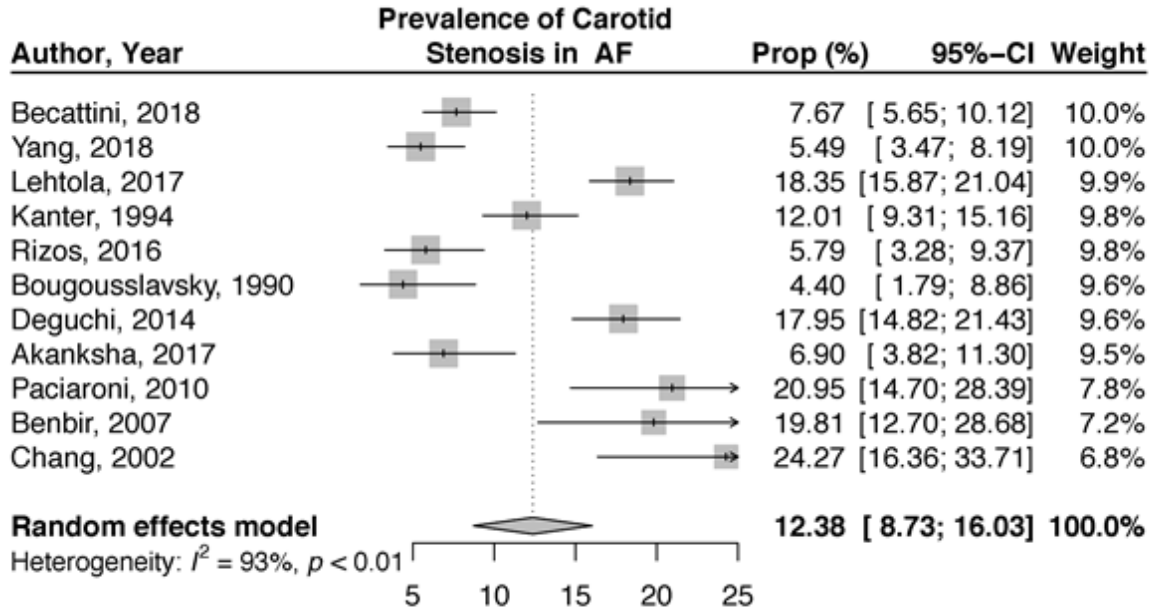
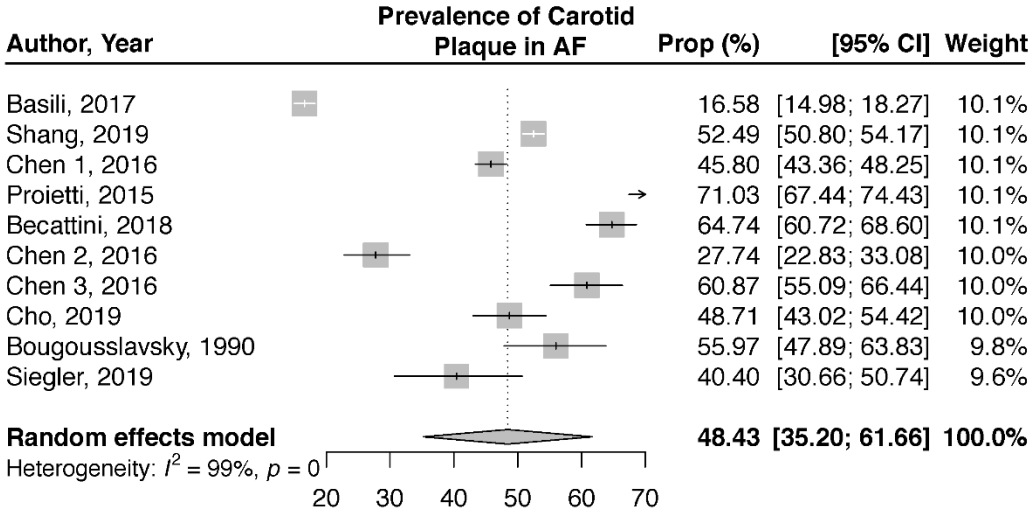


Figure 2. The prevalence of carotid stenosis in patients with atrial fibrillation



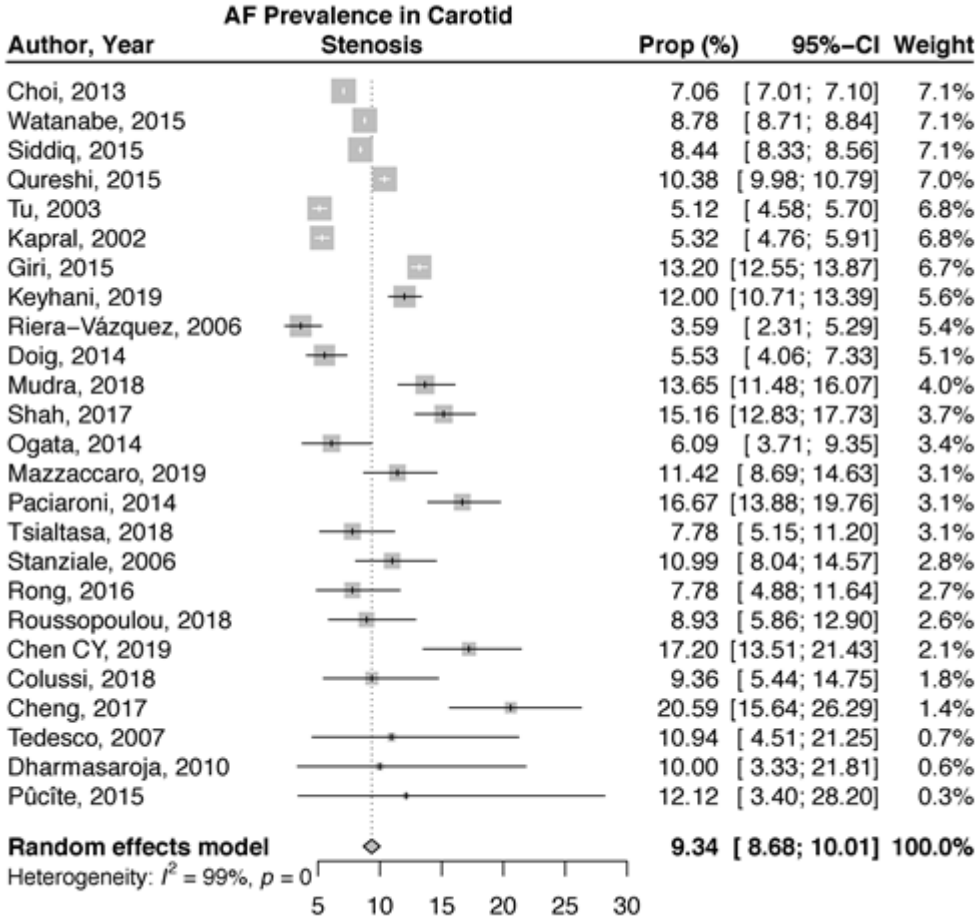
The prevalence of any carotid disease has been presented as a proportion (prop, %) of the overall AF population. The shaded squares indicate the prevalence rates for each study, with the 95% confidence interval (95% CI) shown as horizontal lines traversing each square. The pooled estimate is presented as a shaded diamond, with horizontal line indicating the 95% CI. The plot has been ordered by the weight of each study.

Figure 3. The prevalence of carotid plaque in patients with atrial fibrillation



The prevalence of any carotid plaque has been presented as a proportion (prop, %) of the overall AF population. The shaded squares indicate the prevalence rates for each study, with the 95% confidence interval (95% CI) shown as horizontal lines traversing each square. The pooled estimate is presented as a shaded diamond, with horizontal line indicating the 95% CI. The plot has been ordered by the weight of each study.

Figure 4. The prevalence of AF in patients with carotid stenosis



The prevalence of atrial fibrillation has been presented as a proportion (prop, %) of the overall population with carotid stenosis. The shaded squares indicate the prevalence rates for each study, with the 95% confidence interval (95% CI) shown as horizontal lines traversing each square. The pooled estimate is presented as a shaded diamond, with horizontal line indicating the 95% CI. The plot has been ordered by the weight of each study

5.1.7 Appendix

Supplementary Table 1. Search strategy

	Search strategy
#1	carotid
#2	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#3	#1 AND #2

Supplementary Table 2. Definition of carotid plaque in included studies

Study	**Imaging modality**	**Definition of carotid plaque**
Shang, 2019	Ultrasonography	A focal structure that uplifted into the arterial lumen at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) value; or an IMT greater than 1.5 mm
Siegler, 2019	Computed tomography	Plaque ≥ 3 mm
Proietti, 2015	Ultrasonography	cIMT ≥1.5 mm
Becattini, 2018	Ultrasonography	A protrusion into the vessel lumen of at least 2 mm, as measured from the border between the adventitial and medial layer
Cho, 2020	Ultrasonography	Abnormal wall thickness (cIMT > 1.5 mm); or a focal lesion measuring at least 0.5 mm or 50% of the surrounding cIMT value and protruding into the lumen.
Basili, 2017	Ultrasonography	Focal wall thickening that is at least 50% or greater than that of the surrounding vessel wall; or focal region with carotid intima media thickness >1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary
Chen, 2016 (ARIC)	Ultrasonography	Two of these three criteria: abnormal wall thickness (defined as cIMT >1.5 mm), abnormal shape and abnormal wall texture
Chen, 2016 (MESA)	Ultrasonography	≥25% of the surrounding CIMT value and protruding into the lumen
Chen, 2016 (Rotterdam study)	Ultrasonography	Protrusion into the lumen
Bogousslavsky, 1990	Ultrasonography	Protrusion into the lumen; <50% stenosis

cIMT: carotid intima-media thickness

Supplementary Table 3. Summarized study characteristics

A. Carotid disease in atrial fibrillation

Characteristics	**N = 20**
Total population	49 070
Year of publication, range	1990-2019
Period of inclusion of participants, range	1990-2017
Design	
- Cohort	9
- Cross-sectional	9
- Case-control	1
- Clinical trial	1
Setting	
- Hospital-based	17
- Community-based	3
Data source	
- Registry	13
- Directly from patients	7
Timing of data collection	
- Prospective	9
- Retrospective	11
- Both	0
Regions	
- Asia	7
- Northern America	6
- Europe	6
- Multinational	1
Countries	
- US	6
- Italy	2
- Japan	2
- Korea	2
- China	1
- Finland	1
- Germany	1
- India	1
- Multinational	1
- Taiwan	1
- The Netherland	1
- Turkey	1
Representativeness	
- Local	13
- National	5
- Multinational	2
Type of carotid disease	
- Carotid stenosis	10
- Carotid occlusion	1

B. Atrial fibrillation in carotid disease

Characteristics	**N = 28**
Total population	2 288 265
Year of publication, range	2002-2019
Period of inclusion of participants, range	1990-2018
Design	
- Cohort	18
- Cross-sectional	6
- Clinical trial (RCT)	1
- Clinical trial (non-RCT)	1
Setting	
- Hospital-based	27
- Community-based	1
Data source	
- Registry	17
- Directly from patients	10
Timing of data collection	
- Prospective	12
- Retrospective	16
- Both	1
Regions	
- Europe	12
- Northern America	12
- Asia	4
-	
Countries	
- USA	10
- Italy	5
- Canada	2
- Spain	2
- UK	2
- Germany	1
- Israel	1
- Japan	1
- Latvia	1
- Multinational (Europe)	1
- Taiwan	1
- Thailand	1
Representativeness	
- Local	20
- National	5
- Multinational	1
Type of carotid disease	
- Carotid stenosis	23
- Carotid occlusion	2

- Carotid plaque	7
- Stenosis and plaque	1
- Carotid occlusive disease	1
Risk of bias	
- Low	6
- Moderate	11
- High	3

- Carotid plaque	2
- Stenosis and occlusion	1
Diagnostic cutoff	
- ≥50%	4
- ≥70%	4
- Not reported	20
Risk of bias	
- Low	9
- Moderate	18
- High	1

ND, not determined; RCT, randomized controlled trial

Supplementary Table 4. Individual characteristics of included studies

A. Studies reporting on the prevalence of carotid disease in patients with atrial fibrillation

Author	Year	Country	Design	Setting	Study Level	Data Collection	Data Source	Type of Carotid Disease	Method of AF Diagnosis	Type of Carotid Disease	Carotid Disease Diagnosis	Sample Size
Rizos et al	2016	Germany	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	12-lead ECG, 24-h Holter, and continuous ECG	Carotid stenosis	NR	320
Shibazaki et al	2010	Japan	Cohort	Hospital	Local	Prospective	Patients	Carotid Occlusion	12-lead ECG, 24-h Holter, and continuous ECG	NR	IS and TIA patients with AF within 24 h of onset	221
Yang et al	2018	Korea	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Stenosis	12-lead ECG and 24-h Holter	Carotid stenosis	Carotid Duplex Sonography	401
Shang et al	2019	China	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Plaques	NR	Carotid plaques	Carotid Ultrasound Examination	3435
Siegler et al	2019	USA	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Plaques	ECG	Carotid plaques	CTA	99
Akanksha et al	2017	India	Cohort	Hospital	National		Registry	Carotid Stenosis	ECG	Carotid stenosis	NR	203
Kanter et al	1994	USA	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	NR	Carotid stenosis	Carotid Ultrasonography	508

Lehtola et al	2017	Finland	Cohort	Hospital	National	Retrospective	Registry	Carotid Stenosis	NR	Carotid stenosis	Angiography + CTA	899
Paciaroni et al	2010	Italy	Case-Control	Hospital	Local	Prospective	Patients	Atherosclerosis	NR	Atherosclerosis	NR	148
Proietti et al	2015	Italy	Cross Sectional	Hospital	National	Prospective	Registry	Increased cIMT	NR	Increased cIMT	Ultrasonography	673
Chen et al (1)	2016	USA	Cohort	Community	National	Retrospective	Registry	Carotid Plaque	ECG	Carotid plaque	Ultrasound	1631
Chen et al (2)	2016	USA	Cohort	Community	National	Retrospective	Registry	Carotid Plaque	ECG	Carotid plaque	Ultrasound	310
Chen et al (3)	2016	Netherlands	Cohort	Community	Local	Retrospective	Registry	Carotid Plaque	ECG	Carotid plaque	Ultrasound	299
Benbir et al	2007	Turkey	Cross-Sectional	Hospital	Local	Prospective	Patients	Carotid Stenosis	ECG	Carotid stenosis	Doppler-ultrasonography	106
Bogousslavsky et al	1990	USA	Cross-Sectional	Hospital	Local	Prospective	Patients	Carotid Stenosis and Plaque	ECG	Carotid stenosis and plaque	Doppler-ultrasonography	159
Chang et al	2002	Taiwan	Cross-Sectional	Hospital	Local	Prospective	Patients	Carotid Stenosis	ECG	Carotid stenosis	Doppler-ultrasonography	103
Cho et al	2019	Korea	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Plaque	NR	Carotid plaque	Ultrasonography	310
Deguchi et al	2014	Japan	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Stenosis	ECG and 24-h Holter	Carotid stenosis	MRI and MRA	546
Fox et al	2020	USA, UK, France, Netherlands, Germany	Cohort	Hospital	Multinational	Prospective	Registry	Carotid Occlusive Disease	NR	Carotid occlusive disease	NVAF	24436

		, Canada										
Kochar et al	2017	USA	Clinical Trial	Hospital	Multinational	Retrospective	Registry	Carotid Stenosis	NR	Carotid stenosis	NR	14263

B. Studies reporting on the prevalence of atrial fibrillation in patients with carotid disease

Author	Year	Country	Design	Setting	Study Level	Data Collection	Data Source	Type of Carotid Disease	Method of Carotid Disease Diagnosis	Diagnostic Cut-Off	Type of Carotid Procedure	Sample Size
Qureshi et al	2015	USA	Cohort	Hospital	National	Retrospective	Registry	Carotid Stenosis	ICD Codes (9th Revision)	NR	CAS	22,177
Riera-Vázquez et al	2006	Spain	Cohort	Hospital	Local	Retrospective	Registry	Carotid Stenosis	NR	NR	CEA	669
Rong et al	2016	USA	Cohort	Hospital	Local	Retrospective	Registry	Carotid Stenosis	NR	NR	CEA	270
Roussopoulou et al	2018	Greece, Germany	Cohort	Hospital	Local	Prospective	NR	Carotid Stenosis	Carotid Duplex Ultrasound	≥70%	CEA	280
Shah et al	2017	USA	Cohort	Hospital	Local	Retrospective	NR	Carotid Stenosis	Duplex Sonography	≥50%	NR	864
Siddiq et al	2015	USA	Cross-Sectional	Hospital	National	Retrospective	Registry	Carotid Stenosis	ICD-9-CM codes 433.10 and 433.11	NR	CAS & CEA	225,191
Stanziale et al	2006	USA	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	CTA	≥50%	CAS	360
Tedesco et al	2007	USA	Cohort	Hospital	Local	Retrospective	Registry	Carotid Stenosis	NR	NR	CAS & CEA	64
Tsialtasa et al	2018	Italy	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	NR	≥75%	CEA	334
Tu et al	2003	Canada	Cohort	Hospital	Local	Retrospective	Registry	Carotid Stenosis	Cerebral Angiography and Carotid Doppler	NR	CEA	6038
Watanabe et al	2015	USA	Cohort	Hospital	National	Retrospective	Registry	Carotid Stenosis	ICD-9-CM code 433.11	NR	CAS & CEA	672074

									or without 433.10			
Chen et al	2019	Taiwan	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	Bilateral Carotid Duplex Scan	70-99%	NR	372
Cheng et al	2017	UK	Cross-Sectional	Hospital	Local	Prospective	Patients	Carotid Stenosis	CTA, MRA or Duplex Ultrasonography	50%	CAS & CEA	238
Choi et al	2013	USA	Cross-Sectional	Hospital	National	Retrospective	Registry	Carotid Stenosis and Occlusion	NR	NR	CAS & CEA	1335554
Dharmasaroja et al	2010	Thailand	Cross-Sectional	Hospital	Local	Prospective	Patients	Carotid Stenosis	Carotid Duplex	NR	NR	50
Diaz-Perez et al	2018	Spain	Cross-Sectional	Hospital	Local	Retrospective	Registry	Carotid Artery Occlusion	CT, Angiography, and CTP	NR	Mechanical Thrombectomy	153
Doig et al	2014	UK	RCT	Hospital-Based	Local	Prospective	Patients	Carotid Stenosis	NR	>50%	CEA	814
Pûcîte et al	2015	Latvia	Cross-Sectional	Hospital-Based	Local	Prospective	Patients	Carotid Stenosis	CTA	≥70%	CEA	33
Colussi et al	2018	Italy	Cohort	Hospital Based	Local	Retrospective	Patients	Carotid Stenosis	CTA and MRA	NR	CAS	171
Telman et al	2012	Israel	Cohort	Hospital Based	Local	Retrospective and Prospective	Registry	Carotid Plaques	Duplex Ultrasound	NR	NR	671
Giri et al	2015	USA	Cohort	Hospital Based	National	NR	Registry	Carotid Stenosis	NR	NR	NR	10246
Willeit et al	2013	Italy	NR	Population	NR	Retrospective	NR	Carotid Atherosclerosis	NR	NR	NR	900

Kapral et al	2002	Canada	NR	NR	Local	Retrospective	Registry	Carotid Stenosis	NR	NR	NR	6038
Keyhani et al	2019	USA	Cohort	Hospital	NR	NR	Patients	Carotid Stenosis	Carotid Ultrasonography, MRA, and CTA	NR	NR	2325
Mazzaccaro et al	2019	Italy	Cohort	Hospital	Local	Retrospective	Patients	Carotid Stenosis	Duplex Ultrasound	NR	CEA & CAS	473
Mudra et al	2018	Germany	Cohort	Hospital	Local	Prospective	Patients	Carotid Stenosis	NR	NR	CAS	901
Ogata et al	2014	Japan	Cohort	Hospital	Local	NR	Patients	Carotid Stenosis	Ultrasound	NR	CEA	312
Paciaroni et al	2014	Italy	Therapeutic Trial (non-RCT)	Hospital	Multinational	Retrospective	Registry	Extracranial Internal Artery Occlusion	CTA, MRA, and Carotid Ultrasound & Angiography	NR	NR	648

cIMT, carotid intima-media thickness; CT, computed tomography; CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, CT angiography; CTP, CT perfusion; ECG, electrocardiography; IS, ischemic stroke; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NR, not reported; NVAF, nonvalvular atrial fibrillation; PAF, paroxysmal atrial fibrillation; RCT, randomized controlled trial; TIA, transient ischemic accident

Supplementary Table 5. Clinical characteristics of included studies

A. Studies reporting on the prevalence of carotid disease in patients with atrial fibrillation

Author	Year	Mean Age	Percent Male	Percent Stroke	Percent Hypertension	Percent Diabetes	Percent Smokers	Percent Dyslipidemia	Percent CAD
Rizos et al	2016	77.0	51.6	27.8	88.4	28.8	NR	NR	2.6
Shibazaki et al	2010	76.5	54.8	30.0	67.4	26.7	41.6	20.8	7.2
Yang et al	2018	68.6	65.6	16.5	78.5	29.4	42.6	53.1	NR
Shang et al	2019	NR	38.2	NR	NR	NR	17.1	NR	NR
Siegler et al	2019	78.0	52.0	21.0	76.0	31.0	12.0	45.0	33.0
Akanksha et al	2017	62.0	59.0	NR	87.0	41.0	5.0	32.0	30.0
Kanter et al	1994	77.0	63.0	NR	50.0	15.0	8.0	NR	21.0
Lehtola et al	2017	NR	56.6	20.0	64.6	21.0	NR	47.4	31.4
Paciaroni et al	2010	76.0	47.9	NR	83.8	21.6	21.6	31.1	NR
Proietti et al	2015	72.0	54.0	14.0	80.0	23.0	18.0	37.0	12.0
Chen et al (1)	2016	NR	NR	NR	NR	NR	NR	NR	NR
Chen et al (2)	2016	NR	NR	NR	NR	NR	NR	NR	NR
Chen et al (3)	2016	NR	NR	NR	NR	NR	NR	NR	NR
Benbir et al	2007	68.8	38.7	NR	66.1	25.3	18.9	8.4	ND
Bougousslavsky et al	1990	68.6	56.0	20.0	48.0	14.0	26.0	9.0	55.0
Chang et al	2002	69.0	62.0	28.2	45.6	21.4	42.7	33	NR

Cho et al	2019	67.8	67.1	15.8	67.1	26.5	NR	16.5	9.0
Deguchi et al	2014	75.8	59.3	NR	68.7	21.8	NR	NR	NR
Fox et al	2020	71.0	55.0	9.8	76.8	21.1	NR	37.9	13.5
Kochar et al	2017	74.0	72.0	72.0	93.0	40.0	NR	NR	32.0

CAD, coronary artery disease; NR, not reported

B. Studies reporting on the prevalence of atrial fibrillation in patients with carotid disease

Author	**Year**	**Mean Age**	**Percent Male**	**Percent Stroke**	**Percent Hypertension**	**Percent Diabetes**	**Percent Smoking**	**Percent Dyslipidemia**	**Percent CAD**
Qureshi et al	2015	75.1	57.8	NR	76.5	28.2	NR	31.9	46.7
Riera-Vázquez et al	2006	68.1	86.1	53.4	62.3	33.2	77.4	44.1	9.6
Rong et al	2016	67.2	61.1	NR	81.5	27.8	64.1	45.2	47.4
Roussopoulou et al	2018	68.5	73.2	100.0	86.8	30.4	45.5	62.0	29.6
Shah et al	2017	72	51.5	NR	89.0	24.0	45.0	56.3	62.0
Siddiq et al	2015	70.8	58.2	NR	81.1	28.9	19.6	16	44.6
Stanziale et al	2006	76	59.7	NR	100.0	33.0	65.2	NR	64.6
Tedesco et al	2007	69.5	100.0	41.0	87.5	39.1	82.8	87.5	59.4
Tsialtasa et al	2018	72.6	67.1	14.5	95.2	21.3	57.4	86.2	NR
Tu et al	2003	68.3	65.3	5.7	64.4	23.1	23.1	NR	35.7
Watanabe et al	2015	73.2	39.3	NR	78.4	30.6	NR	NR	1.5

Chen et al	2019	72	73.4	19.4	83.6	47	66.1	NR	20.2
Cheng	2017	74.6	62.2	26.9	68.9	33.2	42.4	65.5	19.3
Choi	2013	70.6	30.7	NR	66.9	26.7	NR	36.4	41.4
Dharmasaroja	2010	70.0	60.0	18.0	60.0	28.0	28.0	88.0	12
Diaz-perez	2018	71.0	59.5	NR	71.9	26.8	26.1	45.8	NR
Doig	2014	NR	71.0	NR	70.3	21.4	23.3	66.2	18.4
Pûcîte	2015	68.5	48.5	NR	NR	24.2	39.4	NR	NR
Colussi	2018	72.0	73.0	NR	85.0	46.0	67.0	71.0	36.0
Telman	2012	70.6	63.0	100.0	80.2	38.8	22.5	45.3	32.5
Giri	2015	70.0	62.4	14.9	91.7	38.3	73.9	89.0	52.7
Willeit	2013	58.0	50.9	NR	65.6	6.6	24.0	NR	4.3.0
Kapral	2002	68.0	65.0	NR	66.0	23.0	69.5	36.0	35.0
Keyhani	2019	73.74	98.8	NR	93.3	40.1	33.5	NR	53.5
Mazzaccaro	2019	84.2	63.0	NR	70.2	44.4	61.3	57.5	34.2
Mudra	2018	71.0	63.3	NR	90.8	32.7	21.5	78.8	63.2
Ogata	2014	70.2	81.7	NR	72.8	41.0	33.4	45.7	18.9
Paciaroni	2014	63.0	63.3	9.9	61.4	21.5	34.3	30.7	NR

CAD, coronary artery disease; NR, not reported

Supplementary Table 6. Risk of bias assessment

A. Assessment of studies reporting carotid disease in AF

Author	Publication Year	External Validity				Internal Validity					Score	RoB Level
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9		
Rizos et al	2016	0	1	1	0	1	1	0	1	1	6	Moderate
Yang et al	2018	0	1	0	0	0	1	1	1	1	5	Moderate
Shibazak et al	2010	0	1	1	1	1	0	1	1	1	7	Low
Shang et al	2019	0	0	0	0	0	0	1	1	1	3	High
Siegler et al	2019	0	1	0	0	0	1	0	1	1	4	Moderate
Basili et al	2017	1	1	0	0	0	1	0	1	1	5	Moderate
Becattini et al	2018	0	1	0	0	1	1	0	1	1	5	Moderate
Chen et al (1)	2016	0	1	0	0	0	1	1	1	1	5	Moderate
Chen et al (2)	2016	1	1	0	0	0	1	1	1	1	6	Moderate
Chen et al (3)	2016	0	1	0	0	0	1	1	1	1	5	Moderate
Benbir et al	2007	0	1	0	0	1	1	1	1	1	6	Moderate
Bogousslavsky et al	1990	0	1	0	0	1	1	1	1	1	6	Moderate
Chang et al	2002	0	1	0	0	1	1	1	1	1	6	Moderate
Cho et al	2019	0	0	0	0	0	0	1	1	1	3	High
Deguchi et al	2014	0	1	0	0	0	1	1	1	1	5	Moderate
Fox et al	2020	1	0	0	0	0	0	0	1	1	3	High

Akanksha et al	2017	0	1	1	1	0	0	0	1	1	5	Moderate
Kanter et al	1994	1	1	1	1	0	1	1	1	1	8	Low
Lehtola et al	2017	1	1	1	1	0	1	0	1	1	7	Low
Paciaroni et al	2010	0	0	1	1	1	0	0	1	1	8	Low
Proietti et al	2015	1	1	1	1	0	1	0	1	1	7	Low
Kochar et al	2017	1	1	1	1	1	0	1	1	1	8	Low

B. Assessment of studies reporting AF in carotid disease

Author	**Publication Year**	**External Validity**				**Internal Validity**					**Score**	**RoB Level**
		Item 1	**Item 2**	**Item 3**	**Item 4**	**Item 5**	**Item 6**	**Item 7**	**Item 8**	**Item 9**		
Qureshi	2015	1	1	1	0	0	1	0	1	1	6	Low
Riera-Vázquez	2006	0	0	0	1	0	1	0	1	1	4	Moderate
Rong	2015	0	0	0	0	0	0	0	1	1	2	High
Roussopoulou	2018	0	0	0	0	1	1	0	1	1	4	Moderate
Shah	2017	0	0	1	0	0	1	0	1	1	4	Moderate
Siddiq	2015	1	1	0	0	0	0	0	1	1	4	Moderate
Stanziale	2006	0	0	1	1	1	1	0	1	1	6	Moderate
Tedesco	2007	0	1	1	1	0	0	1	1	1	6	Moderate
Tsialtasa	2018	0	1	1	1	1	1	1	1	1	8	Low
Tu	2003	0	1	1	1	0	1	0	1	1	6	Moderate

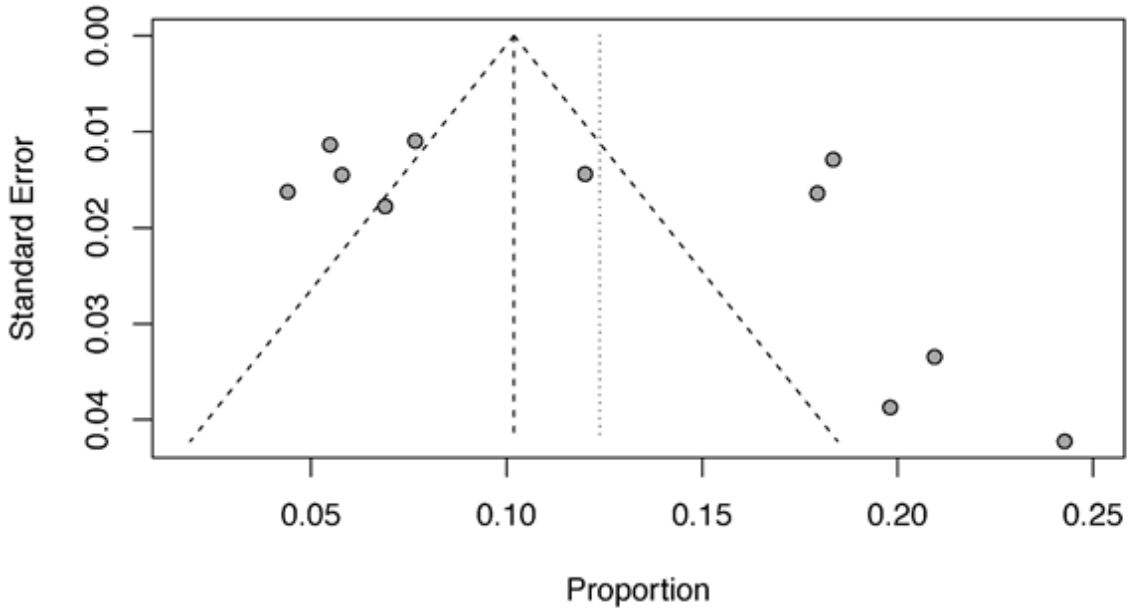
Watanabe	2015	1	1	1	1	0	0	0	1	1	6	Moderate
Yue	2016	1	1	1	0	0	1	1	1	1	7	Low
Chen	2019	0	1	0	0	1	1	1	1	1	6	Moderate
Cheng	2017	0	1	0	0	1	1	0	1	1	5	Moderate
Choi	2013	1	1	0	0	0	1	0	1	1	5	Moderate
Dharmasaroja	2010	0	1	0	0	1	1	0	1	1	5	Moderate
Diaz-Perez	2018	0	1	0	0	0	1	0	1	1	4	Moderate
Doig	2014	0	1	1	1	1	0	0	1	1	6	Moderate
Pûcîte	2015	0	0	0	0	1	1	0	1	1	4	Moderate
Colussi	2018	0	1	1	1	0	1	0	1	1	6	Moderate
Telman	2012	1	1	1	1	0	1	1	1	1	8	Low
Giri	2015	1	1	1	1	0	0	0	1	1	6	Moderate
Willeit	2013	0	1	0	1	0	0	0	1	1	4	Moderate
Kapral	2002	1	1	1	1	0	0	0	1	1	6	Moderate
Keyhani	2019	1	1	1	1	1	1	0	1	1	8	Low
Mazzaccaro	2019	1	1	1	1	1	1	1	1	1	9	Low
Mudra	2018	1	1	1	1	1	0	0	1	1	7	Low
Ogata	2014	1	1	1	1	0	1	0	1	1	7	Low
Paciaroni	2014	1	1	1	1	0	1	1	1	1	8	Low

RoB: risk of bias

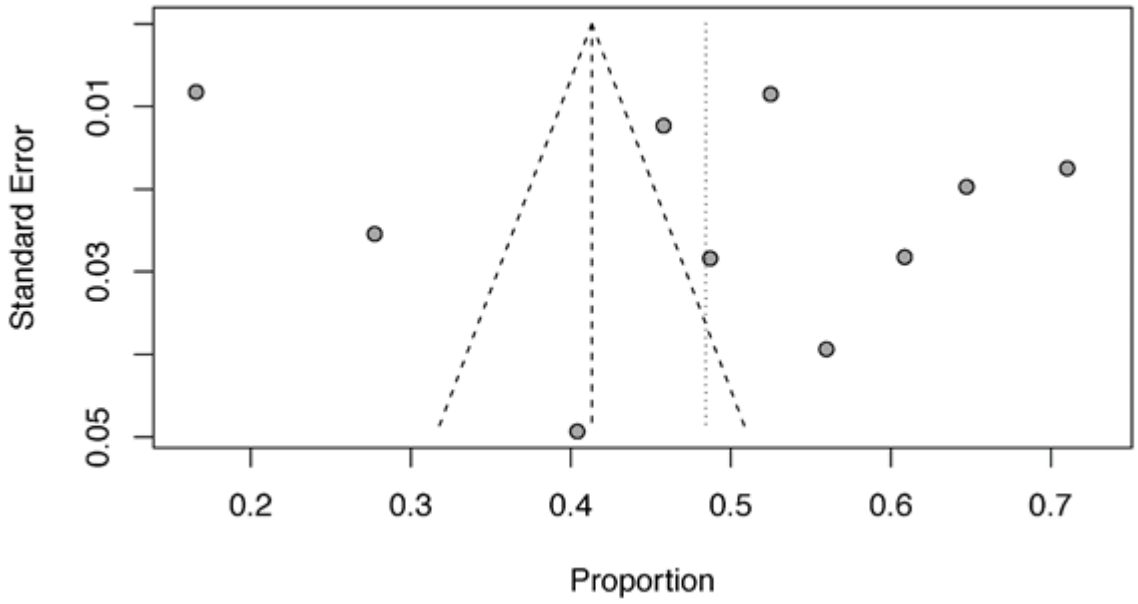
Interpretation of the score

7 – 9: Low Risk of Bias / High-quality study; **4 – 6**: Moderate Risk of Bias / Moderate-quality study; **3 or less**: High Risk of Bias / Low-quality study.

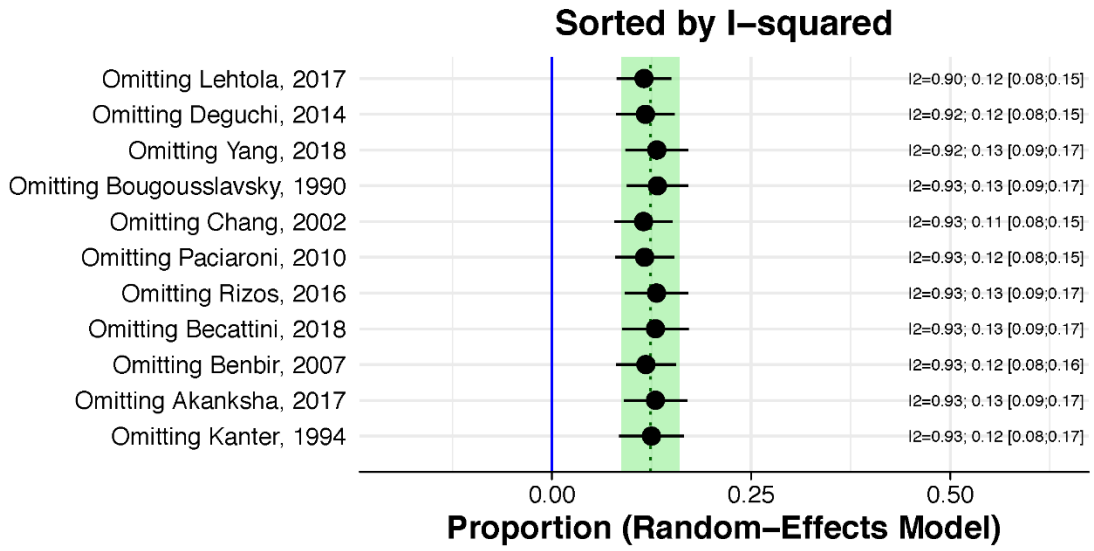
Supplementary Figure 1. Funnel plot of studies reporting on the prevalence of carotid stenosis in patients with atrial fibrillation



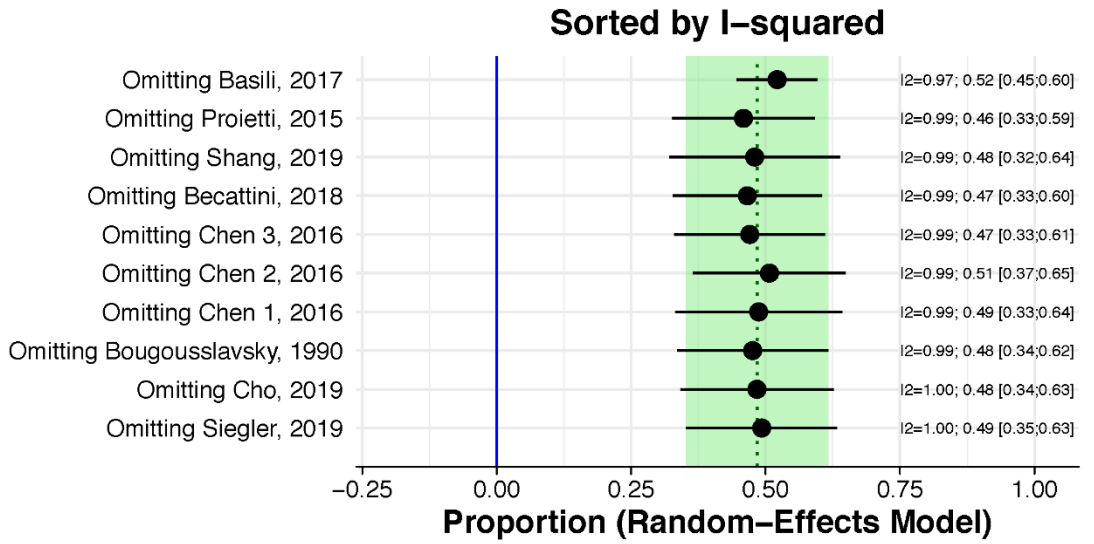
Supplementary Figure 2. Funnel plot of studies reporting on the prevalence of carotid plaque in patients with atrial fibrillation



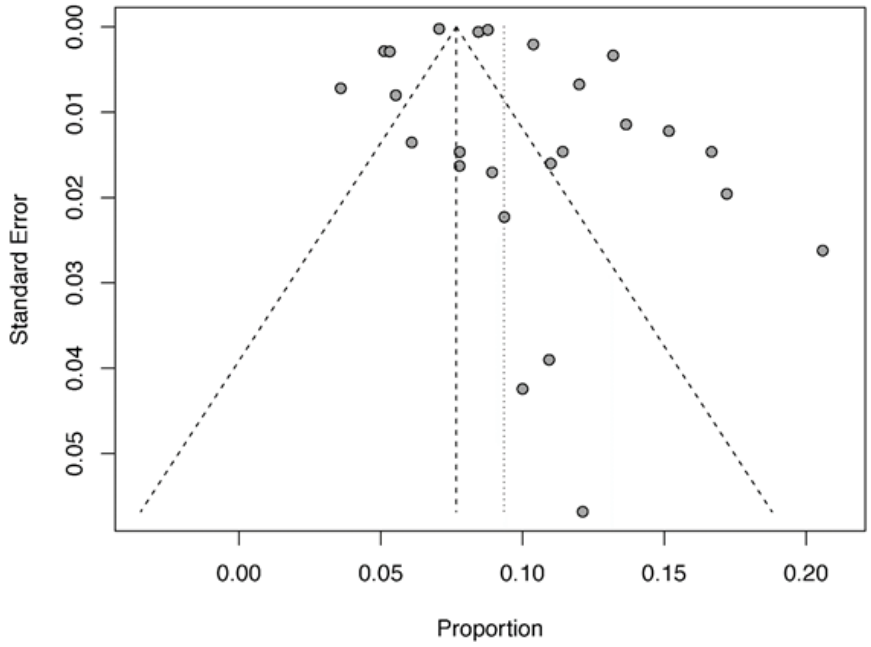
Supplementary Figure 3. The influence of studies on the estimated prevalence rates of carotid stenosis



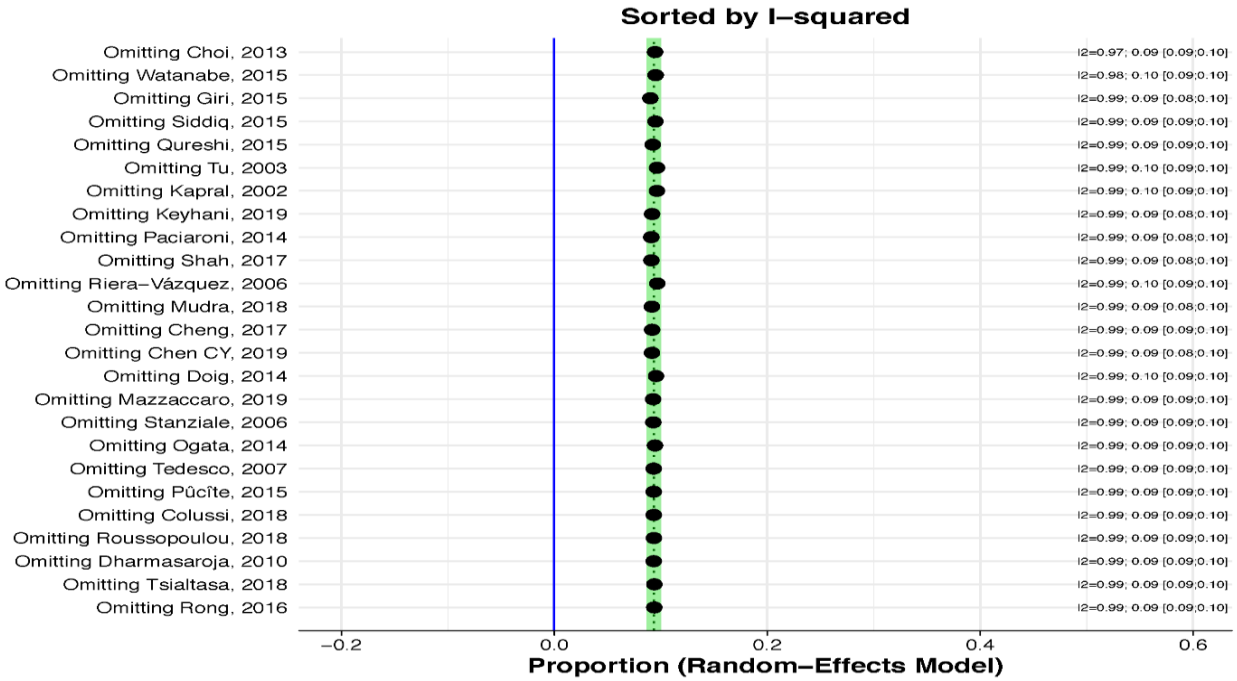
Supplementary Figure 4. The influence of studies on the estimated prevalence rates of carotid plaque



Supplementary Figure 5. Funnel plot of studies reporting on the prevalence of atrial fibrillation in patients with carotid stenosis



Supplementary Figure 6. The influence of studies on the estimated prevalence rates of atrial fibrillation and between study heterogeneity



5.2 Stroke risk associated with carotid and aortic atherosclerosis in patients with atrial fibrillation: A systematic review

5.2.1 Introduction

Stroke prevention is the pillar of atrial fibrillation (AF) management. Currently, this is mainly achieved through oral anticoagulation (OAC) with either vitamin K antagonists, direct oral anticoagulants, or percutaneous left atrial appendage occlusion [261]. The decision to start OAC is guided by an assessment of the risk of stroke and the risk of bleeding. The current stroke risk stratification schemes have limited performance for predicting thromboembolism, especially in AF patients with low-risk [253, 261]. This is partly explained by the fact that these stroke risk prediction tools do not appropriately account for non-cardioembolic causes of stroke such as aortic or carotid atherosclerosis [261]. A recent meta-analysis showed that AF and carotid stenosis frequently coexist, with about one in ten patients with AF having carotid stenosis, and vice versa. Furthermore, about half of patients with AF have non-stenotic carotid disease [542]. Interestingly, severe carotid stenosis accounted for about one fourth of ischemic strokes in a cohort of 103 patients with AF [494]. The CHA_2DS_2-VASc score, which is the most popular stroke risk prediction tool, does not include carotid disease as a risk factor [253]. Although carotid occlusive disease is included in the new GARFIELD-AF risk calculator, its weight in the risk calculation remains unclear [255]. Similar uncertainty remains for aortic atherosclerosis which is included in the CHA_2DS_2-VASc score with peripheral vascular disease and myocardial infarction as a single composite item referred to as vascular disease [253].

This review aimed to summarize the evidence on the risk of thromboembolism associated with carotid and aortic atherosclerosis in patients with AF, and the impact of their inclusion in current stroke risk stratification scores.

5.2.2 Methods

5.2.2.1 Literature search

We searched PubMed/MEDLINE, Excerpta Medica Database (EMBASE) and Web of Science to identify all studies reporting primary data on risk of thromboembolism associated with carotid and aortic atherosclerosis in patients with AF, published until February 28, 2021, without language restriction. The search strategy is available in the appendix (Supplementary Table 1). The reference lists of eligible articles were also scrutinized to identify potential additional data sources.

5.2.2.2 Selection of studies to include in the review

We included cohort studies or randomized controlled trials (RCT) reporting relevant information. We excluded case reports and articles without primary data, such as editorials and reviews. After screening the titles and abstracts of records from bibliographic searches, the full texts of articles deemed potentially eligible were reviewed for final inclusion.

5.2.2.3 Data extraction and charting

We extracted data on first author, year of publication, study design, mean or median duration of follow-up, mean age and proportion of women in the study population, antithrombotic drugs, proportions of patients with various cardiovascular risk factors and co-morbidities and how they were assessed (imaging modality and definition), type and incidence of the

outcomes of interest (stroke or systemic embolism), and risk estimates in the form of hazard ratio (HR) or risk ratio (RR). The risk of bias of included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale [402].

Due to the high heterogeneity across studies, we opted for a narrative summary of our findings.

5.2.3 Results

5.2.3.1 Study selection and characteristics

We identified 3474 records from bibliographic searches, of which 10 are included in this review [471, 535, 538, 543-549] (Figure 1). The characteristics of the included studies are presented in Table 1. There were four retrospective cohorts, three prospective cohorts, and three RCTs. Uptake of different antithrombotic medications and the distribution of risk factors for thromboembolism varied widely across studies. In general, hypertension and heart failure were the most prevalent risk factors in most populations. The risk of bias was low for seven studies and intermediate for three studies. Supplementary Table 2 presents the definitions of carotid and aortic parameters and imaging modalities used in the included studies. In most studies, carotid stenosis was defined as a ≥ 50 % narrowing of the lumen of one segments of the common carotid artery, its bifurcation or the proximal internal carotid artery. Carotid plaque was defined as a protrusion into the vessel lumen with variable cutoffs of carotid intima-media thickness (cIMT) used across studies. Complex aortic plaque defined as ≥ 4-mm-thick, ulcerated or containing mobile thrombi.

5.2.3.2 Carotid stenosis and risk of thromboembolism

Five studies reported on the association of carotid stenosis with stroke, transient ischemic attack (TIA) or systemic embolism [538, 543-546]. In the Stroke Prevention in Atrial Fibrillation (SPAF) II Study, an RCT comparing 508 elderly (age ≥ 70 years) with AF randomly assigned to warfarin or aspirin, carotid stenosis was not associated with incident stroke (adjusted RR 1.3, 95% CI 0.5-3.6) after a mean follow-up of 2.6 years [543]. Data from the ROCKET-AF trial (14263 patients with AF randomly assigned to rivaroxaban or warfarin, $CHADS_2$ score ≥ 2) showed that, after a mean follow-up of 2.5 years, carotid stenosis was not associated with ischemic stroke (adjusted HR 0.93, 95% CI 0.57–1.48) or the composite endpoint of stroke and systemic embolism (adjusted HR 0.99, 95% CI 0.66–1.48) [538]. In patients with AF treated with anticoagulants and followed-up prospectively for a mean of 3.4 years in a hospital in Italy, carotid stenosis was not associated with incident ischemic stroke or TIA (adjusted HR 1.03, 95% CI 0.30-3.45), and not associated with stroke, TIA or systemic embolism (adjusted HR 1.31, 95% CI 0.45-3.81) [544].

In a retrospective cohort of AF patients with and without carotid disease (unspecified) matched for age, sex, hypertension, diabetes, coronary artery disease, and prior stroke, carotid disease was associated with stroke or TIA after a mean follow-up of 5.3 years (adjusted HR 1.49, 95% CI 1.30-1.71) [545]. Another retrospective cohort of patients with AF and a previous stroke or TIA (about half on OAC) showed that carotid stenosis was associated with recurrent stroke (adjusted HR 2.02, 95% CI 1.37–3.01) [546].

5.2.3.3 Carotid plaque and risk of thromboembolism

Four studies reported on the association of carotid plaque with stroke, TIA or systemic embolism [535, 544, 547, 548]. A prospective cohort study of patients with AF on OAC from Italy (mean follow-up of 3.4 years) showed no association between carotid plaque and incident

ischemic stroke or TIA (adjusted HR 1.19, 95% CI 0.52-2.72), and no association with ischemic stroke, TIA or systemic embolism (adjusted HR 1.29, 95% CI 0.53-2.79). In the Atherosclerosis Risk in Communities (ARIC) Study, a population-based prospective cohort of unselected patients with AF (mean follow-up of 8.5 years), carotid plaque was associated with a 56% increase in the risk of incident ischemic stroke (adjusted HR 1.56, 95% CI 1.00-2.54). In the same study, each one standard deviation increase in carotid intima-media thickness (cIMT) was associated with a 23% higher risk of stroke (adjusted HR 1.23, 95% CI 1.04-1.46). The addition of carotid plaque and cIMT to a model including race and CHA_2DS_2-VASc score increased the C-statistic from 0.685 to 0.698, with a significant net reclassification improvement, 0.091 (95% CI 0.012-0.170) [547]. Similarly, in a retrospective analysis of an unselected cohort of patients with AF followed for a mean of 2.6 years, carotid plaque was associated with an increased risk of incident ischemic stroke (adjusted HR 1.1, 95% CI 1.0-1.2). The C-statistic increased from 0.648 (95% CI 0.538-0.757) to 0.716 (95% CI 0.628-0.804) in the CHA_2DS_2-VASc score model after the addition of cIMT and carotid plaque as vascular components ($p = 0.013$) [535]. Another retrospective cohort study (mean follow-up of 3 years) showed that carotid plaque was more frequent in patients in incident stroke or TIA (31.6% vs 16.1%, $p = 0.002$) and discriminated patients who experienced stroke/TIA during the follow-up (Log-Rank: 8.61, $p = 0.003$). The combination of carotid plaque and vascular disease was associated with a 78% higher risk of stroke or TIA (adjusted HR 1.78, 95% CI 1.05-3.01), and had significantly greater C-statistic than conventional vascular disease alone at 24 months (0.609 vs 0.553, $p < 0.001$) and 36 months (0.626 vs 0.591, $p < 0.001$) [548]. [548].

5.2.3.4 Aortic plaque and risk of thromboembolism

Two studies reported on the association of complex aortic plaque with stroke, TIA or systemic embolism [471, 549]. Data from the Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial involving 1251 patients with AF and a $CHADS_2$ score ≥ 1, randomly assigned to apixaban or warfarin [471], showed that after a mean follow-up of 1.8 years, complex aortic plaque did not predict ischemic stroke or systemic embolism (adjusted HR 2.21, 95% CI 0.71–6.85). In a prospective cohort study (mean follow-up of 6.4 years) including patients with AF patients at lower risk ($CHADS_2$ score 0 or 1), a combination of complex aortic plaque with left atrial/left atrial appendage abnormalities (thrombi, spontaneous echo-contrast or reduced flow velocity), referred to as transesophageal echocardiography (TEE) risk, was associated with an increased risk of incident ischemic stroke (adjusted HR 4.0, 95% CI 1.4-11.4) [549].

5.2.4 Discussion

This review shows inconsistent findings across studies reporting on the association of carotid and aortic atherosclerosis with thromboembolism is patients with AF. This might be explained by significant differences in the characteristics of the study populations in terms of risk profiles and use of OAC. On one hand, a comparison of two cohorts of patients with AF with and without carotid stenosis, matched for important stroke predictors and with a relatively low rate of OAC use, showed that carotid stenosis predicts cerebrovascular events [545]. On the other hand, the use of OAC was much higher in the three studies that showed no association between carotid stenosis and incident stroke or TIA [538, 543, 544]. For instance, in the ORBIT trial, all patients received OAC, either warfarin or rivaroxaban [538]. This suggest that OAC might reduce the risk of ischemic stroke associated with carotid stenosis in patients with AF. Findings of the Cardiovascular Outcomes for People Using Anticoagulant Strategies

(COMPASS) trial support this hypothesis and raise the question of whether patients with AF already taking OAC should be switched to a Rivaroxaban-Aspirin combination if they have a carotid atherosclerosis provided that their bleeding risk is low [550]. Further trials would be needed to answer the question and determine how the characteristics of the carotid atherosclerosis (e.g., grade of stenosis, presence of high-risk features) modulate the risk-benefit of the combination therapy [551]. Although aortic atherosclerosis is a recognized independent risk factor for stroke [552, 553], data on the association of aortic plaque with thromboembolism in patients with AF is scarce. This results from the fact that assessment of the aortic arch is limited with transthoracic echocardiography and transesophageal echocardiography is not routinely performed since it is a technically complex and less well-tolerated procedure [261]. Moreover, advanced exploration of alternative embolic sources, including aortic plaques, might often be overlooked in patients for whom AF is perceived by the clinician as the obvious cause of the stroke.

The evidence suggesting that carotid plaque predicts stroke or transient ischemic attack in AF patients are more consistent [535, 547, 548]. The inclusion of carotid plaque and cIMT into stroke risk stratification tools for AF patients could significantly improve their performance. However, it remains unclear whether there are specific features in carotid plaque that are more predictive of cerebrovascular events in AF patients. In fact, carotid plaques with high-risk features such as echolucency, lipid-rich necrotic core, neovascularization, intraplaque hemorrhage or ulcerations, are associated with an increased risk of ipsilateral embolic stroke in non-stenotic carotid atherosclerosis [551]. Data are needed to evaluate whether high-risk carotid plaques could improve stroke risk prediction in AF patients.

From a practical perspective, in patients with AF and peripheral artery diseases including extracranial carotid atherosclerotic disease, current guidelines recommend OAC

when the CHA_2DS_2-VASc is ≥ 2 (Class I, level A), whereas OAC should be considered in all other patients (Class IIa, level B) [554]. However, OAC does not significantly mitigate the risk of ischemic stroke and other adverse cardiovascular events in patients with carotid artery disease [555, 556]. Furthermore, DOAC alone do not reduce the risk of stroke in patients with AF and severe carotid disease [556-558]. Antiplatelet therapy is recommended for all patients with carotid atherosclerotic disease [554]. Therefore, a combination of OAC and single antiplatelet therapy should be considered in patients with AF and carotid atherosclerotic disease to mitigate the risk of stroke attributable to both conditions. However, the concomitant use of OAC and antiplatelet in patients with AF increases the risk of bleeding. There is no practical recommendation on how to approach the combination of OAC and antiplatelet therapy to balance the risk of stroke and the risk of bleeding. Data from both randomized controlled trials and real word settings have shown that the DOAC-antiplatelet use is associated with lower risk of major bleeding, especially intracranial hemorrhage, than vitamin K antagonist (VKA)-antiplatelet combination therapy in patients with AF [559, 560]. Considering that DOAC is either non-inferior or superior to VKA for stroke prevention [343, 559], DOAC should therefore be preferred to VKA when combined with antiplatelet in these patients. Besides OAC, other stroke-reduction strategies should be considered in patients with AF and carotid atherosclerotic disease whenever indicated [554]. Such strategies include carotid revascularization by endarterectomy or carotid stenting for symptomatic carotid stenosis [554]. Rhythm control also has an important role. Indeed, a study showed that AF ablation lowers the risk of stroke or TIA by 64% and the risk of dementia by 49% in patients with AF and carotid stenosis [545].

The main limitations of the evidence presented in this review are the heterogeneity in the composition of study populations and the proportion of OAC users, and the predominance of retrospective and post-hoc analyses with potential reporting bias. This heterogeneity across

studies precluded a meta-analysis. Furthermore, the clinical significance of carotid atherosclerosis and its causal relationship to incident ischemic events remains uncertain in patients with AF treated with anticoagulation. It is also worth mentioning that most of the studies included in this review were conducted in patients on OAC. Because stroke risk stratification is mainly intended to help in the decision to initiate OAC, prediction tools should ideally be derived in patients with AF who are OAC-naïve. However, with the scaling up of the use of OAC in patients with AF, it might be difficult to have unselected cohort of AF patients who remain OAC-naïve for periods long enough to have statistically appropriate rates of incident thromboembolic events.

5.2.5 Conclusion

Available data suggest an association of carotid atherosclerosis with the risk of stroke and transient ischemic attack in patients with AF. Future studies should evaluate whether incorporating cIMT and characteristics of carotid plaques into scoring systems would improve stroke prediction and prevention in patients with AF.

5.2.6 Tables

Table 1. Characteristics of included studies

Table 2. Association between aortic plaque, carotid plaque, carotid stenosis and risk of stroke in patients with atrial fibrillation

Table 1. Characteristics of included studies

Part A

Study	Country	Study design	Study population	Mean or median follow-up (years)	Antithrombotic patterns
Basili, 2017	Italy	Retrospective, hospital-based cohort	Unselected cohort	3.0	None: 15.6%; APT: 19.2%; VKA: 60.7%; APT+VKA: 4.5%
Becattini, 2018	Italy	Prospective, hospital-based cohort study	All patients on OAC	3.4	APT: 7.8% VKA: 100%
Bekwelem, 2016	USA	Prospective, community-based cohort study	Unselected cohort	8.5	VKA: 0%
Bunch, 2020	USA	Retrospective, hospital-based cohort*	Matched for baseline risk factors*	5.3	APT: 48.1% OAC: 36.4%
Cho, 2020	Korea	Retrospective, hospital-based cohort	Unselected cohort	2.6	None: 56.5%; APT: 23.5%; VKA: 13.5%; DOAC: 6.5%
Kanter, 1994	USA	Randomized clinical trial	Age ≥ 70 years	2.6	Randomly assigned to aspirin or warfarin
Kochar, 2018	International	Randomized clinical trial	CHADS2 score ≥ 2	2.5	Randomly assigned to rivaroxaban or warfarin
Lehtola, 2017	Finland	Retrospective, hospital-based cohort	Previous stroke or TIA	2.5	VKA: 46.3%
Sasahara, 2012	Japan	Prospective, hospital-based cohort study	CHADS2 score 0 or 1	6.4	None: 12.1%; APT: 17.9%; VKA: 70.0%;

APT: antiplatelet drug; VKA: vitamin K antagonists; OAC: oral anticoagulant; DOAC: direct oral anticoagulant; NR: not reported;
*Cohort divided in 4 groups matched for cardiovascular risk factors: Atrial fibrillation (AF) and carotid disease (CD), AF and No CD, CD and no AF, no CD and no AF; only the groups AF and CD and AF with no CD were included

Part B

Study	Sample size	Mean age (years)	Male (%)	HPT (%)	DIAB (%)	DYSL (%)	TE (%)	PAD (%)	CAD (%)	HF (%)	Risk of bias
Basili, 2017	2027	73.3	54.7	82.5	27.9	38.5	11.6	NR	NR	20.3	Low
Becattini, 2018	587	74.5	58.6	75.5	17.2	27.6	16.9	NR	14.7	18.5	Low
Bekwelem, 2016	724	63.3	59.9	51.8	23.1	NR	0.0	6.8	4.8	3.2	Low
Bunch, 2020	5786	73	17.8	78.3	28.4	58.5	16.9	26.9	36.7	40.1	Intermediate
Cho, 2020	310	67.8	67.1	67.1	26.5	16.5	15.8	6.8	9.0	31.9	Intermediate
Kanter, 1994	508	77	63	50	15	NR	9	8	21	22	Low
Kochar, 2018	14263	73	60.3	90.5	39.9	NR	54.8	6.0	17.3	62.5	Low
Lehtola, 2017	899	74.3	55.6	64.6	21.0	47.4	20.0	7.9	31.4	15.2	Low
Sasahara, 2012	280	64	71.8	20.4	4.3	NR	NR	NR	NR	12.8	Intermediate
Vinereanu, 2017	1251	NR	NR	NR	NR	NR	NR	NR	NR	NR	Low

HPT: hypertension; DIAB: diabetes mellitus; DYSL: dyslipidemia; TE : previous thromboembolism (stroke or TIA) ; PAD : peripheral artery disease ; CAD : coronary artery disease; HF: heart failure; APT: antiplatelet drug; VKA: vitamin K antagonists; OAC: oral anticoagulant; DOAC: direct oral anticoagulant; NR: not reported;

*Cohort divided in 4 groups matched for cardiovascular risk factors: Atrial fibrillation (AF) and carotid disease (CD), AF and No CD, CD and no AF, no CD and no AF; only the groups AF and CD and AF with no CD were included

Table 2. Association between aortic plaque, carotid plaque, carotid stenosis and risk of stroke in patients with atrial fibrillation

Study	Carotid or aortic parameter	Sample size	Cases of aortic or carotid plaque or stenosis	Mean or median Follow-up (years)	Outcome	Number of events (entire cohort)	Incidence rate (per 100 patient-years)	Adjusted Hazard Ratio (95% CI)*
Basili, 2017	Carotid plaque and vascular disease**	2027	336	3	Stroke and TIA	56	1.17	1.78 (95% CI 1.05-3.01)
Bunch, 2020	Carotid disease	5786	2893	5.3	Stroke or TIA	NR	NR	1.49 (95% CI 1.30-1.71)
Lehtola, 2017	Carotid stenosis ≥ 50 %	899	165	2.5 vs 3.7 (CS vs no CS)	Recurrent stroke	128	8.1 vs 3.6 (CS vs no CS)	2.02 (95% CI 1.37–3.01)
Kanter, 1994	Carotid stenosis ≥ 50 %	508	61	2.6	Stroke	34	NR	1.3 (95% CI 0.5–3.6)
Kochar, 2018	Carotid stenosis ≥ 50 %	14263	493	2.5	Stroke or systemic embolism	575	2.95 vs 2.24 (CS vs no CS)	0.99 (95% CI 0.66–1.48)
					Ischemic stroke	414	2.08 vs 1.61 (CS vs no CS)	0.93 (95% CI 0.57–1.48)
Becattini, 2018	Carotid stenosis ≥ 50 %	587	45	3.4	Ischemic stroke or TIA	30	1.49 (95% CI 0.96- 2.03)	1.03 (95% CI 0.30-3.45)
					Ischemic stroke or TIA or systemic embolism	35	1.59 (95% CI 1.05- 2.14)	1.31 (95% CI 0.45-3.81)
Becattini, 2018	Carotid plaque	587	380	3.4	Ischemic stroke or TIA	30	1.49 (95% CI 0.96- 2.03)	1.19 (95% CI 0.52-2.72)
					Ischemic stroke or TIA or systemic embolism	35	1.59 (95% CI 1.05- 2.14)	1.29 (95% CI 0.54-2.79)
					Ischemic stroke or TIA or death	NR	NR	1.73 (95% CI 1.07-2.79)
					Death	30	1.49 (95% CI	1.99 (95% CI 1.12-3.51)

							0.96- 2.03)	
Bekwelem, 2016	Carotid plaque	724	276	8.5	Ischemic stroke	81	1.09 vs 1.76 (CP vs no CP)	1.56 (95% CI 1.00–2.45)
	Carotid intima-media thickness (cIMT)	724	NA	8.5	Ischemic stroke	81	0.88 vs 2.25 (lowest vs highest cIMT quintiles)	1.23 (95% CI 1.04–1.46) per 1 SD increase
Cho, 2020	Carotid plaque	310	151	2.6	Ischemic stroke	18	NR	3.75 (95% CI 1.11–12.69)
Sasahara, 2012	TEE risk (Left atrial abnormality with/without CAP)	280	143	6.4	Ischemic stroke	20	2.0 vs 0.5 (TEE risk vs no TEE risk)	4.0 (95% CI 1.4-11.4)
Vinereanu, 2017	Complex aortic plaque	1251	241	1.8	Stroke or systemic embolism	21	1.76 vs 0.76 (CAP vs no CAP)	2.21 (95% CI 0.71–6.85)

cIMT: carotid intima-media thickness; TIA: transient ischemic attack; NA: not applicable; TEE: transoesophageal echocardiography; CAP: complex aortic plaque; CS: carotid stenosis

* For the association with the outcome (stroke, TIA, or death). None of the studies included the use of OAC as a covariate in the Cox regression analysis

**Vascular disease: myocardial infarction, aortic plaque or symptomatic peripheral artery disease;

95% CI: 95% confidence interval

Definitions of carotid and aortic parameters are presented in the Supplementary Table 2

5.3 High-risk carotid plaques and stroke risk stratification in patients with atrial fibrillation: the Cardiovascular Health Study

5.3.1 Introduction

Stroke prevention is one of the pillars of atrial fibrillation (AF) management. Currently, this is mainly achieved through oral anticoagulation (OAC) with either vitamin K antagonists, direct oral anticoagulants, or percutaneous left atrial appendage occlusion [261]. The decision to start OAC is guided by an assessment of the risk of stroke and the risk of bleeding. The current stroke risk stratification schemes have limited performance for predicting thromboembolism, especially in patients with AF with low risk [253, 261]. This is partly explained by the fact that these stroke risk prediction tools do not appropriately account for non-cardioembolic causes of stroke such as carotid atherosclerosis [261, 561]. A recent meta-analysis showed that AF and carotid stenosis frequently coexist, with about one in ten patients with AF having carotid stenosis, and vice versa. Furthermore, about half of patients with AF have non-stenotic carotid disease [542]. Interestingly, severe carotid stenosis accounted for about one fourth of ischemic strokes in a cohort of 103 patients with AF [494]. The CHA_2DS_2-VASc score, which is the most popular stroke risk prediction tool, does not include carotid disease as a risk factor [253]. Although carotid occlusive disease is included in the new GARFIELD-AF risk calculator, its weight in the risk calculation remains unclear [255].

There is some evidence suggesting that carotid plaque predicts stroke or transient ischemic attack in patients with AF [535, 547, 548]. The inclusion of carotid plaque and carotid intima-media thickness (cIMT) into stroke risk stratification tools for patients with AF could significantly improve their performance. However, it remains unclear whether there are specific features in carotid plaque that are more predictive of cerebrovascular events in

patients with AF. In fact, carotid plaques with high-risk features such as echolucency, lipid-rich necrotic core, neovascularization, intraplaque hemorrhage or ulcerations, are associated with an increased risk of ipsilateral embolic stroke in non-stenotic carotid atherosclerosis [551].

To the best of our knowledge, no previous study has evaluated whether high-risk carotid plaques could improve stroke risk prediction in patients with AF. This study aimed to determine 1) the prevalence of occlusive and non-occlusive carotid disease in patients with and without AF; 2) the distribution of non-occlusive carotid disease and high-risk features (plaque irregularity, ulceration, and echolucency) in patients with and without AF; 3) the risk of stroke associated with occlusive and non-occlusive carotid disease in patients with and without AF; 4) the added value of high-risk carotid plaques on stroke risk stratification compared to the classical CHA_2DS_2-VASc score. We hypothesized that carotid plaques with high-risk features such as plaque irregularity, ulceration, and echolucency, are associated with an increased risk of stroke in patients with AF, and that high-risk carotid plaques could improve stroke risk prediction in patients with AF.

5.3.2 Methods

5.3.2.1 Study design

This study was performed using data from the Cardiovascular Health Study (CHS). The CHS prospectively enrolled and continues to follow a community-dwelling cohort of men and women aged ≥65 years randomly selected from Medicare eligibility lists in four counties in the USA, California, Maryland, North Carolina, and Pennsylvania. An initial cohort of 5,201 participants was recruited in 1989-1990 and a supplemental cohort of 687 predominantly African American participants was recruited in 1992-1993. Participants returned for annual in-person study visits until 1998-1999 and again in 2005-2006. Throughout follow-up,

participants were contacted via semi-annual telephone calls, and data were linked with Medicare claims. Carotid ultrasound scans were performed at baseline, year 5, and year 11.

5.3.2.2 Participants

For this study, we included all participants with AF and available carotid ultrasound data. Atrial fibrillation was identified from 3 sources: i) participant's self-report; ii) outpatient ECGs obtained yearly at study examinations; iii) hospital discharge primary diagnoses with ICD-9 codes for AF (427.31), excluding diagnosis assigned during the same hospitalization for a cardiac surgery (ICD-9 codes of 35.x, 36.x, or 37.x). Eligible participants were divided in 2 groups depending on when they had AF: Group 1 included participants with AF at baseline; Group 2 included participants without AF at baseline but who developed AF by year 5 (**Figure 1. Panels A and B**). Year 5 was selected because participants had follow-up carotid ultrasound at this time, allowing us to have baseline ultrasound data for participants who developed AF by year 5. The follow-up started at baseline for Group 1 and at year 5 for Group 2 (**Figure 1. Panel B**). Baseline characteristics of each group correspond to their characteristics at the beginning of their specific follow-up period.

5.3.2.3 Exposure variables

The main exposure variables were carotid ultrasound features including the percentage of stenosis, plaque irregularity, and plaque echogenicity. Duplex ultrasonography of both carotid arteries was performed at baseline and at Year 5 with a Toshiba SSA-270A ultrasound device (Toshiba American Medical Systems, Tustin, CA) equipped with 5.0 MHz transducer. We considered carotid ultrasound measurements done at baseline for Group 1 and at Year 5 for Group 2.

- Percentage stenosis was classified as: 0% or Normal, 1-24%, 25-49%, 50-74%, 75-99%, and 100% [562].
- Plaque irregularity was classified as: smooth, mildly irregular, markedly irregular, and ulcerated [562].
- Plaque irregularly was further dichotomized as low-risk (smooth and mildly irregular) and high-risk (markedly irregular and ulcerated).
- Plaque echogenicity was classified as: no lesion, hypoechoic, isoechoic, hyperechoic, and calcified [562].
- Plaque echogenicity was further dichotomized as low-risk (no lesion, isoechoic, hyperechoic, and calcified) and high-risk (hypoechoic).
- Vulnerable plaque was defined as the presence of plaques in either of the carotid arteries with the following high-risk features: hypoechoic, markedly irregular, or ulcerated.

Plaques that were hypoechoic, markedly irregular, or ulcerated are considered of high-risk based on previous studies which showed that these ultrasound features were associated with an increased risk of stroke [551, 563].

Other variables of interest included sociodemographic characteristics; cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, dyslipidemia (**Supplementary Table 1**), heart failure, coronary artery disease, peripheral artery disease, prior stroke or transient ischemic attack (TIA), chronic kidney disease, smoking, alcohol consumption, and use of antithrombotic medication. The CHA_2DS_2-VASc score was calculated for each participant (**Supplementary Table 2**).

5.3.2.4 Outcome variable

The outcome was incident ischemic stroke. Stroke was defined as the rapid onset of focal neurological deficit lasting more than 24 hours or until death, a lesion on computed tomography or magnetic resonance imaging, with the exclusion of brain concussion, tumor, or infection as the cause of the deficit. Ischemic stroke was further defined as: i) a focal neurological deficit without evidence of intracranial hemorrhage on computed tomography, magnetic resonance imaging, or cerebrospinal fluid analysis or ii) imaging evidence of brain ischemia in a location compatible with the presenting symptoms [564]. We consider the start of follow-up as baseline for Group 1, and Year 5 for Group 2.

5.3.2.5 Statistical analysis

Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. We assessed differences between groups using the Student's t-test for continuous variables and the Pearson Chi square test for categorical variables. Time to incident ischemic stroke was assessed using survival analysis. Participants were censored at the time of ischemic stroke, last follow-up, or death. Factors associated with incident ischemic stroke were assessed using univariable and multivariable cox regression analysis, with risk estimates reported as hazard ratio (HR) along with 95% confidence interval (CI). A two-tailed p-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using Stata 16.1 statistical package (Stata Corp, College Station, TX).

5.3.2.6 Ethical considerations

The CHS received approval from institutional review boards of all participating centers and all participants provided written informed consent. In addition, prior to receiving the CHS data, the current study was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network, Adelaide, Australia (CALHN Reference Number: 15839).

5.3.3 Results

5.3.3.1 General characteristics of the study population

Out of 5888 participants in CHS, 1398 with AF were included in the analysis. There were 266 (19.0%) participants with AF at baseline (Group 1) and 1132 (81.0%) without AF at baseline but who developed AF by Year 5 (Group 2) (**Figure 1. Panels A and B**). The general characteristics of the study population are presented in **Table 1**. There were more females (55.2%) than males, and participants aged 65-74 years (61.7%) than those aged ≥75 years. The prevalence of cardiovascular risk factors was 81.4% for dyslipidemia, 62.3% for hypertension, 31.8% for vascular disease, 21.9% for chronic kidney disease, 16.4% for diabetes mellitus, 6.4% for heart failure and, 6.1% for previous stroke or TIA. The median CHA_2DS_2-VASc score was 3 (IQR 2-4).

5.3.3.2 Carotid ultrasound features

5.3.3.2.1 Carotid artery stenosis

Most participants had a normal ultrasound examination or carotid artery stenosis <50% (96.6% on the right and 96.5% on the left). On either the left or the right carotid arteries, the maximum stenosis was <50% in 94.5% of participants, 50-99% in 5% of participants, and 0.5% had carotid occlusion (**Table 2**).

5.3.3.2.2 Carotid plaques

Regarding plaque irregularity, most participants had either smooth carotid arteries (69.3% on the right and 69.6% on the left) or mildly irregular plaques (25.8% and 25.2% on the right side and left side, respectively). Markedly irregular (4.4% and 4.9% on the right side and left side, respectively) and ulcerated plaques (0.4% and 0.3% on the right and left sides, respectively) were much less frequent (**Table 2**). Regarding echogenicity, most participants had either no lesion (32.0% and 33.3% on the right side and left side, respectively) or isoechoic lesion (35.0% and 30.9% on the right side and left side, respectively) (**Table 2**).

The proportion of participants with high-risk plaques was 25.6% based on echogenicity and 8.9% based on plaque irregularity. When considering both irregularity and echogenicity, 33.6% of participants had vulnerable plaques (**Table 2**).

5.3.3.3 Incidence of ischemic stroke according to carotid plaque characteristics

After a median follow-up of 10.9 years (IQR 7.5-15.6), 298 ischemic strokes occurred. There was no difference in the incidence of ischemic stroke according to the degree of carotid artery stenosis (p=0.44, **Figure 2. Panel A**), the echogenicity of plaque (low risk versus high risk, p=0.68, **Figure 2. Panel B**), the irregularity of plaque (low risk versus high risk, p=0.55, **Figure 2. Panel C**), and the vulnerability of the plaque (p=0.86, **Figure 2. Panel D**).

5.3.3.4 Predictors of ischemic stroke

Factors associated with incident ischemic stroke in univariable cox regression analysis included aged ≥75 years, hypertension, diabetes mellitus, vascular disease, previous stroke or TIA, and chronic kidney disease. In multivariable analysis, predictors of ischemic stroke included aged ≥75 years (adjusted hazard ratio [aHR] 1.35, 95% CI: 1.05-1.71, p=0.015),

hypertension (aHR 1.37, 95% CI: 1.06-1.76, p=0.016), diabetes mellitus (aHR 1.95, 95% CI: 1.46-2.62, p<0.001), previous stroke or TIA (aHR 1.59, 95% CI: 1.01-2.51, p=0.045), and chronic kidney disease (aHR 1.33, 95% CI: 1.01-1.76, p=0.043) (**Table 3**). The CHA_2DS_2-VASc score was associated with an increased risk of ischemic stroke (aHR 1.28, 95% CI: 1.18-1.40, p<0.001) (**Table 4**). Both maximum grade of stenosis and plaque vulnerability were not associated with incident ischemic stroke (all p>0.05) (**Tables 3 and 4**).

5.3.3.6 Added value of high-risk carotid plaques to stroke risk stratification

In the absence of an association between all carotid artery ultrasound parameters with incident ischemic stroke, logically these parameters could not improve stroke risk stratification in our cohort. Therefore, the planned receiver operating characteristic (ROC) analysis to compare the performance in predicting incident ischemic stroke of the CHA_2DS_2-VASc score and of a combination of high-risk carotid plaques with the CHA_2DS_2-VASc score was futile.

5.3.4 Discussion

This study aimed to determine the pattern of occlusive and non-occlusive carotid artery disease in patients with AF and assess whether prediction of their stroke risk could be improved by considering the presence of carotid stenosis or vulnerable carotid plaque. We observed that 1) moderate to severe carotid stenosis (≥ 50%) was uncommon, affecting only 5.5% of participants; 2) a third of patients had carotid plaques considered vulnerable or high-risk; 3) the degree of carotid stenosis and the presence of vulnerable plaques were not associated with incident ischemic stroke and therefore, could not have any added value in stroke risk stratification in this cohort of patients.

The prevalence of carotid stenosis in this cohort of patients with AF is much lower than was reported in several previous study. In fact, a meta-analysis of prevalence rates of carotid stenosis in patients with AF showed a pooled prevalence of 13.9% [542], much higher than the 5.5% prevalence in our study. There are few potential explanations for this difference. There was a wide variation in the prevalence of carotid stenosis across the studies included in the meta-analysis, ranging from 4.4% to 24.3% [542]. Subgroup analysis by geographic region showed that the pooled prevalence was 8.2% in studies done in Northern America, an estimate closer to our observation in this cohort from the US, compared with 14.2% and 12.9% in studies done in Asia and Europe, respectively. Hence, variations in the prevalence of carotid stenosis in patients with AF might be partly related to geographic regions. These geographic differences in prevalence rates might be due to variations in the genetic predisposition to risk factors of atherosclerosis, to differences in primary prevention or disease detection. Furthermore, our cohort is quite old, with the first participants enrolled in 1989-1990 (three decades ago). It is possible that the burden of carotid artery disease has increased over time, with recent studies reporting higher prevalence rates. Finally, our cohort consists of people recruited from the general population who likely had a better cardiovascular risk profile than that of patients with AF recruited in hospital settings, hence a lower burden of atherosclerosis including in the carotid arteries. Indeed, the proportions of people with cardiovascular risk factors such as hypertension, diabetes mellitus, previous stroke, or smoking were lower in our cohort compared to other studies on carotid artery disease in patients with AF [542].

Contrary to our hypothesis, the degree of carotid stenosis was not associated with incident ischemic stroke. Studies on the association of carotid stenosis with thromboembolism in patients with AF have shown inconsistent results [561]. Carotid stenosis was found to be associated with stroke or TIA in one retrospective study (aHR 1.49, 95% CI 1.30-1.71, mean

follow-up 5.3 years) [545], and with recurrent stroke in another retrospective cohort of patients with AF and a previous stroke or TIA (aHR 2.02, 95% CI 1.37–3.01) [546]. Dissimilarly, a prospective cohort study in Italy showed no association between carotid stenosis and ischemic stroke or TIA (adjusted HR 1.03, 95% CI 0.30-3.45), and a composite of stroke, TIA, or systemic embolism (adjusted HR 1.31, 95% CI 0.45-3.81, mean follow-up of 3.4 years) [544]. Some inconsistencies have also been reported in studies on the association of carotid plaque with thromboembolism in patients with AF, although most studies suggested an association [561].

In a meta-analysis of 64 studies that enrolled 20751 participants, high-risk plaques were common in patients with asymptomatic carotid stenosis, and the associated annual incidence of ipsilateral ischemic events was higher than the currently accepted estimates [551]. These findings suggested that extending the assessment of asymptomatic carotid stenosis beyond the grade of stenosis is needed in routine practice to improve risk stratification [551]. In the current study, we hypothesized that carotid plaques with high-risk features such as plaque irregularity, ulceration, and echolucency, are associated with an increased risk of stroke in patients with AF, and that high-risk carotid plaques could improve stroke risk prediction in patients with AF. Contrary to our hypothesis, vulnerable plaques defined as the presence of hypoechoic, markedly irregular, or ulcerated plaques were not associated with incident ischemic stroke. Yet, a previous analysis of the CHS showed that risk of incident stroke was associated with two ultrasound features: presence of a hypoechoic plaque in the internal carotid artery and an estimated grade of stenosis ≥50% [563]. Importantly, this previous analysis of the CHS was not restricted to patients with AF, and it excluded all strokes of cardiac origin [563]. Therefore, the absence of association between grade of carotid stenosis or presence of high-risk carotid plaques and incident stroke suggests that carotid disease was probably not an important cause of the stroke events in our cohort of patients with AF. These findings indicate

that vulnerable carotid plaques might not improve stroke risk stratification in patients with AF.

This study has some limitations. First, our study population included only patients aged ≥65 years and mostly whites, hence limiting its generalizability. Second, data was not available for systemic embolism which is a relevant endpoint for our study hypothesis. Third, several parameters could not be considered in our analysis, notably changes in medical therapy over time (antiplatelet, antihypertensive, and lipid-lowering drugs), vascular interventions (endarterectomy because of TIA or amaurosis fugax), and localization of the ischemic stroke that might not be in the relevant territory. Fourth, there was a small proportion of participants with AF affected by moderate to severe carotid stenosis. Hence, the study might have limited power to detect an association between moderate to severe carotid stenosis and incident stroke in this population. Strengths of our study include a well-characterized population and larger than those from previous studies on the association of carotid disease with thromboembolism in patients with AF [561], as well as a meticulous adjudication of the outcome of stroke [564].

5.3.5 Conclusion

Moderate to severe carotid stenosis (≥50%) was uncommon, affecting only 5.5% of participants with AF, whereas a third of patients with carotid atherosclerosis had plaques considered vulnerable or high-risk. Neither the degree of carotid stenosis nor the presence of vulnerable plaques was associated with incident ischemic stroke. This suggests that carotid disease was probably not a significant contributor to ischemic stroke in this population of patients with AF and, therefore, vulnerable carotid plaques might not improve stroke risk stratification in patients with AF.

5.3.6 Tables and figures

Table 1. General characteristics of the study population

Table 2. Carotid artery ultrasound features

Table 3. Association between clinical and carotid ultrasound features and incident ischemic stroke

Table 4. Association between CHA_2DS_2-VASc score and carotid ultrasound features and incident ischemic stroke

Figure 1. Participant selection and follow-up

Figure 2. Incidence of ischemic stroke according to carotid ultrasound features

Table 1. General characteristics of the study population

Variables	**Group 1** (n = 266)	**Group 2** (n =1132)	**Total** (n = 1398)
Age			
65-74 years	145 (54.5%)	718 (63.4%)	863 (61.7%)
≥75 years	121 (45.5%)	414 (36.6%)	535 (38.3%)
Sex			
Male	135 (50.8%)	492 (43.5%)	627 (44.8%)
Female	131 (49.2%)	640 (56.5%)	771 (55.2%)
Body mass index			
<25	120 (45.1%)	405 (35.8%)	525 (37.6%)
25-29.9	101 (38.0%)	464 (41.0%)	565 (40.4%)
≥30	45 (16.9%)	263 (23.2%)	308 (22.0%)
Cardiovascular risk factors			
Hypertension	182 (68.4%)	689 (60.9%)	871 (62.3%)
Diabetes mellitus	59 (22.2%)	170 (15.0%)	229 (16.4%)
Dyslipidemia	221 (83.1%)	917 (81.0%)	1138 (81.4%)
Heart failure	44 (16.5%)	46 (4.1%)	90 (6.4%)
Previous stroke or TIA	28 (10.5%)	57 (5.0%)	85 (6.1%)
Current smoking	20 (7.5%)	14 (1.2%)	34 (2.4%)
CAD	114 (42.9%)	307 (21.7%)	421 (30.1%)
PAD	15 (5.6%)	29 (2.6%)	44 (3.1%)
Vascular disease	121 (45.5%)	323 (28.5%)	444 (31.8%)
Chronic kidney disease	88 (33.1%)	218 (19.3%)	306 (21.9%)
CHA_2DS_2-VASc score			
Median (IQR)	4 (3-5)	3 (2-4)	3 (2-4)
Antithrombotic medication			
Antiplatelet	15 (5.6)	30 (2.7)	45 (3.2)
Oral anticoagulant	30 (11.3)	34 (3.0)	64 (4.6)

CAD: coronary artery disease; IQR: interquartile range; PAD: peripheral artery disease; TIA: transient ischemic attack

Table 2. Carotid artery ultrasound features

Variables	Group 1 (n = 266)	Group 2 (n =1132)	Total (n = 1398)
Percentage stenosis, RIGHT			
Normal	79 (29.7%)	366 (32.3%)	445 (31.8%)
1-24%	73 (27.4%)	360 (31.8%)	433 (31.0%)
25-49%	107 (40.2%)	366 (32.3%)	473 (33.8%)
50-74%	5 (1.9%)	30 (2.7%)	35 (2.5%)
75-99%	1 (0.4%)	8 (0.7%)	9 (0.6%)
100%	1 (0.4%)	2 (0.2%)	3 (0.2%)
Percentage stenosis, LEFT			
Normal	68 (25.6%)	398 (35.2%)	466 (33.3%)
1-24%	81 (30.5%)	334 (29.5%)	415 (29.7%)
25-49%	111 (41.7%)	358 (31.6%)	469 (33.5%)
50-74%	5 (1.9%)	30 (2.7%)	35 (2.5%)
75-99%	0 (0.0%)	8 (0.7%)	8 (0.6%)
100%	1 (0.4%)	4 (0.4%)	5 (0.4%)
Percentage stenosis, MAX			
Normal	37 (13.9%)	220 (19.4%)	257 (18.4%)
1-24%	81 (30.5%)	357 (31.5%)	438 (31.3%)
25-49%	137 (51.5%)	489 (43.2%)	626 (44.8%)
50-74%	9 (3.4%)	44 (3.9%)	53 (3.8%)
75-99%	1 (0.4%)	16 (1.4%)	17 (1.2%)
100%	1 (0.4%)	6 (0.5%)	7 (0.5%)
Plaque irregularity, RIGHT			
No lesion	79 (29.7%)	366 (32.3%)	445 (31.8%)
Smooth	127 (47.7%)	397 (35.1%)	524 (37.5%)
Mildly irregular	55 (20.7%)	306 (27.0%)	361 (25.8%)
Markedly irregular	5 (1.9%)	57 (5.0%)	62 (4.4%)
Ulcerated	0 (0.0%)	6 (0.5%)	6 (0.4%)
Plaque irregularity, LEFT			
No lesion	68 (25.6%)	398 (35.2%)	466 (33.3%)
Smooth	143 (53.8%)	365 (32.2%)	508 (36.4%)
Mildly irregular	54 (20.3%)	297 (26.2%)	351 (25.1%)
Markedly irregular	1 (0.4%)	68 (6.0%)	69 (4.9%)
Ulcerated	0 (0.0%)	4 (0.4%)	4 (0.3%)
Plaque echogenicity, RIGHT			
No lesion	80 (30.1%)	369 (32.6%)	449 (32.1%)
Hypoechoic	44 (16.5%)	167 (14.8%)	211 (15.1%)
Isoechoic	94 (35.3%)	394 (34.8%)	488 (34.9%)
Hyperechoic	42 (15.8%)	161 (14.2%)	203 (14.5%)

Calcified	6 (2.3%)	41 (3.6%)	47 (3.4%)
Plaque echogenicity, LEFT			
No lesion	68 (25.6%)	398 (35.2%)	466 (33.3%)
Hypoechoic	52 (19.5%)	152 (13.4%)	204 (14.6%)
Isoechoic	99 (37.2%)	333 (29.4%)	432 (30.9%)
Hyperechoic	45 (16.9%)	195 (17.2%)	240 (17.2%)
Calcified	2 (0.8%)	54 (4.8%)	56 (4.0%)
Plaque irregularity			
Low risk	260 (97.7%)	1013 (89.5%)	1273 (91.1%)
High risk	6 (2.3%)	119 (10.5%)	125 (8.9%)
Plaque echogenicity			
Low risk	185 (69.5%)	855 (75.5%)	1040 (74.4%)
High risk	81 (30.5%)	277 (24.5%)	358 (25.6%)
Vulnerable plaque			
No	180 (67.7%)	748 (66.1%)	928 (66.4%)
Yes	86 (32.3%)	384 (33.9%)	470 (33.6%)

Table 3. Association between clinical and carotid ultrasound features and incident ischemic stroke

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age						
65-74 years	Ref	-	-	Ref	-	-
≥75 years	1.40	1.11-1.78	0.005	1.35	1.05-1.71	0.015
Sex						
Female	Ref	-	-	Ref	-	-
Male	0.92	0.72-1.16	0.457	0.91	0.71-1.16	0.430
Current smoker						
No	Ref	-	-	Ref	-	-
Yes	1.05	0.39-2.83	0.922	1.22	0.45-3.32	0.697
Body mass index						
<25	Ref	-	-	Ref	-	-
25-29.9	0.92	0.71-1.19	0.503	0.89	0.68-1.17	0.414
≥30	0.96	0.71-130	0.791	0.79	0.58-1.09	0.154
Hypertension						
No	Ref	-	-	Ref	-	-
Yes	1.55	1.22-198	<0.001	1.37	1.06-1.76	0.016
Diabetes mellitus						
No	Ref	-	-	Ref	-	-
Yes	1.96	1.48-2.58	<0.001	1.95	1.46-2.62	<0.001
Dyslipidemia						
No	Ref	-	-	Ref	-	-
Yes	1.20	0.87-1.65	0.261	1.18	0.86-1.63	0.301
Heart failure						
No	Ref	-	-	Ref	-	-
Yes	1.58	0.94-2.67	0.085	1.27	0.74-2.17	0.390
Vascular disease						
No	Ref	-	-	Ref	-	-
Yes	1.30	1.01-1.67	0.044	1.07	0.82-1.40	0.616
Previous stroke or TIA						
No	Ref	-	-	Ref	-	-
Yes	1.81	1.16-2.82	0.009	1.59	1.01-2.51	0.045
Chronic kidney disease						
No	Ref	-	-	Ref	-	-
Yes	1.42	1.09-1.86	0.011	1.33	1.01-1.76	0.043
Percentage stenosis						
Normal	Ref	-	-	Ref	-	-
1-49%	1.21	0.90-1.61	0.202	1.22	0.89-1.67	0.210
50-100%	1.14	0.61-2.13	0.685	1.02	0.53-1.96	0.956
Vulnerable plaque						
No	Ref	-	-	Ref	-	-
Yes	1.02	0.80-1.30	0.867	0.94	0.72-1.22	0.619

95% CI: 95% confidence interval; HR: hazard ratio; Ref: reference category; TIA: transient ischemic attack

Table 4. Association between CHA_2DS_2-VASc score and carotid ultrasound features and incident ischemic stroke

Variables	HR	95% CI	P value
Model 1			
CHA_2DS_2-VASc score (per 1 unit)	1.29	1.18-141	<0.001
Maximum percentage stenosis			
• Normal	Ref	-	-
• 1-49%	1.24	0.93-1.66	0.151
• 50-100%	1.04	0.56-1.95	0.898
Model 2			
CHA_2DS_2-VASc score (per 1 unit)	1.28	1.18-1.40	<0.001
Vulnerable plaque			
• No	Ref	-	-
• Yes	1.00	0.79-1.28	0.972

LCL: 95% lower confidence limit; HR: hazard ratio; TIA: transient ischemic attack; UCL: 95% upper confidence limit

Figure 1. Participant selection and follow-up

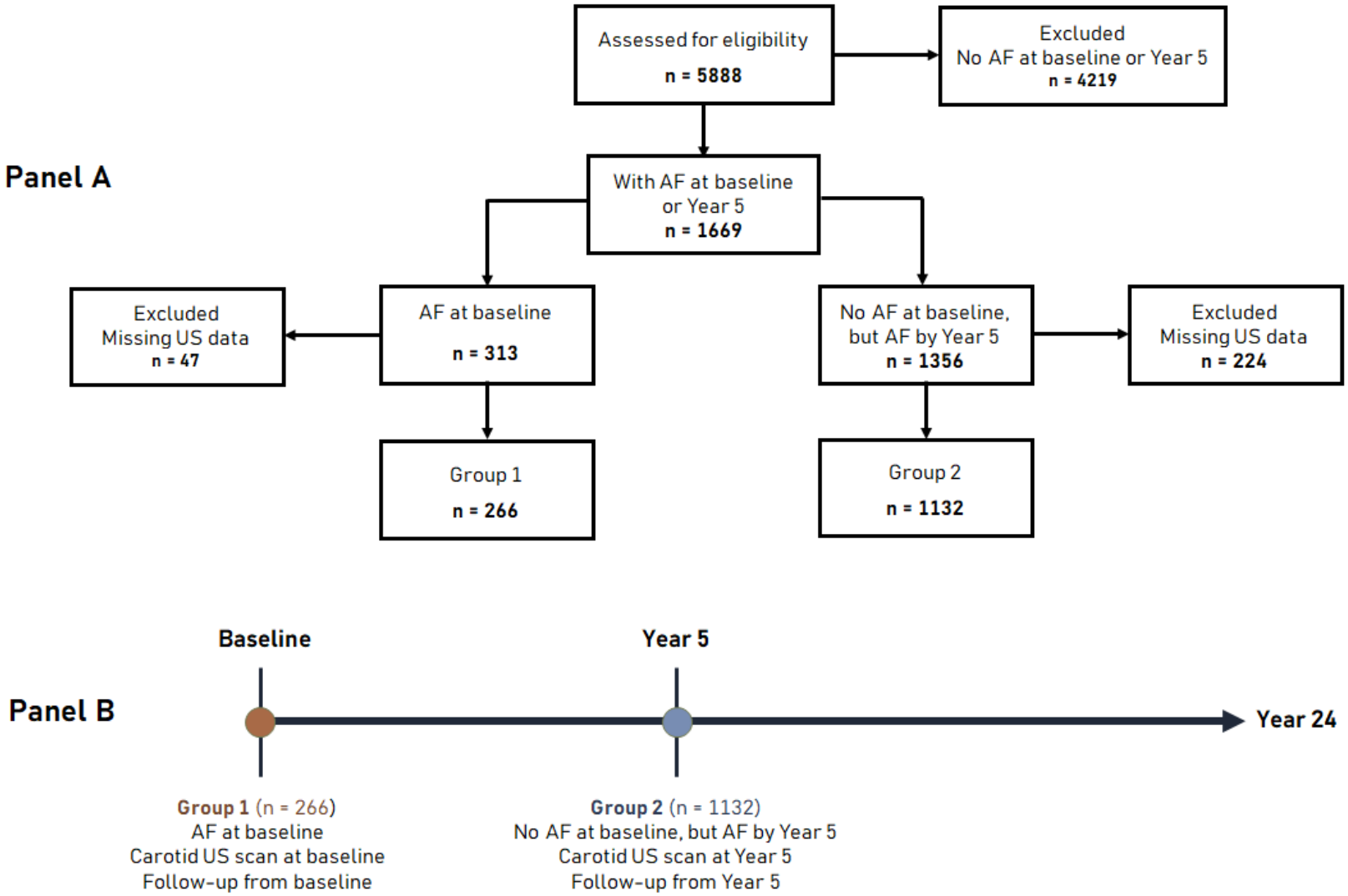


Figure 2. Incidence of ischemic stroke according to carotid ultrasound features

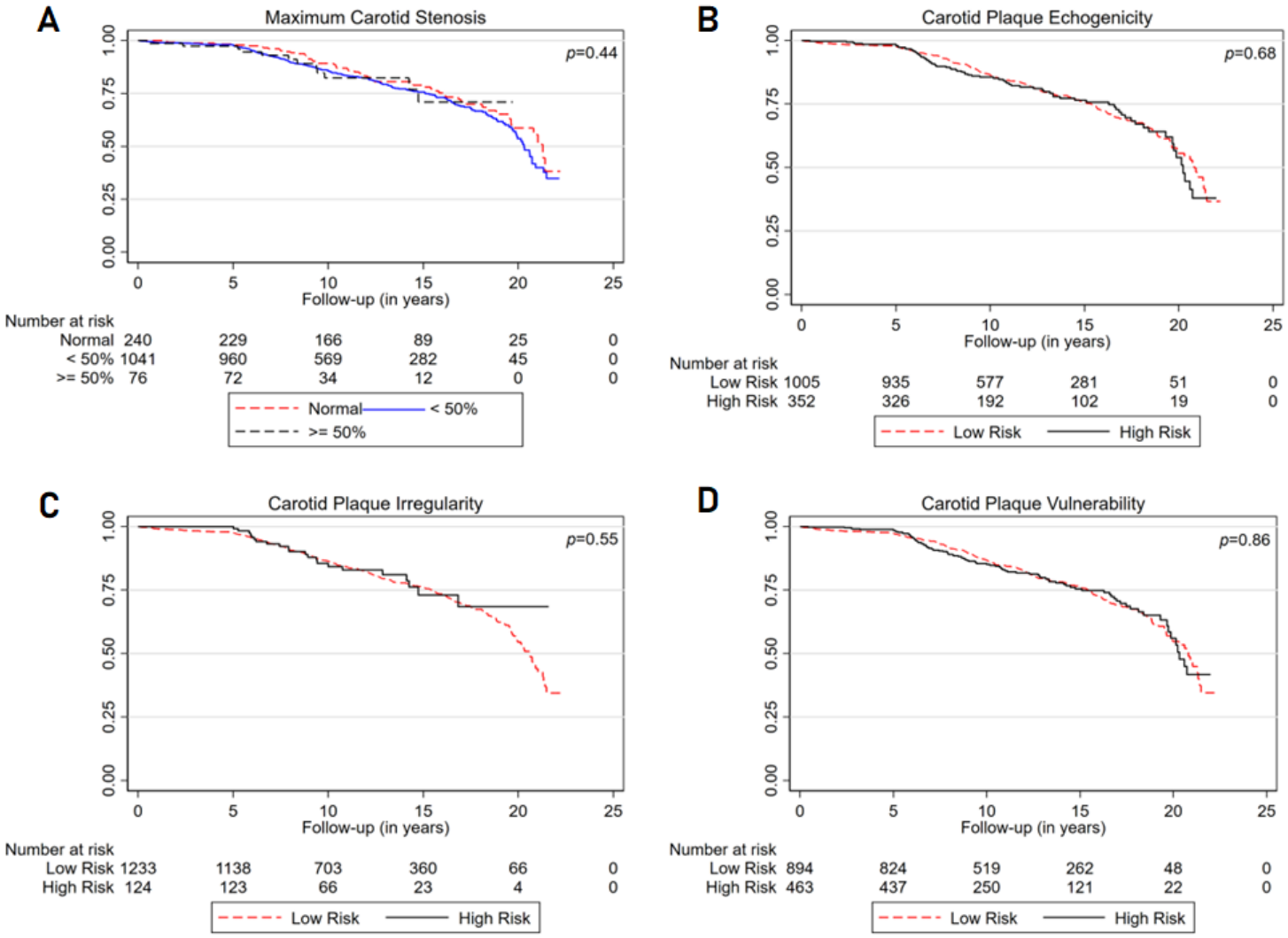
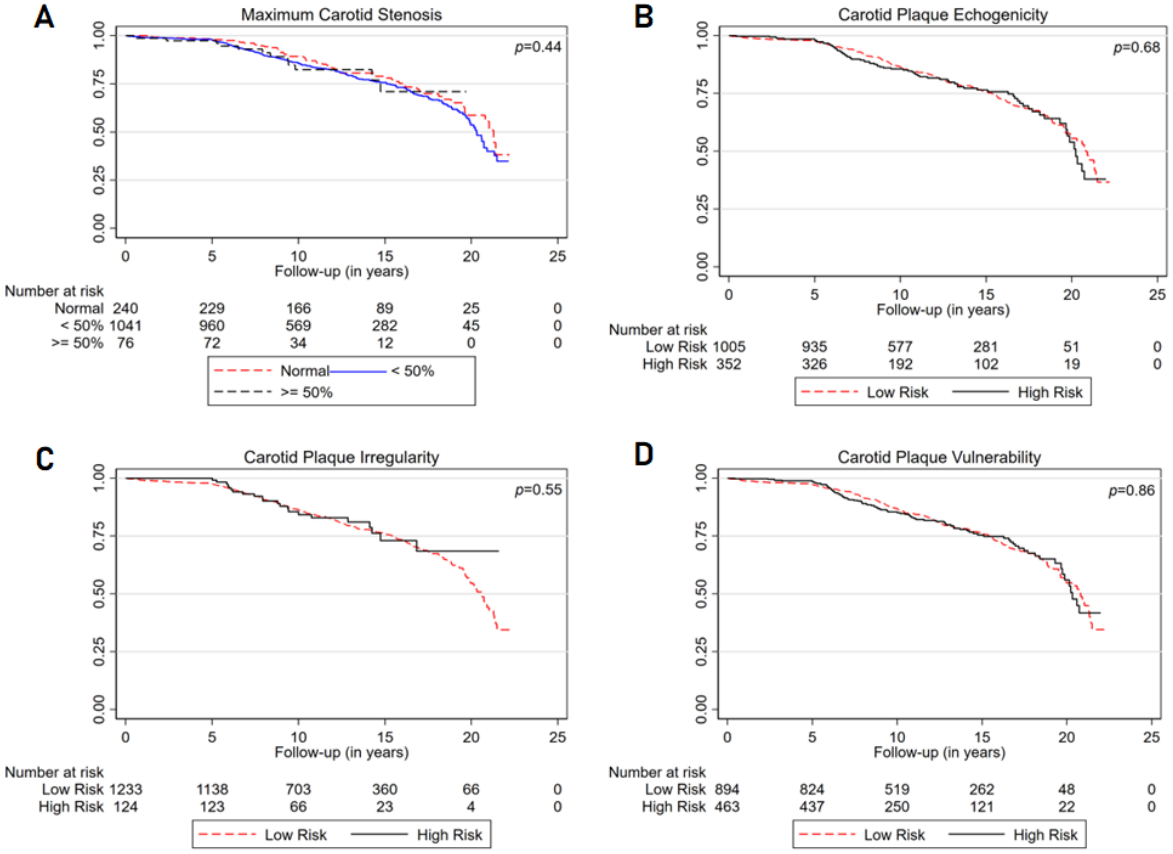


Figure 3. Association of the degree of maximum carotid stenosis with incident ischemic stroke



5.3.7 Appendix

Supplementary Table 1. Definition of variables

Condition	Score
Hypertension	Blood pressure > 140/90 mmHg or medical history of hypertension or ongoing antihypertensive treatment
Diabetes	Fasting blood glucose > 7 mmol/L or history of diabetes mellitus or ongoing treatment with insulin or oral antidiabetic drugs
Dyslipidemia	at least one of the followings: LDL-C > 100 mg/dL (2.6 mmol/L), HDL-C < 50 mg/dL (1.26 mmol/L), triglycerides > 150 mg/dL (1.7 mmol/L), total cholesterol > 200 mg/dL (5.2 mmol/L), treatment with lipid-lowering drugs.
Obesity	Body mass index ≥ 30 kg/m^2

Supplementary Table 2. CHA_2DS_2VASc Comorbidity Point Values

Condition	Score
Sex Category (female)	1
Age 65-74 years	1
Age ≥75 years	2
Stroke, transient ischemic attack, or systemic thromboembolism	2
Vascular disease	1
Congestive Heart Failure	1
Hypertension	1
Diabetes mellitus	1
Maximum Score	9

CHAPTER 6:

Prognostic impact of atrial fibrillation on acute cardiovascular events

Publication 1

Statement of Authorship

Title of Paper	Atrial fibrillation incidence, prevalence, predictors, and adverse outcomes in acute coronary syndromes: A pooled analysis of data from 8 million patients
Publication Status	☒ Published ☐ Accepted for publication ☐ Submitted for publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Noubiap JJ**, Agbaedeng TA, Nyaga UF, Lau DH, Worthley MI, Nicholls SJ, Sanders P. Atrial fibrillation incidence, prevalence, predictors, and adverse outcomes in acute coronary syndromes: A pooled analysis of data from 8 million patients. *J Cardiovasc Electrophysiol*. 2022 Mar;33(3):414-422.

Principal Author

Name of Principal Author (Candidate)	Jean Jacques Noubiap Nzeale		
Contribution to the Paper	Conception and design, literature search, data collection, manuscript drafting, manuscript revision		
Overall percentage (%)	50%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Knowledge, manuscript revision (10%)		
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Publication 2

Statement of Authorship

Title of Paper	Frequency and prognostic significance of atrial fibrillation in acute pulmonary embolism: a pooled analysis
Publication Status	☒ Published ☐ Accepted for publication ☐ Submitted for publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	**Noubiap JJ**, Nyaga UF, Middeldorp ME, Fitzgerald JL, Ariyaratnam JP, Thomas G, Sanders P. Frequency and prognostic significance of atrial fibrillation in acute pulmonary embolism: A pooled analysis. Respir Med. 2022 Aug;199:106862. doi: 10.1016/j.rmed.2022.106862.

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Overall percentage (%)	60%		
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Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Overview

This chapter explores the prognostic impact of AF in patients with two major acute cardiovascular events: acute coronary syndromes and acute pulmonary embolism. It is divided into two sections. The first section is a systematic review and meta-analysis that summarizes data on the overall prevalence of AF in patients with acute coronary syndromes (ACS) in general, and specifically the prevalence of pre-existing AF, and the incidence proportion of newly diagnosed AF; 2) determine the predictors of newly diagnosed AF and; 3) assess the risk of various short-term and long-term adverse outcomes (e.g. death, stroke, re-infarction, heart failure, major bleeding) attributable to AF, according to its temporal patterns in patients with ACS in general. The second section is on acute pulmonary embolism (aPE). It is a systematic review and meta-analysis that summarizes data on 1) the prevalence of pre-existing AF and the incidence proportion of newly diagnosed AF; 2) the predictors of newly diagnosed AF and; 3) the risk of short-term and long-term mortality attributable to AF, according to its temporal patterns in patients with aPE.

6.1 Atrial fibrillation incidence, prevalence, predictors, and adverse outcomes in acute coronary syndromes: a pooled analysis of data from 8 million patients.

6.1.1 Introduction

Acute myocardial infarction (AMI) and atrial fibrillation (AF) are two major contributors to the global burden of cardiovascular disease (CVD). Acute myocardial infarction is the most severe manifestation of ischemic heart disease, which is the leading cause of mortality and disability worldwide [565]. Atrial fibrillation, the most prevalent sustained cardiac arrhythmia [1], frequently co-exists with AMI [566], either as a pre-existing condition resulting from their similar risk factors, or as an acute complication due to several mechanisms including ischemia, systemic inflammation, neurohormonal activation, increased ventricular, and atrial pressures on the background of chronic structural atrial changes [566, 567].

Several studies have suggested that in the setting of AMI, AF is associated with an increased risk of adverse outcomes such as heart failure, ventricular tachyarrhythmias, and death [566]. However, it remains uncertain whether AF is a true prognostic factor or is just a marker of co-morbidities or AMI severity [568]. Furthermore, the risk of adverse outcomes attributable to AF might differ depending on the temporal pattern of AF [568]. For instance, some studies demonstrated that newly diagnosed AF at the time of AMI is associated with higher mortality, whereas pre-existing AF does not increase mortality, or does but to a lesser extent [569-572].

To the best of our knowledge, there is no recent review that provides a comprehensive summary of key aspects of the epidemiology of AF in AMI or acute coronary syndromes (ACS) in general. Therefore, the current systematic review and meta-analysis aimed to: 1) summarize data on the overall prevalence of AF in patients with AMI or ACS in general, and

specifically the prevalence of pre-existing AF, and the incidence proportion of newly diagnosed AF; 2) determine the predictors of newly diagnosed AF and; 3) assess the risk of various short-term and long-term adverse outcomes (e.g. death, stroke, re-infarction, heart failure, major bleeding) attributable to AF, according to its temporal patterns in patients with AMI or ACS in general.

6.1.2 Methods

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines [385] and was prospectively registered on PROSPERO (CRD42020210310).

6.1.2.1 Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science were searched to identify all eligible studies published through August 23, 2020 (date of the last search), without language restriction. The search strategy used a combination of the following terms or their synonyms: “atrial fibrillation”, “myocardial infarction”, or “acute coronary syndrome” (**Supplementary Table 1**). The reference lists of eligible articles were also scrutinized to identify potential additional data sources.

6.1.2.2 Study selection

We included: (1) cross-sectional studies, cohort studies, or RCTs, (2) with more than 100 participants, (3) reporting primary data on the prevalence or incidence of AF, its risk factors, or its association with adverse outcomes in patients with AMI (either ST-elevation myocardial infarction [STEMI] or non-ST myocardial infarction [NSTEMI]) or ACS, irrespective of the treatment received (medical or percutaneous coronary intervention), or studies with enough

data to compute these estimates. Although our primary population of interest was patients with AMI, we extended the study population to ACS that include STEMI, NSTEMI, and unstable angina to cover the maximum number of studies including patients with AMI. We excluded studies including patients with stable coronary artery disease without ACS, or patients who underwent coronary artery bypass graft surgery (to exclude post-operative AF). We also excluded studies in which participants were recruited before the year 2000. The year 2000 was chosen as the cutoff because it almost corresponds to the introduction of the first-generation drug-eluting stent [573]. For studies reporting data from the same primary study or registry (duplicates), we included the single most comprehensive one reporting the largest sample size, or articles presenting complementary data (each article having original information not included in any of the others). Two investigators (JJN and UFN) independently screened records for eligibility based on titles and abstracts. Full texts of articles deemed potentially eligible were retrieved and screened independently by the same investigators for final inclusion. Disagreements were resolved via discussion and consensus.

6.1.2.3 Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by second investigator (UFN). We collected data on study characteristics, study population (AMI, STEMI, NSTEMI, ACS), sample size, mean or median age, proportion of males, proportion of patients with co-morbidities such as hypertension, diabetes, heart failure, prior stroke or TIA, or prior AMI, number of participants with various types of AF. We also gathered information on risk estimate (hazard ratio, odds ratio, or relative risk) with the 95% confidence interval (CI) for each variable assessed as a potential predictor of AF, and risk estimate with the 95% CI for the association of AF with various adverse outcomes such as death, stroke, re-infarction, heart failure, sudden cardiac death, or readmission. For each

study, the risk of bias was assessed using an adapted version of the tool developed by Hoy et al. [386].

6.1.2.4 Definitions

The following definitions of type of AF were used:

- Pre-existing AF: AF diagnosed before the index AMI;
- Newly diagnosed AF: AF diagnosed for the first time during the index presentation for AMI (on admission or during hospitalization), in the absence of a prior history of AF;
- Prevalent AF: total cases of any form of AF (pre-existing or newly diagnosed).

The following definitions of outcomes were used:

- Short-term outcomes: outcomes occurring within 1 month from the index AMI, including in-hospital outcomes;
- Long-term outcomes: outcomes occurring beyond 1 month from the index AMI.

6.1.2.5 Statistical analysis

We performed random-effects meta-analysis of proportions using the inverse variance model. For comparisons with low proportions, we performed variance stabilizing transformation using the Freeman-Tukey double-arcsine transformation [574]. Heterogeneity was assessed by the χ^2 test on Cochran's Q statistic [387], which was quantified by I^2 values, assuming that I^2 values of <25%, 50 – 75%, and >75% respectively represent low, medium, and high heterogeneity [388]. We assessed small-study effect or publication bias by funnel plots and tests of funnel plot asymmetry (Egger's linear regression test). Next, we performed random-effects meta-analyses of unadjusted estimates to assess the association between clinical variables and AF incidence or prevalence, reporting this in odds ratio (OR) and 95% CI. For categorical

variables, number of AF events and non-events were used to calculate OR and 95% CI. For continuous variables, we converted the reported mean and standard deviations (SD) to standardized mean difference and rescaled as OR (95% CI) per SD change in the variable [389]. We then performed random-effects meta-analyses using the most adjusted risk estimates associating clinical variables and AF detection, reporting the results in adjusted hazard ratio (aHR) and 95% CI. Hazard ratio and OR were treated as equivalent measures of risk, as they were all derived from cohort studies. Finally, we analyzed the association of AF on short- and long-term outcomes in ACS. All statistical tests were two-tailed and statistical significance defined as p-value ≤ 0.05. All analyses were conducted with R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Some of the forest plots were exported from R software to Adobe Illustrator (Adobe Inc., San Jose, CA, USA) for editing.

6.1.2.6 Ethical approval

This is a systematic review using published data. Therefore, an ethical clearance is not required.

6.1.3 Results

6.1.3.1 Study selection and characteristics

Database and bibliographic searches retrieved 17,816 records from which 109 articles were finally included (**Figure 1**). The list of included studies and their characteristics are presented in the appendix (**Supplementary Tables 2–4**). The included studies reported data from a pooled sample of 8,239,364 patients, were conducted between 2000 and 2019, and published between 2007 and 2020. Most studies were conducted in Europe (52.3%, n = 57), Asia (17.4%, n = 19), and Northern America (11.9%, n = 13), with the most represented country

being the U.S. (11.0%, n = 12). Most studies had low (50.9%, n = 56) or moderate (46.4%, n = 51) risk of bias (**Supplementary Table 4**).

6.1.3.2 Prevalence/incidence of AF according to temporal patterns

6.1.3.2.1 Pre-existing AF

Thirty-three studies reported on pre-existing AF from a pooled population of nearly half a million patients with ACS (**Table 1**). The overall prevalence of pre-existing AF was 5.8%. The prevalence was 5.5% and 3.7% in patients with AMI and STEMI respectively **(Table 1**).

6.1.3.2.2 Newly diagnosed AF

Sixty-two studies reported on newly diagnosed AF from a pooled population of 501,513 patients with ACS (**Table 1**). The overall prevalence of newly diagnosed AF was 7.3% (**Supplementary Figure 4**). The prevalence was 7.4%, 6.9% and 8.6% in patients with AMI, STEMI, and NSTEMI respectively **(Table 1**).

6.1.3.2.3 Prevalent AF

We obtained data on prevalent (total) AF from 7.2 million participants from 58 studies (**Table 1**). The prevalence of any type of AF was 11.3% in all studies. It was 10.9% and 10.7% in patients with AMI and STEMI **(Table 1**).

6.1.3.2.4 Publication bias, sensitivity analysis, and meta-regression

There was no evidence of publication bias or small-study effect in the pooled analysis of prevalent AF detection (funnel plot asymmetry: p >0.05). However, we detected publication

bias or small study-effect in the analyses for pre-existing and newly diagnosed (funnel plot was asymmetrical: p = 0.03, **Supplementary Figures 1–3**). After correction for publication bias or small-study effect, the prevalence of pre-existing AF increased to 7.9% (missing studies identified: 11, *Egger's* p = 0.95, **Supplementary Figure 4**). In contrast, the prevalence of newly diagnosed AF decreased to 5.3% after bias correction (missing studies identified: 23, *Egger's* p = 0.89, **Supplementary Figure 5**). Bias-corrected funnel plots for pre-existing and newly diagnosed AF are presented in the appendix (**Supplementary Figures 6 and 7**)

Given the high heterogeneity in the pooled analyses, we performed a meta-regression to determine factors influencing the pooled prevalence of AF. We identified prior history of stroke or TIA, diabetes, and hypertension as the predictors of higher pooled prevalence of newly diagnosed AF, accounting for 30.8%, 12.4%, and 9.9% variances in the pooled results, whereas RoB was negatively predictive of the proportion of patients with AF, with a variance of 18.5% (**Supplementary Figure 8**). For pre-existing AF, hypertension and RoB positively predicted the pooled results, whereas male sex negatively predicted prevalence (**Supplementary Figure 9**). Mean age, history of dyslipidemia, and hypertension positively predicted prevalent AF prevalence, explaining 7.6% to 20.8% variances; RoB was not predictive of prevalent AF (**Supplementary Figure 10**). Additionally, we performed subgroup analyses by the quality of each study, with the scores categorized into: Low or Moderate (**Table 1**). The heterogeneity remained high, but lower in the sub-analyses of studies with moderate quality versus low.

6.1.3.3 Predictors of AF in AMI

6.1.3.3.1 Meta-analysis of univariable estimates

Univariable analysis of factors associated with newly diagnosed AF was performed using data from 38 studies reporting data on from a total of 322,711 patients (**Supplementary Figure 11**). The following variables were significantly associated with newly diagnosed AF (p <0.05): age (per yearly increase), LA diameter, LVEF (per unit decrement), estimated glomerular filtration rate (eGFR, per unit decrement), C-reactive protein (CRP), CHA_2DS_2Vasc score, N-terminal proBNP, heart rate, female sex, hypertension, diabetes, previous stroke, heart failure, chronic kidney disease (CKD), previous AMI, cardiac arrest, Killip 2, and Killip 3 or 4 as positive predictors; and smoking history and dyslipidemia the sole negative predictors.

Factors associated with pre-existing and prevalent AF are presented in the appendix (**Supplementary Figures 12 and 13**).

6.1.3.3.2 Meta-analysis of multivariable estimates

We performed a meta-analysis of predictors of newly diagnosed AF from multivariable analysis in 20 studies with a pooled sample of 60,404 patients. Pooled predictors included age (per year increase) (aOR 1.05, 95% CI 1.04–1.06), CRP (aOR 1.49, 95% CI 1.03–2.16), left atrial (LA) diameter (aOR 1.08, 95% CI 1.05–1.11), LA dilatation (aOR 2.32, 95% CI 1.67–3.22), LVEF <40% (aOR 1.82, 95% CI 1.38–2.39), hypertension (aOR 1.87, 95% CI 1.09–3.21), and Killip >1 (aOR 1.85, 95% CI 1.47–2.33) (**Figure 2**).

6.1.3.4 Association of AF with adverse outcomes in AMI

6.1.3.4.1 Short-term outcomes

Newly diagnosed AF was associated with an increased risk of acute heart failure (aHR 3.20, 95% CI 2.91–3.51), acute kidney injury (aHR 3.09, 95% CI 2.73–3.50), re-infarction (aHR 1.96, 95% CI 1.00–3.83), stroke (aHR 2.15, 95% CI 1.67–2.78), major bleeding (aHR 2.93, 95% CI 2.00–4.29), and mortality (aHR 1.82, 95% CI 1.43–2.31). The risks of short-term outcomes were consistently higher for newly diagnosed AF compared to pre-existing AF or prevalent AF (**Figure 3**). Pre-existing AF did not increase the risk of acute heart failure, major bleeding, and stroke (all $p > 0.05$).

6.1.3.4.2 Long-term outcomes

Newly diagnosed AF was associated with an increased risk of heart failure (aHR 2.21, 95% CI 1.47–3.31), stroke (aHR 1.75, 95% CI 1.44–2.12), mortality (aHR 1.67, 95% CI 1.52–1.84), CV mortality (aHR 2.09, 95% CI 1.52–2.88), sudden cardiac death (aHR 1.53, 95% CI 1.24–1.89), and a composite of major adverse cardiovascular events (aHR 1.54, 95% CI 1.30–1.82). Pre-existing AF did not increase the risk of stroke and of a composite of major cardiovascular events (all p >.05) (**Figure 4**).

6.1.4 Discussion

Atrial fibrillation and AMI are known to co-exist, and AF has prognostic implications in patients with AMI or ACS in general. To the best of our knowledge, no prior review has provided a comprehensive summary of key aspects of the epidemiology of AF in AMI. Using a meta-analysis, the current review demonstrates that: 1) the prevalence of pre-existing AF, newly diagnosed AF and prevalent AF are 5.8%, 7.3% and 11.3%, respectively, in patients

with ACS; 2) predictors of newly diagnosed AF include older age, hypertension, diabetes, CKD, heart failure at presentation, reduced LVEF and LA dilatation; 3) AF markedly increases the risk of short-term and long-term adverse outcomes, but this varies according to the timing of AF (**Figure 5**).

This study shows that AF is a common arrhythmia in the setting of AMI, and ACS in general. Some patients have pre-existing AF, but a higher proportion of patients are diagnosed for the first time with AF during the index presentation for AMI. This stresses the importance of continuous electrographic monitoring following AMI to identify AF alongside ventricular tachyarrhythmias. Although the intensity of electrographic monitoring was not reported in most studies, continuous monitoring at least during the acute phase and in the coronary care unit is now considered as standard of care [575]. Considering the high incidence of AF after AMI and its poor prognosis, prolonged outpatient monitoring after hospitalization might be beneficial in high-risk patients. In fact, one study using implantable cardiac monitors revealed an AF incidence of 28% after an average follow-up of 1.9 years among patients who had an AMI and a LVEF ≤40% [576]. Predictors of newly diagnosed AF identified in our study (older age, hypertension, diabetes, CKD, heart failure, reduced LVEF and LA enlargement) could be used to select a subset of patients that have an increased risk of developing AF and who may benefit from intensified clinical follow-up and implantable cardiac monitoring. In view of the increasing availability and ease of use of implantable cardiac monitor in one hand, and the effectiveness of oral anticoagulation in reducing thromboembolic events and mortality in patients with AF on the other hand [407], studies should be conducted to develop and validate AF screening strategies based on risk-stratification that would be cost-effective in patients with AMI.

Indeed, AF was associated with a higher risk of short-term (in-hospital and within 30 days after AMI) adverse outcomes such as death, re-infarction, stroke, acute kidney injury,

acute heart failure, cardiogenic shock and bleeding. There are several potential mechanisms explaining the association of AF with these poor outcomes in the setting of AMI. Hemodynamic derangement induced by AF such as poor atrial contraction, rapid and irregular ventricular rates, and atrioventricular desynchrony lead to reduced cardiac output, and ultimately to acute heart failure, cardiogenic shock, and acute kidney injury [566, 577, 578]. These mechanisms also contribute to further impairment in coronary circulation resulting in worsening myocardial ischemia and eventually re-infarction [566, 577, 578]. These hemodynamic changes, especially blood stasis in the LA, also promote thrombogenesis and cardioembolic stroke [578, 579]. The increased risk of bleeding in AF patients might be due to a higher utilization of antithrombotic therapies [580]. The harmful impact of AF following an AMI extends beyond the index hospitalization, remaining significant even after several years. Considering the strong prognostic impact of AF in the setting of AMI, its incorporation into risk stratification schemes such as the GRACE and TIMI scores should be considered.

This study shows that all types of AF, whether pre-existing or newly diagnosed, might increase the risk of death in patients with AMI. However, newly diagnosed AF seems to be associated with higher risk. Furthermore, unlike newly diagnosed AF, pre-existing AF does not increase the risk of stroke, re-infarction, or acute heart failure (in-hospital). A potential explanation is that a large proportion of patients with pre-existing AF are already receiving oral anticoagulation at the time of the AMI unlike patients with newly diagnosed AF [580]. The anticoagulation probably reduces the extent of acute ischemia and infarction, leading to lower rates of and less severe adverse outcomes in patients with pre-existing AF [580]. Indeed, compared with patients with newly diagnosed AF, those with pre-existing AF have been shown to have lower infarct size as estimated by serum creatinine kinase levels, and lower NT-proBNP levels, an indicator of cardiac strain and left ventricular dysfunction [580].

Our findings highlight the need for effective AF management as part of secondary cardiovascular prevention in AMI survivors, in which antithrombotic therapy is an important aspect. To-date, there is no well-established optimal antithrombotic strategy in patients with AF and AMI. Some RCTs (AUGUSTUS, ENTRUST-AF PCI, WOEST, PIONEER AF-PCI and RE-DUAL PCI) have demonstrated that dual antithrombotic therapy (DAT) is associated with lower bleeding events compared to triple antithrombotic therapy (TAT) in AF patients with AMI and/or undergoing percutaneous coronary intervention (PCI), with similar rates of thromboembolic events (although underpowered) [581-585]. A recent meta-analysis confirmed that DAT significantly reduces bleeding events compared with TAT and probably has a similar effect in preventing ischemic events in AF patients post-PCI or ACS [586]. However, studies are still needed to determine whether the efficacy of DAT is not inferior specifically in patients at high risk of ischemic events. Another important question is whether pre-existing AF and newly diagnosed AF should be managed similarly. In fact, an observational study showed that DAT had a survival benefit in patients with pre-existing AF but not in those with newly diagnosed AF, whereas it showed the opposite scenario for TAT, suggesting that TAT might be more appropriate in patients with newly diagnosed AF [580]. Future studies should also determine the best timing for rhythm control therapy in patients with newly diagnosed AF after AMI, in view of the superiority of early rhythm control therapy over usual care in reducing adverse cardiovascular outcomes among patients with recently diagnosed AF (≤ 1 year) and cardiovascular co-morbidities demonstrated by the recent EAST-AFNET 4 Trial [281].

This study has some limitations. First, there was marked heterogeneity in pooled prevalence estimates. The marked difference in the distribution of risk factors for AF (**Supplementary Table 4**) across studies was likely the main source of this heterogeneity. The prevalence rates were also lower in studies done after year 2000, suggesting that the period of recruitment could be a potential source of heterogeneity, although most of the

included studies (85.5%) were conducted after year 2000. Second, AF burden that has been suggested as a specific prognostic factor was not reported in included primary studies and therefore, not considered in our analysis, as well as information on cardioversion of AF especially in patients with newly diagnosed AF. Furthermore, it is unknown whether a proportion of patients initially in sinus rhythm developed AF during follow-up. However, this scenario would be in favour of a more deleterious effect of AF, hence supporting the conclusion of our study. Third, data used in our analysis span two decades and therefore might not totally reflect contemporary practice. Finally, although primary estimates included in analyses of AF predictors and prognosis were adjusted for potential confounders, there remains a possibility of reverse causation and residual confounding.

Nevertheless, our study has important strengths. It is the most comprehensive and up-to-date summary of data on the incidence, risk factors, and prognosis of AF in AMI. We used more precise definitions of AF according to timing (pre-existing, newly diagnosed, and prevalent AF) than previously reported. We covered several major outcomes categorized as short-term or long-term. We performed robust quantitative synthesis on a large dataset from a population of nearly 9 million individuals.

6.1.5 Conclusion

This study shows that about one in nine patients with AMI has AF, with a high proportion of newly diagnosed AF. Predictors of newly diagnosed AF identified in our study could be used to select high-risk patients who may benefit from prolonged cardiac monitoring. Atrial fibrillation, in particular newly diagnosed AF, is associated with poor short-term and long-term outcomes in patients with ACS. Considering this strong prognostic impact of AF, its incorporation into risk stratification schemes for patients with AMI should be considered.

Studies are needed to determine the benefit of prolonged cardiac monitoring for AF detection in patients with ACS and the optimal antithrombotic strategy in patients with ACS and AF.

6.1.6 Tables and figures

Table 1. Pooled estimates of atrial fibrillation occurrence in acute coronary syndromes

Figure 1. Study selection

Figure 2. Summarized predictors of newly diagnosed atrial fibrillation. Each point estimate represents a pooled result of studies reporting the association between that predictor and AF. ***Legend****: AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; LA: left atrial; LVEF: left ventricular ejection fraction; STEMI: ST elevation myocardial infarction;*

Figure 3. Association of atrial fibrillation types with short-term outcomes in patients with acute myocardial infarction

Figure 4. Association of atrial fibrillation types with long-term outcomes in patients with acute myocardial infarction

Figure 5. Central illustration.

Legend: *ACS: acute coronary syndrome; AF: atrial fibrillation; AMI: acute myocardial infarction; STEMI: ST elevation myocardial infarction*

Table 1. Pooled estimates of atrial fibrillation occurrence in acute coronary syndromes

Subgroup	Number of studies	No. of patients		Detection rate (95% CI)	Heterogeneity		*Egger's* test (*P* value)
		Total	Cases		I^2	*P* value	
Pre-existing AF							
• Overall	33	485,573	38,123	5.75 (7.58 – 7.73)	99.2%	<.001	0.032
• Type of ACS*							
- AMI	24	336,721	27,274	5.41 (4.42 – 6.50)	99.2%	<.001	0.056
- STEMI	6	13,593	500	3.73 (2.34 – 5.42)	95.3%	<.001	0.697
• Level of RoB#							
- Low	21	467,921	37,434	6.59 (5.65 – 7.56)	99.4%	<.001	0.257
- Moderate	12	17,652	689	4.32 (3.12 – 5.70)	94.1%	<.001	0.088
Newly diagnosed AF							
• Overall	62	501,513	31,059	7.30 (6.67 – 7.92)	98.8%	<.001	0.037
• Type of ACS*							
- AMI	46	296,827	20,598	7.44 (6.84 – 8.03)	96.7%	<.001	0.658
- STEMI	18	39,465	2,496	6.87 (5.92 – 7.82)	93.3%	<.001	0.025
- NSTEMI	3	13,315	755	8.57 (3.80 – 15.01)	98.9%	<.001	0.654
• Level of RoB#							
- Low	35	407,855	24,718	5.89 (5.20 – 6.62)	98.7%	<.001	0.342

- Moderate	27	93,658	6,341	9.03 (8.08 – 10.03)	94.8%	<.001	<.001
Prevalent AF							
• Overall	58	7,235,380	1,072,605	11.25 (9.81 – 12.70)	100.0%	<.001	0.151
• Type of ACS*							
- AMI	38	1,881,503	178,422	10.86 (9.57 – 12.14)	99.7%	<.001	0.245
- STEMI	12	1,515,685	131,718	10.72 (9.26 – 12.19)	96.4%	<.001	0.132
• Level of RoB#							
- Low	29	7,139,199	1,064,554	11.02 (9.24 – 12.94)	100.0%	<.001	0.186
- Moderate	28	96,013	8,031	10.9 (9.02 – 12.99)	98.9%	<.001	0.002

Figure 1. Study selection

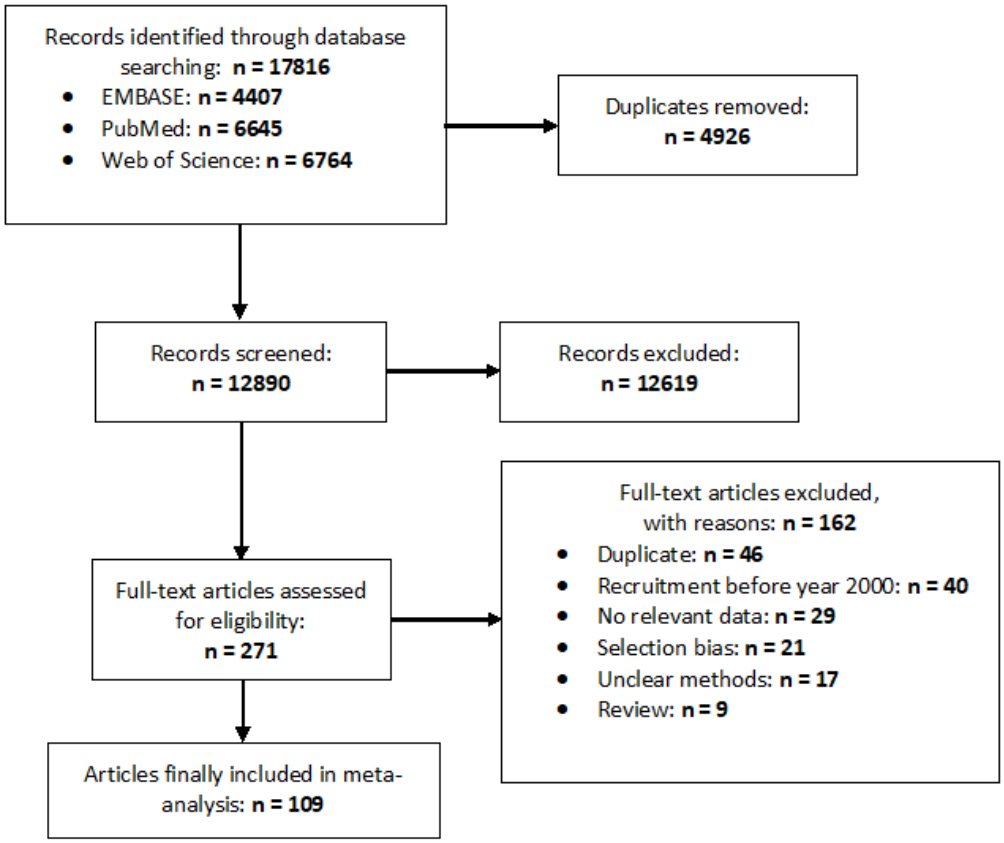
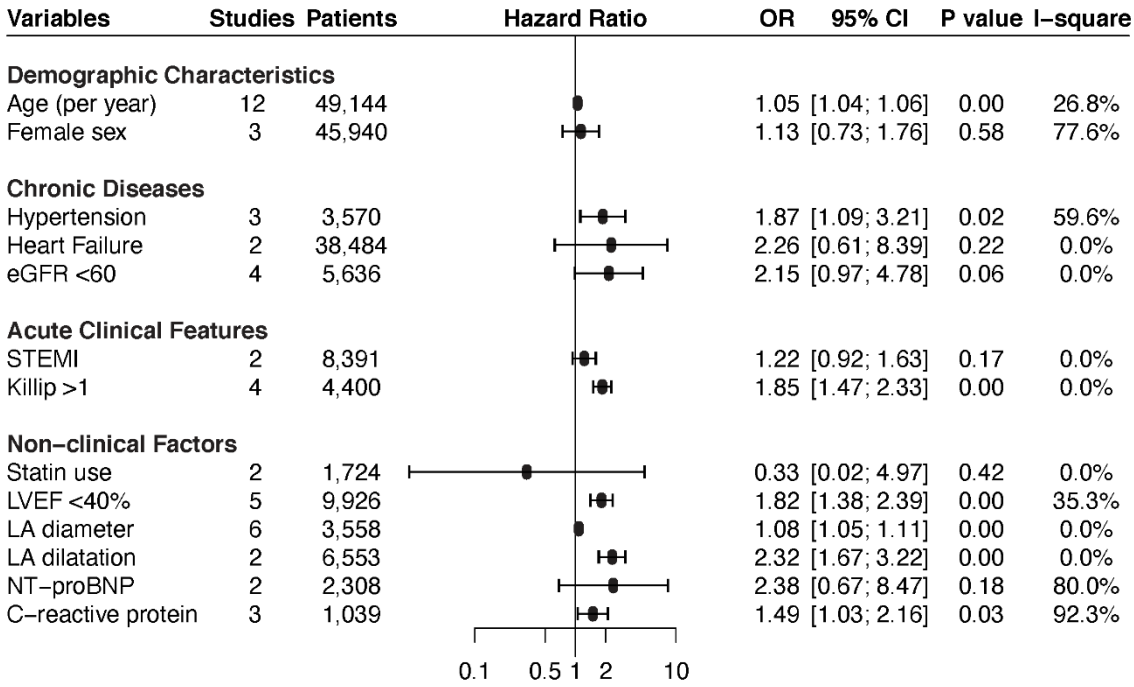


Figure 2. Summarized predictors of newly diagnosed atrial fibrillation. Each point estimate represents a pooled result of studies reporting the association between that predictor and AF.



Legend. AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; LA: left atrial; LVEF: left ventricular ejection fraction; STEMI: ST elevation myocardial infarction

Figure 3. Association of atrial fibrillation types with short-term outcomes in patients with acute myocardial infarction

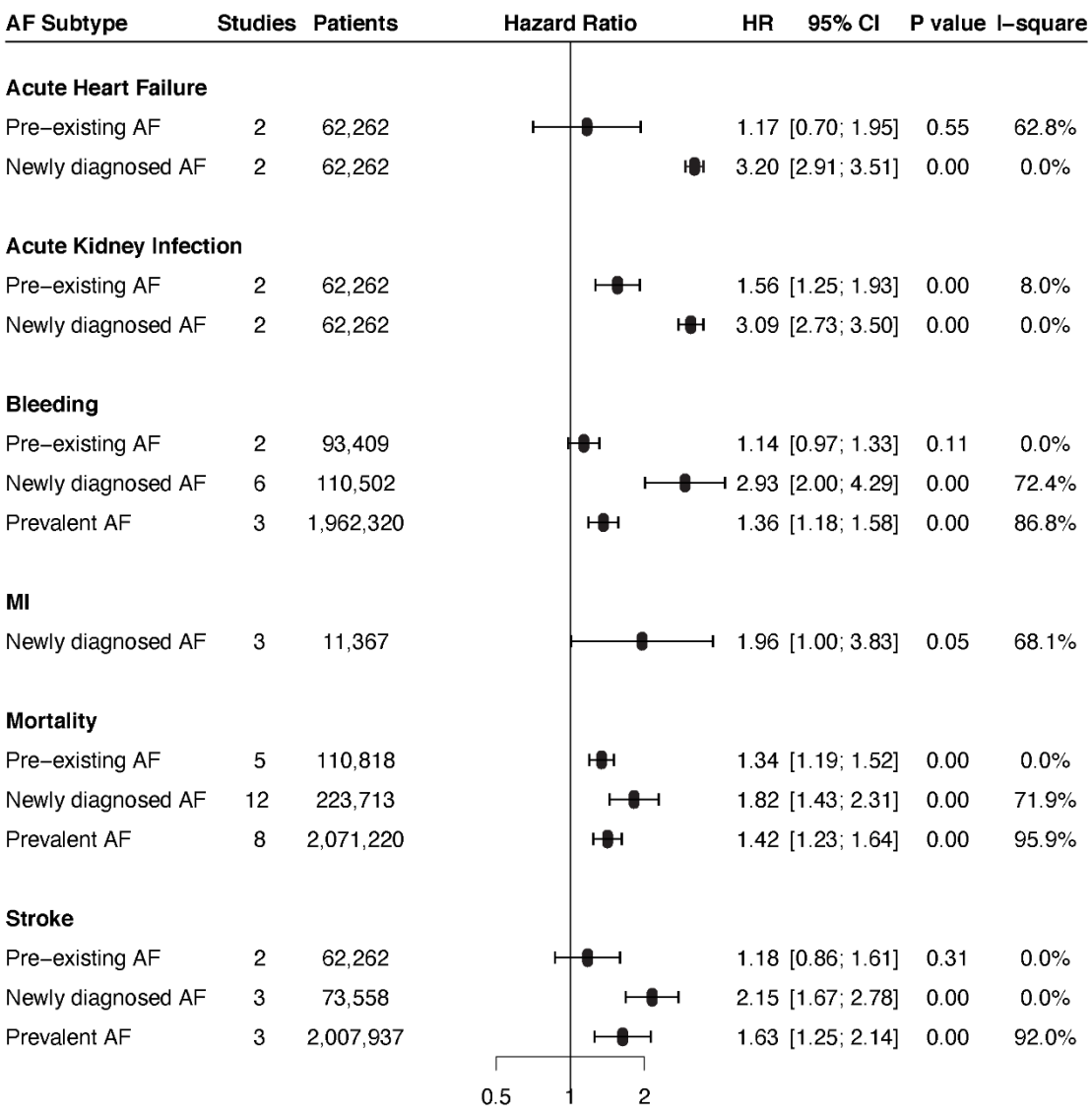


Figure 4. Association of atrial fibrillation types with long-term outcomes in patients with acute myocardial infarction

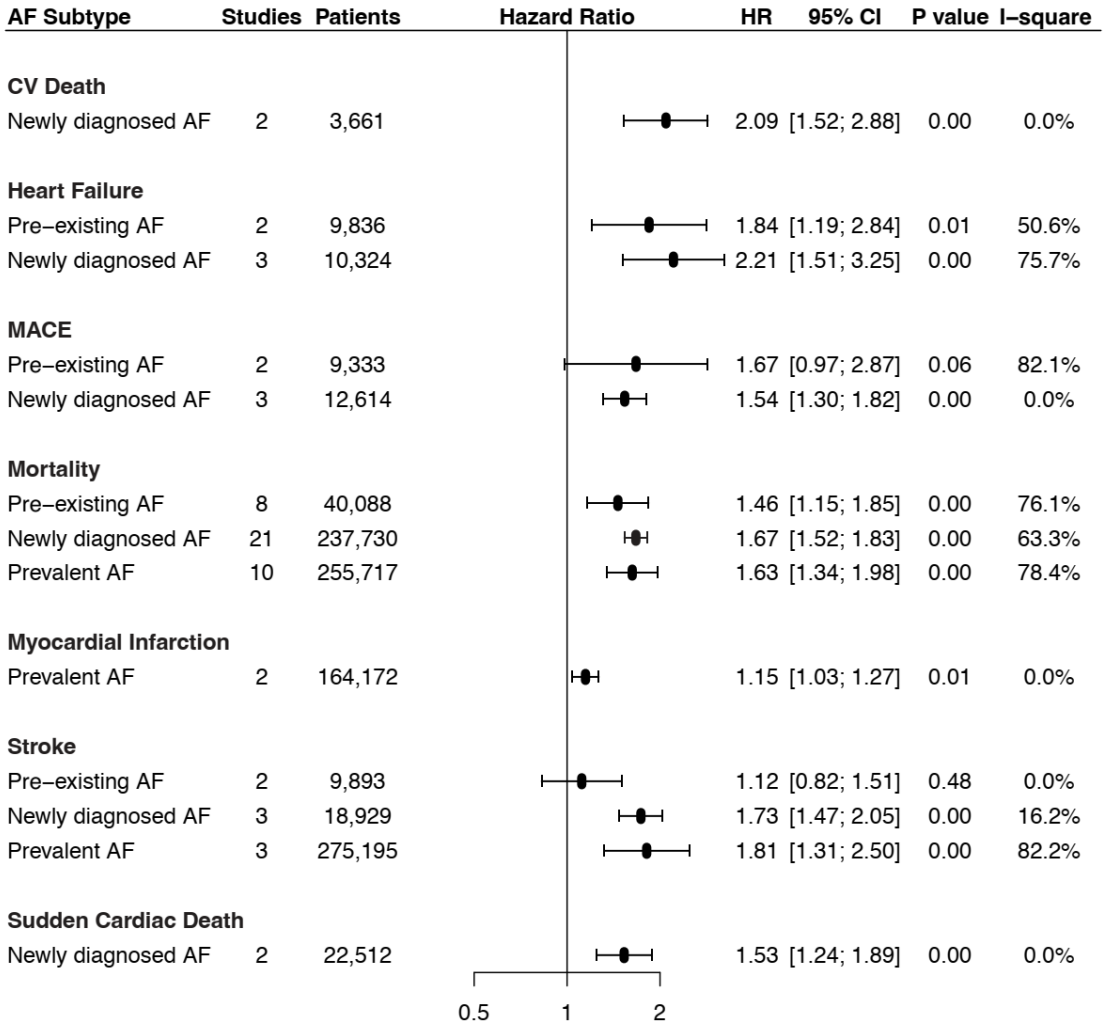
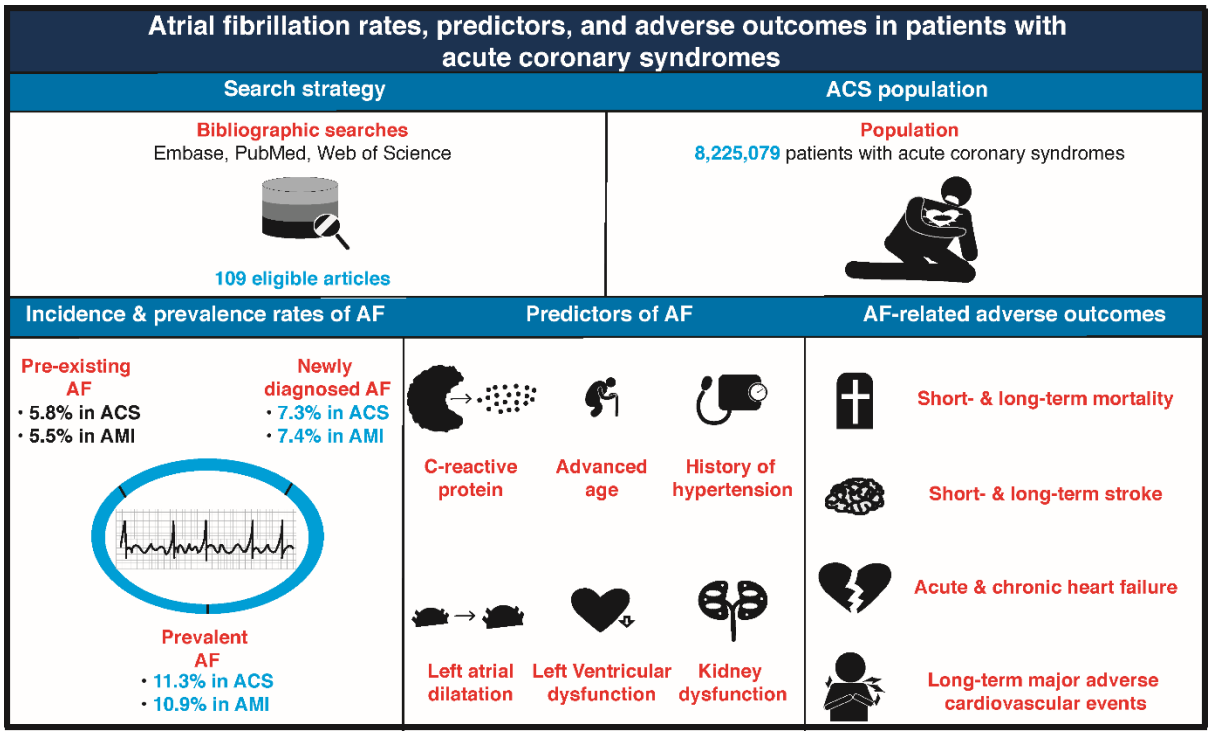


Figure 5. Central illustration



Legend. ACS: acute coronary syndrome; AF: atrial fibrillation; AMI: acute myocardial infarction; STEMI: ST elevation myocardial infarction

6.1.7 Appendix

Supplementary Table 1. Search strategies

	Search strategy for PubMed
#P1	“myocardial infarction” OR “STEMI” OR “NSTEMI” OR “acute coronary”
#P2	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#P3	#P1 AND #P2
	Search strategy for EMBASE
#E1	'myocardial infarction':ab,ti OR 'STEMI':ab,ti OR 'STEMI':ab,ti OR 'NSTEMI':ab,ti OR 'acute coronary':ab,ti
#E2	'atrial fibrillation':ab,ti OR 'auricular fibrillation':ab,ti OR 'AF':ab,ti OR 'AFib':ab,ti
#E3	#E1 AND #E2
#E4	#E3 AND ('article'/it OR 'article in press'/it)
	Search strategy for Web of Science
#W1	“myocardial infarction” OR “STEMI” OR “NSTEMI” OR “acute coronary”
#W2	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#W3	#1 AND #2
#W4	#3 AND limit to articles

Supplementary Table 2. Summarized study characteristics

Characteristics	**N = 109**
Total population	8,239,364
Year of publication, range	2007-2020
Period of inclusion of participants, range	2000-2019
Design	
- Cohort	102
- Randomized controlled trial	7
Data collection	
- Prospective	63
- Retrospective	46
Regions	
- Europe	57
- Asia	19
- Northern America	13
- Middle East	8
- Multiregional	7
- Oceania	3
- South America	2
Countries	
- US	12
- Multinational	9
- Turkey	9
- Spain	8
- China	7
- France	6
- Italy	5
- Israel	5
- Taiwan	5
- Egypt	3
- Korea	3
- Portugal	3
- The Netherlands	3
- Germany	3
- United Kingdom	3
- Japan	2
- Australia	2
- Sweden	2
- Cuba	2
- Pakistan	2
- Poland	2
- Russia	2
- Serbia	2
- Switzerland	2
- Denmark	1
- Austria	1
- Mexico	1

- Montenegro	1
- New Zealand	1
- Norway	1
- Romania	1
Sampling	
- Non-probability	102
- Random	7
Risk of bias	
- Low	56
- Moderate	51
- High	2

Supplementary Table 3. General characteristics of included studies

Author	Year of pub	Period of recruitment	Country	Study design	Sampling	Timing of data collection	Study population	Components of diagnosis of AMI	Methods of diagnosis of AF	AF definition
Aksoy	2019	2014-2015	Turkey	Cohort	Nonprobability	Prospective	STEMI	ECG, troponin	ECG	AF episode > 30 s during hospitalization
Al Khdair	2012	1999-2008	Multinational	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Alasady	2011	2004-2009	Australia	Cohort	Nonprobability	Retrospective	AMI	ESC/ACC 2003	72-hour telemetry post-MI and then daily ECG	AF episode > 30 s during hospitalization
Alexander	2017	2013-2015	USA	Cohort	Nonprobability	Retrospective	NSTEMI	NR	ECG	NR
Almendro-Delia	2014	2001-2011	Spain	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Álvarez-Álvarez	2014	2004-2010	Spain	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Antoni	2010	2004-2005	Netherlands	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Ariyarajah	2008	2004-2005	USA	Cohort	Nonprobability	Prospective	NSTEMI	ESC/ACC 2003	ECG	NR
Aronson	2007	2001-2005	Israel	Cohort	Nonprobability	Prospective	AMI	ESC/ACC 2000	ECG	NR
Athar	2011	2003-2007	USA	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Axelrod	2020	2002-2014	Israel	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	AF episode > 30 s during hospitalization
Barra	2013	2006-2011	UK	Cohort	Nonprobability	Retrospective	AMI	ESC/ACCF/AHA/WHF 2007	24-hour Holter, ECG	NR
Batra	2016	2000-2009	Sweden	Cohort	Nonprobability	Retrospective	AMI	NR	ECG	NR
Bejot	2011	2005-2008	France	Cohort	Nonprobability	Prospective	ACS	NR	ECG	NR
Biasco	2019	2004-2015	Switzerland	Cohort	Nonprobability	Prospective	AMI	NR	ECG	NR
Bloch Thomsen	2010	2001-2009	Europe	Cohort	Nonprobability	Prospective	Low LVEF (<40) AMI	ECG, cardiac biomarkers	ICM	NR

Braga	2014	2009-2011	Portugal	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Butala	2011	2009-2010	Egypt	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	NR	NR
Calabro	2018	2016-2017	Italy	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	NR	NR
Cerrato	2017	2007-2013	Italy	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	NR	NR
Chen HY	2016	2000-2011	USA	Cohort	Nonprobability	Retrospective	AMI	NR	NR	NR
Chen SY	2014	2002-2006	USA	Cohort	Nonprobability	Retrospective	ACS	NR	NR	NR
Cinier	2018	2015-2016	Turkey	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Cirakoglu	2019	2015-2017	Turkey	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	NR	NR
Congo	2019	2010-2017	Portugal	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	NR	NR
Cordero	2019	2003-2016	Spain	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Cosentino	2020	2010-2018	Italy	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	AF episode > 30 s during hospitalization
Dai	2017	2013-2014	China	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry or 12-lead ECG	NR
Danchin	2010	2005	France	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
De Luca	2017	2001-2014	Italy	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Dorje	2013	2008-2011	China	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Erez	2017	2000-2013	Israel	Cohort	Nonprobability	Prospective	AMI	NR	ECG	NR
Gal	2016	2006-2007	Netherlands	RCT	Random	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Gal	2015	2006-2007	Netherlands	RCT	Random	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Garg	2018	2003-2013	USA	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Gonzalez-Pacheco	2015	2006-2013	Mexico	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Gourronc	2019	2004-2015	France	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Green	2016	2009-2012	Denmark	Cohort	Nonprobability	Retrospective	AMI	NR	NR	NR
Guenancia	2018	2012-2015	France	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	AF episode > 30 s
Hachet	2014	2001-2010	France	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR

Hersi	2012	2008-2009	Multinational	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Ho	2020	2017-2018	New Zealand	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Huang SS	2013	2002-2005	Taiwan	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Hwang	2011	2005-2007	Korea	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Ibrahim	2019	After 2016	Egypt	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Iqbal	2019	2014-2015	Pakistan	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	AF episode > 30 s
Jackson	2016	2008-2012	Multinational	RCT	Random	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Jortveit	2019	2013-2016	Norway	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	NR	NR
Karatas	2016	2009-2013	Turkey	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Kayapinar	2018	2009-2014	Turkey	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Khalfallah	2020	2017-2019	Egypt	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Khan	2017	2016	Pakistan	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Kim	2018	2010-2014	USA	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Koracevic	2008	2000-2005	Serbia	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Kundu	2016	1999-2011	USA	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Lau DH	2009	2005-2007	Australia	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	NR
Li CY	2018	2008-2012	Taiwan	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Li K	2008	2001-2006	China	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Lin	2011	2005-2009	Taiwan	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Liu	2011	2009-2010	Taiwan	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Lopes	2013	2004-2008	Multinational	RCT	Random	Prospective	NSTEMI	ECG, cardiac biomarkers	ECG	NR
Lopes	2012	2008-2009	USA	Cohort	Nonprobability	Retrospective	AMI	NR	ECG	NR
Lopes	2009	2004-2006	Multinational	RCT	Random	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Loudon	2016	2000-2013	UK	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Luca	2020	2005-2010	Italy	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Luo	2020	2014-2018	China	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	AF episode >

										30 s
Maagh	2010	2004-2007	Germany	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Mai	2019	2013-2018	China	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	Holter, ECG	NR
Maier	2014	2008-2012	Germany	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Malay	2017	2014	Russia	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Manzano-Fernández	2016	2012-2015	Spain	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Martsevich	2014	2005-2007	Russia	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
McManus	2012	2000-2007	Multinational	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Melendo-Viu	2020	2011-2015	Spain	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	NR
Mohamed	2019	2004-2014	USA	Cohort	Nonprobability	Retrospective	NSTE-ACS	ECG, cardiac biomarkers	ECG	NR
Moss	2019	2009-2014	UK	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Mrdovic	2011	2006-2009	Serbia	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Nagai	2019	2008-2012	Japan	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Ozaydin	2010	2004-2007	Turkey	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Parashar	2013	2005-2008	USA	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	AF episode > 30 s
Pilgrim	2013	2002-2009	Switzerland	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Podolecki	2017	2004-2014	Poland	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Ramani	2007	2001-2006	USA	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Raposeiras Roubín	2015	2008-2012	Spain	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Reinstadler	2018	2008-2011	Germany	RCT	Random	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Rene	2014	2005-2007	Multinational	RCT	Random	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Rhyou	2018	2009-2015	Korea	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Ribeiro	2014	2008-2010	Portugal	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Rodríguez-Jiménez	2020	2013-2018	Cuba	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR

Rodríguez-Jiménez	2017	2013-2015	Cuba	Cohort	Nonprobability	Retrospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Rohla	2015	2003-2012	Austria	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Sagnard	2020	2001-2014	France	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	AF episode > 30 s
Sandowski	2010	2005-2006	Poland	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Serban	2019	2011-2016	Romania	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Shiyovich	2019	2002-2012	Israel	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	ECG	AF episode > 30 s during hospitalization
Topaz	2017	2008-2014	Israel	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Torres	2008	2003-2005	Spain	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Ulvenstam	2018	2009-2013	Sweden	Cohort	Nonprobability	Retrospective	AMI	ECG, cardiac biomarkers	NR	NR
Viliani	2012	2004-2008	Spain	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Vukmirović	2017	2009-2010	Montenegro	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Wang	2019	2005-2009	Taiwan	Cohort	Nonprobability	Retrospective	ACS	ECG, cardiac biomarkers	ECG	NR
Wi	2016	2005-2012	Korea	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	NR
Xue	2019	2014-2017	China	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	24-hour Holter and ECG	NR
Yesin	2018	2016-2017	Turkey	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Yildirim, Erkan	2019	2018	Turkey	Cohort	Nonprobability	Prospective	NSTE-ACS	ECG, cardiac biomarkers	Telemetry, 12-lead ECG	AF episode > 30 s
Yildirim, Ersin	2019	2017-2018	Turkey	Cohort	Nonprobability	Prospective	STEMI	ECG, cardiac biomarkers	ECG	NR
Yoshizaki	2012	2005-2010	Japan	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	Telemetry, ECG	NR
Zeymer	2019	2010-2011	Multinational	Cohort	Nonprobability	Prospective	ACS	ECG, cardiac biomarkers	ECG	NR
Zhang	2014	2005-2007	China	Cohort	Nonprobability	Prospective	AMI	ECG, cardiac biomarkers	ECG	AF episode > 30 s

ACS: acute coronary syndromes; AF: atrial fibrillation; AMI: acute myocardial infarction; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; NR: not reported; NSTEMI: non-ST elevation myocardial infarction; pub: publication; RCT: randomized controlled trial; STEMI: ST elevation myocardial infarction;

Supplementary Table 4. Clinical characteristics of participants in the included studies

Author	Year of Publ	Total sample	Mean age (years)	Males (%)	HPT (%)	Diabetes (%)	DYSL (%)	Obesity (%)	Smokers (%)	CKD (%)	Prior stroke or TIA (%)	Heart failure (%)	Prior MI (%)	CAD (%)	STEMI	Risk of bias
Aksoy	2019	696	62.6	80	51	25.1	21.7		56							Low
Al Khdair	2012	14285	67	66.6	59.9	27.2	53.2		26.7				32.6		28.1	Low
Alasady	2011	2460														Low
Alexander	2017	322	65.4	72.3	72	32.3	56.5		63.4		10.9			36.6		High
Almendro-Delia	2014	39237	64.3	73.8	52.2	31.8		10.8	36.4			4.6	17.6		59.9	Low
Álvarez-Álvarez	2014	4229	66.9	62.1	57.1	26.5	45.2				6.8			23.1	35.1	Low
Antoni	2010	613	60	78	29	10	20		51				7			Moderate
Ariyarajah	2008	462														Moderate
Aronson	2007	1209	61.9	77.4	52.6	29			15.8				22.6		70.4	Low
Athar	2011	1594	62.1													Moderate
Axelrod	2020	12535														Low
Barra	2013	1852	68.3	65.7		33.7					8.9					Moderate
Batra	2016	155071	70.5	64.1	51.4	22.2					7.8	12.2	26.2		37.1	Low
Bejot	2011	525419														Low
Biasco	2019	34377														Moderate
Bloch Thomsen	2010	297	64	77	43.4	19.9										Moderate
Braga	2014	902	64	77.5	61.5	25.8	53		28.9	7						Moderate
Butala	2011	1177		79	51.8	44	20.7					4.6	16.8		70.6	Moderate
Calabro	2018	1171		72.3	69.7	26.3	52.1		47.7		6.5		18.2		48.4	Moderate
Cerrato	2017	1372	66.6	70.4	51.9	17.4			25.1						100	Moderate
Chen HY	2016	4810	68.9	58.2												Moderate

Chen SY	2014	795	76	49.2	68.1											Moderate
Cinier	2018	198	57	87.4	40.4	30.8		20.2	66.7							Moderate
Cirakoglu	2019	692	63.1	74	76.6	22.4	74.9		45.7					49.6	46.1	Moderate
Congo	2019	6325		75.8	59.6	23.7	51.1	20.1	38.6	2.9	5.4	1.4	10.1	8.5		Low
Cordero	2019	8771	66.9	62.5	57.9	28.2	48		30.6	23.5	6.4	4		21.3	35.3	Moderate
Cosentino	2020	244	68	73.9	65.1	22.4	50		52.7				26.5		47	Low
Dai	2017	24658	63	74.2	51.5	20	8		54.7	1.4	9.5		7.7	28.2	75.7	Moderate
Danchin	2010	3396	66.5	68.9	58.3	35.5	48.4		30.3						51.9	Low
De Luca	2017	16803														Low
Dorje	2013	268	64.2	83.6	67.5	26.5	13.1		49.6							Moderate
Erez	2017	13297	63	76.8	50	35			36.6				30			Moderate
Gal	2016	830														Low
Gal	2015	861														Low
Garg	2018	1493859	61.2													Low
Gonzalez-Pacheco	2015	6705														Low
Gourronc	2019	3173	65	72.8	50.7	22.2	51.2		37.2	3.3	4.6			10.7		Low
Green	2016	7104														Moderate
Guenancia	2018	1282	65.6	67.8	52.7	20	43.6	17.9			5			13		Low
Hachet	2014	8485	70	29.8	53.4	22.8	44.8		27.8		5.8		13.1			Moderate
Hersi	2012	7930	56.8	78.7	47.2	39.5	37.5		52.9		4.3	6.7	19.2	38.4	45.6	Low
Ho	2020	9489	66.1	68.9		23.2			22.5			4.1	23.7		27.7	Low
Huang SS	2013	724	67	80.4	64.1	36.6					12.2	5.9	10.9			Moderate
Hwang	2011	401	62	73												Moderate
Ibrahim	2019	440	56.6	65.9	46.6	61.4	50		54.5							Moderate
Iqbal	2019	216	50.8	54.2	75.9	64.5			28.2						44.9	Moderate
Jackson	2016	9101	65.5	60.9	81.7	37.9	56		19.9			17.4	42.6			Low
Jortveit	2019	47204	69.3	63.1	47	18.6			27.7		8.7	8.5	23.7			Low
Karatas	2016	621	57	74.7	41.7	19.3			65.9							Moderate

Kayapinar	2018	4086														Moderate
Khalfallah	2020	530	62.3	56.2	31.3	41.5	41.7		20.2				10.6			Moderate
Khan	2017	207	59.09	74.7	55.1	35.6	36.2	15.5	22.2						51.7	Moderate
Kim	2018	709548	62.9	69	65.1	28.2	63.1		46.5	9.7		19.6	8.4	84.9	100	Low
Koracevic	2008	543	63.8	54.9	69.9	25.8			59.4				45.6		53.8	Moderate
Kundu	2016	6384	70.2	56												Moderate
Lau DH	2009	3230	64.9	64.1	64.3	26.7	60.5				6.8					Low
Li CY	2018	29452	66.5	74	65.5	37.8	37.7			10.6	19.5	14.9	8.6			Low
Li K	2008	967	74	63												Moderate
Lin	2011	783	61.3	83.1	55.3	36.2	57.2		56.1		7.9		7.9			Moderate
Liu	2011	6663	63	74.5												High
Lopes	2013	9242	67.5	69	71	30.5			26.5		5.1	12.2	27.6	30		Low
Lopes	2012	69255	64.1													Low
Lopes	2009	5726	61.1	77	49.4	15.8			43.3			3.6		16.4		Low
Loudon	2016	25287	66.6	64.2	45.1	21.6	24.8					18.4		48.9		Low
Luca	2020	12288	66.9	70.2	56.2	26.4			31.4	36.7	6	3.3	19.9			Low
Luo	2020	2075	65.2	77.3	63	36.8	26.4		44.7	8.4	11.3	5.3	6.5		60.8	Low
Maagh	2010	375	64	73.9												Moderate
Mai	2019	3612	61.6	60.9	37	17.9	35.3		22	2.6	2.4					Moderate
Maier	2014	11068														Moderate
Malay	2017	321			80	22	67									Moderate
Manzano-Fernández	2016	1587	67	72	73	46			31		10	5	34			Moderate
Martsevich	2014	1133		54.5												Moderate
McManus	2012	59032	66	67	61.9	25	48.3		57.2			10	29.7		37	Low
Melendo-Viu	2020	2158	63.3	76.2	59.1	26.3				6.6					41.8	Moderate
Mohamed	2019	4668737	69	56.9	69.9	30	48.8	12.5			3.4	0.8	9.6			Low
Moss	2019	1645	62	71.7	32.5	12.9	40.1		58.7		4		9.8			Moderate
Mrdovic	2011	2096	59.6	72.6	65.2	18.1	48.4		53.8				9.5			Low

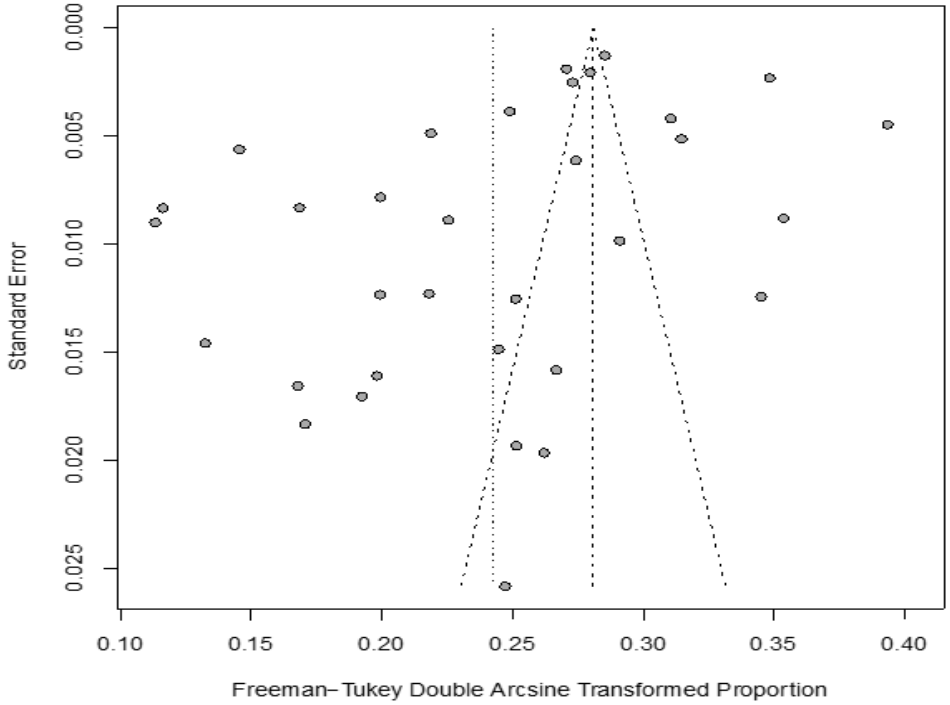
Nagai	2019	648	67.9	78	70.4	37.5	57.6		37.2	33	11.6		10.6		69.3	Moderate
Ozaydin	2010	1000	61.1	75.5	55	23.6			54.3							Moderate
Parashar	2013	2370	57.8	68.3	65.3	31.1	46.9		42.4	6.4	4.5			30	44.5	Low
Pilgrim	2013	6041	63.9	75.4	57.6	17.7	53.5		51.4						47.6	Low
Podolecki	2017	4099	61.7	69.6	54.3	32.6	49.1				4.7		20.1			Moderate
Ramani	2007	1526	66	96	69.4	39.8	50.3		68.6		11.4	17.6		50.5		Low
Raposeiras Roubín	2015	1520	67.1	69.9	57.4	25.1									34.4	Low
Reinstadler	2018	786	61.5	75.7	68.1	20.2	38.6		46.7				6			Low
Rene	2014	3281	59.8	77.2	52.4	16	42.9						10.4			Low
Rhyou	2018	527	60.6	80.6	50.3	29	75.7									Low
Ribeiro	2014	2334														Low
Rodríguez-Jiménez	2020	667	67.4	66.1	79.3	30	14.4	27.4	57							Moderate
Rodríguez-Jiménez	2017	326		55.2												Moderate
Rohla	2015	1456	61.8	68	77	25	83						13			Low
Sagnard	2020	2040														Low
Sandowski	2010	26035	64.7	65.5	59.8	20.5	39.5	17	37.2				15			Moderate
Serban	2019	629	60.8	70.4	63.6	21.3				22.6		7.5	0			Moderate
Shiyovich	2019	5946	64.8	70	48.3	36	65.1	21.1	42.8					73.9	56.2	Low
Topaz	2017	1657	61.4	80.3	42.8	21.7	46.9		50.2			8.1	10.7			Low
Torres	2008	1183	64.5	72.4	58.2	25.9	42.8	16.9	24		6.1		17.2			Low
Ulvenstam	2018	34931	67	72	50	19			26.5		5.5	4				Low
Viliani	2012	913	62.9	77.7	49	22.9	39									Low
Vukmirović	2017	600	63.6	70.3	49	27.8	32.8		49.3	31.2		6.5	22.3		48.3	Moderate
Wang	2019	6663	66.6	67.8	71.7	40.2	41.9			10.6	10.6	11.2				Low
Wi	2016	2105	63.8	73	55	31			42		6		7	18	46	Low
Xue	2019	985	63.4	79.9	49.8	19.5				1.4	5.6		3.3			Low
Yesin	2018	171	63	83	52	35.7			64.3							Moderate

Yildirim, Erkan	2019	448	61.7	60.7	68.5	49.1	34.8									Moderate
Yildirim, Ersin	2019	706	57.4	80.5	39.1	24.5	15.6		32.3		3.7					Low
Yoshizaki	2012	176														Moderate
Zeymer	2019	10568														Low
Zhang	2014	1035	65.2	70	51.9	23.8			38.4		12.3	25.7	9.6		85.3	Low
Aksoy	2019	696	62.6	80	51	25.1	21.7		56							Low
Al Khdair	2012	14285	67	66.6	59.9	27.2	53.2		26.7				32.6		28.1	Low
Alasady	2011	2460														Low
Alexander	2017	322	65.4	72.3	72	32.3	56.5		63.4		10.9			36.6		High
Almendro-Delia	2014	39237	64.3	73.8	52.2	31.8		10.8	36.4			4.6	17.6		59.9	Low
Álvarez-Álvarez	2014	4229	66.9	62.1	57.1	26.5	45.2				6.8			23.1	35.1	Low
Antoni	2010	613	60	78	29	10	20		51				7			Moderate
Ariyarajah	2008	462														Moderate
Aronson	2007	1209	61.9	77.4	52.6	29			15.8				22.6		70.4	Low
Athar	2011	1594	62.1													Moderate
Axelrod	2020	12535														Low
Barra	2013	1852	68.3	65.7		33.7					8.9					Moderate
Batra	2016	155071	70.5	64.1	51.4	22.2					7.8	12.2	26.2		37.1	Low
Bejot	2011	525419														Low
Biasco	2019	34377														Moderate
Bloch Thomsen	2010	297	64	77	43.4	19.9										Moderate
Braga	2014	902	64	77.5	61.5	25.8	53		28.9	7						Moderate
Butala	2011	1177		79	51.8	44	20.7					4.6	16.8		70.6	Moderate
Calabro	2018	1171		72.3	69.7	26.3	52.1		47.7		6.5		18.2		48.4	Moderate
Cerrato	2017	1372	66.6	70.4	51.9	17.4			25.1						100	Moderate
Chen HY	2016	4810	68.9	58.2												Moderate

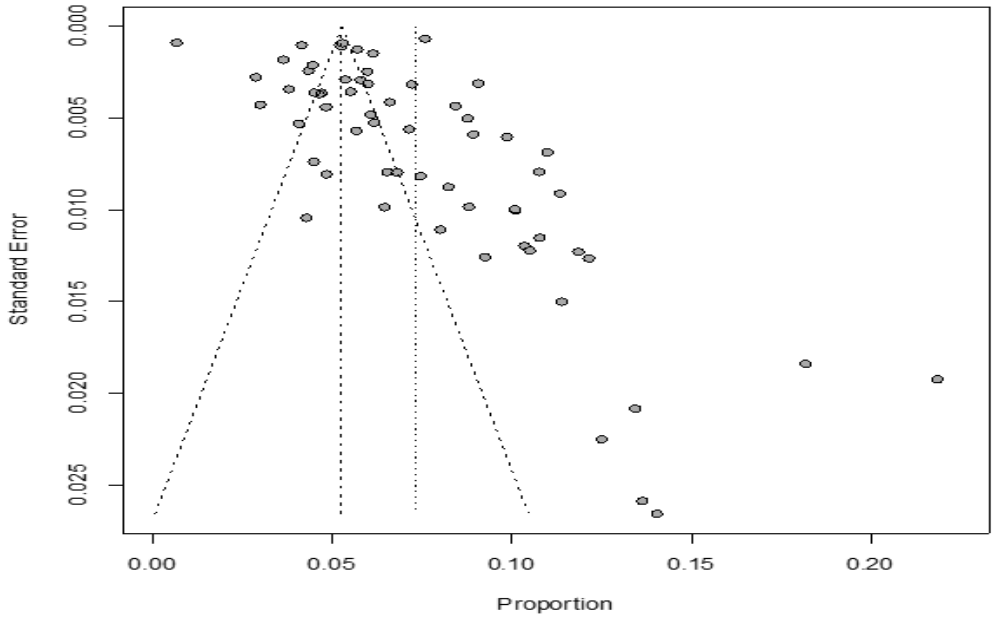
Chen SY	2014	795	76	49.2	68.1										Moderate
Cinier	2018	198	57	87.4	40.4	30.8		20.2	66.7						Moderate
Cirakoglu	2019	692	63.1	74	76.6	22.4	74.9		45.7					49.6	46.1	Moderate
Congo	2019	6325		75.8	59.6	23.7	51.1	20.1	38.6	2.9	5.4	1.4	10.1	8.5		Low
Cordero	2019	8771	66.9	62.5	57.9	28.2	48		30.6	23.5	6.4	4		21.3	35.3	Moderate
Cosentino	2020	244	68	73.9	65.1	22.4	50		52.7				26.5		47	Low
Dai	2017	24658	63	74.2	51.5	20	8		54.7	1.4	9.5		7.7	28.2	75.7	Moderate
Danchin	2010	3396	66.5	68.9	58.3	35.5	48.4		30.3						51.9	Low
De Luca	2017	16803														Low
Dorje	2013	268	64.2	83.6	67.5	26.5	13.1		49.6							Moderate
Erez	2017	13297	63	76.8	50	35			36.6				30			Moderate
Gal	2016	830														Low
Gal	2015	861														Low
Garg	2018	1493859	61.2													Low
Gonzalez-Pacheco	2015	6705														Low
Gourronc	2019	3173	65	72.8	50.7	22.2	51.2		37.2	3.3	4.6			10.7		Low
Green	2016	7104														Moderate
Guenancia	2018	1282	65.6	67.8	52.7	20	43.6	17.9			5			13		Low
Hachet	2014	8485	70	29.8	53.4	22.8	44.8		27.8		5.8		13.1			Moderate

CKD; chronic kidney disease; HPT: hypertension; STEMI: ST elevation myocardial infarction; TIA: transient ischemic attack
Risk of bias assessed using an adapted version of the tool developed by Hoy et al.

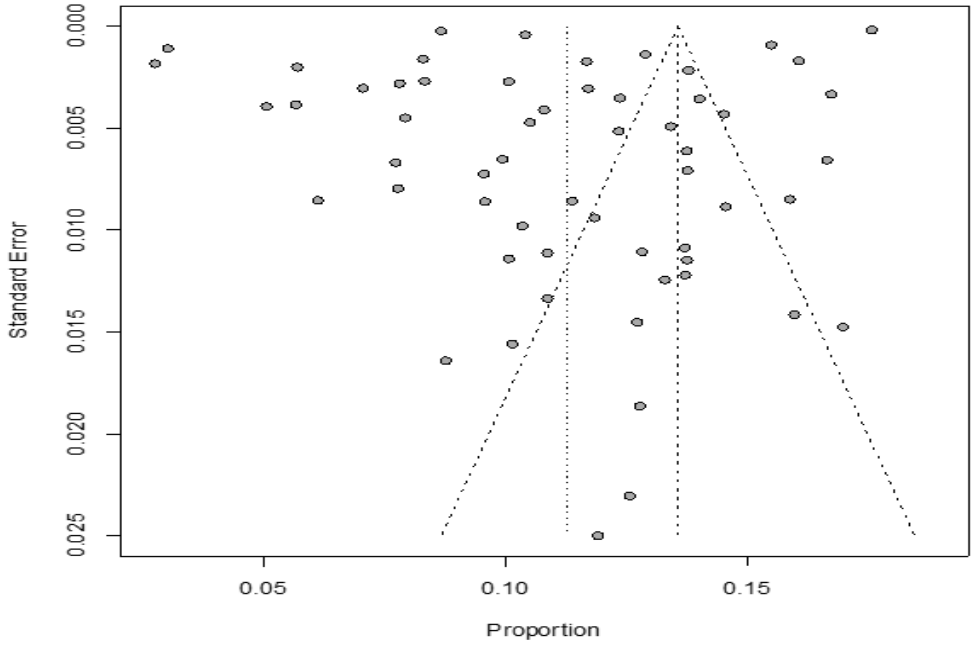
Supplementary Figure 1. Funnel plot for the meta-analysis of prevalence of pre-existing atrial fibrillation in patients with acute coronary syndromes



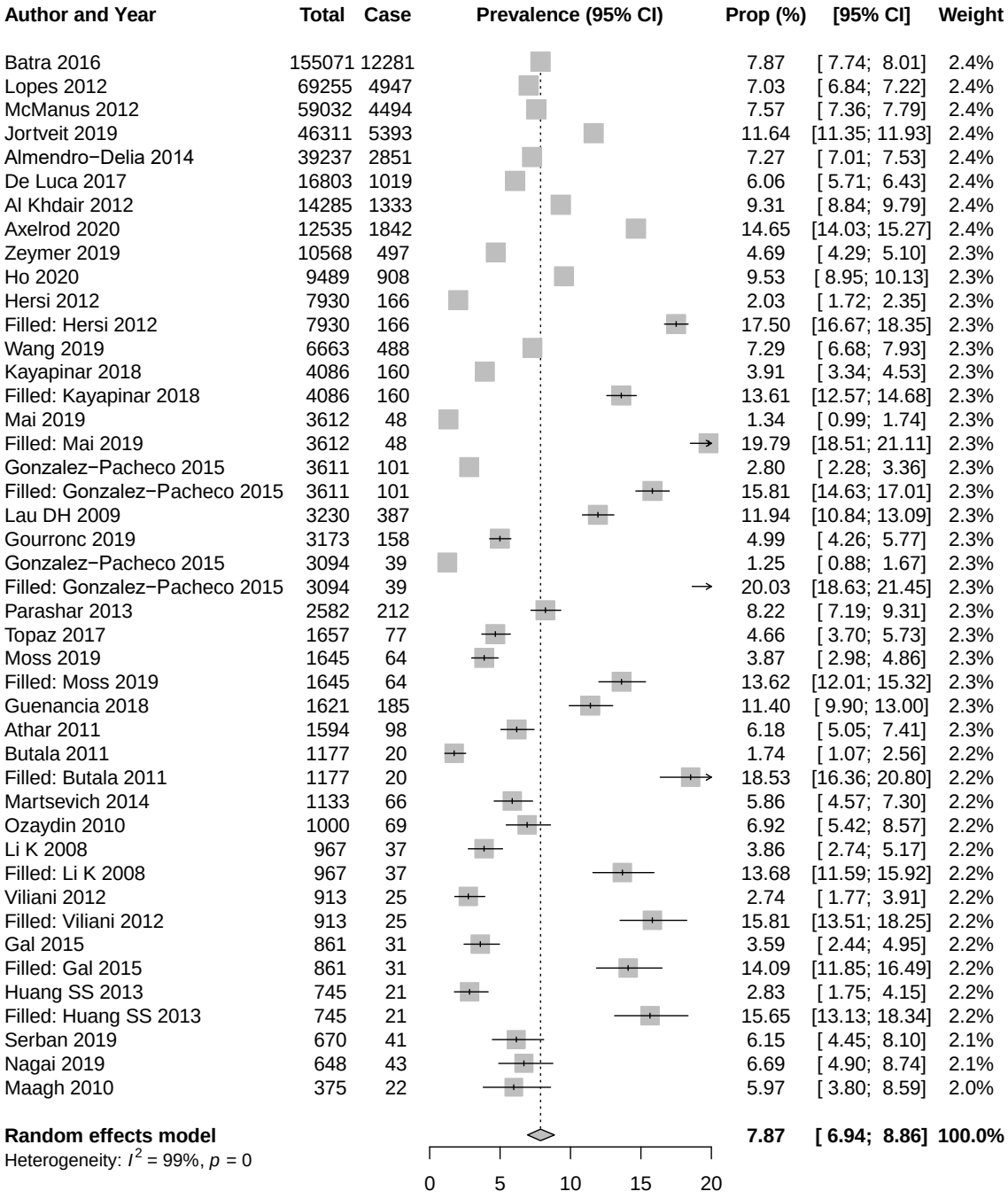
Supplementary Figure 2. Funnel plot for the meta-analysis of prevalence of newly diagnosed atrial fibrillation in patients with acute coronary syndromes



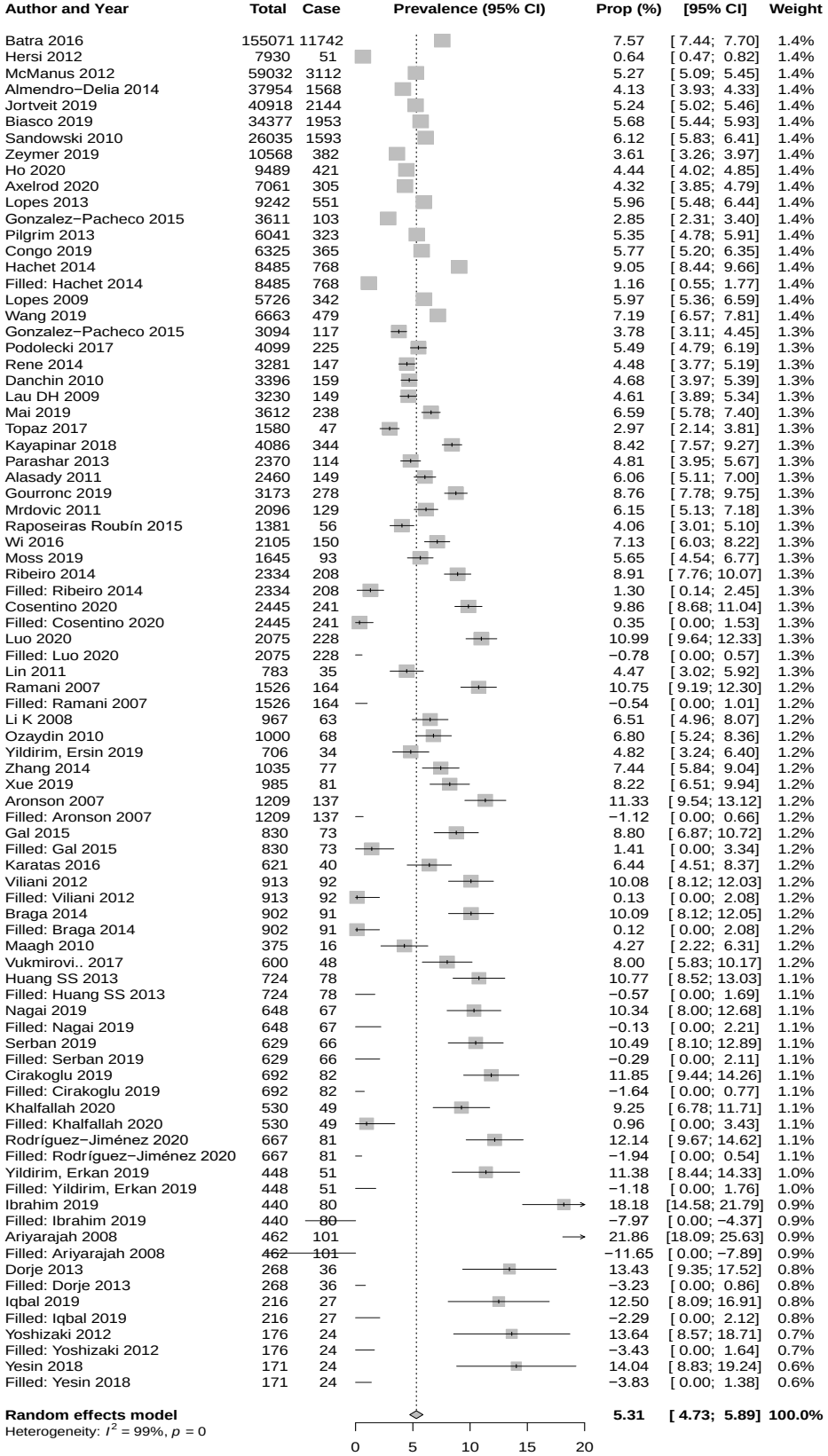
Supplementary Figure 3. Funnel plot for the meta-analysis of rate of prevalent atrial fibrillation in patients with acute coronary syndromes



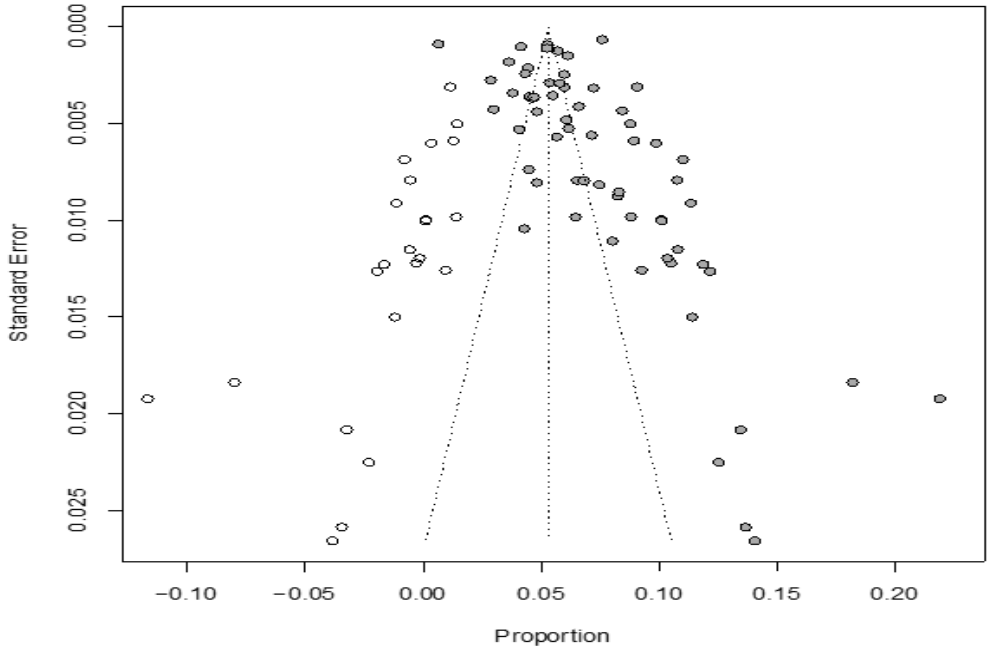
Supplementary Figure 4. Bias-corrected rate of pre-existing atrial fibrillation in patients with acute coronary syndromes



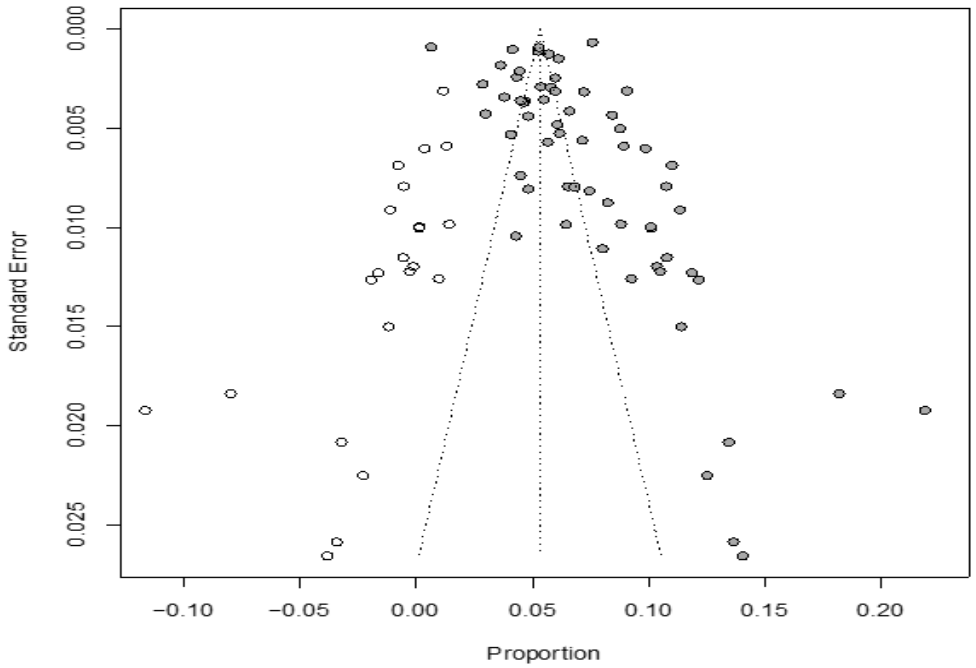
Supplementary Figure 5. Bias-corrected funnel plot for the meta-analysis of rate of newly diagnosed atrial fibrillation in patients with acute coronary syndromes



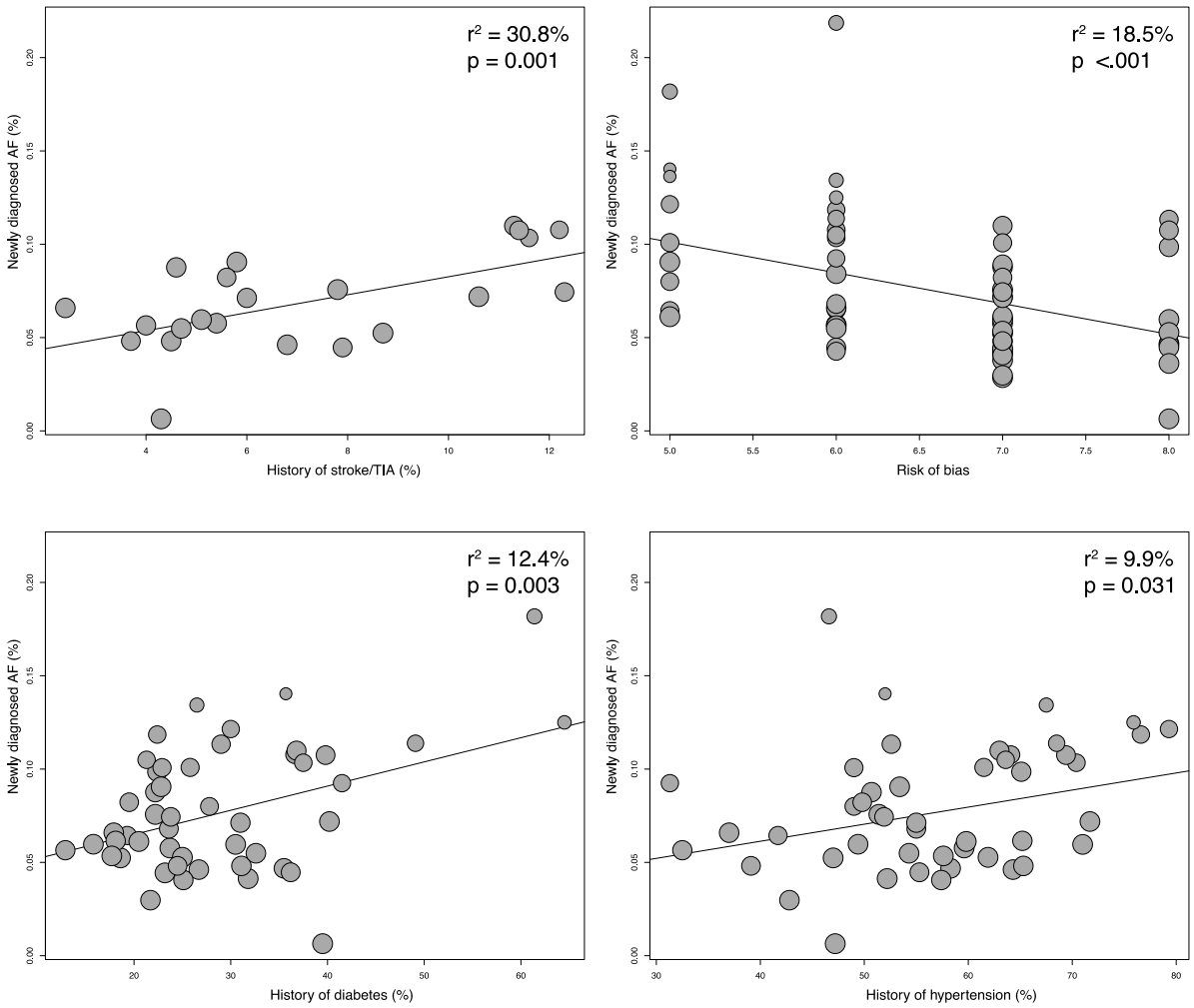
Supplementary Figure 6. Bias-corrected funnel plot for the meta-analysis of rate of pre-existing atrial fibrillation in patients with acute coronary syndromes



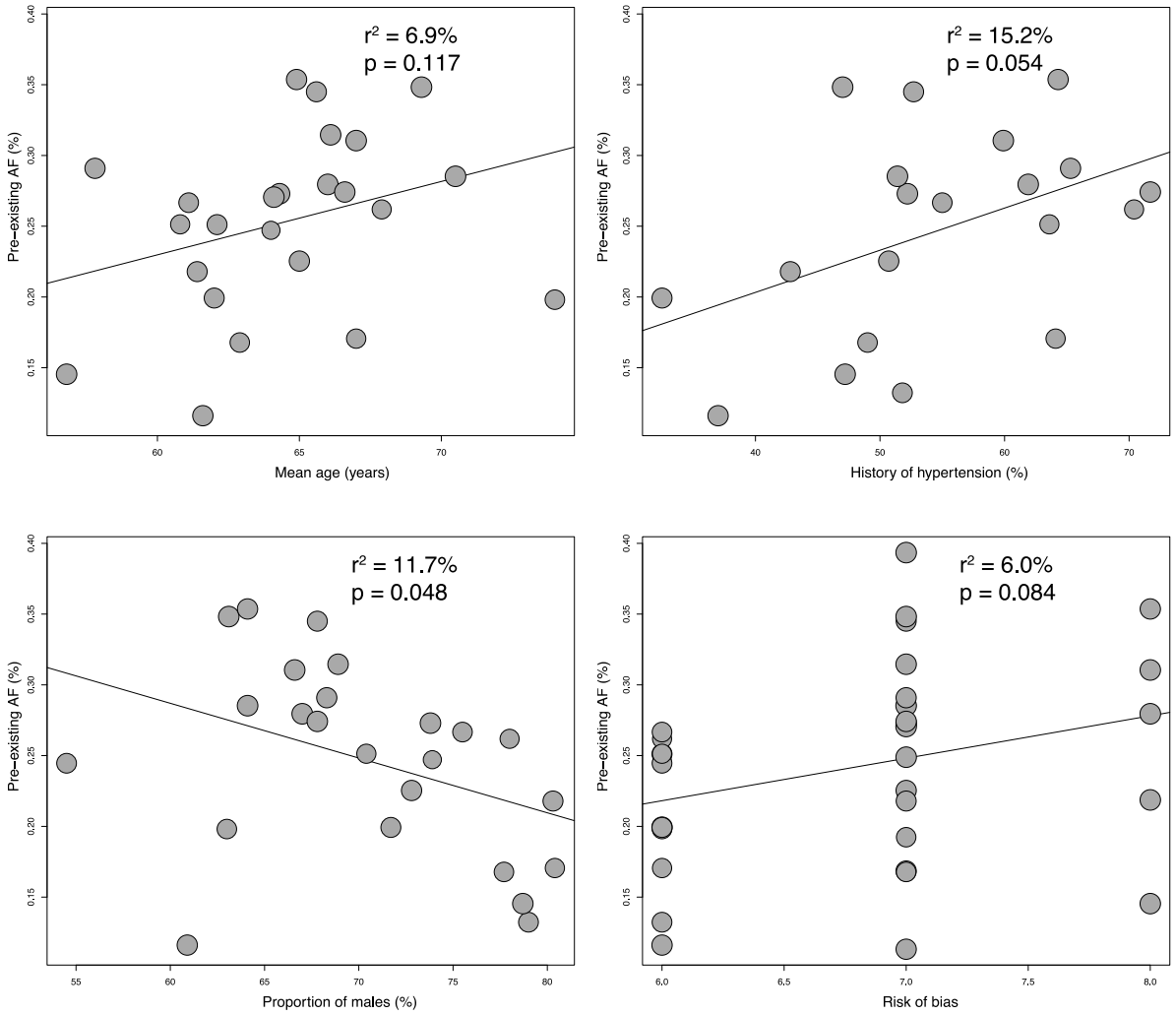
Supplementary Figure 7. Bias-corrected funnel plot for the meta-analysis of rate of newly diagnosed atrial fibrillation in patients with acute coronary syndromes



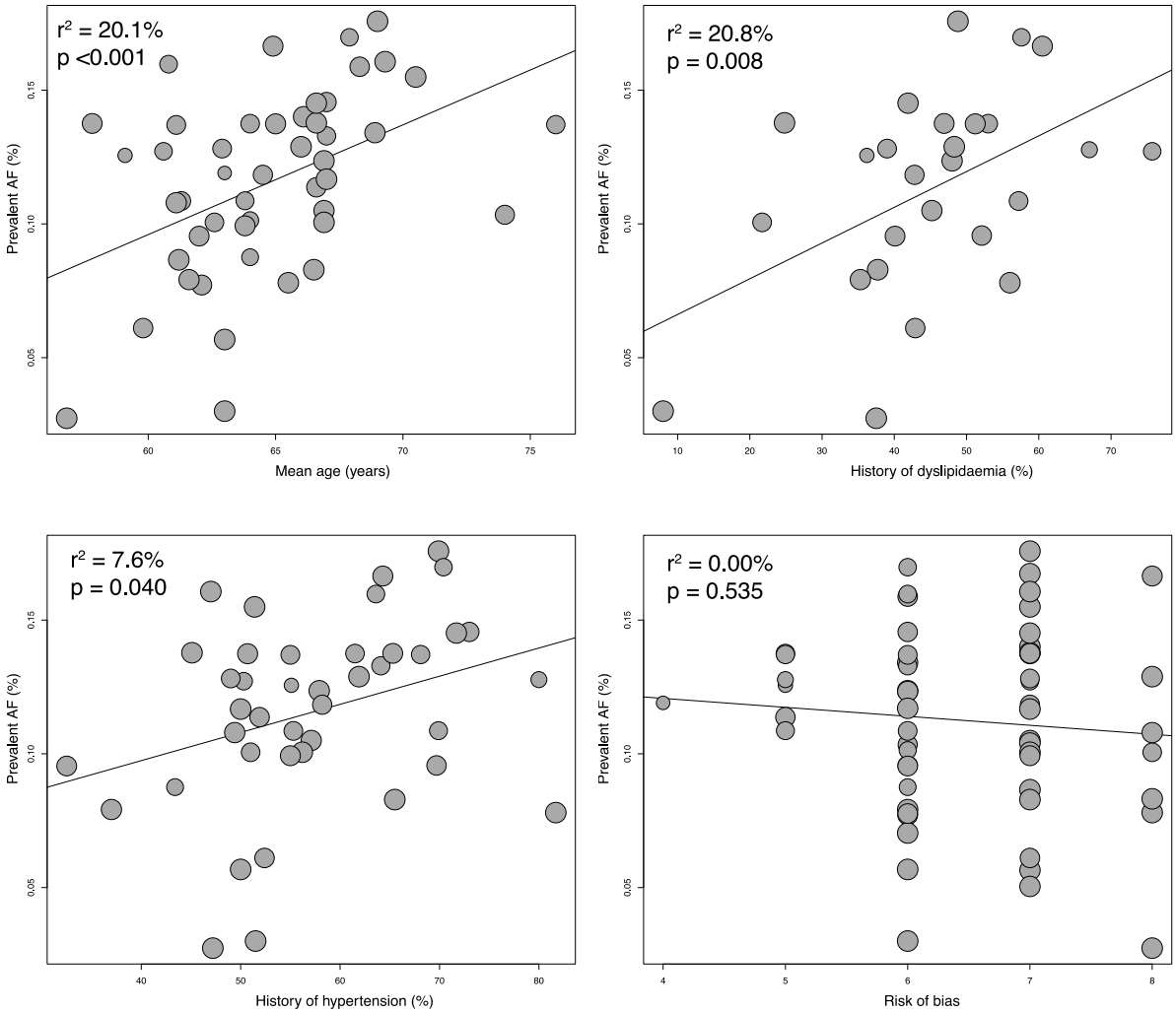
Supplementary Figure 8. Meta-regression plots of newly diagnosed atrial fibrillation in patients with acute coronary syndromes



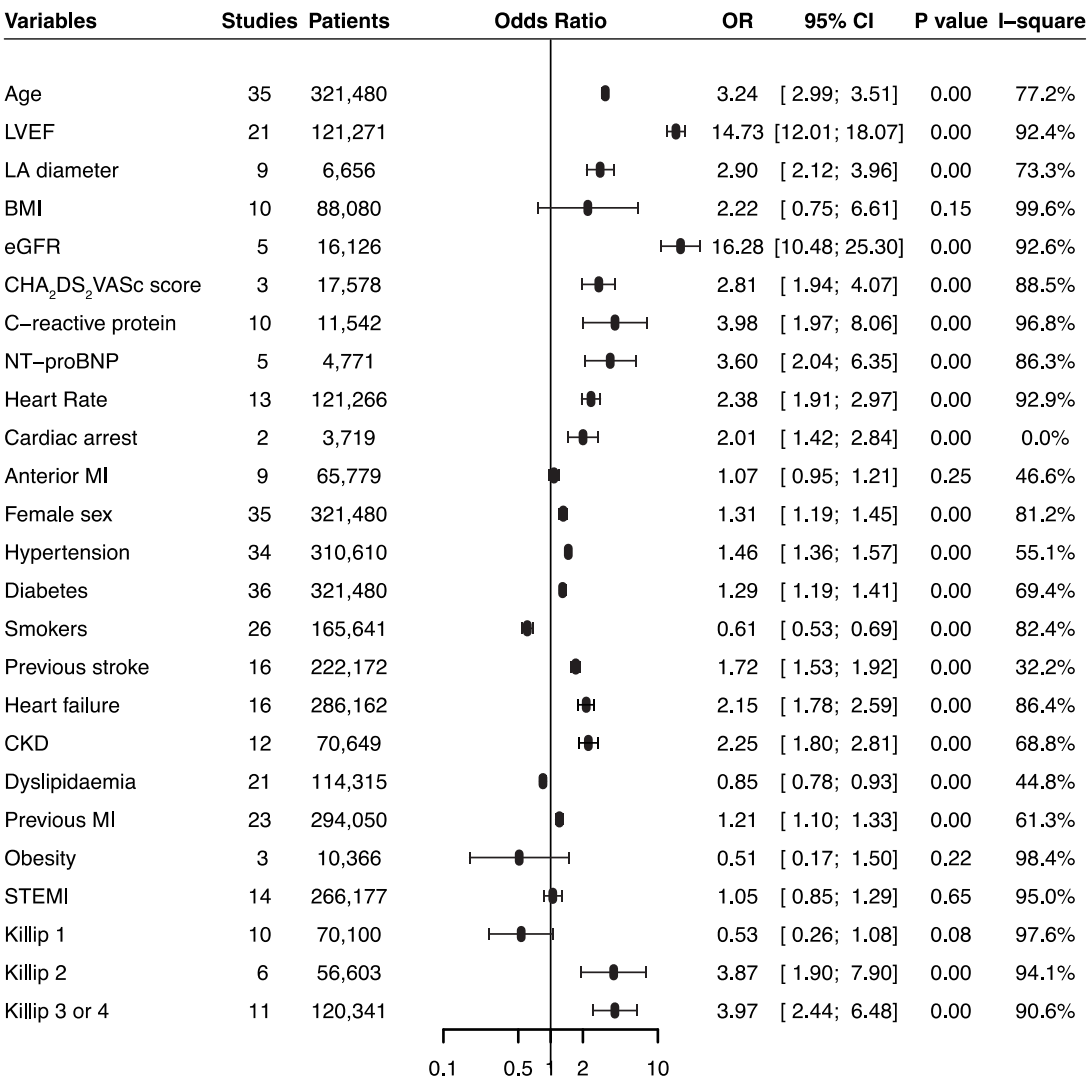
Supplementary Figure 9. Meta-regression plots of pre-existing atrial fibrillation in patients with acute coronary syndromes



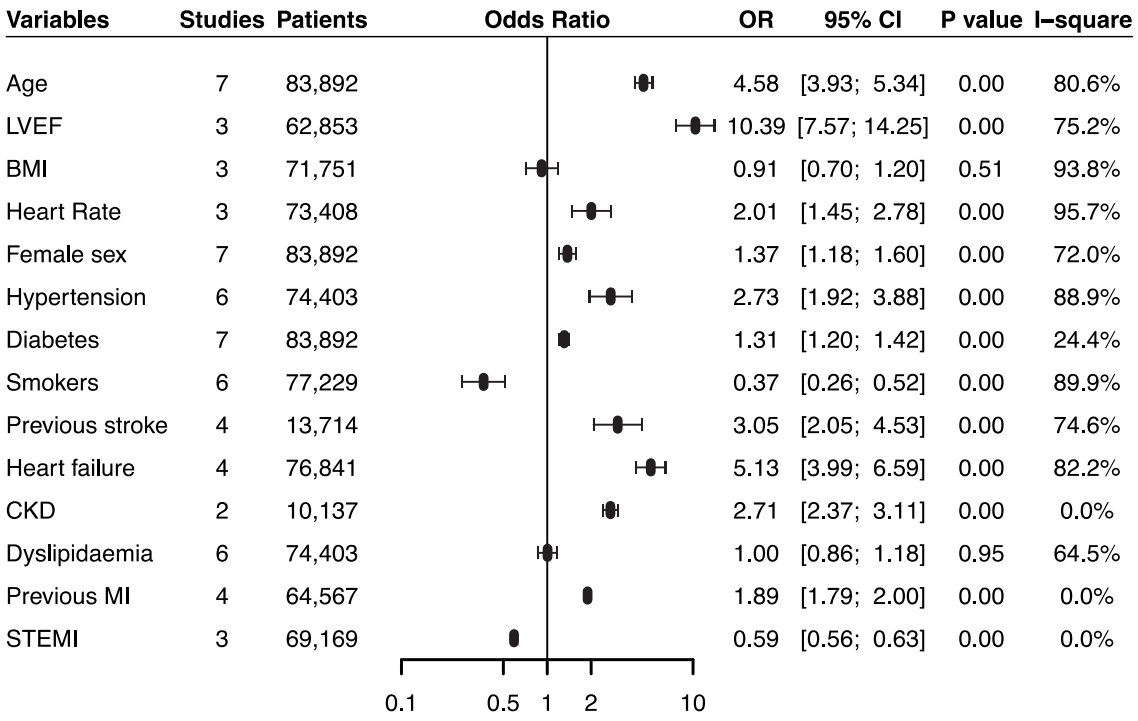
Supplementary Figure 10. Meta-regression plots of prevalent atrial fibrillation in patients with acute coronary syndromes



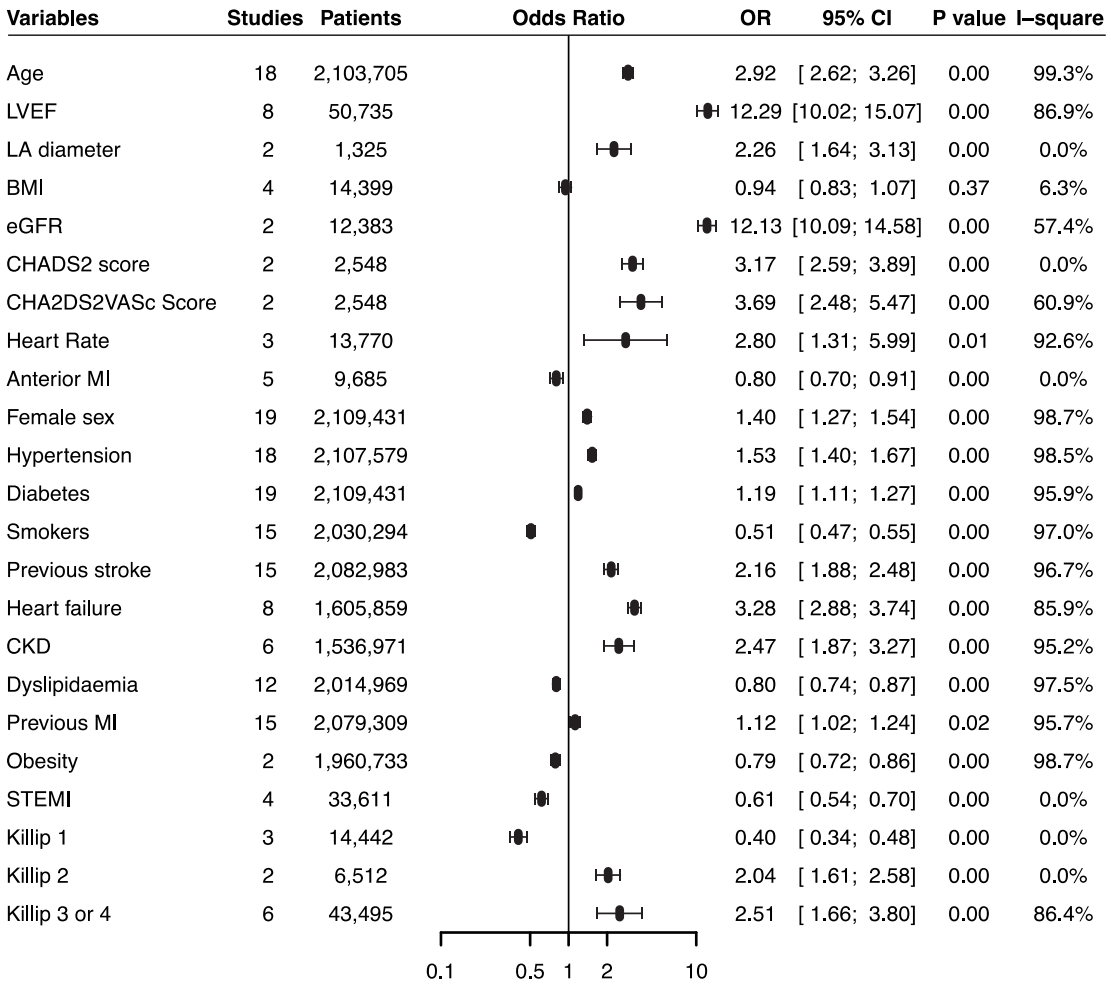
Supplementary Figure 11. Pooled univariable correlates of newly diagnosed atrial fibrillation in patients with acute coronary syndromes



Supplementary Figure 12. Pooled univariable correlates of pre-existing atrial fibrillation in patients with acute coronary syndromes



Supplementary Figure 13. Pooled univariable correlates of prevalent atrial fibrillation in patients with acute coronary syndromes



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6.2 Frequency and prognostic significance of atrial fibrillation in acute pulmonary embolism: a pooled analysis

6.2.1 Introduction

Acute pulmonary embolism (aPE) and atrial fibrillation (AF) are common cardiovascular conditions with substantial mortality and disability. In Europe and the United States, there are an estimated one million cases of aPE, leading to approximately 0.3 million deaths annually [587-589]. Atrial fibrillation is the most common arrhythmia, affecting more than 38 million individuals (0.51% of global population) [1], and is associated with markedly increased risk of stroke, systemic embolism, and death [70, 167]. Due to shared risk factors such as ageing, obesity, hypertension, and heart failure, AF and aPE frequently co-exist [172]. Atrial fibrillation is strongly associated with an increased risk of venous thromboembolism (VTE) including aPE, especially during the first months after AF diagnosis [173, 174]. Conversely, multiple arrhythmias including new-onset AF occur after an aPE [172].

Atrial fibrillation affects the prognosis of patients with a wide range of cardiovascular events. For instance, AF, especially newly diagnosed AF, is associated with poor short-term and long-term outcomes in patients with acute coronary syndromes [590]. This observation has led to the development of tailored interventions to address the thromboembolic and hemorrhagic risk in patients with AF [582, 583]. Studies investigating the prognostic impact of AF in patients with aPE have shown conflicting results [591-594]. Indeed, whether AF truly increases the risk of death in patients with aPE or is just a marker of co-morbidities or aPE severity remain uncertain. Furthermore, similar to acute myocardial infarction, the prognostic value of AF might differ depending on the temporal pattern of AF, either pre-existing or newly diagnosed [590]. Hence, the current systematic review and meta-analysis aimed to summarize data on 1) the prevalence of pre-existing AF and the incidence proportion of newly diagnosed

AF; 2) the predictors of newly diagnosed AF and; 3) the risk of short-term and long-term mortality attributable to AF, according to its temporal patterns in patients with aPE.

6.2.2 Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [595]. A protocol was prospectively registered on PROSPERO (CRD42022299194).

6.2.2.1 Literature search

We searched Excerpta Medica Database (EMBASE), PubMed/MEDLINE, and Web of Science to identify relevant studies published through December 12, 2021 (date of the last search), without language restriction. The search strategy used a combination of "atrial fibrillation", "pulmonary embolism", or their synonyms (**Supplementary Table 1**). Additional hand searches were also carried out by tracking citations and reference chaining of identified studies.

6.2.2.2 Study selection

We included cross-sectional studies, cohort studies, or RCTs reporting primary data on the prevalence or incidence of AF (or atrial flutter), its risk factors, or its association with mortality in patients with aPE. We excluded studies with less than 100 participants. For articles reporting data from the same primary study or registry (duplicates), we included the single most comprehensive one reporting the largest sample size. Two reviewers (JJN and UFN) independently screened the titles and abstracts of identified citations and then performed a detailed review of all selected full texts to ascertain eligibility. Disagreements were resolved through discussion and consensus.

6.2.2.3 Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by another investigator (UFN). We collected data on study characteristics including sample size, mean or median age, proportion of males, proportion of patients with co-morbidities such as hypertension, diabetes, obesity, heart failure, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, and risk factors for VTE such as cancer, recent surgery, immobilization, previous VTE. We also gathered information on total sample size and number of participants with various types of AF to compute prevalence or incidence proportion; on risk estimate (hazard ratio [HR], odds ratio [OR], or risk ratio [RR]) with the 95% confidence interval (CI) for each variable assessed as a potential predictor of AF and; on risk estimate with the 95% CI for the association of AF with mortality. Each study was evaluated for risk of bias using an adapted version of the tool developed by Hoy et al. [386].

6.2.2.4 Definitions

AF was classified as:

- Pre-existing AF: AF diagnosed before the index aPE;
- Newly diagnosed AF: AF diagnosed for the first time during the index presentation for aPE (on admission or during hospitalization), in the absence of a prior history of AF;
- Prevalent AF: total cases of any form of AF (pre-existing or newly diagnosed).

Mortality was classified as:

- Short-term mortality: death occurring within 3 months from the index aPE, including in-hospital mortality;

- Long-term mortality: death occurring beyond 3 months from the index aPE.

6.2.2.5 Statistical analysis

All analyses were conducted using the R statistical software (version 3.5.03, The R Foundation for statistical computing, Vienna, Austria). We performed random-effects meta-analysis of proportions using the inverse variance model. We then performed both random-effects meta-analyses using the most adjusted risk estimates associating AF and mortality, reporting the results in adjusted odds ratio (aOR) and 95% CI. Hazard ratio, OR, and RR were treated as equivalent measures of risk, as they were all derived from cohort studies. In case a study did not find a significant association between AF and mortality in univariable analysis and therefore did not report an adjusted risk estimate, we considered the unadjusted risk estimate to avoid biasing the analysis with the inclusion of only significant estimates. All statistical tests were two-tailed and statistical significance defined as p-value ≤ 0.05. Heterogeneity was assessed by the χ^2 test on Cochran's Q statistic [387], which was quantified by I^2 values, assuming that I^2 values of <25%, 50 – 75%, and >75% respectively represent low, medium, and high heterogeneity [388]. The influence of each study on the overall estimates and heterogeneity was assessed through *Leave-One-Out* influencer analysis model. We assessed small-study effect or publication bias by funnel plots and tests of funnel plot asymmetry (Egger's linear regression test).

6.2.2.6 Ethical approval

This is a systematic review using published data. Therefore, an ethical clearance is not required.

6.2.3 Results

6.2.3.1 Study selection and characteristics

Bibliographic searches retrieved 7126 records and reference scanning identified 13 additional records, from which 27 articles were finally included [591-594, 596-618]. The study selection is summarized in **Figure 1**. The list of included studies and their characteristics are presented in the appendix (**Supplementary Tables 2–4**). The included studies reported data from a pooled sample of 819,380 patients with aPE, were conducted between 2000 and 2020 (except for one study) and published between 1999 and 2021. Most studies were conducted in Europe (59.3%, n = 16). Most studies had low (63.0%, n = 17) or moderate (25.9%, n = 7) risk of bias (**Supplementary Table 5**).

6.2.3.2 Prevalence/incidence of AF according to temporal patterns

6.2.3.2.1 Pre-existing AF

Four studies reported on pre-existing AF from a pooled population of 17,661 patients with aPE. The overall prevalence of pre-existing AF was 11.3% (95% CI: 6.2-17.7), ranging from 4.8% to 21.1% (**Figure 2, Panel A**). Considering the high heterogeneity (I^2 97.4%), we performed influencer analysis using a leave-one-out approach. The omission of none of the studies significantly reduced the level of heterogeneity (**Supplementary Figure 1**). There was publication bias or small-study effect (*Egger's* p = 0.029).

6.2.3.2.2 Newly diagnosed AF

Six studies reported on newly diagnosed AF from a pooled population of 18,604 patients with aPE. The overall prevalence of newly diagnosed AF was 4.7% (95% CI: 3.3-6.2), ranging

from 2.7% to 7.2% (**Figure 2, Panel B**). There was high heterogeneity between studies (I^2 90.4%). Leave-one-out influencer showed that the omission of the study by Bikeli et al. reduced the level of heterogeneity from 90.4% to 43% (**Supplementary Figure 2**). There was no evidence of publication bias or small-study effect (*Egger's* p = 0.066).

6.2.3.2.3 Prevalent AF

Twenty-one studies reported on prevalent AF from a pooled population of 815,010 patients with aPE. The overall prevalence of pre-existing AF was 13.2% (95% CI: 11.5-14.9) ranging from 7.5% to 23.5% (**Figure 3**). Considering the high heterogeneity (I^2 99.5%), we performed influencer analysis. The omission of none of the studies significantly reduced the level of heterogeneity (**Supplementary Figure 3**). There was no evidence publication bias or small-study effect (*Egger's* p = 0.472).

6.2.3.3 Predictors of AF in aPE

Only one study reported on predictors of newly diagnosed AF after aPE from multivariable analysis [610]. These predictors included congestive heart failure (aOR 3.33, 95% CI: 1.81-6.12, p <0.001), ischemic heart disease (aOR 3.25, 95% CI: 1.65-6.39, p <0.001), massive PE (aOR 2.67, 95% CI: 1.19-5.99, p = 0.017).

6.2.3.4 Association of AF with mortality in patients with aPE

6.2.3.4.1 Short-term mortality

Overall, AF was associated with increased risk of short-term mortality (aOR 1.54, 95% CI: 1.44-1.64). There was low heterogeneity (I^2 6%). There was no evidence publication bias or small-study effect (*Egger's* p = 0.846). In subgroup analyses, all types of AF were associated

with increased risk of short-term mortality: pre-existing AF (aOR 1.90, 95% CI: 1.59-2.27), newly diagnosed AF (aOR 1.51, 95% CI: 1.18-1.93), and prevalent AF (aOR 1.50, 95% CI: 1.42-1.60). There was low heterogeneity in all subgroup analyses (all I^2 <5%).

6.2.3.4.2 Long-term mortality

AF increased the risk of long-term mortality (aOR 1.58, 95% CI: 1.26-1.97). There was moderate heterogeneity between studies (I^2 60%). In leave-one-out influencer analysis, the omission of none of the studies reduced the level of heterogeneity below 50% (**Supplementary Figure 4**). There was no evidence of publication bias or small-study effect (*Egger's* p = 0.854). In subgroup analyses, pre-existing AF (aOR 2.08, 95% CI: 1.27-3.42) and prevalent AF (aOR 1.29, 95% CI: 1.02-1.63) were associated with higher long-term mortality, whereas for newly diagnosed AF there was a trend towards a higher risk of mortality (aOR 1.46, 95% CI: 0.96-2.22).

6.2.4 Discussion

This review aimed to summarize data on the prevalence/incidence, risk factors and prognosis of AF in patients with aPE. We found that: 1) the prevalence of pre-existing AF, newly diagnosed AF and prevalent AF were 11.3%, 4.7% and 13.2%, respectively 2) predictors of newly diagnosed AF from one study included congestive heart failure, ischemic heart disease, and massive aPE; 3) irrespective of its timing, AF markedly increased the risk of short-term and long-term mortality in patients with aPE (**Figure 6**).

According to this study, AF is frequent in patients with aPE. AF might be the cause of aPE in a significant proportion of cases. Embolization of thrombi from veins in the lower legs to the pulmonary arteries is the main mechanism of aPE. However, it has been shown that

only 50%-70% of patients with aPE have concomitant deep vein thrombosis [619]. This suggests that there are aetiopathogenic mechanisms other than VTE, including AF, in about 30%-50% of cases of aPE. In fact, one study reported a 53.8% proportion of AF in patients with aPE and no history of VTE [619]. Some studies have suggested that isolated aPE may be due to right atrial thrombus caused by AF [608, 620, 621]. In one study, the prevalence of right atrial or ventricular thrombus was markedly higher in patients with paroxysmal or permanent AF compared to those in sinus rhythm [608].

Atrial fibrillation is newly diagnosed in about 5% of patients with aPE. This newly diagnosed AF might be new onset, triggered by acute precipitants such as right ventricular failure or stretch injuries [622]. Only one study reported on risk factors for newly diagnosed AF based on multivariable analysis. It identified massive aPE, congestive heart failure, and ischemic heart disease as predictors of new-onset AF [610]. In view of the poor prognosis associated with AF, continuous electrographic monitoring to identify AF alongside ventricular tachyarrhythmias might be beneficial in patients with aPE, especially in those with risk factors such as massive aPE, acute heart failure, or history of ischemic heart disease. It is worth mentioning that none of the studies that contributed to the pooled estimate of newly diagnosed AF reported the use of continuous electrocardiographic monitoring [592, 593, 596, 608, 610, 617]. This means that the incidence of new-onset AF might have been underestimated by 12-lead ECG done only at admission or few times during the hospital stay. Further studies are needed to explore predictors of new-onset or newly diagnosed AF, and adequate electrocardiographic monitoring strategies in patients with aPE.

This review shows that AF is associated with increased risk of mortality in the short- and long-term. There are several potential mechanisms underlying the adverse impact of AF in the setting of aPE. AF induces hemodynamic disturbances such as poor atrial contraction, rapid and irregular ventricular rates, and atrioventricular desynchrony that reduce cardiac

output and ultimately cause acute heart failure, cardiogenic shock, and acute kidney injury [577, 578, 623]. This hemodynamic instability also results in blood stasis and possibly thrombus formation in both atria, with a risk of embolization to the brain or the lungs [578, 594, 624, 625]. The simplified PE severity index (sPESI) which is used for the risk stratification of patients with aPE includes heart rate ≥ 110 as a severity criterion, but not AF [626]. However, the addition of AF to the sPESI was shown to increase the predictive value of sPEPI for adverse in-hospital outcomes [626]. This finding should be explored in other cohorts of patients with aPE.

All types of AF, whether pre-existing or newly diagnosed, were found to increase the risk of death in patients with aPE. No information was provided on the use of oral anticoagulation in patients with AF who had an aPE. Atrial fibrillation is strongly associated with an increased risk of VTE including aPE, especially during the first months after AF diagnosis, suggesting that the introduction of oral anticoagulation soon after AF diagnosis might reduce the risk of both VTE and ischemic stroke [173, 174]. The CHA_2DS_2-VASc does not take into consideration previous PE in the risk stratification of patients with AF who are candidates for oral anticoagulation. However, oral anticoagulation might be beneficial in low-risk AF patients (based on a low CHA_2DS_2-VASc score) with unprovoked aPE, beyond the duration of anticoagulation recommended for aPE alone. Additionally, patients with newly diagnosed AF after aPE might also be good candidates for early rhythm control therapy, considering the lower adverse cardiovascular outcomes associated with early rhythm control therapy than usual care among patients recently diagnosed with AF (≤ 1 year) and cardiovascular conditions [281]. These hypotheses need to be investigated.

This study has some limitations. First, data synthesized in this review span two decades and therefore might not be fully representative of the current clinical epidemiology of aPE. Second, there was high heterogeneity in pooled prevalence estimates. This might be due to substantial difference in patients' risk profile across studies. Unfortunately, the limited

number of studies reporting pre-existing and newly diagnosed AF, and the infrequent reporting of key risk factors for AF in the included studies (**Supplementary Table 4**) precluded meta-regression analysis to explore sources of prevalence variability across studies. Third, AF burden that is increasingly considered as a stronger predictor of adverse outcomes than AF as a binary entity (present vs absent) was not reported in the included studies and therefore not examined in this review. Finally, in some primary studies, AF was not included in multivariable regression analysis when there was no significant association of AF with mortality in univariable analysis. In such studies only unadjusted risk estimates were available. We included these estimates to avoid excluding systematically studies showing no association between AF and mortality. Although, this allowed to have more realistic estimates, it increased the likelihood of residual confounding.

6.2.5 Conclusion

About one in eight patients with aPE has AF, with a significant proportion of newly diagnosed AF. Irrespective of its temporal patterns, AF is associated with increased short- and long-term mortality. Searching for AF is therefore crucial in the context of aPE. Studies are needed to determine the appropriate rhythm monitoring strategies in patients with aPE. In view of the strong prognostic value of AF, its incorporation into risk stratification schemes for patients with aPE should be considered.

6.2.6 Figures

Figure 1. Study selection

Figure 2. Proportion of patients with pre-existing and newly diagnosed atrial fibrillation

Figure 3. Proportion of patients with prevalent atrial fibrillation

Figure 4. Association of atrial fibrillation types with short-term mortality

Figure 5. Association of atrial fibrillation types with long-term mortality

Figure 6. Graphical abstract

Figure 1. Study selection

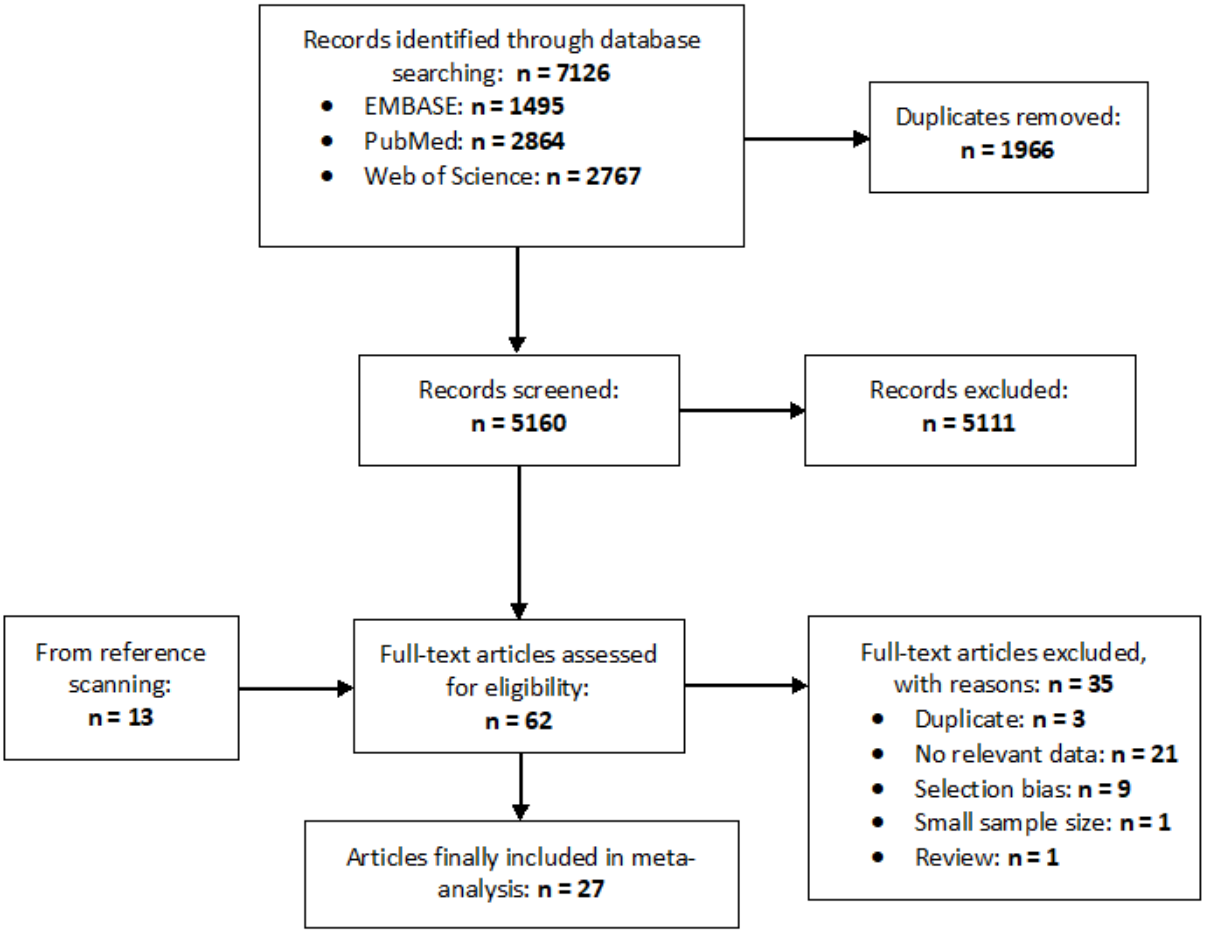


Figure 2. Proportion of patients with pre-existing and newly diagnosed atrial fibrillation

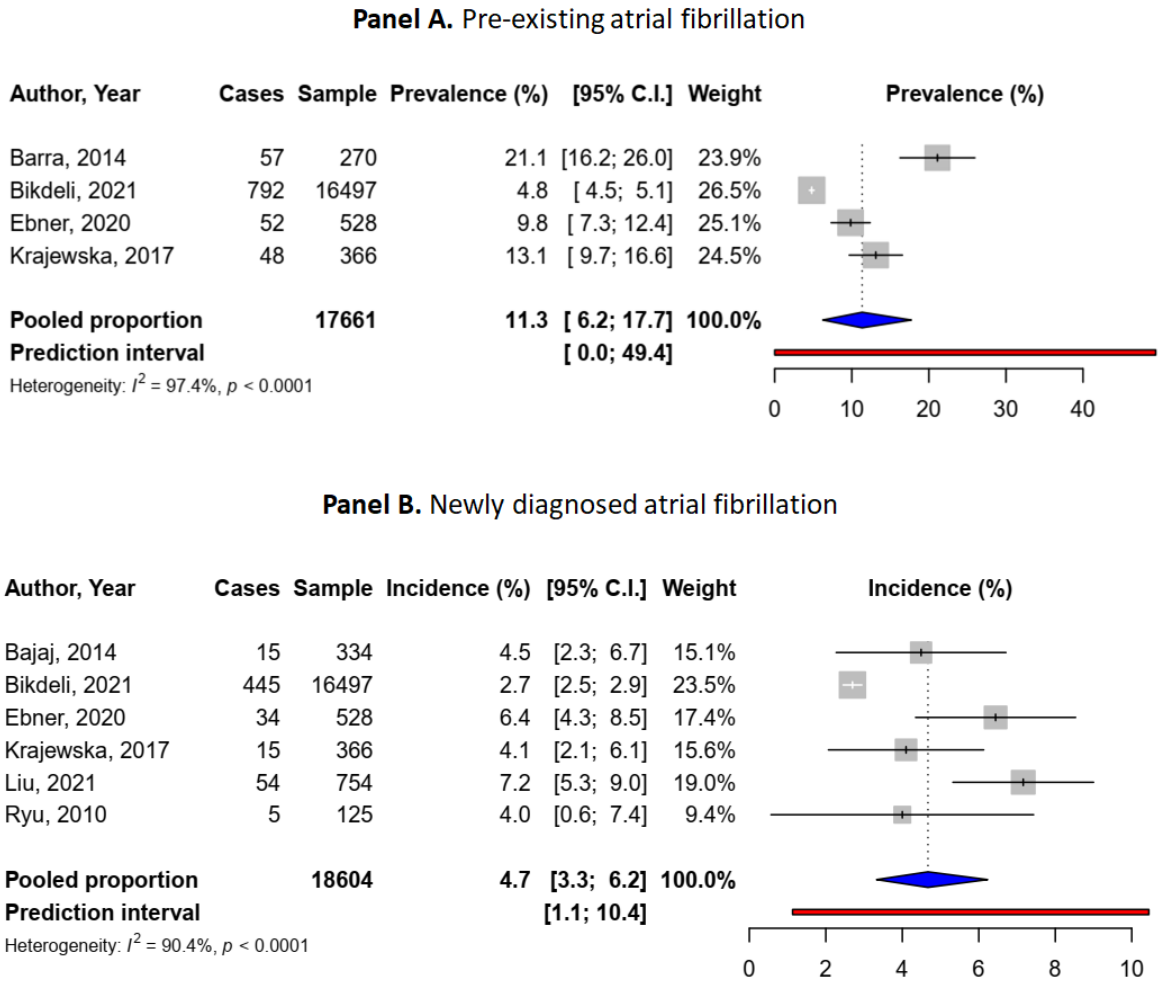


Figure 3. Proportion of patients with prevalent atrial fibrillation

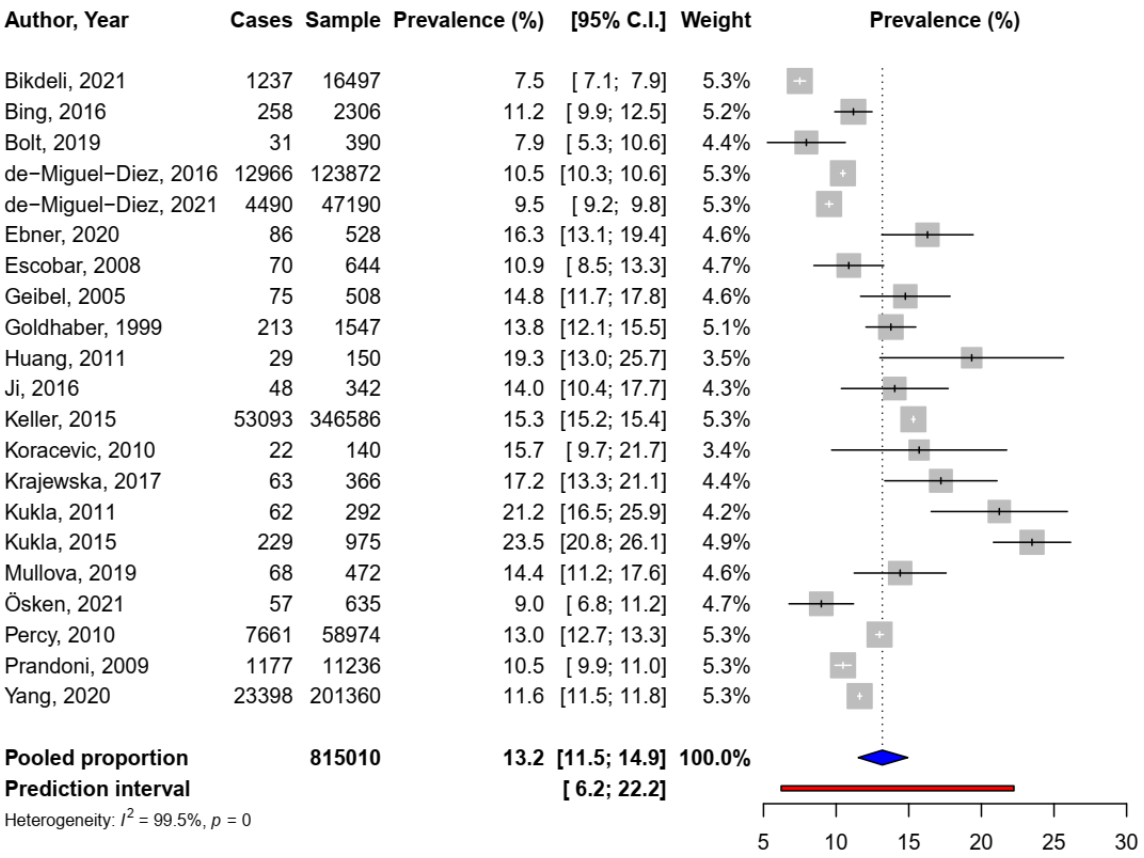


Figure 4. Association of atrial fibrillation types with short-term mortality

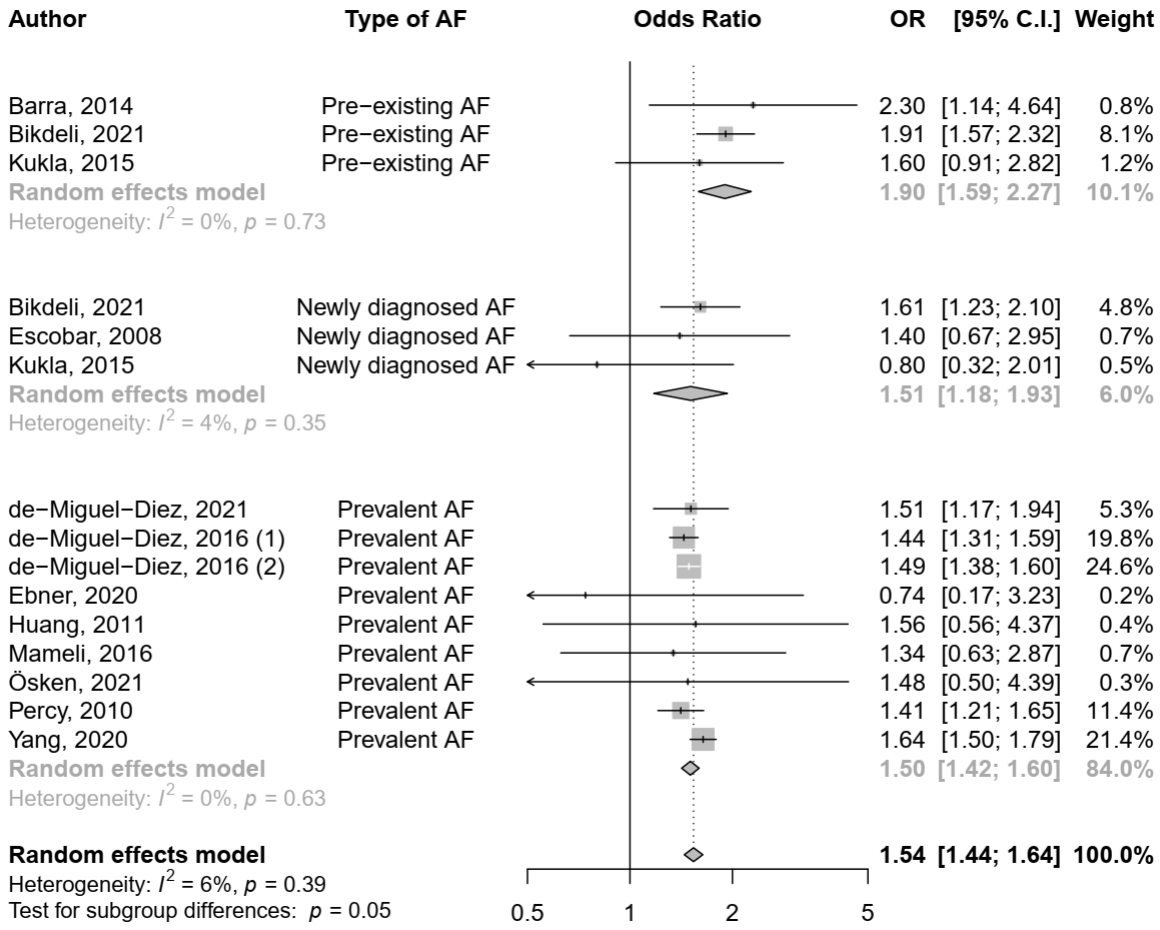


Figure 5. Association of atrial fibrillation types with long-term mortality

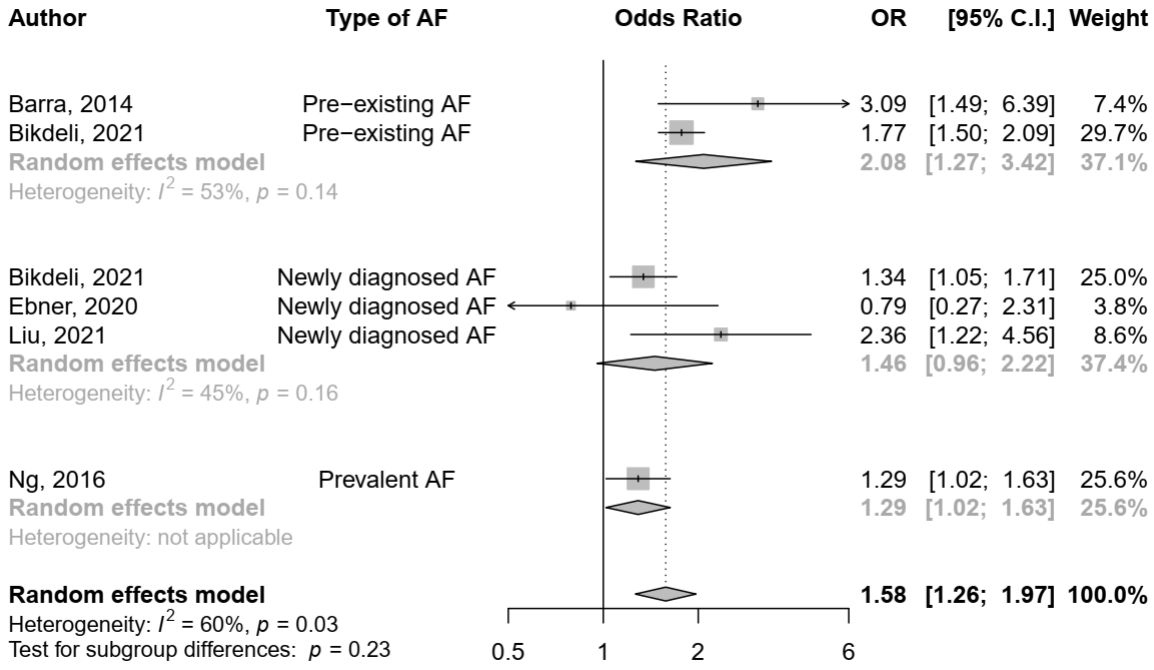
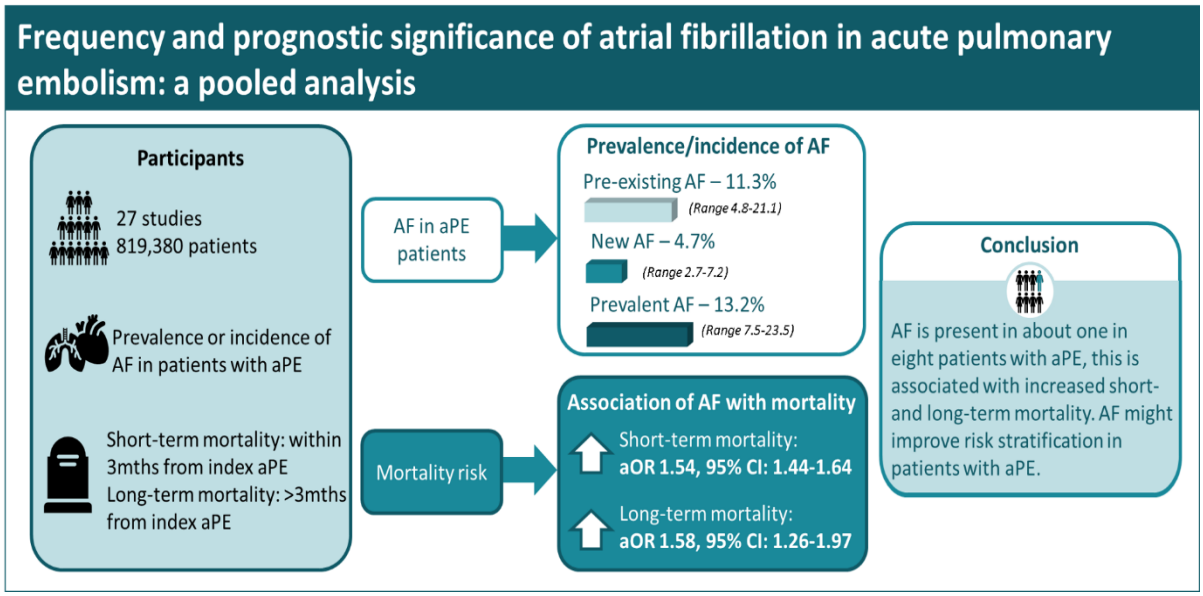


Figure 6. Graphical abstract



6.2.7 Appendix

Supplementary Table 1. Search strategies

	PUBMED
#P1	"deep vein thrombosis" OR "venous thrombosis" OR "pulmonary embolism" OR "venous thromboembolism" OR "pulmonary thromboembolism" OR "venous thromboembol*"
#P2	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#P3	#P1 AND #P2
	EMBASE
#E1	‘deep vein thrombosis’:ab,ti OR ‘venous thrombosis’:ab,ti OR ‘pulmonary embolism’:ab,ti OR ‘venous thromboembolism’:ab,ti OR ‘pulmonary thromboembolism’:ab,ti
#E2	'atrial fibrillation':ab,ti OR 'auricular fibrillation':ab,ti OR 'AF':ab,ti OR 'AFib':ab,ti
#E3	#E1 AND #E2
#E4	#E3 AND ('article'/it OR 'article in press'/it)
	WEB OF SCIENCE
#W1	"deep vein thrombosis" OR "venous thrombosis" OR "pulmonary embolism" OR "venous thromboembolism" OR "pulmonary thromboembolism"
#W2	“atrial fibrillation” OR “auricular fibrillation” OR “AF” OR “Afib”
#W3	#1 AND #2
#W4	#3 AND limit to articles

Supplementary Table 2. Summarized study characteristics

Characteristics	**N = 27**
Total population	819,380
Year of publication, range	1999-2021
Period of inclusion of participants, range	1995-2020
Design	
- Cohort	27
Data collection	
- Prospective	8
- Retrospective	19
Regions	
- Europe	16
- Asia	4
- Northern America	3
- Multiregional	2
- Oceania	2
Countries	
- US	3
- Spain	3
- Germany	3
- Poland	3
- Multinational	2
- China	2
- Italy	2
- Australia	2
- Russia	1
- Serbia	1
- Switzerland and Germany	1
- Taiwan	1
- Turkey	1
- Portugal	1
Sampling	
- Non-probability	27
- Random	0
Risk of bias	
- Low	17
- Moderate	7
- High	3

Supplementary Table 3. General characteristics of included studies

Author	Year of publ	Year of recruitment	Country	Study design	Sampling	Data collection	Methods of diagnosis of pulmonary embolism	Arrhythmia type
Bajaj	2014	2007-2010	USA	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Barra	2014	2007-2011	Portugal	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Bikdeli	2021	2014-2020	Multinational	Cohort	Nonprobability	Prospective	CT pulmonary angiography	AF
Bing	2016	2000-2012	Australia	Cohort	Nonprobability	Prospective	V/Q scan or CT pulmonary angiography	AF or AFl
Bolt	2019	2009-2013	Switzerland and Germany	Cohort	Nonprobability	Prospective	V/Q scan or CT pulmonary angiography	AF or AFl
de-Miguel-Diez	2016	2004-2013	Spain	Cohort	Nonprobability	Retrospective	NR	AF
de-Miguel-Diez	2021	2016-2018	Spain	Cohort	Nonprobability	Retrospective	NR	AF
Ebner	2020	2008-2017	Germany	Cohort	Nonprobability	Prospective	CT pulmonary angiography	AF
Escobar	2008	2003-2006	Spain	Cohort	Nonprobability	Prospective	CT pulmonary angiography	Atrial arrhythmias
Geibel	2005	NR	Germany	Cohort	Nonprobability	Retrospective	V/Q scan or CT pulmonary angiography	AF or AFl
Goldhaber	1999	1995-1996	Multinational	Cohort	Nonprobability	Prospective	V/Q scan or CT pulmonary angiography	AF
Huang	2011	2004-2009	Taiwan	Cohort	Nonprobability	Prospective	CT pulmonary angiography	AF
Ji	2016	2012-2015	China	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Keller	2015	2011-2013	Germany	Cohort	Nonprobability	Prospective	NR	AF or AFl
Koracevic	2010	2003-2008	Serbia	Cohort	Nonprobability	Retrospective	NR	AF
Krajewska	2017	2004-2013	Poland	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Kukla	2011	NR	Poland	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Kukla	2015	2004-2012	Poland	Cohort	Nonprobability	Retrospective	CT pulmonary	AF

							angiography	
Liu	2021	2017-2019	China	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Mameli	2016	2009-2011	Italy	Cohort	Nonprobability	Retrospective	V/Q scan or CT pulmonary angiography	AF
Mullova	2019	2003-2014	Russia	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Ng	2016	2001-2012	Australia	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF or AFl
Ösken	2021	2014-2020	Turkey	Cohort	Nonprobability	Retrospective	CT pulmonary angiography	AF
Percy	2010	2010-2014	USA	Cohort	Nonprobability	Retrospective	NR	AF
Prandoni	2009	2000-2006	Italy	Cohort	Nonprobability	Retrospective	NR	AF or AFl
Ryu	2010	2001-2008	Korea	Cohort	Nonprobability	Retrospective	V/Q scan or CT pulmonary angiography	AF or AFl
Yang	2020	2012-2014	USA	Cohort	Nonprobability	Retrospective	NR	AF or AFl

AF: atrial fibrillation; AFl: atrial flutter; CT: computed tomography; ECG: electrocardiogram; NR: not reported; Publ: publication; V/Q: ventilation/perfusion scan

Supplementary Table 4. Clinical characteristics of participants in the included studies

Author	Year of publ	Total sample	Mean or median age	Males (%)	HPT (%)	Diabetes (%)	Obesity (%)	Smoking (%)	COPD (%)	Heart failure (%)	Cancer (%)	Recent Surgery (5)	Previous DVT/PE (%)	Stroke (%)
Bajaj	2014	334	65.8	46			37.4	27.2	10.5	9.3	27	14.7	19.2	3.9
Barra	2014	270	70.1	40.1						23.3	22.2		23.3	16.7
Bikdeli	2021	16497												
Bing	2016	2306			25.5	14		12.8	11.1	9.3	49.3			2.3
Bolt	2019	390	74	54					13	12	15			
de-Miguel-Diez	2016	123872	70.34	45.5	40									
de-Miguel-Diez	2021	47190	73	46.6	42.4	16.5	12.5				18.6	1.8		
Ebner	2020	528	70	46.8	63.6	17.6			15.3	14.5	14.4			
Escobar	2008	644		43					8.2	7.6	21.3	9.6	10.1	
Geibel	2005	508	63	42.1					10		12.4		28.9	4.9
Goldhaber	1999	2454	62.3	45										
Huang	2011	150	71.3	64	47.3	20			14	15.3	30.7	6.7	10	
Ji	2016	342	71.4	58.5	44.2	8.2		34.2	36.8		12	15.2		
Keller	2015	346586	72	46.7	45	16.1	8.7		18.5	21.9	20	51.1		
Koracevic	2010	140	63.2	31.4										
Krajewska	2017	366	66.1	45.9	55.2	14.5	36.9		5.5		17.2		5.7	
Kukla	2011	292	65.4	37.3			31.5		8.2	12.3	7.5			
Kukla	2015	1006	66	41			19		10	12	13			
Liu	2021	590	67	48.6		4.7			8	21	11.2		30.5	13.4
Mameli	2016	971	71.5	36.8										
Mullova	2019	472	58.1	49.6										
Ng	2016	1142	67.2	45	22.3	13.1		8.4	9.8	10	21.6			
Ösken	2021	635	61.8	45.8	55	28		40.8	15.3	10.6	5.8	10.7	5.7	
Percy	2010	58974	59	50.6	52	19	25	27	19	14	11			

Prandoni	2009	11236	70	39	14	1.3			9					
Ryu	2010	125	62.7	45	28	18					28	14		
Yang	2020	201360	61	48										

COPD: chronic obstructive pulmonary disease; DVP: deep vein thrombosis; HPT: hypertension; PE: pulmonary embolism; Publ: publication

Supplementary Table 5. Risk of bias assessment

Author	Year of publication	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Total score	Level of bias
Bajaj	2014	0	1	1	1	0	1	1	1	1	7	Low
Barra	2014	0	1	1	1	0	1	1	1	1	7	Low
Bikdeli	2021	1	1	1	1	1	1	1	1	1	9	Low
Bing	2016	0	1	1	1	0	1	0	1	1	6	Moderate
Bolt	2019	0	0	1	1	1	1	1	1	1	7	Low
de-Miguel-Diez	2016	0	1	1	1	0	0	0	1	0	4	High
de-Miguel-Diez	2021	0	1	1	1	0	0	0	1	0	4	High
Ebner	2020	0	1	1	1	1	1	1	1	1	8	Low
Escobar	2008	0	0	1	1	1	1	0	1	1	6	Moderate
Geibel	2005	0	1	1	1	0	1	1	1	1	7	Low
Goldhaber	1999	0	1	1	1	1	1	1	1	1	8	Low
Huang	2011	0	0	1	1	1	1	1	1	1	7	Low
Ji	2016	0	0	1	1	0	1	0	1	1	5	Moderate
Keller	2015	1	1	1	1	0	1	1	1	1	8	Low
Koracevic	2010	0	0	1	1	0	0	0	1	1	4	High
Krajewska	2017	0	1	1	1	0	1	1	1	1	7	Low
Kukla	2011	0	1	1	1	0	1	1	1	1	7	Low
Kukla	2015	0	1	1	1	0	1	1	1	1	7	Low
Liu	2021	0	1	1	1	0	1	1	1	1	7	Low
Mameli	2016	0	0	1	1	0	1	0	1	1	5	Moderate
Mullova	2019	0	0	1	1	1	1	1	1	1	7	Low
Ng	2016	0	1	1	1	0	1	1	1	1	7	Low
Ösken	2021	0	1	1	1	0	1	1	1	1	7	Low
Percy	2010	0	1	1	1	0	0	1	1	1	6	Moderate
Prandoni	2009	1	1	1	1	0	1	1	1	1	8	Low

Ryu	2010	0	0	1	1	0	1	1	1	1	6	Moderate
Yang	2020	0	1	1	1	0	0	1	1	1	6	Moderate

RoB: risk of bias

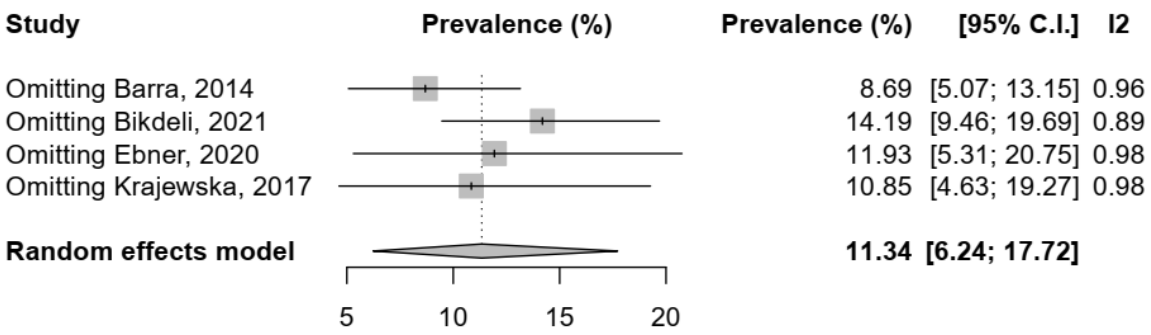
Interpretation of the score

7 – 9: Low Risk of Bias / High-quality study. Further research is very unlikely to change our confidence in the estimate.

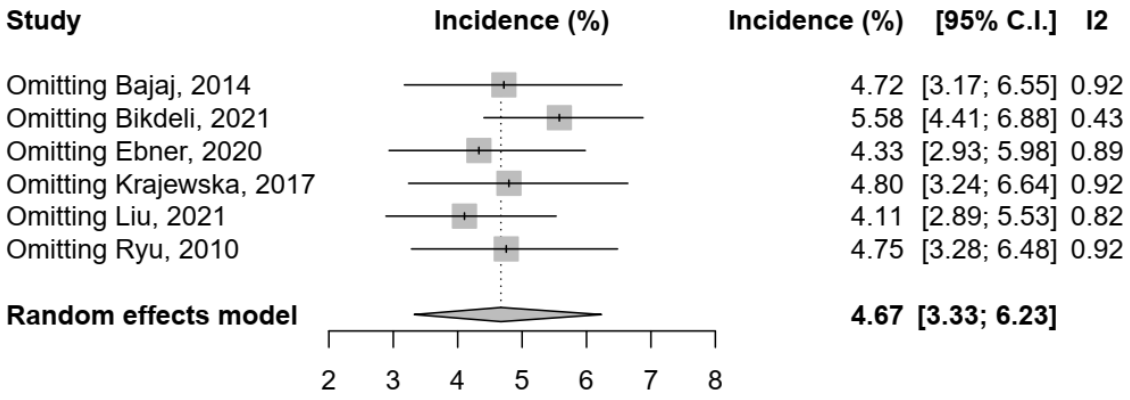
4 – 6: Moderate Risk of Bias / Moderate-quality study. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.

3 or less: High Risk of Bias / Low-quality study. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate. Further research is mandatory.

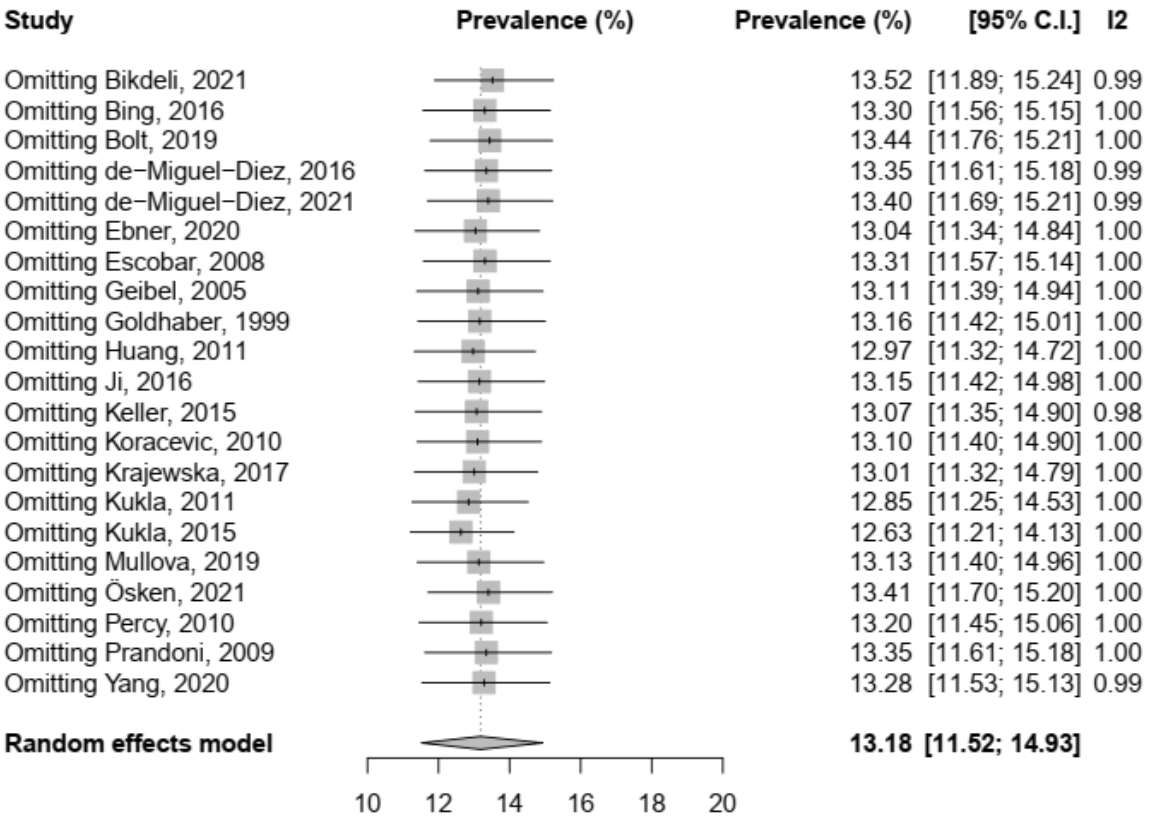
Supplementary Figure 1. Influencer analysis for studies reporting on pre-existing atrial fibrillation



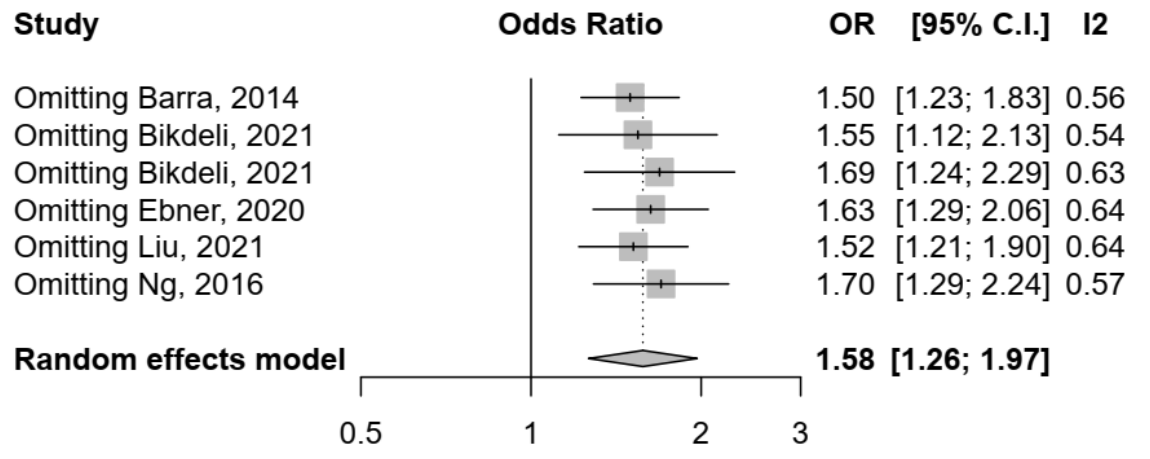
Supplementary Figure 2. Influencer analysis for studies reporting on newly diagnosed atrial fibrillation



Supplementary Figure 3. Influencer analysis for studies reporting on prevalent atrial fibrillation



Supplementary Figure 4. Influencer analysis for studies reporting on the association between atrial fibrillation and long-term mortality



CHAPTER 7:

Sex disparities in enrolment and reporting of outcomes by sex in contemporary clinical trials of atrial fibrillation

Statement of Authorship

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Contribution to the Paper	Conception and design, bibliographic searches, data collection, data analysis, data interpretation, manuscript drafting, manuscript revision		
Overall percentage (%)	60%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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7.1 Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, is an increasingly important threat to global health owing to its rapidly growing prevalence [1] and associated devastating complications including stroke, heart failure, and death [70, 167]. There are significant sex differences in the epidemiology of AF [627]. Women have a lower prevalence of AF compared to men: of the 37.6 million individuals with AF globally in 2017, 17.8 million (47.3%) were women [1]. Furthermore, AF has been shown to be a stronger risk factor for stroke, cardiovascular mortality, and all-cause mortality in women compared with men [329].

Sex differences in disease pathophysiology, clinical patterns and response to treatment should be considered in the design, analysis, and reporting of research studies [628, 629]. Recent analyses have shown inadequate enrolment of women in randomized controlled trials (RCTs) of various cardiovascular diseases [630-632]. Given the well-established importance of sex in the epidemiology of AF [627], the underrepresentation of women in RCTs of therapies for patients with AF might undermine their generalizability and consequently the validity of the evidence guiding treatment of women. Furthermore, reporting of trial results in women and men separately is essential to determine when sex-specific therapeutic strategies should be applied. Despite the call for reporting of trial results by sex made by several initiatives over more than a decade [633, 634], a number of previous studies have observed that results of most trials are not reported according to sex [631, 635-637]. The current study, which focuses on recent RCTs of AF, aims to measure the sex disparities in participants' recruitment, determine associated factors, and describe the frequency of reporting of primary endpoint results by sex.

7.2 Methods

This project was registered with PROSPERO (CRD42021291258).

7.2.1 Literature search

PubMed/MEDLINE was searched to identify all RCTs of AF published between January 1, 2011, and November 20, 2021 in top journals (based on Clarivate Analytics impact factor 2020) of general medicine (New England Journal of Medicine [NEJM], The Lancet, Journal of the American Medical Association [JAMA], JAMA Internal Medicine and British Medical Journal [BMJ]), of general cardiology (European Heart Journal [EHJ], Circulation, Journal of the American College of Cardiology [JACC], and JAMA Cardiology), and of cardiac electrophysiology (JACC Clinical Electrophysiology [JACC CE], Circulation Arrhythmia and Electrophysiology [Circ AE], Hearth Rhythm, Europace, and Journal of Cardiac Electrophysiology [JCE]). The search strategy was built based on the combination of relevant terms related to atrial fibrillation, clinical trials, and the names of the targeted journals (**Supplementary Table 1**). One investigator (JJN) conducted the bibliographic searches. The reference lists of eligible articles were also scrutinized and ClinicalTrial.gov to identify additional relevant RCTs.

7.2.2 Selection of studies to include in the review

The inclusion criteria were: 1) studies reporting final primary results of an RCT; 2) published in one of the 12 abovementioned target journals between January 1, 2011, and November 20, 2021; 3) trial population consisting of patients with atrial fibrillation. The exclusion criteria were: 1) sample size of less than 100 participants; 2) articles not reporting primary results such as subsequent analyses of trial data; 3) RCTs of AF screening or detection in at risk populations such as elderly or patients with stroke. Two investigators (JJN and UFN) independently selected records from bibliographic searches based on title and abstract screening. Full texts of articles deemed potentially eligible were retrieved and screened

independently by the same investigators for final inclusion. Selection discrepancies were solved through discussion and consensus.

7.2.3 Data extraction and management

Data were extracted using a standardized data abstraction form and included: name of the first author, year of publication, period of participants' recruitment, whether it was a single or multicenter trial, total trial population size, whether participants were recruited in one or multiple countries, trial name, trial registration number, trial phase (as reported by the investigators), masking (unmasked, single-blinded, or double-blinded trial), type of intervention, primary outcome, involvement of industry, involvement of 1 or more females represented in trial leadership, total sample size, number of enrolled females, whether trial results were reported by sex, and whether there was a sex difference in the trial results. Detailed variable definitions are provided in the appendix (**Supplementary Table 2**). Data were extracted by one investigator (JJN). This study did not aim to assess treatment efficacy in the included RCTs. Therefore, we did not assess risk of bias.

7.2.4 Assessment of sex enrolment disparities

To measure enrolment of females, we used a modified version of the enrolment disparity difference (EDD), a metric which accounts for sex prevalence inequalities in the general population, initially developed to characterize enrolment disparities in lung cancer treatment RCTs [638], and also used in a recent study of sex enrolment disparities in RCTs of acute stroke therapies [630]. For each RCT, we calculated the proportion of females enrolled in the trial (PFT), and estimated the proportion of females with AF among the general population (PFG) using data from the Global Burden of Disease (GBD) database (https://gbd2017.healthdata.org/gbd-search/). Each trial was matched to GBD prevalence data

on the basis of the approximate median year of the trial recruitment period and geographic area. Because data in the GBD database were available up to year 2017, data for 2017 were attributed to all trials in which participants were recruited from 2017 onward. For trials conducted in one country, we considered the GBD estimates of that country. For trials conducted in two or more countries, if they were in the same GBD region, we included estimates for the corresponding region, otherwise we considered the global estimates. We abstracted the number of people with AF and associated 95% uncertainty interval for females, males, and both.

The EDD was calculated as the difference between the PFT and PFG. We also calculated the standard errors (SE) of the PFT, PFG, and EDD. The following calculations were performed:

$$PFT = \frac{\text{Number of females in the trial}}{\text{Number of participants in the trial}}$$

$$PFG = \frac{\text{Number of females with AF in the general population}}{\text{Number of people (males and females) with AF in the general population}}$$

$$SE(PFT) = \sqrt{\text{PFT x } \frac{(1 - \text{PFT})}{\text{Number of participants in the trial}}}$$

$$EDD = PFT - PFG$$

$$SE(EDD) = \sqrt{SE(PFT)^2 + SE(PFG)^2}$$

To calculate the standard error of the PFG, we accounted for the uncertainty of the estimates from the GBD. For each trial, we used the matched number of males and females with AF and the associated 95% uncertainty intervals from the GBD to fit γ distributions and drew 100,000 samples from each of the γ distributions to compute the corresponding PFG and its standard error.

7.2.5 Statistical analysis

Sex disparities in enrolment across RCTs were summarized using a random-effects meta-analysis of the EDDs. We conducted subgroup analyses according to trial characteristics including journal categories (general medicine, general cardiology, and cardiac electrophysiology), period of publication, sample size category, geographical region, type of trial intervention, presence of females in a leadership position, and industry involvement. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic [387], which was quantified by I^2 values, assuming I^2 values of 25, 50 and 75% respectively representing low, medium and high heterogeneity [388]. We performed univariable and multivariable meta-regression to explore factors associated with enrolment of females. Analyses were conducted using the R statistical software (version 3.5.03, The R Foundation for statistical computing, Vienna, Austria) and IBM SPSS Statistics version 27.0 (Chicago, Illinois, USA).

7.3 Results

7.3.1 Study selection and characteristics

From 1133 records identified from bibliographic search and additional sources, we finally included 142 articles reporting trial data from a total of 133,532 participants (Figure 1). The list of included trials and their individual characteristics (**Supplementary Tables 3 and 4**) are presented in the appendix. These articles were most frequently published in Circ AE (14.8%), EHJ (14.1%), Europace (12.7%), NEJM (11.3%), and Heart Rhythm (10.6%). Most RCTs were conducted in multiple centers (71.8%), or in one country (59.2%). About a third of RCTs were conducted in several regions, whereas the single most represented region was Europe (31.0%). Most RCTs did not have a woman in a leadership role (86.6%), and industry (for-profit entity) was involved in 46.5% of them. The number of participants enrolled in the

included trials ranged from 100 to 21,105, with a median of 222 (interquartile range 150-501.5). The most common interventions evaluated in the RCTs were catheter ablation (49.3%), any adjuvant therapy to catheter ablation or electrical cardioversion (12.7%), preprocedural oral anticoagulation (9.9%), long-term oral anticoagulation (7.7%), and risk factor management or integrated care (7.7%) (**Table 1**).

7.3.2 Enrolment disparity differences

There were wide variations in the PFT and PFG across studies (**Figure 1**). The PFT ranged from 10.0% to 72.8% (median 30.9%, interquartile range 24.6%-38.1%), whereas the PFG ranged from 34.7% to 55.9% (median 45.3%, interquartile range 40.6%-47.2%). The random-effects pooled EDD of the 142 trials was −0.125 (95% CI, −0.143 to −0.108), representing an under-enrollment of females by an absolute difference of 12.5 percentage points relative to their representation in the general populations of people with AF. Female enrolment varied significantly across trials (I^2 88%). The results of subgroup analysis according to journals, publication period, sample size, region, type of intervention tested in the trial, industry involvement, and whether female(s) had a leadership role in the trial are presented in **Figure 2** and the appendix (**Supplementary Table 5**).

In univariable meta-regression analysis, an age limit for participants' inclusion in the trial, the mean age of participants, and the period of publication of the trial's results were associated with female enrolment, whereas a trend towards an association was noted for sample size, and industry involvement (**Table 3**). In multivariable analysis (Model 1), larger sample sizes were associated with an increased likelihood of female enrolment (categories <250 vs >750: adjusted odds ratio [aOR] 1.065, 95% CI: 1.008-1.125). Compared to trials conducted in Europe, those in North America (USA or Canada) were associated with lower female enrolment (aOR 0.945, 95% CI: 0.898-0.995). Because the periods of recruitment of

trials were very heterogeneous and difficult to categorize, we used the period of publication of the trial results as a surrogate of the period of recruitment. The participation of females was higher in trials published in 2020 or 2021 compared to those published between 2011 and 2013 (aOR 1.058, 95% CI: 1.004-1.115). Higher mean age of the trial population was also significantly associated with a greater likelihood of female enrolment (aOR 1.006, 95% CI: 1.002-1.009; Model 2).

7.3.3 Reporting of results by sex

Out of 142 trials, 36 (25.4%) reported primary endpoint results by sex. Reporting by sex was higher ($p < 0.001$) in general medicine journals (64.5%), compared to general cardiology journals (27.3%) and cardiac electrophysiology journals (7.5%). The NEJM (87.5%) and Lancet (50.0%) had the highest reporting rates. Reporting also differed by period of publication, geographic region, sample size, intervention, and industry involvement. Trials published in 2020 and 2021 were more commonly reported by sex compared to those published between 2011 and 2019 (40.0% vs 21.4%, $p = 0.038$). Reporting rates were higher in trials conducted in more than one country or more than one region compared to those conducted in a single country (36.2% vs 17.9%, $p = 0.013$) or a single region (43.5% vs 16.7, $p < 0.001$). Increased sample size was associated with more frequent reporting, with 66.6% of trials with more than 750 participants reporting compared to only 32.4% of trials with less than 250 participants ($p < 0.001$). Trials evaluating long-term oral anticoagulation (81.8%), left atrial appendage occlusion (75.0%), and risk factor management or integrated care interventions (63.6%) had significantly higher reporting rates compared to trials on other interventions ($p < 0.001$). Reporting was higher in trials with industry involvement compared to those with no industry involvement (34.5% vs 15.8%, $p = 0.007$). Twenty-nine of the 36

trials (80.6%) that reported results by sex performed statistical testing of the sex-by-treatment interaction (**Supplementary Table 4**).

7.4 Discussion

This study aimed to describe sex disparities in participants' recruitment and associated factors, and to describe the frequency of primary endpoint results reported by sex in contemporaneous RCTs of AF. Our major findings are: i) females were substantially less represented, with an absolute difference of 12.5 percentage points relative to their representation in the general populations of people with AF; ii) more recently published trials, those conducted in Europe, with larger sample sizes, and with a higher mean age of participants were associated with a greater likelihood of female enrolment; iii) only one quarter of trials reported sex-specific primary endpoint results; reporting by sex was more common in general medicine journals (mainly NEJM and Lancet), in multinational trials, those with higher sample sizes, those with industry involvement, those evaluating long-term oral anticoagulation, left atrial appendage occlusion, and risk factor management or integrated care interventions, and in the most recently published trials (2020 and 2021) (**Figure 4**).

The marked underrepresentation of females in RCTs of AF is a major issue considering that females have poor AF-related outcomes including more frequent strokes, cardiovascular and all-cause deaths compared with men [329]. This underrepresentation of females also raises concerns about the applicability and generalizability of trial results to females. For instance, the enrolment of females was lowest in RCTs of catheter ablation. A recent analysis of the Get With The Guidelines-AF registry in the United States found sex differences in AF ablation strategies that are not supported by current evidence [639],

highlighting the need for data to inform optimal ablation strategies by sex. This requires an appropriate representation of females in clinical trials.

We observed that trials with an upper age limit of 80 years or less had lower female representation in their study population. Furthermore, a younger mean age was associated with a reduced likelihood of female enrolment. Because females with AF are generally older than their male counterparts and diagnosed later in life [317], trials that include younger patients by chance or by design are likely to recruit fewer females. Therefore, an upper age limit as a selection criterion in trials of AF should be considered only if medically indicated. If age is used as a surrogate of age-related health condition such as frailty, it would be desirable to exclude participants based on a formal assessment of the condition rather than age [630, 640]. We also observed that smaller trials enrolled fewer females. Special attention is required to ensure appropriate female representation in such trials. Overall, trials published in 2020 and 2021 had enrolled significantly more females compared to those published in 2011-2013. Although the recruitment in these trials might have occurred several years before publication of their results, it is likely that the enrolment of females in RCTs of AF has increased in recent years. More efforts are needed to further increase the enrolment of females in future trials.

Reporting of sex-specific endpoint results has increased in recent years. This may be due to growing awareness of sex disparities in the epidemiology of disease in general, and particularly AF. Indeed, the number of publications on sex differences in diseases has substantially increased in the last decade (trends data from PubMed). Similar increasing temporal trends were observed in two recent analyses of reporting of results by sex in clinical trials of acute stroke therapies and Alzheimer's disease [635, 641]. However, the reporting of outcomes by sex is still largely suboptimal as only 40% of RCTs of AF published in 2020 and 2021 reported sex-specific outcomes. We observe higher rates of reporting in NEJM (87.5%) and Lancet (50.0%), in keeping with a 2016 review on sex-related reporting in RCTs in the

NEJM and Lancet journals in which 48% of trials reported results by sex [637], and with a more recent review on trials of acute stroke therapies which showed 61% and 40% sex-specific reporting in trials published in the NEJM and Lancet, respectively [635]. This likely reflects editorial policies in these journals that strongly recommend reporting sex-specific outcomes. Consideration of such reporting recommendations should be strongly encouraged among authors and journals, especially those with lower rates of sex-specific reporting. This can be achieved by including reporting by sex as a requirement in journals' reporting guidelines as recommended by the International Committee of Medical Journal Editors [642]. We also observed that increased sample size was associated with more frequent sex-specific reporting. This suggests that perhaps trials that are more statistically powered are more likely to have sex-stratified data reported. Indeed, potential sex differences in endpoints should be considered early in the design of trials.

The findings of this study should be interpreted with caution. Because we focused on trials published in selected high-impact journals, some important RCTs could have been missed. However, RCTs with the greatest impact of AF management are more likely to be published in journals we selected. Furthermore, the precision of the measurement of enrolment disparities might have been influenced by the source of data for the representation of females in the general population. Indeed, data from the GBD are estimates derived from modeling analysis and therefore have some degree of imprecision. Nevertheless, the GBD data were the most suitable for this study considering their disaggregation by year and geographic areas. Our study is an important contribution as it is the first description of the frequency of reporting by sex in RCTs of AF. Furthermore, we used a strong metric to measure sex enrolment disparities, accounting for the sex distribution of people with AF in the general population. We also provide important information on factors associated with female enrolment in these trials using adjusted meta-regression analysis.

7.5 Conclusion

Despite recent progress, females remain substantially less represented in RCTs of AF. This calls into question the generalizability of these trials and the validity of the evidence guiding the treatment of females. More efforts are needed to increase female enrolment, with a special attention in trials conducted in Northern America and those with lower sample size. Avoiding the exclusion of older individuals may also improve female representation. Furthermore, sex-stratified reporting of primary outcomes infrequently occurs in RCTs of AF, with the exception of top tier general medical journals. Reporting by sex should become a requirement in journals' reporting guidelines in a bid to reduce the sex disparity observed in enrolment and reporting of major trials in AF.

7.6 Tables and figures

Table 1. Characteristics of included trials

Characteristics	Number	Percentage
Journal		
• NEJM	16	11.3
• Lancet	6	4.2
• JAMA	8	5.6
• JAMA Internal Medicine	1	0.7
• European Heart Journal	20	14.1
• Circulation	14	9.9
• JACC	9	6.3
• JAMA Cardiology	1	0.7
• JACC Clinical Electrophysiology	7	4.9
• Circulation Arrhythmia and Electrophysiology	21	14.8
• Heart Rhythm	15	10.6
• Europace	18	12.7
• Journal of Cardiovascular Electrophysiology	6	4.2
Journal category		
• General medicine	31	21.8
• General cardiology	44	40.0
• Cardiac electrophysiology	67	47.2
Year of publication		
• 2011-2013	27	19.0
• 2014-2015	34	23.9
• 2016-2017	24	16.9
• 2018-2019	27	19.0
• 2020-2021	30	21.1
Sample size		
• Less than 250	81	57.0
• 250 to 750	37	26.1
• More than 750	24	16.9
Centers		
• Multicenter	102	71.8
• Single center	40	28.2
Multinational		
• Yes	58	40.8
• No	84	59.2
Region		
• Asia Pacific	26	18.3
• Europe	44	31.0
• North America	25	17.6
• South America	1	0.7
• Multiregional	46	32.4
Intervention		
• Catheter ablation	70	49.3
• Electrical cardioversion	3	2.1
• Surgical ablation	2	1.4

• Adjuvant to catheter ablation or electrical cardioversion	18	12.7
• Periprocedural oral anticoagulation	14	9.9
• Long-term oral anticoagulation	11	7.7
• Left atrial appendage occlusion	4	2.8
• Antiarrhythmic drugs	4	2.8
• RFM/integrated care	11	7.7
• Others	5	3.5
Industry involvement		
• Yes	66	46.5
• No	76	53.5
Female(s) in trial leadership role		
• Yes	19	13.4
• No	123	86.6

RFM: risk factor management

Table 2. Study-level characteristics associated with reporting of sex-specific trial results

Characteristics	Number of trials (N)	Results reported by sex, n (%)	No results reported by sex, n (%)	P value
Total	142	36 (25.4)	106 (74.6)	
Journal				< 0.001
• NEJM	16	14 (87.5)	2 (12.5)	
• Lancet	6	3 (50.0)	3 (50.0)	
• JAMA	8	3 (37.5)	5 (62.5)	
• JAMA Internal Medicine	1	0 (0.0)	1 (100.0)	
• European Heart Journal	20	5 (25.0)	15 (75.0)	
• Circulation	14	5 (28.6)	10 (71.4)	
• JACC	9	2 (22.2)	7 (77.8)	
• JAMA Cardiology	1	0 (0.0)	1 (100.0)	
• JACC Clinical Electrophysiology	7	0 (0.0)	7 (100.0)	
• Circulation Arrhythmia and Electrophysiology	21	2 (9.5)	19 (90.5)	
• Heart Rhythm	15	0 (0.0)	15 (100.0)	
• Europace	18	3 (16.7)	15 (83.3)	
• Journal of Cardiovascular Electrophysiology	6	0 (0.0)	6 (100.0)	
Journal category				< 0.001
• General medicine	31	20 (64.5)	11 (35.5)	
• General cardiology	44	12 (27.3)	32 (72.7)	
• Cardiology electrophysiology	67	5 (7.5)	62 (92.5)	
Year of publication				0.133
• 2011-2013	27	6 (22.2)	21 (77.8)	
• 2014-2015	34	4 (11.8)	30 (88.2)	
• 2016-2017	24	7 (29.3)	17 (70.8)	
• 2018-2019	27	7 (25.9)	20 (74.1)	

• 2020-2021	30	12 (40.0)	18 (60.0)	
Year of publication (Binary)				0.038
• 2011-2019	112	24 (21.4)	88 (78.6)	
• 2020-2021	30	12 (40.0)	18 (60.0)	
Sample size				
• Less than 250	81	12 (32.4)	25 (67.6)	< 0.001
• 250 to 750	37	8 (9.9)	73 (90.1)	
• More than 750	24	16 (66.6)	8 (33.3)	
Centers				
• Multicenter	102	30 (29.4)	72 (70.6)	0.076
• Single center	40	6 (15.0)	34 (85.0)	
Multinational				0.013
• Yes	58 (40.8)	21 (36.2)	37 (63.8)	
• No	84 (59.2)	15 (17.9)	69 (82.1)	
Region				0.003
• Asia Pacific	26 (18.3)	4 (15.4)	22 (84.6)	
• Europe	44 (31.0)	6 (13.6)	38 (86.4)	
• North America	25 (17.6)	5 (20.0)	20 (80.0)	
• South America	1 (0.7)	1 (100.0)	0 (0.0)	
• Multiregional	46 (32.4)	20 (43.5)	26 (56.5)	
Region (Binary)				< 0.001
• Single region	96	16 (16.7)	80 (83.3)	
• Multiregional	46 (32.4)	20 (43.5)	26 (56.5)	
Intervention				< 0.001
• Catheter ablation	70 (49.3)	9 (12.9)	61 (87.1)	
• Electrical cardioversion	3 (2.1)	0 (0.0)	3 (100.0)	
• Surgical ablation	2 (1.4)	0 (0.0)	2 (100.0)	
• Adjuvant to catheter ablation or electrical cardioversion	18 (12.7)	3 (16.7)	15 (83.3)	
• Periprocedural oral anticoagulation	14 (9.9)	3 (21.4)	11 (78.6)	

• Long-term oral anticoagulation	11 (7.7)	9 (81.8)	2 (18.2)	
• Left atrial appendage occlusion	4 (2.8)	3 (75.0)	1 (25.0)	
• Antiarrhythmic drugs	4 (2.8)	1 (25.0)	3 (75.0)	
• RFM/integrated care	11 (7.7)	7 (63.6)	4 (36.4)	
• Others	5 (3.5)	1 (20.0)	4 (80.0)	
Industry involvement				0.007
• Yes	66 (46.5)	24 (36.4)	42 (63.6)	
• No	76 (53.5)	12 (15.8)	64 (84.2)	
Female(s) in a trial leadership role				0.258
• Yes	19 (13.4)	7 (36.8)	12 (63.2)	
• No	123 (86.6)	29 (23.6)	94 (76.4)	

RFM: risk factor management

Table 3. Random-effects multivariable meta-regression analysis of the enrolment disparity difference in trials of atrial fibrillation

	Univariable				Multivariable model 1				Multivariable model 2			
	OR	**95% CI**		**P value**	**OR**	**95% CI**		**P value**	**OR**	**95% CI**		**P value**
		LCL	**UCL**			**LCL**	**UCL**			**LCL**	**UCL**	
Upper age limit												
• ≤ 80 years	Ref											
• > 80 years or no limit	1.045	1.007	1.086	0.021	1.036	0.995	1.078	0.083				
Mean age (per 1 year increase)	1.007	1.004	1.010	<0.001					1.006	1.002	1.009	0.002
Sample size												
• < 250	Ref											
• 250 to 750	1.041	1.000	1.084	0.052	1.054	1.012	1.097	0.011	1.041	1.000	1.084	0.050
• > 750	1.047	0.999	1.097	0.054	1.065	1.008	1.125	0.025	1.042	0.986	1.102	0.144
Female(s) in a leadership role												
• No												
• Yes	1.006	0.956	1.059	0.814	0.983	0.933	1.034	0.502	0.976	0.928	1.026	0.340
Industry involvement												
• No	Ref											
• Yes	0.966	0.933	1.000	0.050	0.968	0.928	1.010	0.138	0.960	0.922	1.000	0.053
Intervention												
• Non-invasive	Ref											
• Invasive	0.961	0.925	0.999	0.043	0.971	0.927	1.017	0.211	0.986	0.941	1.032	0.542
Region												
• Europe	Ref											
• Asia Pacific	0.994	0.944	1.046	0.813	0.981	0.932	1.032	0.448	0.990	0.942	1.040	0.681

• North America	0.961	0.912	1.013	0.138	0.945	0.898	0.995	0.033	0.958	0.912	1.007	0.091
• Multiple region	0.964	0.923	1.007	0.100	0.939	0.890	0.991	0.023	0.951	0.903	1.001	0.055
Period of publication												
• 2011-2013	Ref											
• 2014-2015	0.997	0.946	1.050	0.901	1.017	0.965	1.071	0.537	1.018	0.968	1.071	0.483
• 2016-2017	0.975	0.921	1.032	0.39	0.994	0.939	1.051	0.829	0.993	0.940	1.049	0.793
• 2018-2019	0.987	0.934	1.043	0.644	0.999	0.946	1.056	0.982	1.003	0.951	1.057	0.923
• 2020-2021	1.057	1.001	1.115	0.046	1.058	1.004	1.115	0.035	1.047	0.994	1.103	0.081

CI: confidence interval; LCL: lower confidence limit; OR: odds ratio; UCL: upper confidence limit.
Due to collinearity, the variables “highest permitted age of participants” and “mean age” could not be analyzed together. Therefore, two separate multivariable models including each of these variables were conducted. Model 1 and Model 2 are fully adjusted, with Model 1 including “highest permitted age of participants” whereas Model 2 includes “mean age”.

Figure 1. Study selection

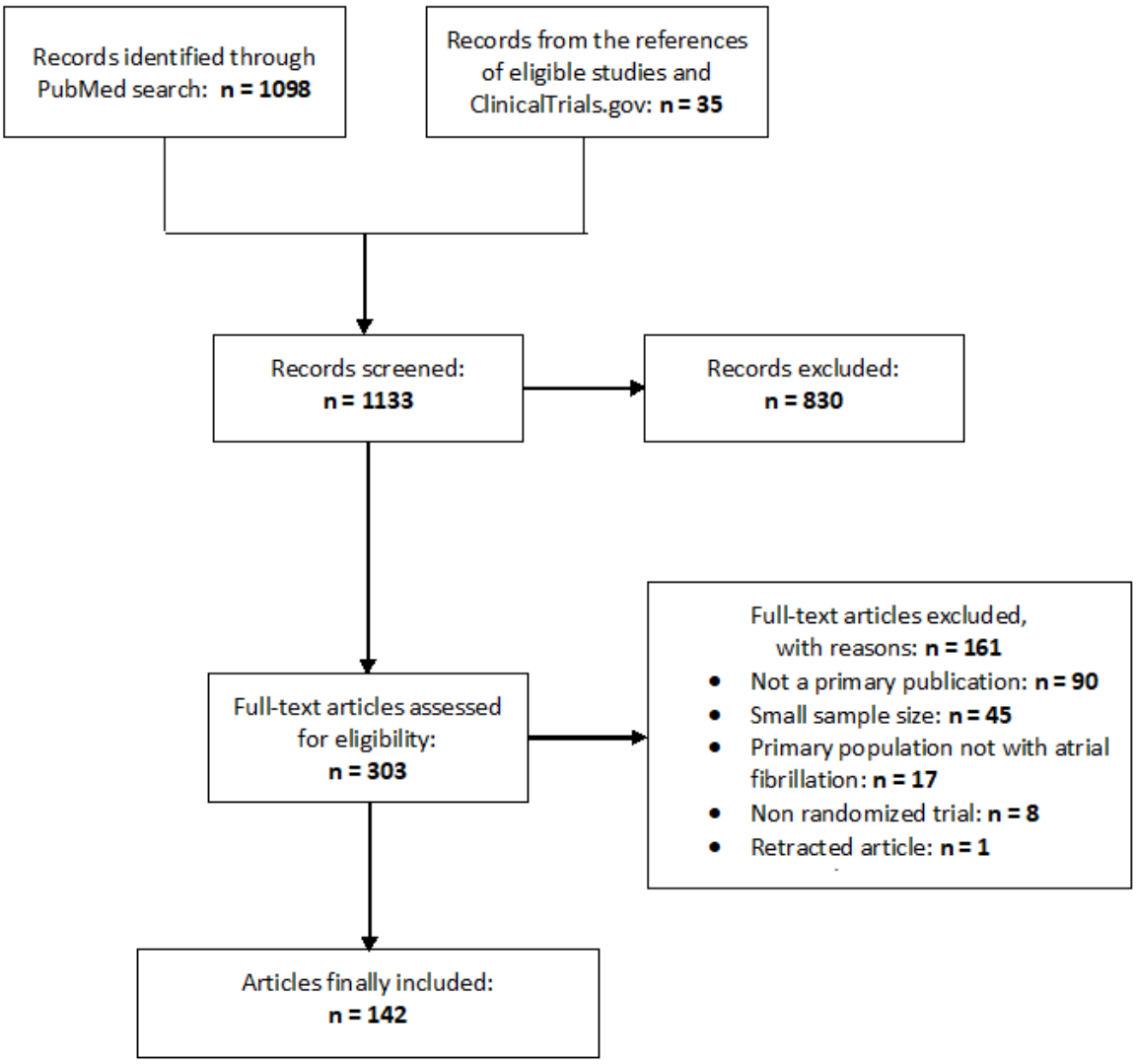


Figure 2. Proportions of females in trials and matched Global Burden of Disease populations with atrial fibrillation

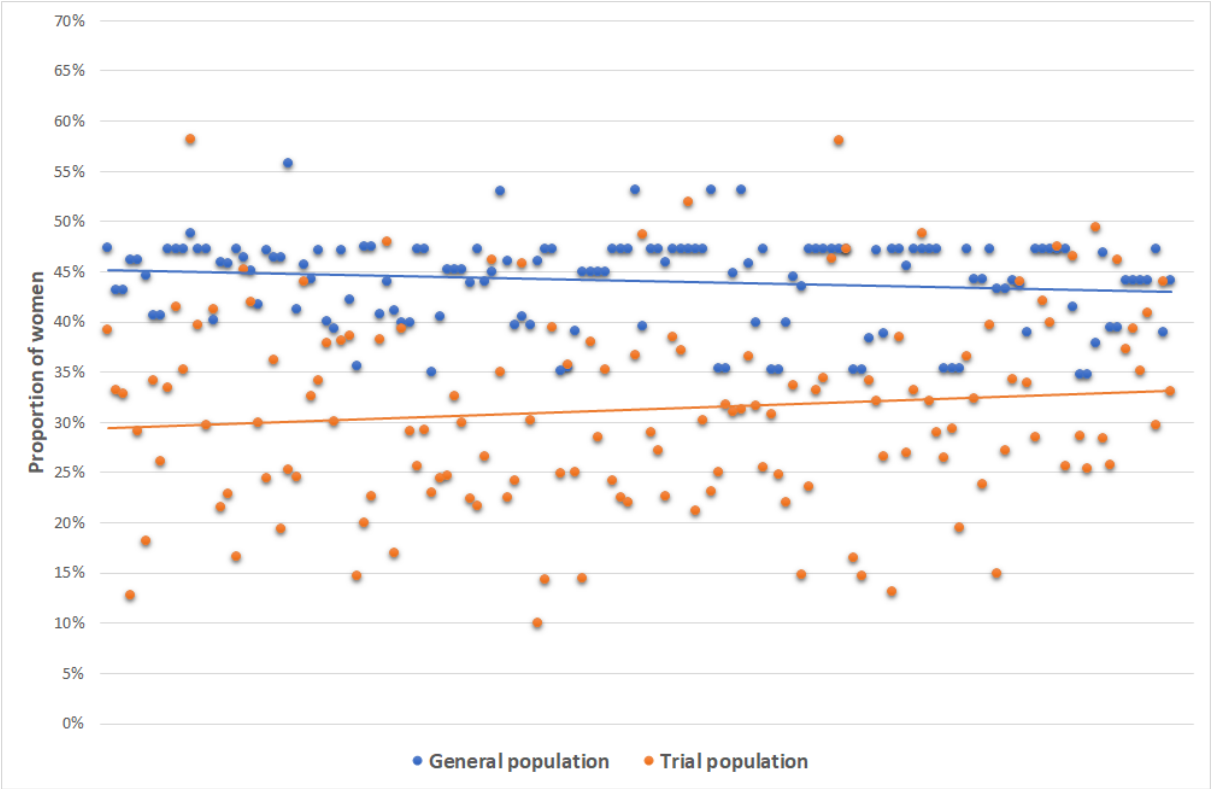


Figure 3. Random-effects pooled enrolment disparity difference in trials of atrial fibrillation

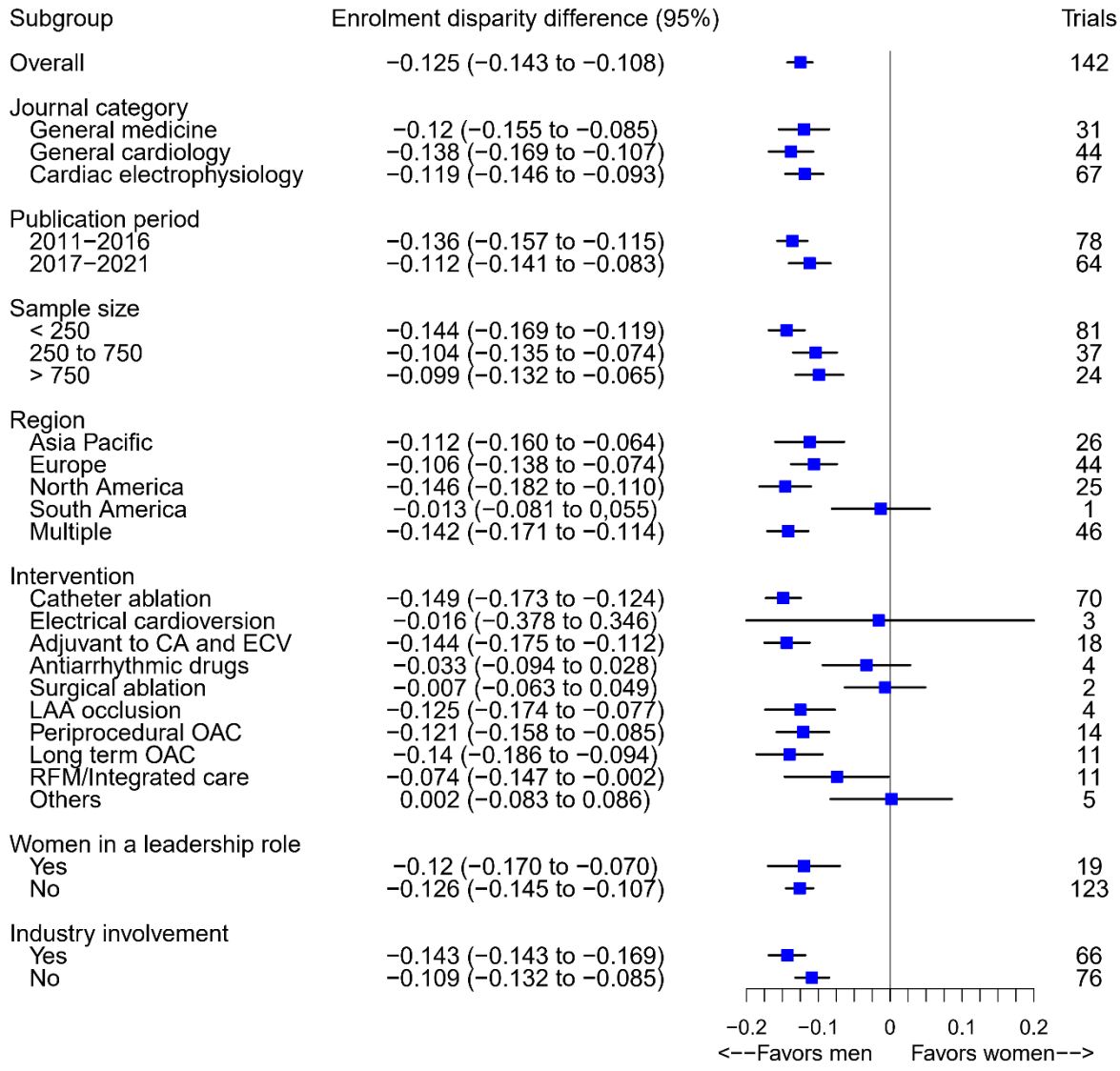
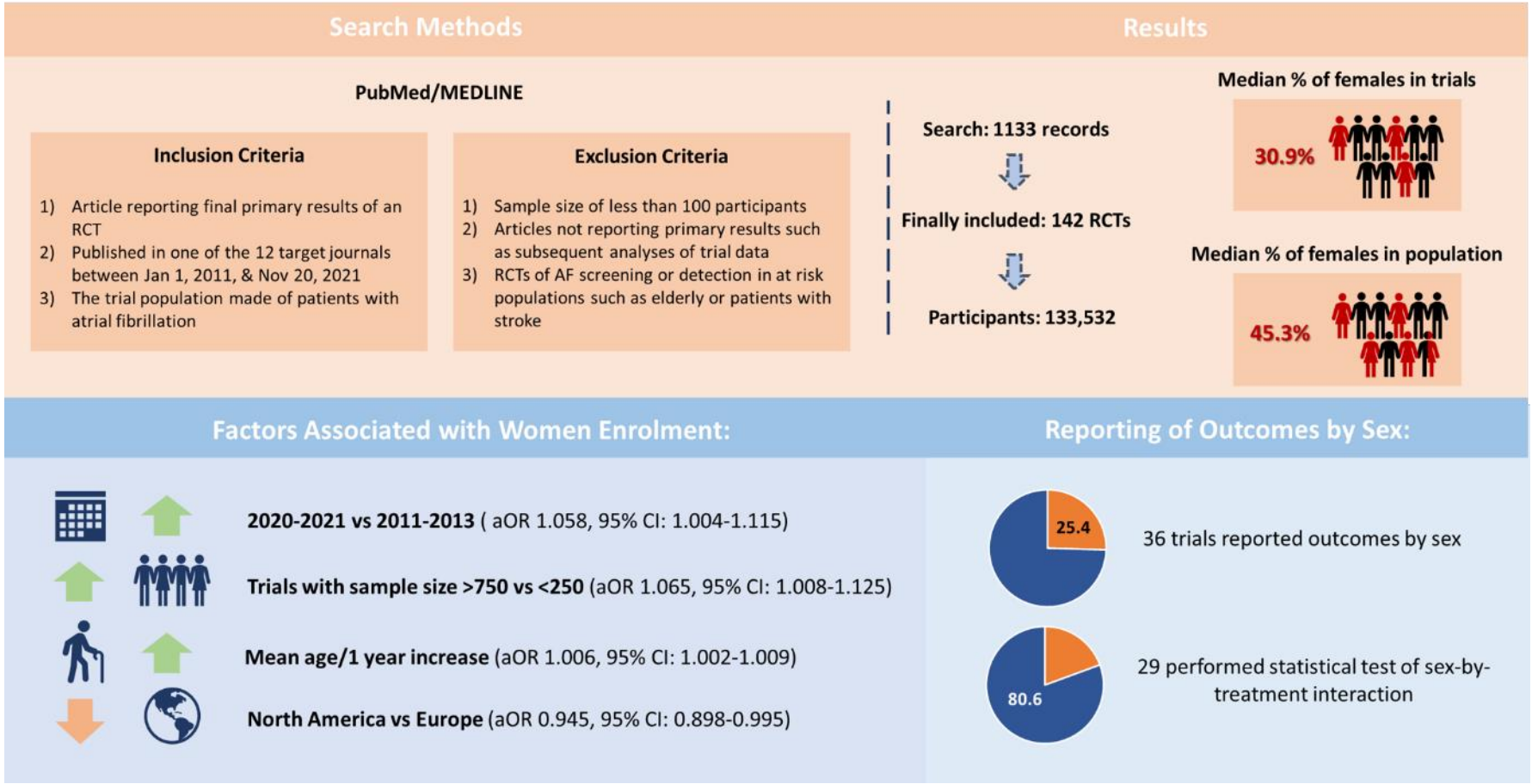


Figure 4. Graphical abstract



7.7 Appendix

Supplementary Table 1. Search strategy

	PUBMED
#P1	“atrial fibrillation” [tiab]
#P2	“controlled trial” [tiab] OR “clinical trial” [tiab] OR “randomized trial” [tiab] OR randomized [tiab]
#P3	JAMA [journal] OR "N Engl J Med" [journal] OR Lancet [journal] OR “BMJ” [journal] OR “Ann Intern Med” [journal] OR “JAMA Intern Med” [journal] OR Circulation [journal] OR "Eur Heart J" [journal] OR "J Am Coll Cardiol" [journal] OR “JAMA Cardiol” [journal] OR “Heart Rhythm” [journal] OR “Europace” [journal] OR "JACC Clin Electrophysiol" [journal] OR "Circ Arrhythm Electrophysiol" [journal] OR "J Cardiovasc Electrophysiol" [journal]
#P4	#P1 AND #P2 AND #P3
#P5	Limit #P4: Publication date [2011 to 2021]

Supplementary Table 2. Definitions of variables

Variables	Definitions
General medicine journals	New England Journal of Medicine, The Lancet, British Medical Journal, JAMA Internal Medicine
General cardiology journals	European Heart Journal, Circulation, Journal of American College of Cardiology, JAMA Cardiology
Cardiac electrophysiology journals	JACC Clinical Electrophysiology, Circulation Arrhythmia and Electrophysiology, Hearth Rhythm, Europace, Journal of Cardiac Electrophysiology
Period of recruitment	The year when participants' recruitment started and the year when it stopped. This information was collected from the published article, or from the trial registration web page if not available in the article.
Multinational	Whether (yes) or not (no) the trial was conducted in more than one country
Region	The region of the country where the trial was conducted. If the trial was conducted in several countries: it was classified in a specific region if all the countries involved were from that same region, or classified as multiregional if the countries were from several regions.
Intervention type	Trials were classified into one of 10 types based on the primary intervention tested: catheter ablation, surgical ablation, electrical cardioversion, adjuvant therapies to catheter ablation and electrical cardioversion, antiarrhythmic drugs, left atrial appendage occlusion, oral anticoagulation, risk factor modification/integrated care, and others
Intervention: catheter ablation	If the treatment tested was any form of catheter ablation for atrial fibrillation
Intervention: periprocedural oral anticoagulation	If the treatment tested was an oral anticoagulant given around either catheter ablation or electrical cardioversion for stroke prevention
Intervention: long-term oral anticoagulation	If the treatment tested was an oral anticoagulant given for long term stroke prevention
Intervention: adjuvant to catheter ablation or electrical cardioversion	If the treatment tested was given in patients undergoing catheter ablation or electrical cardioversion to enhance their efficacy
Intervention: risk factor modification or integrated care	If the intervention tested was aimed at: i) controlling the comorbid cardiovascular risk factors of patients with atrial fibrillation; ii) improving adherence to therapies or monitoring, and health-related outcomes or; ii) providing a holistic approach to chronic management of patients with atrial fibrillation
Intervention: others	Any intervention that did not fall into the categories: catheter ablation, surgical ablation, electrical cardioversion, adjuvant therapies to catheter ablation and electrical cardioversion, antiarrhythmic drugs, left atrial appendage occlusion, oral anticoagulation, and risk factor modification/integrated care
Invasive intervention	If the therapy tested was either an invasive procedure (e.g., catheter ablation, surgical ablation) or a therapy associated with

	an invasive procedure (e.g., periprocedural oral anticoagulation for catheter ablation)
Non-invasive intervention	If the therapy tested was not directly associated with a break in the skin or a contact with an internal body cavity beyond a natural or artificial body orifice (e.g., oral medications, behavioral therapies, risk factor modification)
Female(s) in a trial leadership role	At least one female listed as first or last author (including joint authorship) on the article reporting trial results. Determination of the sex of first and last authors was based given names or on profile pictures available via internet.
Industry involvement	Provision of financial support (funding) and/or of material (e.g., drug, device) used in the trial by a for-profit entity such as a pharmaceutic or medical device company.
Highest permitted age for participant inclusion	Any upper limit on the age of participants that defined eligibility. For the purpose of meta-regression analysis, this variable was categorized as upper age limit ≤ 80 years (e.g., 80 years, 75 years or 65 years) and > 80 years or no upper age limit
Reporting by sex	Whether or not the primary endpoint results were reported by sex (males versus females) in the main article or in the appendix
Test of sex-by-treatment interaction	Whether a formal test of interaction between the treatment and sex was performed and reported in the main article or in the appendix, with a p value or a statement that no interaction was found

Supplementary Table 3. Characteristics of included studies (Part 1)

First author	Journal	Year of publ	Period of recruitment	Center	Country	Multinational	Region	Trial name	Trial registration	Intervention
Abed	JAMA	2013	2010-2011	Single	Australia	No	Asia Pacific	None	ACTRN 12610000497000	Risk factor modification
ACTIVE I investigators	NEJM	2011	2003-2009	Multiple	International	Yes	Multiple	ACTIVE I	NCT00249795	Angiotensin receptor antagonist
Ahmed	JACC CE	2020	2018-2019	Single	USA	No	North America	ABCD-AF		No urinary catheter peri-catheter ablation
Andrade	Circulation	2019	2014-2018	Multiple	International	Yes	Multiple	CIRCA-DOSE	NCT01913522	Catheter ablation
Atienza	JACC	2014	2009-2012	Multiple	Spain	No	Europe	RADAR-AF	NCT00674401	Catheter ablation
Bisbal	Circ AE	2020	2016-2019	Single	Spain	No	Europe	ALICIA	NCT02698631	Catheter ablation
Blomström-Lundqvist	JAMA	2019	2008-2017	Multiple	Finland and Sweden	Yes	Europe	CAPTAF	EudraCT Number:2008-001384-11	Catheter ablation
Boersma	Circulation	2012	2007-2011	Multiple	Netherlands and Spain	Yes	Europe	FAST	NCT00662701	Catheter ablation
Boersma	Circ AE	2016	2011-2014	Multiple	Netherlands	No	Europe	MYSTIC-PAF	NCT01696136	Catheter ablation
Brignole	EHJ	2021	2014-2021	Single	Italy	No	Europe	APAF-CRT	NCT02137187	Atrioventricular junction ablation and cardiac resynchronization therapy
Budera	EHJ	2012	2007-2012	Multiple	Czech Republic	No	Europe	PRAGUE-12	NCT00665587	Surgical ablation
Cannon	NEJM	2017	2014-2017	Multiple	International	Yes	Multiple	RE-DUAL PCI	NCT02164864	Long term OAC
Cappato	EHJ	2015	2013-2014	Multiple	International	Yes	Multiple	VENTURE-AF	NCT01729871	Periprocedural OAC (catheter ablation)
Cappato	EHJ	2014	2012-2014	Multiple	International	Yes	Multiple	X-VeRT	NCT01674647	Periprocedural OAC (electrical

										cardioversion)
Chun	Circ AE	2021	2017-2020	Single	Germany	No	Europe	None		Catheter ablation
Connolly	EHJ	2013	NR	Multiple	International	Yes	Multiple	Explore-Xa	NCT00742859	Long term OAC
Connolly	NEJM	2011	2007-2010	Multiple	International	Yes	Multiple	AVERROES	NCT00496769	Long term OAC
Conti	Heart Rhythm	2018	NR	Multiple	Canada	No	North America	TOUCH AF	NCT01851525	Catheter ablation
Damiano	Heart Rhythm	2014	2007-2011	Multiple	US	No	North America	CURE-AF	NCT00431834	Surgical ablation
Darkner	EHJ	2014	2009-2014	Multiple	Denmark	No	Europe	AMIO-CAT	NCT00826826	Antiarrhythmic drug
De Ferrari	Heart Rhythm	2015	2012-2014	Multiple	International	Yes	Europe	RAFFAELLO	NCT01534962	Adjuvant to electrical cardioversion
Deftereos	Heart Rhythm	2014	2009-2012	Multiple	Greece	No	Europe	None		Adjuvant to Catheter ablation
DeLurgio	Circ AE	2020	2013-2019	Multiple	UK and USA	Yes	Multiple	CONVERGE	NCT01984346	Catheter ablation
Di Biase	JACC	2016	2010-2014	Multiple	USA	No	North America	BELIEF	NCT01362738	Catheter ablation
Di Biase	Circulation	2014	2010-2013	Multiple	USA	No	North America	COMPARE	NCT01006876	Periprocedural OAC (catheter ablation)
Di Biase	Circulation	2016	2008-2014	Multiple	International	Yes	Multiple	AATAC	NCT00729911	Catheter ablation
Dittrich	Heart Rhythm	2015	2012-2013	Multiple	Israel and Russia	Yes	Multiple	COR-ART	NCT01691313	Pharmacological cardioversion
Dixit	Circ AE	2012	2006-2009	Single	USA	No	North America	RASTA	NCT00379301	Catheter ablation
Dukkipati	JACC	2015	2012-2014	Multiple	USA	No	North America	HeartLight	NCT01456000	Catheter ablation
Efremedis	JCE	2016	2014-2015	Single	Greece	No	Europe	None		Adjuvant to Catheter ablation
Ezekowitz	EHJ	2018	2014-2017	Multiple	International	Yes	Multiple	EMANATE	NCT02100228	Periprocedural OAC (electrical cardioversion)
Faustino	Heart Rhythm	2015	2007-2013	Single	Italy	No	Europe	PAFA-SP	ACTRN 12614001231639	Catheter ablation

Ferrero-de-Loma-Osorio	Circ AE	2017	2015-2016	Single	Spain	No	Europe	plusONE	NCT02789358	Catheter ablation
Gallagher	Europace	2021	2012-2016	Single	UK	No	Europe	None		Catheter ablation
Ghanbari	Heart Rhythm	2016	2011-2013	Single	USA	No	North America	None		Adjuvant to catheter ablation
Ghannam	Heart Rhythm	2018	2017-2018	Single	USA	No	North America	None	NCT03140631	Periprocedural OAC reversal (catheter ablation)
Giannopoulos	Circulation	2014	2012-2013	Multiple	Greece	No	Europe	None	NCT01791699	Adjuvant to Catheter ablation
Giannopoulos	JCE	2019	2017-2017	Multiple	Greece	No	Europe	Cryo-LAEF	NCT02611869	Catheter ablation
Gibson	NEJM	2016	2013-2016	Multiple	International	Yes	Multiple	PIONEER AF-PCI	NCT01830543	Long term OAC
Gillinov	NEJM	2015	2010-2015	Multiple	Canada and USA	Yes	North America	CTSN	NCT00903370	Surgical ablation of atrial fibrillation
Giugliano	NEJM	2013	2008-2013	Multiple	International	Yes	Multiple	ENGAGE AF-TIMI 48	NCT00781391	Long term OAC
Goette	Lancet	2016	2014-2016	Multiple	International	Yes	Multiple	ENSURE-AF	NCT02072434	Periprocedural OAC (electrical cardioversion)
Granger	NEJM	2011	2006-2011	Multiple	International	Yes	Multiple	ARISTOTLE	NCT00412984	Long term OAC
Haldar	EHJ	2020	2015-2019	Multiple	UK	No	Europe	CASA-AF	NCT02755688	Catheter ablation
Hayashi	Europace	2014	2010-2013	Single	Japan	No	Asia Pacific	None		Antiarrhythmic drug
Hendriks	EHJ	2012	2006-2010	Multiple	Netherlands	No	Europe	AFClinic	NCT00391872	Risk factor modification /integrated care
Hohnloser	EHJ	2019	2017-2018	Multiple	International	Yes	Multiple	ELIMINATE-AF	NCT02942576	Periprocedural OAC (catheter ablation)
Holmes	JACC	2014	2010-2013	Multiple	USA	No	North America	PREVAIL	NCT01182441	Left atrial appendage occlusion
Hummel	Heart Rhythm	2014	2007-2010	Multiple	USA and Netherlands	Yes	North America	TTOP-AF	NCT00514735	Catheter ablation
Kaitani	EHJ	2016	2011-2014	Multiple	Japan	No	Asia	EAST-AF		Antiarrhythmic

							Pacific			drug
Kautzner	JACC CE	2021	2017-2019	Multiple	International	Yes	Multiple	DIAMOND-AF	NCT03334630	Catheter ablation
Kim	Europace	2015	NR	Single	Korea	No	Asia Pacific	None		Catheter ablation
Kim	JACC CE	2016	2012-2015	Single	Korea	No	Asia Pacific	COHERE	NCT01935557	Periprocedural OAC (catheter ablation)
Kimura	JACC CE	2018	2014-2016	Multiple	Japan	No	Asia Pacific	ASCERTAIN		Periprocedural OAC (catheter ablation)
Kircher	Europace	2018	2010-2011	Single	Germany	No	Europe	None		Catheter ablation
Kirchhof	Lancet	2012	2007-2010	Multiple	Germany	No	Europe	Flec-SL	ISRCTN62728742	Post-cardioversion antiarrhythmic drug
Kirchhof	EHJ	2018	2015-2017	Multiple	International	Yes	Multiple	AXAFA-AFNET 5	NCT02227550	Periprocedural OAC (catheter ablation)
Kirchhof	NEJM	2020	2011-2020	Multiple	International	Yes	Multiple	EAST-AFNET 4	NCT01288352	Early rhythm control (catheter ablation and antiarrhythmic drug)
Knight	JACC CE	2019	2012-2017	Multiple	USA and Canada	Yes	North America	STOP AF PAS	NCT01456949	Catheter ablation
Kotecha	JAMA	2020	2016-2019	Multiple	UK	No	Europe	RATE-AF	NCT02391337	Rate control therapy
Kuck	NEJM	2016	2011-2016	Multiple	International	Yes	Multiple	FIRE AND ICE	NCT01490814	Catheter ablation
Kuck	Circ AE	2016	2006-2010	Multiple	Germany	No	Europe	AFNET-B04-1	NCT00293943	Catheter ablation
Kuck	Europace	2021	2012-2018	Multiple	International	Yes	Multiple	ATTEST	NCT01570361	Catheter ablation
Kuck	Circ AE	2019	2008-2017	Multiple	Hungary, Spain, Germany	Yes	Europe	AMICA	NCT00652522	Implantable cardiac defibrillator/cardiac resynchronization therapy and catheter ablation

Kumar	Heart Rhythm	2012	NR	Single	Australia	No	Asia Pacific	None		Adjuvant to electrical cardioversion
Kuniss	Europace	2021	2014-2019	Multiple	International	Yes	Multiple	Cryo-FIRST	NCT01803438	Catheter ablation
Kunneman	JAMA Int Med	2020	2016-2021	Multiple	USA	No	North America	SDM4Afib	NCT02905032	Behavioral (decision aid)
Kuwahara	JCE	2016	NR	Multiple	Japan	No	Asia Pacific	None		Periprocedural OAC (catheter ablation)
Lakkireddy	Circulation	2021	2016-2020	Multiple	International	Yes	Multiple	Amulet IDE	NCT02879448	Left atrial appendage occlusion
Lau	Circulation	2013	2005-2012	Multiple	International	Yes	Asia Pacific	SAFETY	NCT00419640	Pacing
Lee	Europace	2019	2009-2011	Single	Korea	No	Asia Pacific	None		Catheter ablation
Leong-Sit	Circ AE	2011	2006-2009	Multiple	USA	No	North America	5A study	NCT00408200	Antiarrhythmic drug
Lim	Circ AE	2012	NR	Single	Australia	No	Asia Pacific	None	ACTRN 12606000467538	Catheter ablation
Lin	JCE	2012	NR	Single	Korea	No	Asia Pacific	None		Catheter ablation
Lopes	NEJM	2019	2015-2018	Multiple	International	Yes	Multiple	AUGUSTUS	NCT02415400	Antithrombotic (OAC, antiplatelet)
Luik	Circulation	2015	2008-2014	Single	Germany	No	Europe	FreezeAF	NCT00774566	Catheter ablation
Lüker	Circulation	2019	2014-2018	Multiple	Australia and Germany	Yes	Multiple	Cologne Cardioversion Study	NCT02241382	Electrical cardioversion
Macchia	JACC	2013	2008-2011	Multiple	Argentina	No	South America	FORWARD	NCT00597220	Adjuvant to electrical cardioversion
Macle	Lancet	2015	2009-2013	Multiple	International	Yes	Multiple	ADVICE	NCT01058980	Adjuvant to Catheter ablation
Malmborg	Europace	2013	NR	Single	Sweden	No	Europe	AF-COR		Catheter ablation
Marcus	JAMA Cardiol	2021	2018-2020	Single	USA	No	North America	I-STOP-Afib	NCT03323099	Behavioral

Marrouche	NEJM	2018	2008-2017	Multiple	International	Yes	Multiple	CASTLE-AF		Catheter ablation
Masuda	Europace	2018	2014-2015	Single	Japan	No	Asia Pacific	DRAGON	UMIN000015332	Catheter ablation
Matsumura-Nakano	Circulation	2019	2013-2017	Single	Japan	No	Asia Pacific	OAC-ALONE	NCT01962545	Long term OAC
McCready	Europace	2014	2007-2013	Single	UK	No	Europe	None	NCT00678340	Catheter ablation
McLellan	EHJ	2015	NR	Multiple	Australia, New Zealand, UK	Yes	Multiple	MINIMAX	ACTRN 12610000863033	Catheter ablation
Mohanty	Circulation	2013	2011-2013	Multiple	USA and Italy	Yes	Multiple	APPROVAL	NCT01439386	Catheter ablation
Mohanty	Heart Rhythm	2015	2010-2014	Multiple	USA	No	North America	SPECULATE	NCT01173809	Antiarrhythmic drug
Mont	EHJ	2014	2009-2011	Multiple	Spain	No	Europe	SARA	NCT00863213	Catheter ablation
Morillo	JAMA	2014	2006-2012	Multiple	International	Yes	Multiple	RAAFT	NCT00392054	Catheter ablation
Mörtsell	Europace	2018	2014-2016	Single	Sweden	No	Europe	None		Catheter ablation
Nakamura	Europace	2019	2015-2017	Single	Japan	No	Asia Pacific	None		Periprocedural OAC (catheter ablation)
Nodari	Circulation	2011	2006-2008	Single	Italy	No	Europe	None	NCT01198275	Adjuvant to electrical cardioversion
Nölker	JCE	2016	2012-2013	Multiple	USA, Belgium, Germany	Yes	Multiple	VERSATILE	NCT01656772	Catheter ablation
Osmancik	JACC	2020	2015-2019	Multiple	Czech Republic	No	Europe	PRAGUE-17	NCT02426944	Left atrial appendage occlusion
Packer	JAMA	2019	2009-2017	Multiple	International	Yes	Multiple	CABANA	NCT00911508	Catheter ablation
Packer	JACC	2013	2006-2010	Multiple	USA and Canada	Yes	North America	STOP AF	NCT00523978	Catheter ablation
Pak	Circ AE	2021	NR	Single	Korea	No	Asia Pacific	CRAFT	NCT03920917	Catheter ablation
Pappone	Circ AE	2011	2005-2010	Single	Italy	No	Europe	APAF	NCT00340314	Catheter ablation
Parkash	Circulation	2017	2009-2016	Single	Canada	No	North	SMAC AF	NCT00438113	Risk factor

							America			modification
Patel	NEJM	2011	2006-2010	Multiple	International	Yes	Multiple	ROCKET AF	NCT00403767	Long term OAC
Petra Wijtvliet	EHJ	2020	2012-2018	Multiple	Netherlands	No	Europe	RACE 4	NCT01740037	Integrated care
Pokushalov	Circ AE	2013	2007-2012	Single	Russia	No	Europe	None	NCT01709682	Catheter ablation
Rajagopalan	Circ AE	2016	2012-2014	Single	USA	No	North America	MICA	NCT01597557	Adjuvant to electrical cardioversion
Reddy	JAMA	2014	2005-2012	Multiple	International	Yes	Multiple	PROTECT AF	NCT00129545	Left atrial appendage occlusion
Reddy	Circulation	2015	2011-2013	Multiple	USA	No	North America	TOCCASTAR	NCT01278953	Catheter ablation
Reiffel	Circ AE	2015	2012-2014	Multiple	International	Yes	Multiple	HARMONY	NCT01522651	Antiarrhythmic drug
Reynolds	JACC CE	2018	2015-2017	Multiple	USA	No	North America	AEIOU	NCT02608099	Periprocedural OAC (catheter ablation)
Rienstra	EHJ	2018	2009-2018	Multiple	International	Yes	Multiple	RACE 3	NCT00877643	Risk factor modification
Rillig	JACC CE	2017	2009-2018	Multiple	International	Yes	Multiple	The Man and Machine Trial	NCT00982475	Catheter ablation
Rónaszéki	Europace	2011	2009	Multiple	International	Yes	Europe	None	NCT00915356	Pharmacological cardioversion
Rostock	Circ AE	2013	2009-2013	Single	Germany	No	Europe	None	NCT01896570	Catheter ablation
Schmidt	Circ AE	2017	2013-2016	Multiple	Czech Republic, Spain, Germany	Yes	Europe	None	NCT01863472	Catheter ablation
Shoene	Europace	2020	2017-2019	Single	Germany	No	Europe	OPERA	NCT03246594	Intra-esophageal temperature monitoring (catheter ablation)
Singh	EHJ	2016	2009-2015	Multiple	USA, Canada, Korea	Yes	Multiple	MAGIC-AF	NCT01014741	Catheter ablation

Sohara	JACC	2016	NR	Multiple	Japan	No	Asia Pacific	None		Catheter ablation
Squara	Heart Rhythm	2021	2017-2020	Multiple	France	No	Europe	None		Electrical cardioversion
Steinberg	JAMA	2020	2013-2019	Multiple	USA and Russia	Yes	Multiple	ERADICATE-AF	NCT01873352	Adjuvant to catheter ablation
Steward	Lancet	2015	2010-2012	Multiple	Australia	No	Asia Pacific	SAFETY	ANZCTR 12610000221055	Integrated care
Su	Heart Rhythm	2020	2017-2019	Multiple	USA, Japan, and Canada	Yes	Multiple	STOP Persistent AF	NCT03012841	Catheter ablation
Suleiman	Heart Rhythm	2012	2008-2009	Single	USA	No	North America	None		Adjuvant to catheter ablation
Theis	Circ AE	2015	2012-2014	Single	Germany	No	Europe	None	NCT02238392	Catheter ablation
Valderrábano	JAMA	2020	2013-2019	Multiple	USA	No	North America	VENUS	NCT01898221	Adjuvant to Catheter ablation
van den Dries	EHJ	2020	2016-2019	Multiple	Netherlands	No	Europe	ALL-IN	NL5407	Integrated care
Van Mieghem	NEJM	2021	2017-2021	Multiple	International	Yes	Multiple	ENVISAGE-TAVI AF	NCT02943785	Long term OAC
Verma	NEJM	2015	2010-2014	Multiple	Australia and Canada	Yes	Multiple	STAR AF II	NCT01203748	Catheter ablation
Vinereanu	Lancet	2017	2014-2017	Multiple	International	Yes	Multiple	IMPACT-AF	NCT02082548	Educational support
Vogler	JACC	2015	2010-2014	Single	Germany	No	Europe	CHASE-AF	NCT01580124	Catheter ablation
Voskoboinik	NEJM	2020	2016-2018	Multiple	Australia	No	Asia Pacific	ETOH-AF	ACTRN 12616000256471	Risk factor modification
Voskoboinik	JCE	2018	2016-2018	Multiple	Australia	No	Asia Pacific	None		Electrical cardioversion
Vranckx	Lancet	2019	2017-2019	Multiple	International	Yes	Multiple	ENTRUST-AF PCI	NCT02866175	Long term OAC
Walfridsson	Europace	2015	2005-2014	Multiple	Denmark	No	Europe	MANTRA-PAF	NCT00133211	Catheter ablation
Wang	Heart Rhythm	2016	NR	Multiple	China	No	Asia Pacific	None	ChiCTR-TRC-14004841	Adjuvant to Catheter ablation
Wazni	NEJM	2021	2017-2020	Multiple	USA	No	North	STOP AF	NCT03118518	Catheter ablation

							America	First		
Wintgens	Europace	2021	2015-2018	Multiple	Germany and Netherlands	Yes	Europe	GOLD FORCE		Catheter ablation
Wong	Circ AE	2015	2010-2013	Multiple	UK	No	Europe	BOCA	NCT01711047	Catheter ablation
Wu	Europace	2021	NR	Multiple	China	No	Asia Pacific	CAPA		Catheter ablation
Yamagata	Europace	2018	2016	Multiple	Czech Republic and Japan	Yes	Multiple	ULTRA-FAST	NCT02834221	Real-time ultrasound-guided puncture
Yang	Circ AE	2017	2013-2014	Multiple	International	Yes	Asia Pacific	STABLE-SR	NCT01761188	Catheter ablation
Yu	Circ AE	2020	NR	Multiple	Korea	No	Asia Pacific	None	NCT02176616	Catheter ablation
Yu	EHJ	2019	2015-2019	Multiple	Korea	No	Asia Pacific	None	NCT02504177	Periprocedural OAC (catheter ablation)
Zhang	EHJ	2014	NR	Single	China	No	Asia Pacific	None		Catheter ablation

Circ AE: Circulation Arrhythmia and Electrophysiology; EHJ: European Heart Journal; JACC: Journal of the American College of Cardiology; JCE: Journal of Cardiovascular Electrophysiology; NEJM; New England Journal of Medicine; OAC: oral anticoagulation; Publ: publication

Supplementary Table 4. Characteristics of included studies (Part 2)

First author	Year of publication	Industry involvement	Female(s) in a leadership position	Sample size	Number of females	Highest permitted age for inclusion (years)	Mean age (years)	Reporting by sex	Test of sex-by-treatment interaction
Abed	2013	No	No	150	49	75	60	No	
ACTIVE I investigators	2013	Yes	No	9016	3541	None	69.5	No	
Ahmed	2011	No	No	160	53	None	63	No	
Andrade	2020	Yes	No	346	115	None	59	No	
Atienza	2019	No	No	230	46	None	53	No	
Bisbal	2014	No	No	155	44	None	59	Yes	Yes
Blomström-Lundqvist	2020	Yes	Yes	155	35	70	56	No	
Boersma	2019	Yes	No	124	24	70	56	No	
Boersma	2012	No	No	120	30	70	56.5	No	
Brignole	2016	No	No	133	62	None	73.05	Yes	Yes
Budera	2021	No	No	224	94	None	70.4	No	
Cannon	2012	Yes	No	3489	825	None	70.8	Yes	Yes
Cappato	2017	Yes	No	248	72	None	59.6	No	
Cappato	2015	Yes	No	1504	410	None	64.8	No	
Chun	2014	No	No	200	88	80	65.75	No	
Connolly	2021	Yes	No	508	170	None	73	No	
Connolly	2013	Yes	No	5599	2322	None	70	Yes	Yes
Conti	2011	No	No	128	19	None	61	No	
Damiano	2018	Yes	No	150	66	None	70	No	
Darkner	2014	No	Yes	212	36	None	61	No	
De Ferrari	2014	Yes	No	238	54	None	65	No	

Deftereos	2015	No	No	206	62	80	62.2	No	
DeLurgio	2014	Yes	No	153	56	80	64.2	No	
Di Biase	2020	No	No	173	25	None	61.5	No	
Di Biase	2016	No	No	1584	392	None	61	Yes	Yes
Di Biase	2014	No	No	203	52	75	63.9	No	
Dittrich	2016	Yes	No	104	41	None	66.5	No	
Dixit	2015	No	No	156	20	None	59	No	
Dukkipati	2012	Yes	No	353	115	75	60	No	
Efremedis	2015	No	No	161	51	None	55.42	No	
Ezekowitz	2016	Yes	No	1500	498	None	64.6	No	
Faustino	2018	No	No	150	58	None	62.8	No	
Ferrero-de-Loma-Osorio	2015	No	No	140	45	75	56	No	
Gallagher	2017	No	No	100	22	None	63	No	
Ghanbari	2021	No	No	129	49	None	59.3	No	
Ghannam	2016	No	No	150	56	None	63	No	
Giannopoulos	2018	No	No	291	88	80	60	No	
Giannopoulos	2014	No	No	120		80	60.4	No	
Gibson	2019	Yes	No	2124	543	None	70	Yes	Yes
Gillinov	2016	No	No	260	120	None	69.5	No	
Giugliano	2015	Yes	No	21105	8040	None	72	Yes	Yes
Goette	2013	Yes	No	2199	756	None	64	Yes	No
Granger	2016	Yes	No	18201	6416	None	70	Yes	Yes
Haldar	2011	No	No	120	31	None	62.3	No	
Hayashi	2020	No	No	126	29	None	63	No	
Hendriks	2014	No	No	712	294	None	66.5	Yes	Yes
Hohnloser	2012	Yes	No	614	175	None	60.5	No	
Holmes	2019	Yes	No	407	122	None	74.3	No	
Hummel	2014	Yes	No	210	35	70	60	No	

Kaitani	2014	No	No	2038	508	80	63.3	No	
Kautzner	2016	Yes	No	482	203	None	62.5	No	
Kim	2021	No	No	100	25	None	56.38	No	
Kim	2015	No	No	333	106	None	61.5	No	
Kimura	2016	No	No	127	21	80	60	No	
Kircher	2018	No	No	124	47	None	62.5	No	
Kirchhof	2018	Yes	No	635	217	None	63.7	No	
Kirchhof	2012	Yes	No	633	309	None	70.3	Yes	Yes
Kirchhof	2018	Yes	No	2789	1293	None	64	Yes	No
Knight	2020	Yes	No	344	116	None	60.2	No	
Kotecha	2019	No	No	160	74	None	76	No	
Kuck	2020	Yes	No	762	293	85	62.4	Yes	Yes
Kuck	2016	Yes	No	233	61	75	65.8	No	
Kuck	2016	Yes	No	255	148	75	60	Yes	Yes
Kuck	2021	Yes	No	140	14	None	67.7	No	
Kumar	2019	Yes	No	178	40	None	62	No	
Kuniss	2012	Yes	No	218	70	75	52.3	No	
Kunneman	2021	No	Yes	922	363	None	71	No	
Kuwahara	2020	No	No	200	53	None	65.5	No	
Lakkireddy	2016	Yes	No	1878	750	None	75	Yes	Yes
Lau	2021	Yes	No	385	224	None	70	No	
Lee	2013	No	No	150	22	None	55.9	Yes	Yes
Leong-Sit	2019	No	No	110	32	None	55	No	
Lim	2011	No	No	220	40	None	58	No	
Lin	2012	No	No	126	45	None	54.5	No	
Lopes	2012	Yes	No	4614	1337	None	64	Yes	Yes
Luik	2019	No	No	315	124	75	61	No	
Lüker	2015	Yes	No	213	28	None	69	No	
Macchia	2019	No	No	586	265	None	66.1	Yes	Yes

Macle	2013	Yes	No	534	156	None	59	No	
Malmborg	2015	No	Yes	110	27	None	60.5	No	
Marcus	2013	No	No	446	157	None	58	No	
Marrouche	2021	Yes	No	363	52	None	64	Yes	Yes
Masuda	2018	No	No	156	48	None	67.4	No	
Matsumura-Nakano	2018	Yes	Yes	690	102	None	75	Yes	Yes
McCready	2019	No	No	188	72	None	62	No	
McLellan	2014	No	No	234	80	None	59	No	
Mohanty	2015	No	Yes	360	87	75	62	No	
Mohanty	2013	No	Yes	112	32	75	61	No	
Mont	2015	Yes	No	146	33	70	55	No	
Morillo	2014	Yes	No	127	31	75	55	No	
Mörtsell	2014	No	Yes	139	37	75	65.1	No	
Nakamura	2018	No	No	844	248	None	65	No	
Nodari	2019	No	Yes	199	66	80	69	No	
Nölker	2011	Yes	No	120	27	80	62.54	No	
Osmancik	2016	No	No	402	138	None	73	Yes	Yes
Packer	2020	Yes	No	2204	819	75	57	Yes	Yes
Packer	2019	Yes	No	245	56	None	68	No	
Pak	2013	No	No	314	90	80	59.9	No	
Pappone	2021	No	No	198	65	70	56	No	
Parkash	2011	No	Yes	184	49	None	60	Yes	Yes
Patel	2017	Yes	No	14264	5663	None	73	Yes	Yes
Petra Wijtvliet	2011	Yes	Yes	1354	463	None	64	Yes	Yes
Pokushalov	2020	No	No	154	39	65	66.5	No	
Rajagopalan	2013	No	Yes	261	81	None	65.5	Yes	Yes
Reddy	2016	Yes	No	707	210	None	71	Yes	No
Reddy	2014	Yes	No	295	104	None	60.3	No	

Reiffel	2015	Yes	No	131	68	None	72	No	
Reynolds	2015	Yes	No	590	191	None	63.5	No	
Rienstra	2018	Yes	Yes	245	52	None	64.5	Yes	Yes
Rillig	2018	Yes	No	258	78	75	63	No	
Rónaszéki	2017	Yes	No	171	62	80	65	No	
Rostock	2011	No	No	110	32	85	63	No	
Schmidt	2013	No	No	134	49	80	65.5	No	
Shoene	2017	No	Yes	180	61	85	63	No	
Singh	2020	Yes	No	200	44	None	60	No	
Sohara	2016	No	No	143	28	75	59.2	No	
Squara	2016	No	No	100	44	None	70.2	No	
Steinberg	2021	No	No	302	120	None	60	No	
Steward	2020	No	Yes	335	161	None	72	Yes	No
Su	2015	Yes	No	165	49	None	65	No	
Suleiman	2020	Yes	No	125	27	None	57	No	
Theis	2012	No	Yes	152	74	None	64	No	
Valderrábano	2015	No	No	343	82	85	66.5	Yes	Yes
van den Dries	2020	Yes	Yes	1240	613	None	77	No	
Van Mieghem	2020	Yes	No	1426	678	None	82.1	Yes	No
Verma	2021	Yes	No	589	128	None	60	Yes	Yes
Vinereanu	2015	Yes	No	2281	1079	None	70	Yes	Yes
Vogler	2017	Yes	Yes	153	37	80	61.7	No	
Voskoboinik	2015	No	No	140	21	85	62.3	Yes	No
Voskoboinik	2020	No	No	125	91	85	60.5	No	
Vranckx	2018	Yes	No	1506	386	None	69.5	No	
Walfridsson	2019	No	No	294	88	70	55	No	
Wang	2015	No	No	256	94	80	60	No	
Wazni	2016	Yes	No	203	83	80	61	Yes	No
Wintgens	2021	Yes	Yes	208	56	75	60.4	Yes	Yes

Wong	2021	No	No	131	32	75	61	No	
Wu	2015	No	No	648	227	75	64.1	No	
Yamagata	2021	No	No	319	123	None	63	No	
Yang	2018	Yes	No	229	53	80	57	No	
Yu	2017	No	No	113	28	None	60.4	No	
Yu	2020	No	No	326	83	80	58	No	
Zhang	2019	No	No	201	63	None	59.1	No	

Supplementary Table 5. Overall and subgroup random-effects pooled enrolment disparity differences

Subgroup	Number of Studies	Enrolment disparity difference (95% CI)	Heterogeneity		Between group difference
			I^2 (%)	*P* value	
Overall	142	-0.125 [-0.143; -0.108]	88.0	< 0.0001	NA
Period of publication					0.1975
• 2011-2016	78	-0.136 [-0.157; -0.115]	84.6	< 0.0001	
• 2017-2021	64	-0.112 [-0.141; -0.083]	90.5	< 0.0001	
Period of publication					0.0171
• 2011-2013	27	-0.129 [-0.169; -0.090]	87.4	< 0.0001	
• 2014-2015	34	-0.133 [-0.166; -0.100]	84.2	< 0.0001	
• 2016-2017	24	-0.154 [-0.187; -0.122]	82.6	< 0.0001	
• 2018-2019	27	-0.141 [-0.191; -0.091]	91.7	< 0.0001	
• 2020-2021	30	-0.074 [-0.109; -0.040]	84.8	< 0.0001	
Journals					0.1573
• NEJM	16	-0.128 [-0.180; -0.075]	92.4	< 0.0001	
• Lancet	6	-0.093 [-0.174; -0.013]	91.1	< 0.0001	
• JAMA	8	-0.134 [-0.202; -0.067]	83.5	< 0.0001	
• JAMA IM	1	-0.048 [-0.103; 0.007]	NA	NA	
• EHJ	20	-0.120 [-0.168; -0.072]	90.0	< 0.0001	
• Circulation	14	-0.148 [-0.206; -0.089]	90.3	< 0.0001	
• JACC	9	-0.168 [-0.228; -0.108]	84.8	< 0.0001	
• JAMA Cardiology	1	-0.090 [-0.153; -0.027]	NA	NA	
• JACC CE	7	-0.110 [-0.151; -0.069]	57.4	0.0288	
• Circ AE	21	-0.147 [-0.199; -0.095]	88.5	< 0.0001	
• Heart Rhythm	15	-0.147 [-0.197; -0.096]	81.5	< 0.0001	
• Europace	18	-0.102 [-0.138; -0.065]	74.3	< 0.0001	
• JCE	6	-0.013 [-0.158; 0.133]	93.3	< 0.0001	
Journal category					0.6257
• General medicine	31	-0.120 [-0.155; -0.085]	90.3	< 0.0001	
• General cardiology	44	-0.138 [-0.169; -0.107]	89.2	< 0.0001	
• Cardiac EP	67	-0.119 [-0.146; -0.093]	85.8	< 0.0001	
Multinational					0.0327
• Yes	58	-0.148 [-0.175; -0.121]	90.0	< 0.0001	
• No	84	-0.109 [-0.132; -0.087]	85.6	< 0.0001	
Number of sites					0.3700
• Single center	40	-0.113 [-0.143; -0.084]	81.3	< 0.0001	
• Multicenter	102	-0.130 [-0.151; -0.108]	89.5	< 0.0001	
Region					0.0053
• Asia Pacific	26	-0.112 [-0.160; -	89.4	< 0.0001	

		0.064]			
• Europe	44	-0.106 [-0.138; -0.074]	86.9	< 0.0001	
• North America	25	-0.146 [-0.182; -0.110]	83.6	< 0.0001	
• South America	1	-0.013 [-0.081; 0.055]	NA	NA	
• Multiregional	46	-0.142 [-0.171; -0.114]	89.3	< 0.0001	
Highest permitted age of participants					0.0119
• 80 years or less	43	-0.157 [-0.184; -0.129]	81.9	< 0.0001	
• > 80 years or no limit	99	-0.112 [-0.143; -0.108]	89.2	< 0.0001	
Sample size					0.0486
• Less than 250	81	-0.144 [-0.169; -0.119]	86.4	< 0.0001	
• 250 to 750	37	-0.104 [-0.135; -0.074]	87.6	< 0.0001	
• More than 750	24	-0.099 [-0.132; -0.065]	89.7	< 0.0001	
Intervention					< 0.0001
• Catheter ablation	70	-0.149 [-0.173; -0.124]	85.8	< 0.0001	
• Electrical cardioversion	3	-0.016 [-0.378; 0.346]	98.4	< 0.0001	
• Surgical ablation	2	-0.007 [-0.063; 0.049]	0.0	0.4499	
• Adjuvant to CA or ECV	18	-0.144 [-0.175; -0.112]	70.7	< 0.0001	
• Periprocedural OAC	14	-0.121 [-0.158; -0.085]	79.8	< 0.0001	
• Long-term OAC	11	-0.140 [-0.186; -0.094]	89.1	< 0.0001	
• LAA occlusion	4	-0.125 [-0.174; -0.077]	62.6	0.0454	
• AAD	4	-0.033 [-0.094; 0.028]	54.6	0.0853	
• RFM/integrated care	11	-0.074 [-0.147; -0.002]	91.7	< 0.0001	
• Others	5	0.002 [-0.083; 0.086]	83.7	< 0.0001	
Type of intervention					0.0595
• Invasive	102	-0.137 [-0.156; -0.118]	85.2	< 0.0001	
• Non-invasive	40	-0.097 [-0.134; -0.060]	91.5	< 0.0001	
Industry involvement					0.0503
• Yes	66	-0.143 [-0.169; -0.118]	90.2	< 0.0001	
• No	76	-0.109 [-0.132; -0.085]	84.9	< 0.0001	
Female(s) in a leadership role					0.8203
• Yes	19	-0.120 [-0.170; -0.070]	89.6	< 0.0001	
• No	123	-0.126 [-0.145; -0.107]	87.8	< 0.0001	

AAD: antiarrhythmic drugs; CA: catheter ablation; CI: confidence interval; Circ AE: Circulation Arrhythmia and Electrophysiology; ECV: electrical cardioversion; EHJ: European Heart Journal; JACC: Journal of the American College of Cardiology; JCE: Journal of Cardiovascular Electrophysiology; LAA: left atrial appendage; NEJM; New England Journal of Medicine; OAC: oral anticoagulation; RFM: risk factor modification

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CHAPTER 8:

Sex differences in outcomes of an intensive risk factor modification program in patients with atrial fibrillation

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8.1 Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice.[1] Cardiometabolic risk factors such as obesity, hypertension, diabetes mellitus, and obstructive sleep apnea are important drivers of the development of AF and its progression from paroxysmal to more persistent forms.[55] The control of these risk factors is now recognized in major clinical guidelines as a pillar of AF management.[144, 288] Indeed, several studies have shown a substantial impact of risk factor modification on AF outcomes.[144, 288, 290, 291, 293] Notably, we previously showed in the LEGACY (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up), the CARDIO-FIT (Impact of CARDIOrespiratory FITness on arrhythmia Recurrence in obese individuals with AF), and the REVERSE-AF (PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation) studies that aggressive management of obesity and other risk factors reduces AF symptoms, reverses the type and natural progression of AF, and improves long-term freedom from AF.[291, 293]

Sex differences have been shown in the incidence and outcomes of AF.[3, 303, 643] AF is about 1.5 times more common in men than women of middle age or older.[3] In an analysis from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe), the higher risk of AF in men was partially explained by factors such as body mass index (BMI) and total cholesterol.[303] This suggests that the impact of BMI on AF incidence might be higher in men than in women. However, no previous study has assessed whether there is a sex difference in the impact of weight-loss on AF outcomes. Hence, in a cohort of patients with AF undergoing intensive weight and risk factor modification, the current study aimed to assess the association between sex and weight-loss, cardiorespiratory fitness gain, AF symptoms, progression and recurrence of AF.

8.2 Methods

8.2.1 Study population

This is an ancillary analysis of data from the LEGACY study whose methods have been previously presented in details.[291] Patients referred to the Centre for Heart Rhythm Disorders at The University of Adelaide for the management of symptomatic AF, with a BMI ≥ 27 kg/m^2, in the study were included. They were excluded if they had a history of myocardial infarction or cardiac surgery in the previous 12 months, significant cardiac valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal or hepatic failure, and <24 months of follow-up.

8.2.2 Weight-loss and risk factor management

All participants were enrolled in a physician-led clinic devoted to weight reduction and control of cardiovascular risk factors. Details on our personalized, goal-directed, motivational weight and risk factor modification program are presented elsewhere.[290, 291] In brief, patients received face-to-face counseling with regular visits, every 3 months initially or more frequently if needed. An initial goal of >10% weight-loss was first attempted. Advice initially utilized the individuals own diet with a gradual change as required to a meal plan consisting of high protein and low glycemic index, calorie-controlled foods, and behavioral changes. After a >10% weight reduction was achieved, the next goal was a BMI ≤25 kg/m^2. Hypertension was managed with salt restriction and pharmacotherapy as required. Home-based blood pressure monitoring was performed by patients, with 2–3 measurements daily. In addition, exercise-induced hypertension was assessed by exercise stress testing. Blood pressure targets were: <130/80 mmHg for at least 80% of home blood pressure readings; <130/80 mmHg and <200/100 mmHg during rest and exercise, respectively. This was corroborated by in office blood pressure readings, and 24-h ambulatory monitoring if needed.

Dyslipidemia and glucose intolerance were managed with lifestyle measures and pharmacotherapy as required. Patients were screened for obstructive sleep apnea and offered therapy with continuous positive airway pressure if the apnea–hypopnea index was ≥30/h or if AHI ≥20/h with hypertension. Smoking cessation was encouraged and alcohol reduction to ≤30 g/week was advised.

8.2.3. Exercise program and evaluation of cardiorespiratory fitness

An individualized, structured exercise program was designed in accordance with the American Heart Association guidelines.[644] Details on the program have been presented previously.[645] In brief, after a baseline exercise stress test to ascertain cardiorespiratory fitness, patients were proposed a tailored exercise program with safely achievable goals considering patient's age and physical ability. The program was a combination of aerobic and resistance/strength exercises for progressive fitness gain, consisting of 20 min low-intensity exercise thrice weekly initially, and progressively increased to moderate intensity activity of at least 200 min weekly.

Cardiorespiratory fitness, in sex-specific metabolic equivalents (METs), was evaluated at baseline and final follow-up using the Bruce protocol treadmill exercise test. Test time was used to calculate METs.[646] If patients achieved only a fraction of the stage of exercise, credit for exercise capacity was "pro-rated." Age- and sex-predicted peak METs were calculated using the Veterans Affairs referral model (METs = 18 - [0.15 x age]) for men, and the St. James model (METs = 14.7 - [0.13 x age]) for women.[647]

8.2.4. Arrhythmia management

Management of AF was done in a concurrently conducted arrhythmia clinic which was separate from the risk factor management clinic. The use of rate and rhythm control strategies

was at the discretion of the treating physician according to guidelines. Atrial fibrillation was assessed at least annually by clinical review, 12-lead electrocardiogram, and 7-day Holter monitoring. Catheter ablation was offered to patients who remained symptomatic despite anti-arrhythmic drugs and risk factor modification. The ablation protocol used at our institution has been previously described.[648] Procedural success was determined after a 3-month blanking period, with recurrent arrhythmia defined as any atrial arrhythmia ≥30s and the data of recurrence corresponding to the earliest date of documented atrial arrhythmia. Repeat ablation was offered in case of recurrent symptomatic AF. Patients received oral anticoagulation according to guidelines. All patients had serial echocardiographic examinations. To assess AF symptom burden in all patients at baseline and final follow-up we used the AF Severity Scale (AFSS, University of Toronto, Canada) that quantitates 3 domains of AF-related symptoms (frequency, duration, and severity), and provides a symptom subscale and global well-being score.[649]

8.2.5 Outcomes

The primary outcome was freedom from AF ascertained with 7-day Holter monitoring, including freedom from AF without the use of rhythm control strategies ("ablation and drug free" AF freedom) and total arrhythmia-free survival. Secondary outcomes included weight-loss, cardiorespiratory fitness gain, AF symptom burden assessed with the AFSS questionnaire, change in AF type, change in AF risk factors, change in left atrial volume, left ventricular wall thickness, and diastolic function from echocardiographic studies.

8.2.6 Statistical analysis

Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as mean with standard deviation (SD) or median with interquartile

range (IQR) as appropriate. Differences between women and men at baseline and follow-up were assessed using paired t-test for continuous variables, and the chi-squared test for categorical variables. The interaction between sex and time was assessed using analysis of variance. Time-to-recurrence following the last ablation procedure between men and women was assessed using survival analysis. The association between weight-loss, fitness gain and outcomes of AF freedom was assessed using cox regression analysis. For this purpose, the study population was divided in groups according to the percentage of weight-loss (≥10% weight-loss [WL] versus <10% WL) and the cardiorespiratory fitness gain (≥2 MET gain versus <2 MET gain), as previously reported.[291, 645] Variables with $p < 0.1$ in univariable analyses were included in the multivariable cox regression models. A two-tailed p-value of < 0.05 was considered significant. All analyses were performed using Stata 15 statistical package (Statacorp, College Station, TX).

8.2.7 Ethical approval and registration

The LEGACY study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital (reference number: HREC/13/RAH/158). and registered with the Australian New Zealand Clinical Trials Registry (ANZCTR Clinical Trial Registration: ACTRN12614001123639). The current secondary analysis of data from the LEGACY study was also granted approval by the Central Adelaide Local Health Network (CAHLN) Human Research Ethics Committee (reference number 16784).

8.3 Results

8.3.1 Baseline characteristics

From 1,415 consecutive patients with symptomatic AF, of which 825 patients had a BMI ≥27 kg/m^2, 355 patients were included in the current analysis (**Figure 1**). There were 234 males

(65.9%). Compared to males, females were older (65.5±10.4 vs 62.5±10.6 years, p=0.013), had had higher BMI (34.1±5.4 vs 32.6±4.1 kg/m^2, p=0.003) but were less likely to consume alcohol in excess (5.8% vs 44.4%, p<0.001) and were less likely to have a smoking history (24.8% vs 38.0%, p=0.012). This was associated with more frequent paroxysmal AF (67.8% vs 48.3%, p<0.001) and more severe symptoms (7.22±1.49 vs 6.81±1.74, p=0.041) in females. There was no sex difference in baseline cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, and obstructive sleep apnea (**Table 1**). There was similar risk factor clinic attendance between males and females (58.7% vs 60%, p=0.820).

8.3.2 Impact of the aggressive risk factor management program

8.3.2.1 Changes in risk factor profile

There were significant changes in most parameters between baseline and final follow-up (**Table 2**). Weight decreased in males (104.7±14.6 to 97.3±15.7 kg, p<0.001) and females (91.4±17.2 to 84.4±17.2 kg, p<0.001), with no sex differences (p for group-time interaction = 0.86) (**Table 2, Figure 2A and 2B**). Cardiorespiratory fitness increased in males (7.09±1.72 to 8.74±2.42 MET, p<0.001) and females (6.11±1.98 to 7.48±2.51 kg, p<0.001), with no sex differences (p=0.44) (**Table 2, Figure 2C and 2D**). Systolic blood pressure significantly decreased in males (p<0.001) and females (p<0.001), with no sex difference (p=0.55). The proportion of patients with excessive alcohol consumption significantly decreased in males (p<0.001) and females (p<0.001), but more in males (p=0.01). There was significantly less smokers at the end of follow-up than at baseline in males (p<0.001) and females (p<0.001), with no sex difference (p=0.76). The proportion of patients with OSA also significantly decreased in males (p<0.001) and females (p<0.001), with no sex difference (p=0.97). Low-density Lipoprotein (LDL) cholesterol significantly decreased whereas high-density

lipoprotein (HDL) cholesterol increased in both sexes, but significantly more females than males (p=0.020 and p=0.001, respectively) (**Table 2**). Indexed left atrial volume increased, left ventricular end-diastolic diameter, and E/E' ratio decreased in both males and females, with no sex difference (all p>0.05). In terms of treatment, the number of antihypertensive and antiarrhythmic drugs taken by patients, as well as the number of patients on statins were reduced between baseline and final follow-up in both males and females, with no sex difference (all p >0.05). There was no difference in electrical cardioversion utilization between baseline and final follow-up in males (p=0.211) and females (p=0.168). The number of catheter ablation was similar between males and females (p=0.86) (**Table 2**).

8.3.2.2 Changes in atrial fibrillation symptoms

On the AFSS, frequency, duration, severity and symptoms significantly improved for males and females between baseline and final follow-up, with no between sex difference (all p >0.05, **Table 2**).

8.3.2.3 Changes in atrial fibrillation type

At baseline, paroxysmal AF was significantly more common in females than males (67.8% vs 48.3%, p<0.001) (**Figure 3**). Although more females progressed from paroxysmal to persistent AF, the difference was not significant (26.4% vs 22.6%, p=0.427). There was a trend towards more common reversal from persistent to paroxysmal AF in males compared to females (21.8% vs 14.0%, p=0.079). There no sex difference in AF freedom at the end of follow-up (p=0.877) (**Figure 3**).

8.3.3 Association of weight loss and fitness gain with atrial fibrillation freedom outcomes

8.3.3.1 Total arrhythmia-free survival

There was no sex difference in total AF freedom (p=0.47) (**Supplementary Figure 1A**). Weight-loss was associated with AF recurrence for both sexes in univariable analysis (**Supplementary Table 1, Figure 4A and 4B**). In multivariable analysis (**Table 3**), weight-loss (≥10% compared with <10%) was associated with lower AF recurrence in males (HR 0.41, 95% CI: 0.23-0.73, p=0.002) and females (HR 0.41, 95% CI: 0.20-0.83, p=0.010), with no sex difference (p=0.980). Fitness gain was associated with lower risk of AF recurrence in both sex in univariable regression analysis (**Supplementary Table 1, Figure 4C and 4D**). In multivariable analysis, fitness gain (≥2 MET compared with <2 MET) was associated with lower AF recurrence in females (HR 0.13, 95% CI: 0.05-0.30, p<0.001) but not in males (HR 0.63, 95% CI: 0.38-1.04, p=0.07) (p for sex difference = 0.002). When analyzing fitness as a continuous variable (**Table 3**), fitness gain was associated with lower AF recurrence in females (HR 0.69, 95% CI: 0.59-0.81, p<0.001) and males (HR 0.88, 95% CI: 0.78-0.98, p=0.02) but the association was stronger in females (p for sex difference = 0.019).

8.3.3.2 Freedom from AF without the use of rhythm control strategies

There was no sex difference in "ablation and drug free" AF freedom (p=0.49) (**Supplementary Figure 1, Panel B**). Weight-loss was associated with "ablation and drug free" AF freedom for both sexes in univariable analysis (**Supplementary Table 1, Figure 5A and 5B**). In multivariable analysis (**Table 3**), weight-loss (≥10% compared with <10%) was associated with lower AF recurrence in males (HR 0.45, 95% CI: 0.26-0.76, p=0.003) and females (HR 0.30, 95% CI: 0.14-0.67, p=0.003) (p for sex difference = 0.449). Fitness gain was not associated with a decrease in AF recurrence in both males (p=0.23) and females

(p=0.28) in univariable regression analysis (**Supplementary Table 1, Figure 5C and 5D**). However, in multivariable analysis (**Table 3**), fitness gain (≥2 MET compared with <2 MET) was associated with lower AF recurrence in males (HR 0.57, 95% CI: 0.35-0.93, p=0.02) but not in females (HR 1.36, 95% CI: 0.65-2.86, p=0.41) (p for sex difference = 0.056).

8.4 Discussion

In this study we investigated sex differences in weight-loss, risk factors, cardiorespiratory fitness gain, AF symptoms, progression and recurrence of AF in a cohort of patients undergoing intensive weight and risk factor modification. Four important findings emerge (**Figure 6**):

1. First, although females were older, with greater BMI and normalized cardiorespiratory fitness at baseline, there was no sex difference in weight-loss or fitness gain at follow-up.
2. Second, weight-loss and fitness gain were associated with a significant increase in "ablation and drug free" AF freedom and total AF freedom in both males and females.
3. Third, improvement in fitness had a much greater benefit for total arrhythmia freedom for females than males.
4. Fourth, there was a trend towards higher rates of AF reversal from persistent AF to paroxysmal AF in males compared to females.

Differences in outcomes of risk factor modification between males and females with AF might be influenced by differences in their risk profiles and the way they are managed. For instance, in patients hospitalized for AF in the United States, females were reported to be older, with higher prevalence of hypertension and heart failure. Whereas, diabetes mellitus, vascular disease, and obstructive sleep apnea were more common in males.[316] Furthermore,

lower utilization of rhythm control strategies in females, especially electrical cardioversion and catheter ablation, has been reported in multiple studies across the globe.[316, 348-350] These differences between males and females with AF have been shown to impact their outcomes.[316] In the current study, besides older age and higher BMI in females, and excess alcohol consumption in males, there was no other substantial differences in cardiovascular risk factors between sexes. In addition, there was no difference in clinic attendance, in the use of antiarrhythmic drugs, electrical cardioversion, and catheter ablation during follow-up between sexes.

Several studies have suggested a difference in weight-loss and maintenance between males and females. Data from older adults with obesity from two studies in the US and the UK showed that females had generally better weight control than males.[650] In contrast, in a meta-analysis of 49 randomized controlled trials of weight-loss interventions, males showed greater weight-loss than females.[651] This inconsistency regarding sex difference in weight control could be partially explained by differences in weight-loss interventions (diet alone, exercise alone, or diet + exercise), durations of programs, and baseline characteristics such as age, BMI status, and co-morbidities between males and females.[652] Regarding cardiorespiratory fitness, males are generally more fit than females.[653] Our study demonstrates that individualized, structured, goal-directed, motivational weight reduction and exercise programs are equally effective in reducing weight and improving cardiorespiratory fitness in males and females with AF.

Atrial fibrillation is a progressive disease determined by continuous atrial remodeling resulting from various underlying risk factors. Without appropriate intervention, most patients progress from paroxysmal to persistent and then permanent AF over time. In the REVERSE-AF study, we demonstrated that aggressive weight-loss and risk factor modification may reverse the natural progression of AF. In the current analysis, we observed a trend towards

higher rates of AF reversal from persistent AF to paroxysmal AF in males compared with females (p=0.079). This might be explained by differences in AF mechanisms or AF substrate between males and females. Tissue fibrosis plays a major role in the development and progression of AF. It has been shown that female sex is independently associated higher left atrial fibrosis burden in patients with AF.[308, 627, 654] Furthermore, epicardial fat is associated with decreased left atrial voltage and left atrial transport function, and AF substrate remodeling.[627, 655] Hence, the increase in epicardial fat resulting from post-menopausal hormonal changes[655] could also explain the higher left atrial fibrosis burden and a lower tendency to reverse from persistent AF to paroxysmal AF in females with AF compared with males, as observed in our study. We could not perform multivariable regression analysis to account for potential confounders due to limited number of individuals in the subgroups and a high number of co-variates. It is possible that female sex is not truly associated with a lower reversal from persistent AF to paroxysmal AF, and that this apparent association is driven by the older age and more co-morbidities in females than in males.

In the LEGACY and the Cardiorespiratory Fitness (CARDIO-FIT) studies[291, 645], we demonstrated that long-term sustained weight-loss and cardiorespiratory fitness are associated with significant reduction of AF burden and maintenance of sinus rhythm. The current analysis shows that weight-loss and fitness gain have beneficial effects in males and females. Specifically, “ablation and drug free” AF freedom the overall freedom from AF did not differ in males and females. Several studies have shown sex differences in outcomes of catheter ablation. A meta-analysis of 19 observational studies (151,370 patients; 34% women) showed a 25% increased likelihood of atrial arrhythmias recurrence after catheter ablation in females compared with males.[349] The reason for this difference in outcomes is not entirely clear. One potential reason is that females who undergo catheter ablation usually have higher CHA_2DS_2-VASc score and longer duration of AF, both of which have been shown to directly correlate

with a higher atrial arrhythmia recurrence after catheter ablation.[656] Furthermore, during ablation, females have more non-pulmonary vein triggers than males.[352, 656] The presence of non-pulmonary vein triggers, especially those that are unable to be mapped and cannot be ablated, is a risk factor for atrial arrhythmia recurrence.[656, 657] Our study suggests that the reversal of the structural and electrical remodeling of the atria that forms the AF with aggressive weight-loss, physical exercise and control of other risk factors might be an important strategy to reduce the sex disparity in the outcomes of catheter ablation, as both males and females experienced benefit from our dedicated risk factor modification program. Moreover, early and aggressive weight and risk factor intervention could halt the progression of the AF disease and prevent the need for catheter ablation. Nevertheless, it is worth noting that improvement in fitness had a much greater benefit for total arrhythmia freedom for females than males. This reinforces the crucial role of fitness gain in females.

Our study has some limitations. First, the study was not designed and powered to detect sex differences in the study outcomes. Hence, the absence of statistical significance does not necessarily imply a lack of association but may rather signal an indeterminate result. Larger studies are needed to confirm our findings. Second, we did not perform prolonged continuous rhythm monitoring using implantable monitoring devices. With the higher prevalence of paroxysmal AF in females compared with males at baseline, AF burden assessment using 7-day Holter monitoring may have resulted in imprecise quantification of AF burden, especially in females. Third, changes in AF types between baseline and final follow-up could not be investigated with multivariable analysis due to limited numbers of individuals in each subgroup and a high number of co-variates.

8.5 Conclusion

Despite sex differences at baseline with regards to age, AF type, BMI, and cardiorespiratory fitness, the benefits of weight-loss and fitness gain were favorable for both males and females. However, improvement in fitness had a much greater benefit for total arrhythmia freedom for females, whereas there was a trend towards more common regression from persistent to paroxysmal AF in males. This study reinforces the need to address lifestyle risk factors to minimize arrhythmia recurrence and reduce symptom severity for all individuals.

8.6 Tables and figures

Table 1. Baseline characteristics

Variable	Males (n = 234)	Females (n = 121)	P value
Age, years	62.5 (10.6)	65.5 (10.4)	0.013
Anthropomorphic parameters			
• Weight, kg	104.7 (14.6)	91.4 (17.2)	<0.001
• BMI, kg/m^2	32.6 (4.1)	34.1 (5.4)	0.003
• SBP, mm Hg	145.3 (17.0)	145.1 (18.4)	0.92
Atrial fibrillation			
• Paroxysmal	113 (48.3%)	82 (67.8%)	<0.001
• Non-paroxysmal	121 (51.7%)	39 (32.2%)	
Cardiometabolic risks			
• Hypertension	175 (75.1%)	99 (82.5%)	0.11
• Diabetes mellitus	63 (29.4%)	35 (31.0%)	0.69
• Glucose intolerance	26 (12.1%)	8 (7.1%)	0.17
• Hyperlipidemia	100 (43.5%)	56 (46.7%)	0.57
• Coronary artery disease	32 (13.7%)	12 (9.9%)	0.3
• Valvulopathy	14 (6.0%)	5 (4.1%)	0.46
• AHI >30	32 (30.8%)	10 (20.4%)	0.18
• Alcohol excess (>30 g/week)	104 (44.4%)	7 (5.8%)	<0.001
• Current smoker	15 (6.4%)	4 (3.3%)	0.22
• Ex-smoker	89 (38.0%)	30 (24.8%)	0.012
Medication use			
• Median number of AAD (IQR)	1 (0, 1)	1 (0, 1)	0.34
• Median number of anti-HTN drugs (IQR)	1 (0, 1)	1 (0, 1)	0.32
• Patients on statins	100 (46.7%)	52 (46.4%)	0.96
Lipid profile			
• LDL, mg/L	2.80 (0.93)	3.01 (1.01)	0.084
• HDL, mg/L	1.16 (0.33)	1.28 (0.37)	0.005
• Total cholesterol, mg/L	4.67 (1.07)	5.01 (1.05)	0.01
• Triglycerides, mg/L	1.59 (0.73)	1.57 (0.61)	0.76
Echocardiographic parameters			
• LAVI, mL/m^2	37.61 (7.62)	37.84 (6.65)	0.83
• LV IVS, cm	1.28 (0.63)	1.10 (0.44)	0.009
• LVEDD, cm	5.06 (0.86)	4.69 (0.75)	<0.001
• E/E' ratio	1.06 (0.16)	0.99(0.19)	<0.001
Atrial Fibrillation Severity Scale			
• Frequency (1-10)	6.96 (1.58)	7.10 (1.51)	0.47
• Duration (1-10)	6.96 (1.92)	7.00 (1.51)	0.84
• Severity (1-10)	6.81 (1.74)	7.22 (1.49)	0.041
• Symptoms (0-35)	15.46 (7.44)	17.24 (6.66)	0.081

Values are expressed as mean with standard deviation (SD), median with interquartile range (IQR), or frequency with percentage (%)
AAD: anti-arrhythmic drugs; AHI: apnea–hypopnea index; Anti-HPT drugs: anti-hypertensive drugs; BMI: body mass index; HDL: high-density lipoprotein; IQR: interquartile

range; LAVI: left atrium volume indexed; LDL: low-density lipoprotein; LVEDD: left ventricular end-diastolic diameter; LV IVS: left ventricular interventricular septum; SBP: systolic blood pressure; TG: triglyceride.

Table 2. Parameters changes between baseline and final follow-up

	Males (n=234)			Females (n=121)			
	Baseline	Follow-up		Baseline	Follow-up		
Variable	**Mean (SD) or median (IQR) or n (%)**	**Mean (SD) or median (IQR) or n (%)**	**P value**	**Mean (SD) or median (IQR) or n (%)**	**Mean (SD) or median (IQR) or n (%)**	**P value**	**P value for sex difference**
Anthropomorphic parameters							
• Weight, kg	104.7 (14.6)	97.3 (15.7)	<0.001	91.4 (17.2)	84.4 (17.2)	<0.001	0.86
• BMI, kg/m^2	32.5 (4.2)	30.6 (4.6)	<0.001	34.2 (5.5)	31.6 (5.7)	<0.001	0.53
• SBP, mm Hg	145.3 (17.0)	133.6 (15.9)	<0.001	145.1 (18.4)	134.8 (13.5)	<0.001	0.55
Lifestyle factors							
• Cardiorespiratory fitness, MET	7.09 (1.72)	8.74 (2.42)	<0.001	6.11 (1.98)	7.48 (2.51)	<0.001	0.44
• Alcohol excess	103 (44.40)	63 (27.16)	<0.001	7 (5.83)	5 (4.17)	<0.001	0.01
• Current smoker	15 (6.47)	7 (3.02)	<0.001	4 (3.31)	1 (0.83)	<0.001	0.76
• OSA	115 (54.50)	82 (38.86)	<0.001	54 (49.09)	36 (32.73)	<0.001	0.97
Treatment							
• Number of anti-HTN	1 (0,1)	0 (0, 1)	0.04	1 (0, 1)	0(0, 1)	0.03	0.54
• Number of AAD	1 (0, 1)	0 (0, 1)	<0.001	1 (0, 1)	0 (0, 1)	<0.001	0.67
• Patients on statins	100 (46.5)	109 (51.57)	<0.001	52 (46.43)	60 (53.57)	<0.001	0.808
• Cardioversion (yes)	55 (35.48)	21 (13.55)	0.211	15 (20.83)	11 (15.28)	0.168	0.164
• Catheter ablation (yes)	-	106 (49.53)		-	59 (52.21)		0.64
• Number of ablations	-	1 (0, 1)		-	1 (0, 1)		0.86
Lipid profile							
• LDL, mg/L	2.82 (0.94)	2.53 (0.86)	0.001	3.06 (1.05)	2.40 (0.70)	<0.001	0.020
• HDL, mg/L	1.14 (0.30)	1.22 (0.33)	0.03	1.29 (0.35)	1.60 (0.43)	<0.001	0.001
• Triglycerides, mg/L	1.55 (0.74)	1.34 (0.78)	0.01	1.53 (0.61)	1.27 (0.66)	0.009	0.52
Echocardiographic parameters							
• LAVI, mL/m^2	37.66 (7.62)	34.85 (9.50)	<0.001	37.84 (6.65)	33.63 (8.69)	<0.001	0.98

• LV IVS, cm	1.28 (0.63)	1.08 (0.17)	<0.001	1.10 (0.44)	1.02 (0.16)	0.09	0.08
• LVEDD, cm	5.06 (0.85)	4.90 (0.88)	0.001	4.69 (0.75)	4.54 (0.76)	0.01	0.95
• E/E' ratio	11.54 (3.94)	9.74 (4.49)	0.001	12.78 (4.67)	10.33 (4.21)	<0.001	0.39
Atrial Fibrillation Severity Scale							
• Frequency (1-10)	6.96 (1.53)	3.54 (1.88)	<0.001	7.17 (1.32)	4.03 (1.77)	<0.001	0.21
• Duration (1-10)	6.92 (1.91)	4.68 (2.37)	<0.001	6.98 (1.50)	5.01 (2.30)	<0.001	0.63
• Severity (1-10)	6.81 (1.72)	4.17 (2.16)	<0.001	7.24 (1.49)	4.35 (1.86)	<0.001	0.49
• Symptoms (0-35)	16.24 (7.08)	9.40 (6.04)	<0.001	17.4 (6.60)	11.3 (6.54)	<0.001	0.37

Values are expressed as mean with standard deviation (SD), median with interquartile range (IQR), or frequency with percentage (%)
AAD: anti-arrhythmic drugs; anti-HTN: antihypertensive medications; BMI: body mass index; Excess alcohol: consumption >30 g/week; HDL: high-density lipoprotein; LAVI: left atrium volume indexed; LDL: low-density lipoprotein; LVEDD: left ventricular end-diastolic diameter; LV IVS: left ventricular interventricular septum; MET: metabolic equivalent; OSA: obstructive sleep apnea; SBP: systolic blood pressure; TG: triglyceride.

Table 3. Association between cardiorespiratory fitness gain, weight loss, and atrial fibrillation recurrence (multivariable analysis)

	Overall		Females		Males		
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**P value for sex difference**
Total AF freedom*							
Fitness gain (per 1 MET)	0.83 (0.76-0.91)	<0.001	0.69 (0.59-0.81)	<0.001	0.88 (0.78-0.98)	0.02	0.019
Fitness gain (≥2 MET vs <2MET)	0.44 (0.29-0.67)	<0.001	0.13 (0.05-0.30)	<0.001	0.63 (0.38-1.04)	0.07	0.002
Weight loss (per 1 kg)	0.96 (0.94-0.98)	<0.001	0.97 (0.94-1.01)	0.09	0.95 (0.92-0.97)	<0.001	0.278
Weight loss (≥10% kg vs <10% kg)	0.45 (0.29-0.69)	<0.001	0.41 (0.20-0.83)	0.01	0.41 (0.23-0.73)	0.002	0.980
"Ablation and drug free" AF freedom **							
Fitness gain (per 1 MET)	0.93 (0.84-1.03)	0.19	1.05 (0.88-1.25)	0.01	0.88 (0.76-1.02)	0.09	0.132
Fitness gain (≥2 MET vs <2MET)	0.72 (0.49-1.06)	0.09	1.36 (0.65-2.86)	0.41	0.57 (0.35-0.93)	0.02	0.056
Weight loss (per 1 kg)	0.95 (0.93-0.97)	<0.001	0.94 (0.89-0.98)	0.008	0.95 (0.93-0.98)	0.001	0.506
Weight loss (≥10% kg vs <10% kg)	0.39 (0.25-0.60)	<0.001	0.30 (0.14-0.67)	0.003	0.45 (0.26-0.76)	0.003	0.449

Atrial fibrillation; MET: metabolic equivalents; 95% CI: 95% confidence interval; HR: hazard ratio
Variables with p<0.1 in univariable analyses were included in the multivariable cox regression models.
* Adjusted for: hypertension, diabetes mellitus, tobacco use, baseline left ventricular interventricular septum
** Adjusted for: hypertension, obstructive sleep apnea, tobacco use, number of antiarrhythmic drugs, baseline left ventricular interventricular septum, and E/E' ratio

Figure 1. CONSORT diagram of participant selection

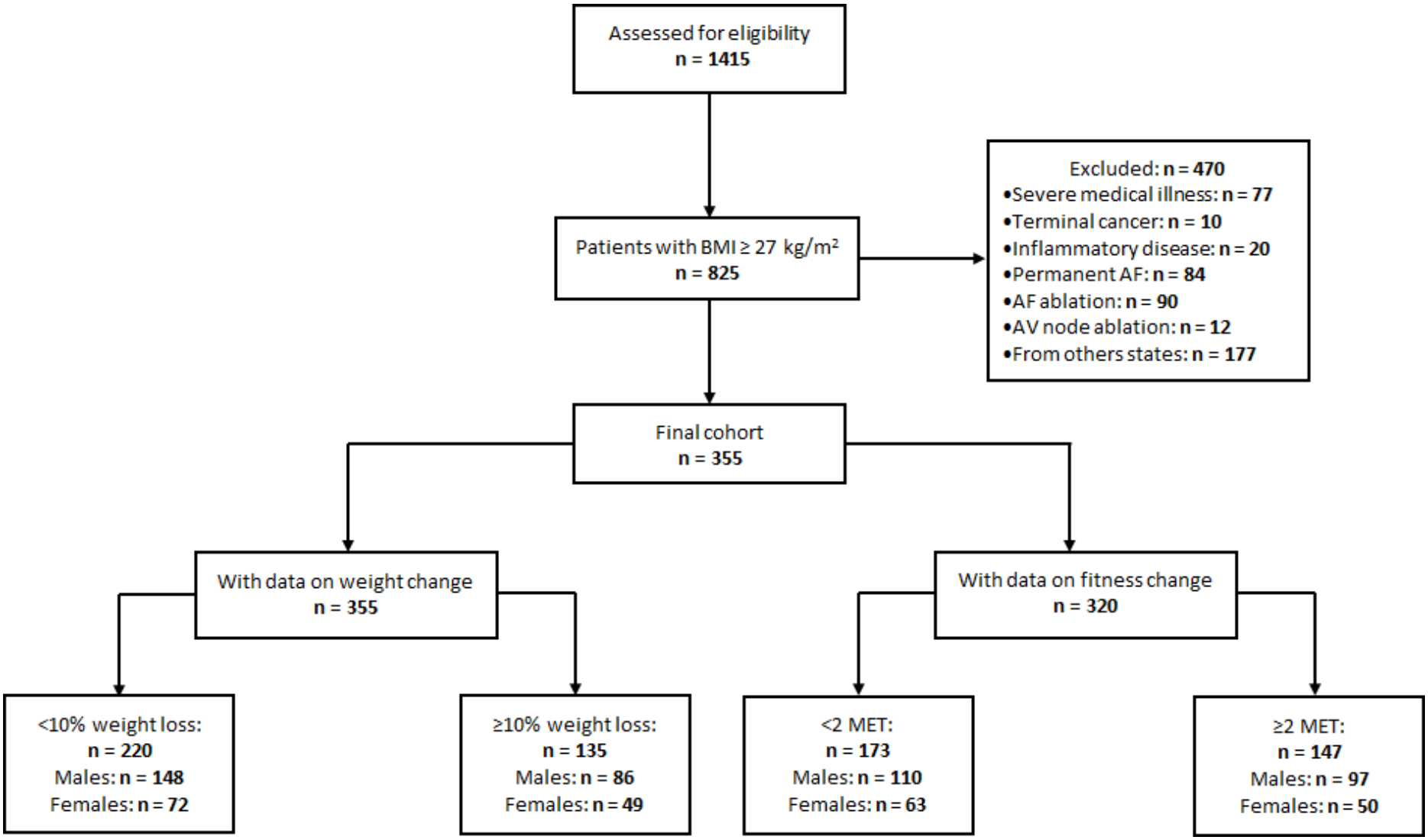


Figure 2. Weight and cardiorespiratory fitness changes in males and females

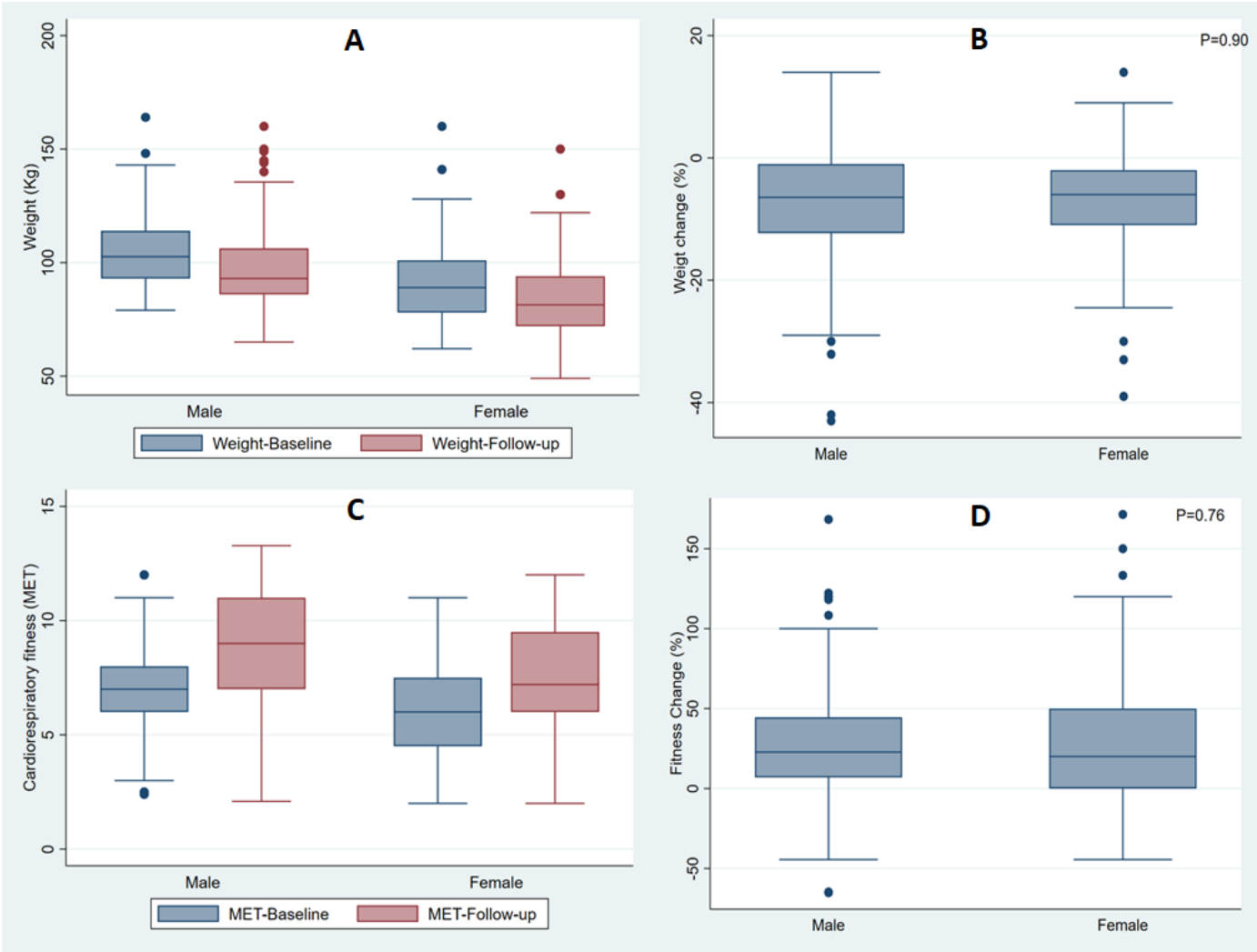


Figure 3. Changes in atrial fibrillation type

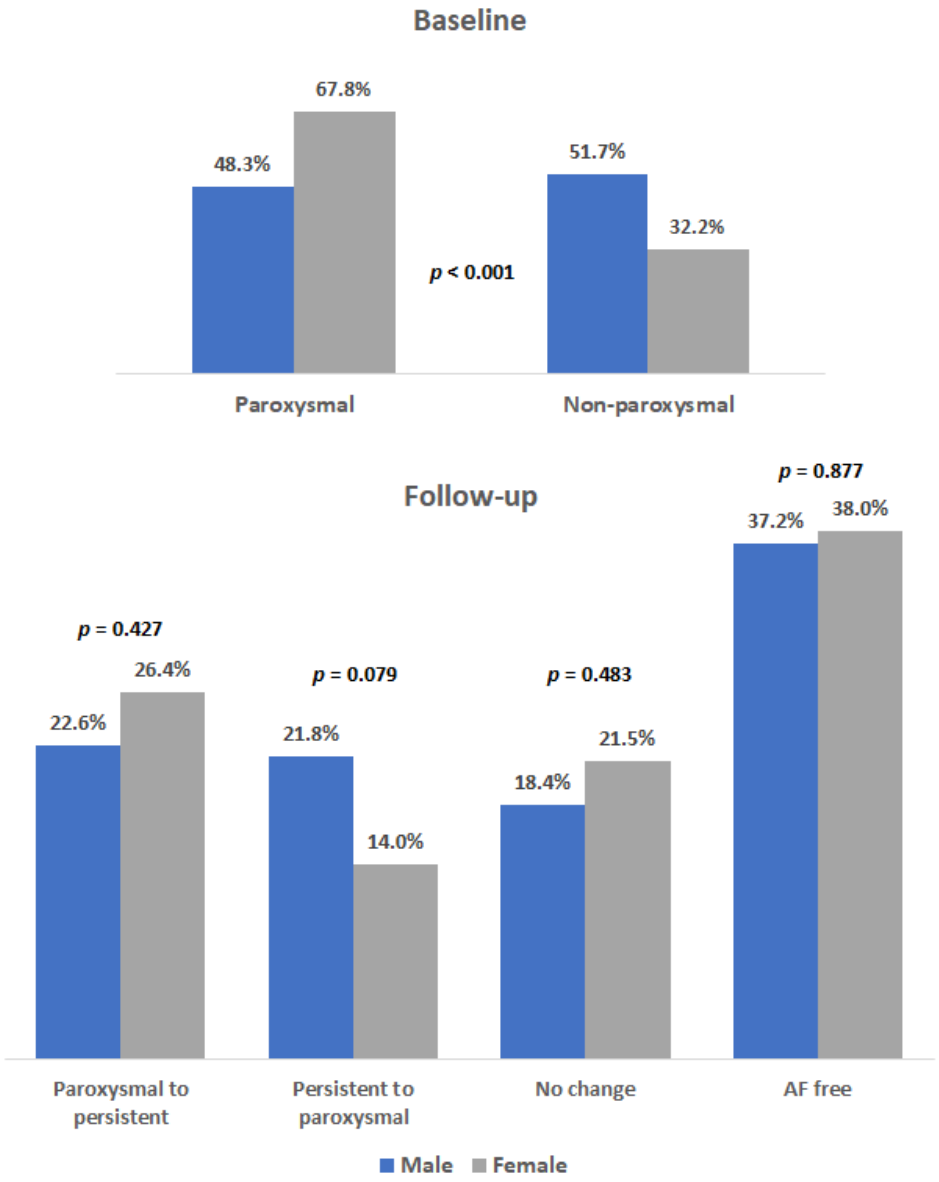


Figure 4. Total atrial fibrillation freedom in males and females according to weight loss and fitness gain categories

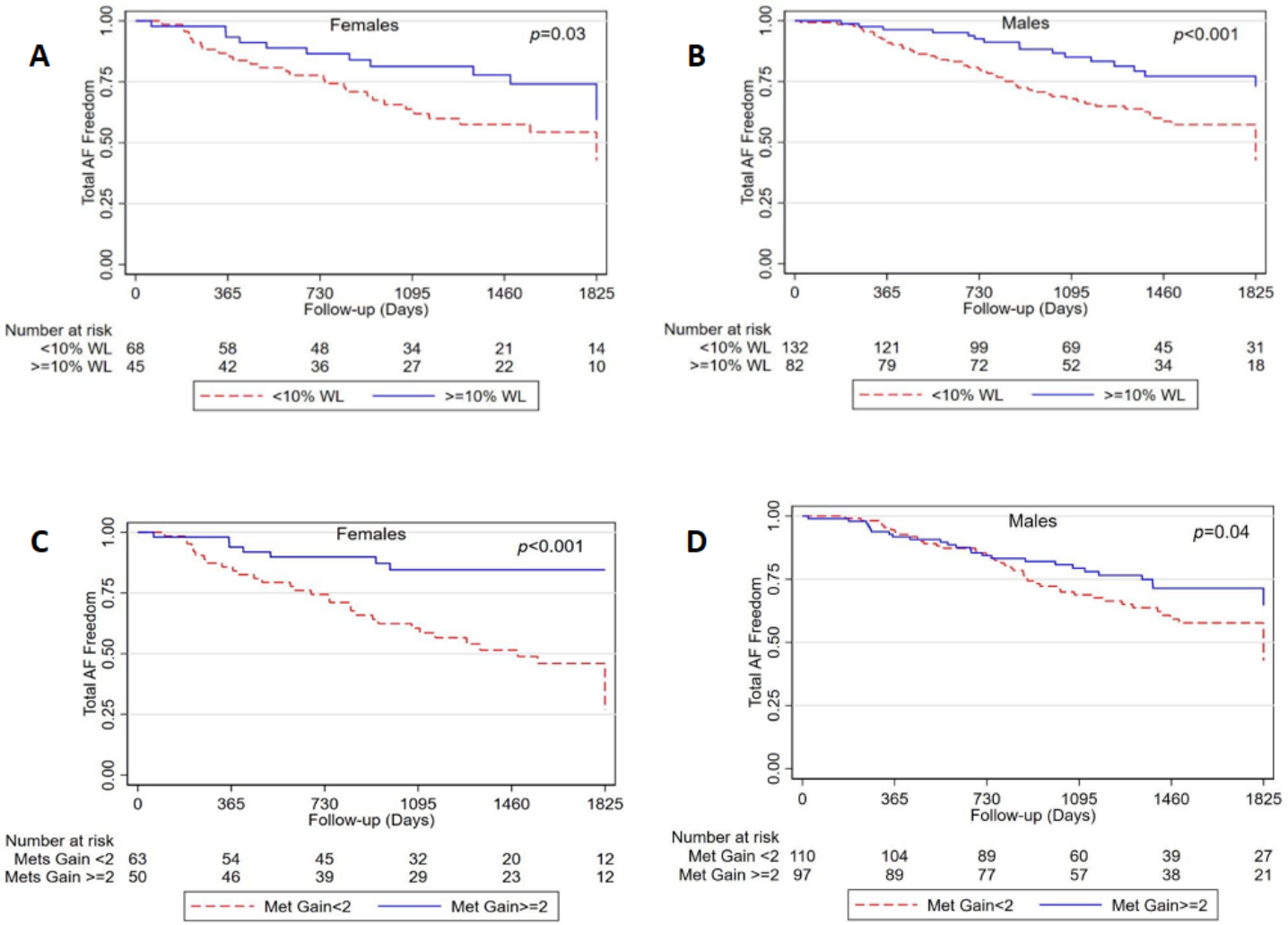


Figure 5. Freedom from AF ablation and drugs in males and females according to weight loss and fitness gain categories

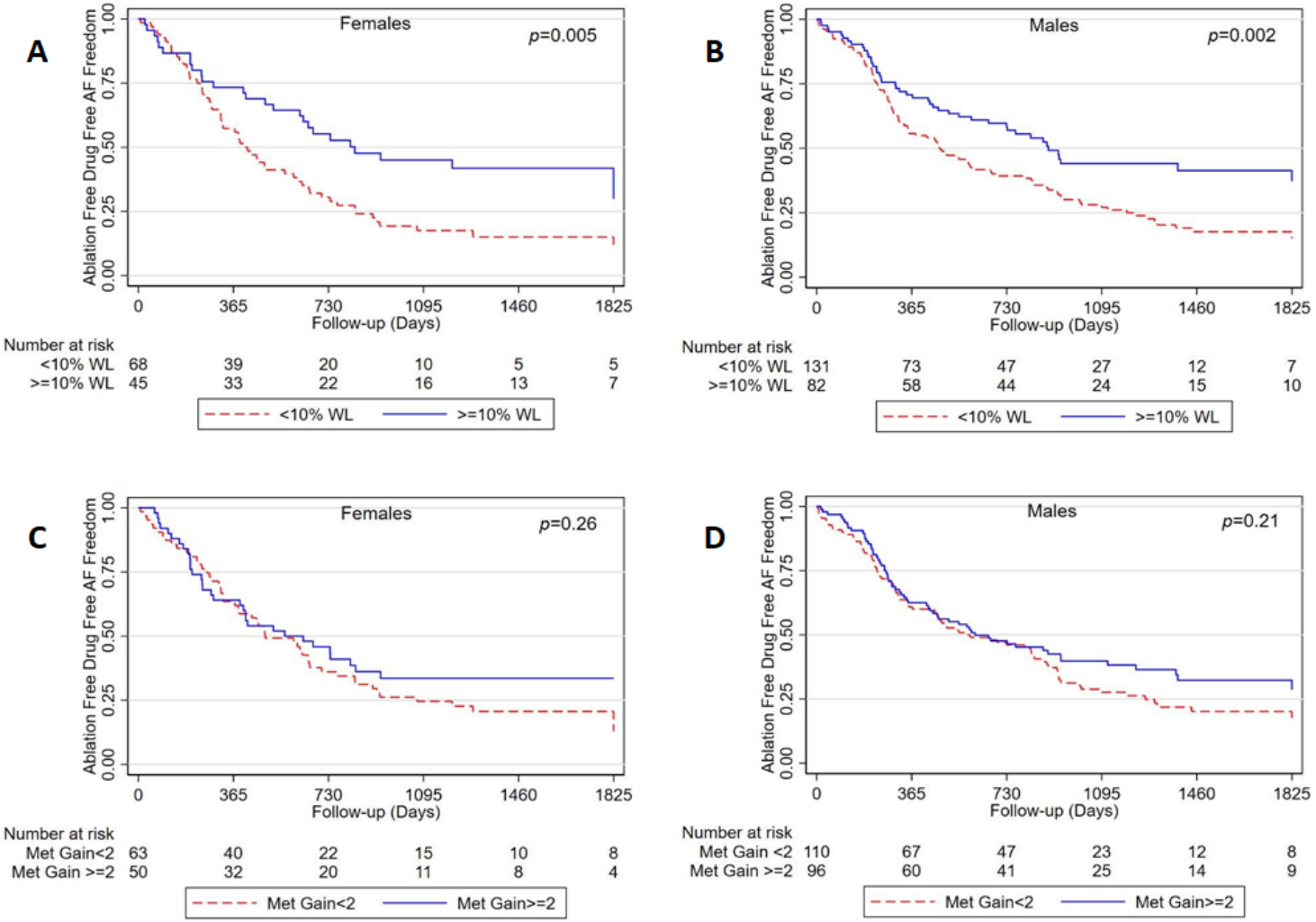
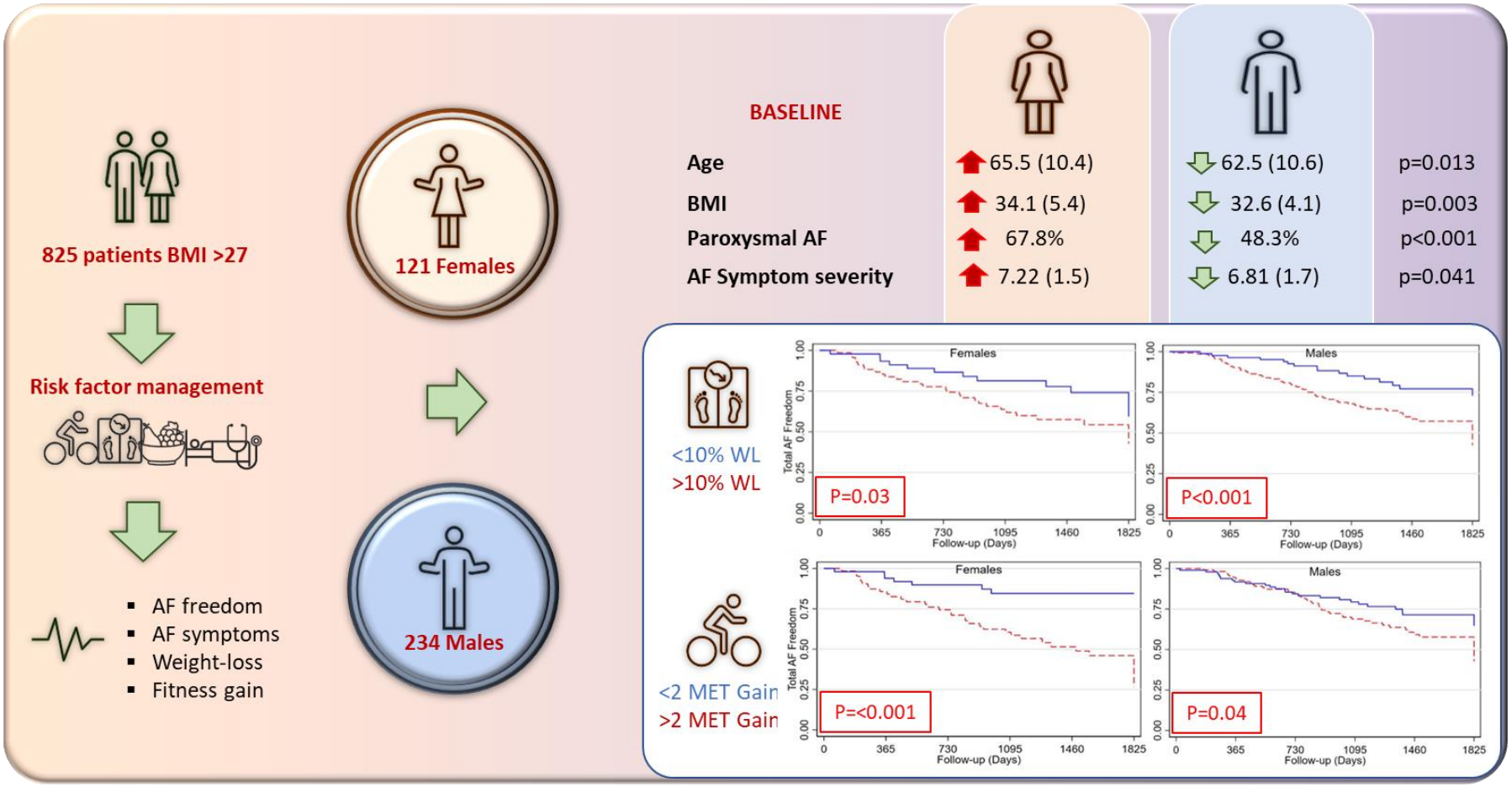


Figure 6. Graphical abstract

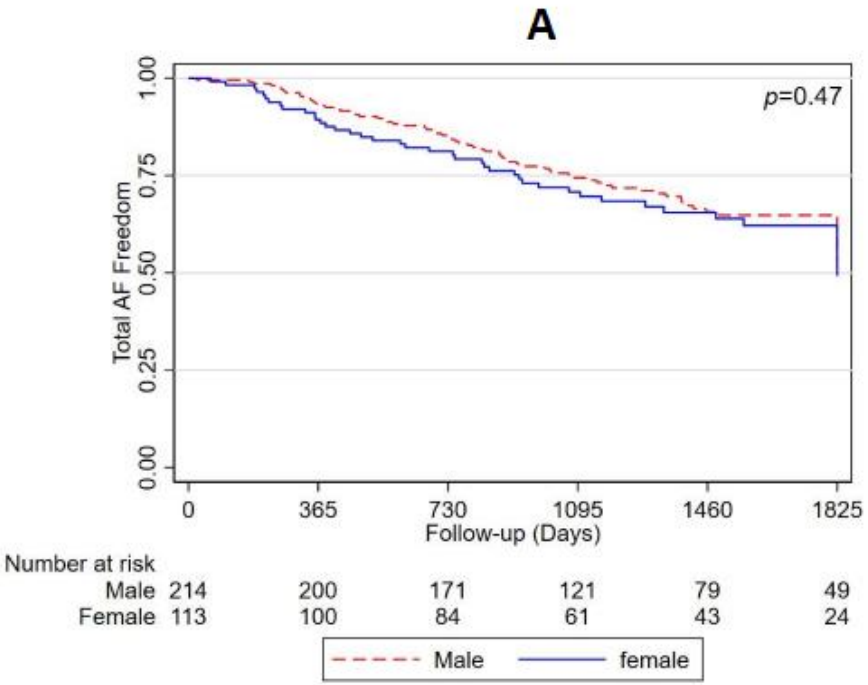


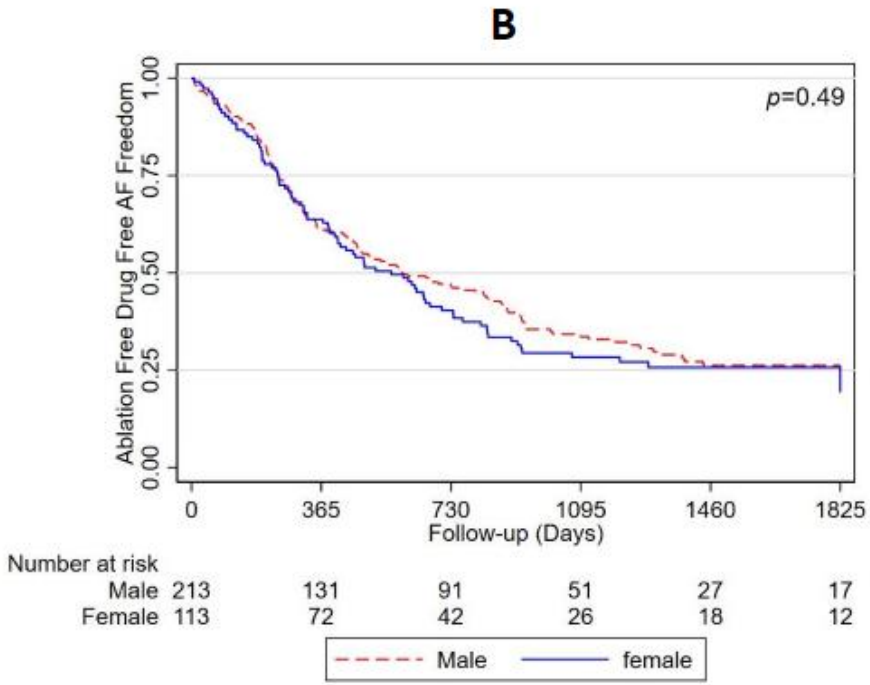
8.7 Appendix

Supplementary Table 1. Association between cardiorespiratory fitness gain, weight loss, and atrial fibrillation recurrence (univariable analysis)

	Overall		Females		Males	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Total AF freedom*						
Fitness gain (per 1 MET)	0.85 (0.78-0.92)	<0.001	0.80 (0.70-0.92)	0.002	0.88 (0.79-0.98)	0.02
Fitness gain (≥2 MET vs <2MET)	0.45 (0.30-0.67)	<0.001	0.24 (0.11-0.54)	0.001	0.60 (0.37-0.98)	0.04
Weight loss (per 1 kg)	0.96 (0.94-0.97)	<0.001	0.97 (0.94-1.04)	0.232	0.95 (0.92-0.97)	<0.001
Weight loss (≥10% kg vs <10% kg)	0.44 (0.29-0.67)	<0.001	0.48 (0.25-0.95)	0.036	0.40 (0.23-0.70)	0.001
"Ablation and drug free" AF freedom **						
Fitness gain (per 1 MET)	0.96 (0.90-1.02)	0.19	0.95 (0.86-1.05)	0.315	0.96 (0.88-1.05)	0.35
Fitness gain (≥2 MET vs <2MET)	0.81 (0.62-1.05)	0.115	0.79 (0.51-1.22)	0.284	0.82 (0.59-1.13)	0.233
Weight loss (per 1 kg)	0.97 (0.96-0.98)	<0.001	0.98 (0.96-1.01)	0.159	0.96 (0.95-0.98)	<0.001
Weight loss (≥10% kg vs <10% kg)	0.58 (0.42-0.74)	<0.001	0.52 (0.33-0.82)	0.005	0.58 (0.41-0.83)	0.003
AF: atrial fibrillation; MET: metabolic equivalents; LCL: 95% lower confidence limit; HR: hazard ratio; UCL: 95% upper confidence limit						

Supplementary Figure 1. Outcomes of AF freedom in males and females





CHAPTER 9:

Sex differences in clinical profile, management, and outcomes of patients hospitalized for atrial fibrillation in the United States

Statement of Authorship

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Overall percentage (%)	60%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		**Date**	3/12/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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9.1 Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting more than 38 million individuals (0.51% of global population) [1]. The occurrence of AF is driven mainly by aging, and cardiometabolic risk factors such as obesity, hypertension, diabetes mellitus, and obstructive sleep apnea [55]. AF substantially increases the risk of stroke, systemic embolism, heart failure, and death [70, 167]. Some studies have shown sex differences in the incidence of AF and related adverse outcomes. For instance, AF is about 1.5 to 2 times more frequent in middle-aged and older men compared with women of the same age group [3, 303, 643]. Furthermore, AF has been shown to be a stronger risk factor for stroke, cardiovascular mortality, and all-cause mortality in women compared with men [329]. Hence, female sex is a component in several cardioembolic risk scores for patients with non-valvular AF including the CHA_2DS_2-VASc score [264]. However, some studies, especially in Asian populations, have shown a similar risk of stroke in women and men with AF [658]. Moreover, results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe) that includes four community-based European studies (FINRISK, DanMONICA, Molisani, Northern Sweden), confirmed the increased risk of AF in men, and showed that this sex difference in the risk of AF was partially explained by factors such as body mass index and total cholesterol [303]. However, there was no significant sex difference in mortality associated with incident AF [303].

These conflicting data highlight the need for more studies to explore sex differences in various aspects of the epidemiology of AF and unravel the potential underlying mechanisms. The current study aimed to investigate the impact of sex on the clinical profile, utilization of rhythm control therapies, in-hospital mortality, length of stay (LOS), and cost of hospitalization in patients admitted for AF in the United States. We hypothesized that there are sex differences in outcomes of hospital admissions for AF.

9.2 Methods

9.2.1 Study design and data source

We conducted a cohort-based observational study using data from the Nationwide Inpatient Sample (NIS) for the year 2018. The NIS is the largest publicly available inpatient healthcare dataset in the United States. It is part of the Healthcare Cost and Utilization Project (HCUP) developed by the Agency for Healthcare Research and Quality (AHRQ) [659]. The NIS records approximately 35 million weighted hospitalizations per year, which represents a 20% stratified systemic sample of all discharges from urban and rural US community hospitals from the 46 participating states, with the exclusion of rehabilitation centers and long-term care facilities [659]. It is representative of more than 97% of the US population [659].

9.2.2 Study population and diagnosis ascertainment

Diagnoses and procedures were identified through the International Classification of Diseases, Tenth Revision (ICD-10) codes. The list of codes used in the study is presented in the appendix (**Supplementary Table 1**). We included all patients aged 18 years or more, admitted with a primary diagnosis of AF. We excluded patients with known AF but not admitted specially for AF (AF listed as secondary diagnoses), and patients admitted for a primary diagnosis of atrial flutter. Because the ICD-10 codes for ablation are not specific to catheter ablation and may represent atrioventricular nodal ablation and pacemaker implantation, we excluded patients with ICD-10 codes of ablation and pacemaker implantation.

9.2.3 Study variables and outcomes

We gathered information on patients' demographics including age, sex, race, admission type, median household income, primary expected payer and comorbidities. Comorbidities of interest included hypertension, diabetes mellitus, obesity, dyslipidemia, heart failure [including the categories heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) whenever available], vascular disease, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and previous stroke or transient ischemic attack (TIA). We also retrieved data on tobacco smoking and alcohol abuse. The CHA_2DS_2-VASc score was calculated for each patient (**Supplementary Table 2**). The primary outcome of interest was in-hospital mortality. Secondary outcomes included the use of rhythm control therapies (electrical cardioversion and ablation), LOS, and cost of hospitalization.

9.2.4 Statistical analysis

Categorical variables were expressed as frequencies and percentages (excluding missing data) while continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. We assessed differences between men and women using the Student's t-test for continuous variables and the Pearson Chi square test for categorical variables. For the primary outcome, in-hospital mortality, we performed univariable and multivariable logistic regression analysis in the entire population. To assess any difference in factors associated with in-hospital mortality, we also performed univariable and multivariable regression analysis in men and women separately. In multivariable regression analysis, we reported a full model adjusted for age, sex (for the analysis on the entire population), race, median household income, co-morbidities, tobacco smoking and alcohol abuse, and rhythm control procedures (catheter ablation or electrical cardioversion).

Similar logistic regression analyses were performed for the secondary outcomes including LOS (> median), cost of hospitalization (> median), and use of catheter ablation and electrical cardioversion. For these analyses on secondary outcomes, we only reported measures of association for sex (male versus female). Associations between outcomes and explanatory variables were presented as odds ratios (OR) with 95% confidence interval (95% CI). A p-value of ≤ 0.05 was considered significant. All analyses were performed using Stata 15 statistical package (Statacorp, College Station, TX).

9.2.5 Ethical considerations

This study used de-identified patient information from the NIS. Therefore, ethical approval was not required.

9.3 Results

9.3.1 Sociodemographic and clinical characteristics

We included 82592 patients aged 18 years or more admitted with a primary diagnosis of AF during the year 2018 of the NIS database. Women represented 50.8% (n = 41971) of the cohort. Women were significantly older than men (mean age 74 (SD 12) years vs 67 (SD 13) years, p <0.001, had lower household income (p = 0.033), and were more likely to have Medicare insurance (p <0.001) (**Table 1**).

There were sex differences in the prevalence of most risk factors (**Table 2**). Tobacco smoking and alcohol abuse were more frequent in men (both p <0.001). Hypertension and heart failure were more common in women (both p <0.001), whereas diabetes mellitus, obesity, vascular disease, OSA (all p <0.001), and CKD (p = 0.007) were more frequent in men. Heart failure with preserved ejection fraction was more common in women (p <0.001), with no difference for heart failure with reduced ejection fraction (p = 0.290). There was no

difference with respect to COPD (p = 0.960) and history of stroke or TIA (p = 0.670). Overall, women had a higher CHA_2DS_2-VASc score (median 4 [IQR 3,5] vs 2 (IQR 1,4), p <0.001). Furthermore, women had more paroxysmal AF than men (p <0.001).

9.3.2 In-hospital mortality

Women had a trend towards higher in-hospital mortality (0.9% vs 0.8%, p = 0.070) (**Table 3**). In multivariable regression analysis female sex was not associated with an increased risk of in-hospital mortality (adjusted OR [aOR] 1.11, 95% CI 0.95-1.30). (**Table 4**). In sex-specific univariable logistic regression analysis, in-hospital mortality was influenced by age, obesity, hypertension, dyslipidemia, OSA, COPD, previous stroke or TIA, heart failure, vascular disease, chronic kidney disease, and use of electrical cardioversion and catheter ablation in both men and women (**Table 5**). In multivariable regression analysis, regarding women, increased age (adjusted OR [aOR] 1.05, 95% CI 1.04-1.07; per one year increase), COPD (aOR 1.44, 95% CI 1.13-1.85), previous stroke or TIA (aOR 5.17, 95% CI 3.52-7.61), heart failure (aOR 2.04, 95% CI 1.53-2.71), vascular disease (aOR 1.42, 95% CI 1.15-1.77), CKD (2.11, 95% CI 1.65-2.70), and chronic AF (aOR 1.50, 95% CI 1.07-2.11) were associated with risk of in-hospital mortality, whereas dyslipidemia (aOR 0.70, 95% CI 0.56-0.86) and OSA (aOR 0.47, 95% CI 0.27-0.80) were associated with a lower risk (**Table 6**). Specifically in men, the likelihood of in-hospital mortality was increased by increased age (adjusted OR [aOR] 1.05, 95% CI 1.04-1.06; per one year increase), Black race (aOR 2.19, 95% CI 1.53, 3.16) and Asian or Pacific Islander ethnicity (aOR 3.37, 95% CI 1.89-6.00), alcohol abuse (aOR 1.57, 95% CI 1.03-2.38), COPD (aOR 1.64, 95% CI 1.26-2.12), previous stroke or TIA (aOR 3.57, 95% CI 2.19-5.84), heart failure (aOR 2.16, 95% CI 1.61-2.90), CKD (aOR 2.15, 95% CI 1.63-2.83) and was decreased by dyslipidemia (aOR 0.59, 95% CI 0.46-0.75) (**Table 6**).

9.3.3 Utilization of rhythm control therapies

Women were less likely to receive catheter ablation (3.7% vs 5.2%, p <0.001) and electrical cardioversion (16.0% vs 21.4%, p <0.001) (**Table 3**). After adjusting for potential confounders, female sex was associated with lower likelihood of receiving catheter ablation (aOR 0.69, 95% CI 0.64-0.74) and electrical cardioversion (aOR 0.69, 95% CI 0.67-0.72) (**Table 4**).

9.3.4 Length of stay and costs

Women had longer duration of hospitalization (3 [IQR 2,4] days vs 2 [IQR 1,4] days, p <0.001) but lower cost of hospitalization (25036 [IQR 14442, 47034] vs 25839 [IQR 14675, 52877] US dollars, p <0.001) compared with men (**Table 3**). After adjusting for confounders, female sex was associated with a longer length of stay (aOR 1.33, 95% CI 1.28-1.37), whereas sex had no influence of hospitalization costs (p = 0.339) (**Table 4**).

9.4 Discussion

In this study we investigated sex differences in the clinical profile, utilization of rhythm control therapies, in-hospital mortality, LOS, and cost of hospitalization among patients admitted for AF in the United States. We observed significant disparities in risk factors between men and women. Women were older and with significantly higher CHA_2DS_2-VASc score. Although women had a trend towards higher crude mortality rate, after adjusting for confounders, female sex was not associated with increased in-hospital mortality. Both sexes shared numerous risk factors for in-hospital mortality including increased age, COPD, previous stroke, heart failure, and CKD (**Figure 1**). However, some factors were sex-specific, such as vascular disease in women, race and alcohol abuse in men. Dyslipidemia was

associated with a lower risk of in-hospital mortality in both sexes, whereas OSA was associated with a lower risk only in women. Women were significantly less likely to receive catheter ablation and electrical cardioversion, and had a longer hospital stay.

The higher CHA_2DS_2-VASc score in women likely stems from the inclusion of female sex in this score, the older age of women (especially the proportion of those aged ≥ 75 years) and their higher prevalence of risk factors such as hypertension and heart failure. One of the most striking differences between women and men is age. The mean age on admission was 74 years in women and 67 years in men. Similar age distribution between women and men was reported in other studies in people with AF including the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry (72 vs 68 years)[317], the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry (77 vs 73 years) [319], and the Euro Heart Survey on Atrial Fibrillation (70 vs 64 years) [320], the Monitoring and Observing the Value of Exercise (MOVE) study (67 vs 71 years) [321], and the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study (67 vs 71 years) [318]. Furthermore, the differences in co-morbidities burden between men and women in our study were similar to what was reported in various studies [317-321].

In our study, women had a 27% reduced likelihood to have catheter ablation for AF. Several studies have also shown a lower utilization of rhythm control procedures for AF in women [348-350]. In most studies, women represented about only a third of patients who underwent catheter ablation [348-350]. However, these studies have shown conflicting results on whether women are less likely to undergo catheter ablation when accounting for potential confounders. For instance, in the ORBIT-AF registry, despite having more symptoms, more functional impairment, and worse quality of life, women had lower crude rates of catheter ablation [319]. Nevertheless, after risk adjustment similar rates of AF ablation were observed between women and men [319]. An analysis of Quebec administrative databases showed that the

annual proportion of women who had received AF ablation between 2003 and 2021 had not surpassed 30%, and that men had a 54% higher likelihood of undergoing ablation than did women [348]. Consistent with our findings, lower rates of electrical cardioversion in women compared with men have been reported in several studies [319, 320, 350].

We observed a trend toward a higher crude in-hospital mortality rate in women. However, after risk adjustment female sex did not emerge as a predictor of in-hospital mortality in this large cohort of patients with AF. This suggests that the relatively higher mortality rate in women was due to their higher comorbidity burden and older age. Our sex-specific regression analyses showed similarities and disparities in risk factors for mortality in men and women. This highlights the importance of disaggregating data to better explore predictors of outcomes in specific groups, and that prediction of outcomes using sex-specific risk stratification tools might be more efficient than tools that do not differentiate women from men. A notable finding is the association of dyslipidemia with lower risk of in-hospital mortality in both sexes. This might be due to the benefit of statin therapy in patients with AF. A meta-analysis showed 41 % and 25 % reduction in all-cause and cardiovascular mortality, respectively, in patients with AF [660]. Furthermore, the absence of a significant impact of catheter ablation on in-hospital mortality might be due to the fact that its survival benefit is apparent in the long-term [661]. Another striking finding is the substantially higher risk of in-hospital mortality associated with Black and Asian or Pacific Islander races in men, whereas there was no effect of race of in-hospital mortality in females. It is well-established that Black populations in the US have significantly higher risk of all-cause mortality compared to White populations,[662] due to a worse risk profile and lower access to healthcare in Black people.[663] However, the sex disparity in the impact of race on in-hospital mortality in patients hospitalized for AF deserves further investigation.

We found that women had a longer hospital stay. This might be due to more common frailty in women due to their higher comorbidity burden and older age. Frailty is a well-known predictor of long hospital stay [664]. The cost of hospitalization was higher in men compared with women. However, after adjusting for potential confounders, the difference was no longer significant, suggesting that the sex-disparity in cost of hospitalization might be due to procedures such as catheter ablation that were more commonly performed in men.

Our findings have some clinical implications. Women have a more conservative treatment, with significantly less rhythm control than men. The criteria underpinning the decision to perform catheter ablation for AF in many centers might preclude women from having appropriate therapy. In fact, patients undergoing catheter ablation tend to be younger and have fewer baseline comorbidities [348]; hence, women who are usually older and with higher comorbidities might be less frequently offered catheter ablation. Catheter ablation should be considered more often in women, especially in view of their higher symptom burden and functional impairment, and worse quality of life than men [319, 320]. Furthermore, the disparities in the risk profile and predictors of outcomes between men and women highlight the need for more consideration of sex specificities in the risk stratification and management of patients with AF.

Our study has some limitations. First, because this study was retrospective and was based on an administrative database using diagnosis codes, there is a potential of selection bias and ascertainment bias from coding errors and disease misclassification. Second, it was not possible to obtain some information including whether AF was non-valvular or valvular, the duration of AF or when AF was diagnosed, key drug therapies for AF such as anticoagulant, rate and rhythm control medications. These factors are known to impact outcomes in patients with AF, and could have influenced our estimates. Third, this study only examined in-hospital outcomes; therefore, it could not capture the full extent of the impact of

sex on AF outcomes, especially long-term outcomes. Finally, although we performed multivariable analysis to assess factors independently associated with in-hospital mortality, hidden confounders may not have all been accounted for.

9.5 Conclusion

There were differences in the risk profile, management, and outcomes between men and women hospitalized for AF. Women were older, with a higher comorbidity burden, and were less likely to undergo catheter ablation or electrical cardioversion. Although women had a relatively higher mortality rate, after risk adjustment, female sex was not a predictor of mortality. There were similarities and disparities in risk factors for mortality between men and women. Finally, women also had significantly longer hospital stay. Sex specificities need more consideration in research in the AF population.

9.6 Tables and figures

Table 1. Sociodemographic characteristics of the study population

Table 2. Clinical profile of the study population

Table 3. Management and outcomes

Table 4. Outcomes of atrial fibrillation hospitalization among women compared with men

Table 5. Factors associated with in-hospital mortality among women and men in univariable logistic regression analysis

Table 6. Factors associated with in-hospital mortality among women and men in multivariable logistic regression analysis

Figure 1. Graphical abstract

Table 1. Sociodemographic characteristics of the study population

Variables	**Women** (N = 41971)	**Men** (N = 40621)	**P value**
Age at admission (years)*	74 (12)	67 (13)	<0.001
• <45	689 (1.6%)	2122 (5.2%)	<0.001
• 45-64	7127 (17.0%)	13727 (33.8%)	
• 65-74	11280 (26.9%)	12004 (29.6%)	
• >=75	22875 (54.5%)	12768 (31.4%)	
Race			
• White	33557 (81.6%)	32536 (81.9%)	0.002
• Black	3316 (8.1%)	2984 (7.5%)	
• Hispanic	2599 (6.3%)	2579 (6.5%)	
• Asian or Pacific Islander	674 (1.6%)	598 (1.5%)	
• Native American	141 (0.3%)	170 (0.4%)	
• Other	813 (2.0%)	872 (2.2%)	
Household income (national quartile)			
• Quartile 1	11172 (27.0%)	10442 (26.2%)	0.033
• Quartile 2	11514 (27.8%)	11138 (27.9%)	
• Quartile 3	10385 (25.1%)	10039 (25.2%)	
• Quartile 4	8320 (20.1%)	8257 (20.7%)	
Primary expected payer (uniform)			
• Medicare	33177 (79.1%)	24299 (59.9%)	<0.001
• Medicaid	1895 (4.5%)	3076 (7.6%)	
• Private insurance	5869 (14.0%)	10547 (26.0%)	
• Self-pay	603 (1.4%)	1378 (3.4%)	
• No charge	62 (0.1%)	121 (0.3%)	
• Other	332 (0.8%)	1146 (2.8%)	
Census Division of hospital			
• New England	2206 (5.3%)	2060 (5.1%)	
• Middle Atlantic	5774 (13.8%)	5735 (14.1%)	
• East North Central	7320 (17.4%)	6866 (16.9%)	

• West North Central	2957 (7.0%)	2868 (7.1%)	0.046
• South Atlantic	9758 (23.2%)	9429 (23.2%)	
• East South Central	3030 (7.2%)	2791 (6.9%)	
• West South Central	4550 (10.8%)	4450 (11.0%)	
• Mountain	2268 (5.4%)	2281 (5.6%)	
• Pacific	4108 (9.8%)	4141 (10.2%)	

*Expressed as mean (standard deviation)

Table 2. Clinical profile of the study population

Variables	**Women** (N = 41971)	**Men** (N = 40621)	**P value**
Tobacco smoking	3185 (7.6%)	5830 (14.4%)	<0.001
Alcohol abuse	682 (1.6%)	3543 (8.7%)	<0.001
Hypertension	18577 (44.3%)	17064 (42.0%)	<0.001
Diabetes mellitus	11627 (27.7%)	12089 (29.8%)	<0.001
Obesity	9077 (21.6%)	9441 (23.2%)	<0.001
Dyslipidemia	21598 (51.5%)	21227 (52.3%)	0.022
Chronic kidney disease	7627 (18.2%)	7676 (18.9%)	0.007
COPD	7548 (18.0%)	7300 (18.0%)	0.960
Obstructive sleep apnea	4505 (10.7%)	7467 (18.4%)	<0.001
Previous stroke or TIA	685 (1.6%)	648 (1.6%)	0.67
Vascular disease	15099 (36.0%)	18394 (45.3%)	<0.001
Heart failure	17283 (41.2%)	16079 (39.6%)	<0.001
HFrEF	5542 (13.2%)	5466 (13.5%)	0.290
HFpEF	5785 (13.8%)	5114 (12.6%)	<0.001
Atrial fibrillation type			
• Paroxysmal	18112 (43.2%)	15673 (38.6%)	<0.001
• Persistent	5185 (12.4%)	6599 (16.2%)	
• Chronic	4025 (9.6%)	3978 (9.8%)	
• Unspecified	14649 (34.9%)	14371 (35.4%)	
CHA_2DS_2-VASc score*	4 (3, 5)	2 (1, 4)	<0.001

COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; TIA: transient ischemic attack

*Expressed as median (interquartile range)

Table 3. Management and outcomes

Variables	**Women** (N = 41971)	**Men** (N = 40621)	**P value**
Catheter ablation	1556 (3.7%)	2093 (5.2%)	<0.001
Electrical cardioversion	6731 (16.0%)	8712 (21.4%)	<0.001
Length of stay, median (IQR)	3 (2, 4)	2 (1, 4)	<0.001
Cost (US dollar), median (IQR)	25036 (14442, 47034)	25839 (14675, 52877)	<0.001
Died during hospitalization	376 (0.9%)	317 (0.8%)	0.070

IQR: interquartile range

Table 4. Outcomes of atrial fibrillation hospitalization among women compared with men

Outcomes	Unadjusted				Adjusted			
	OR	LCL	UCL	P value	OR	LCL	UCL	P value
Mortality	1.15	0.99	1.33	0.070	1.11	0.95	1.30	0.199
LOS ≥ median	1.24	1.20	1.27	<0.001	1.33	1.28	1.37	<0.001
Cost ≥ Median	0.94	0.92	0.97	<0.001	1.01	0.98	1.04	0.339
Catheter ablation	0.71	0.66	0.76	<0.001	0.69	0.64	0.74	<0.001
Electrical cardioversion	0.70	0.68	0.72	<0.001	0.69	0.67	0.72	<0.001

LCL: 95% lower confidence limit; LOS: length of stay; OR: odds ratio; UCL: 95% upper confidence limit
Outcome variables adjusted for: age, sex, race, income, tobacco smoking, alcohol abuse, obesity, diabetes, hypertension, dyslipidemia, OSA, COPD, heart failure, vascular disease, CKD, catheter ablation, and electrical cardioversion

Table 5. Factors associated with in-hospital mortality among women and men in univariable logistic regression analysis

Variables	Female				Male			
	OR	**LCL**	**UCL**	**P value**	**OR**	**LCL**	**UCL**	**P value**
Age	1.07	1.05	1.08	<0.001	1.05	1.04	1.07	<0.001
Race								
• White (reference)	1.00							
• Black	0.78	0.52	1.19	0.253	1.97	1.40	2.76	<0.001
• Hispanic	0.79	0.50	1.26	0.327	1.07	0.67	1.72	0.763
• Asian or Pacific Islander	0.48	0.15	1.50	0.208	3.22	1.83	5.67	<0.001
• Native American	2.34	0.74	7.38	0.147	3.49	1.28	9.49	0.014
• Other	1.07	0.53	2.16	0.853	0.84	0.34	2.03	0.691
Household income								
• Quartile 1	1.03	0.76	1.40	0.827	1.44	1.02	2.04	0.038
• Quartile 2	1.10	0.81	1.48	0.552	1.43	1.01	2.01	0.042
• Quartile 3	1.05	0.77	1.42	0.773	1.28	0.90	1.83	0.168
• Quartile 4 (reference)	1.00							
Tobacco smoking	0.90	0.61	1.35	0.621	0.89	0.64	1.23	0.469
Alcohol abuse	1.15	0.54	2.44	0.716	1.02	0.69	1.50	0.940
Obesity	0.54	0.40	0.73	<0.001	0.57	0.42	0.78	<0.001
Diabetes mellitus	1.05	0.84	1.32	0.656	1.12	0.88	1.42	0.345
Hypertension	2.46	1.98	3.05	<0.001	2.05	1.64	2.57	<0.001
Dyslipidemia	0.80	0.65	0.98	0.034	0.68	0.54	0.84	0.001
Obstructive sleep apnea	0.34	0.20	0.58	<0.001	0.58	0.41	0.82	0.002
COPD	1.66	1.32	2.09	<0.001	2.06	1.62	2.61	<0.001
Previous stroke or TIA	5.62	3.86	8.19	<0.001	3.79	2.34	6.14	<0.001
Heart failure	2.60	2.11	3.22	<0.001	2.39	1.91	3.00	<0.001
Vascular disease	1.77	1.44	2.17	<0.001	1.37	1.09	1.70	0.006
Chronic kidney disease	2.73	2.21	3.37	<0.001	2.90	2.31	3.64	<0.001
Atrial fibrillation type								

• Paroxysmal (reference)	1.00				1.00			
• Persistent	1.17	0.81	1.69	0.407	1.00	0.70	1.44	0.984
• Chronic	2.43	1.74	3.41	<0.001	1.57	1.05	2.33	0.027
• Unspecified	1.99	1.57	2.51	<0.001	1.56	1.21	2.02	0.001
Catheter ablation	0.42	0.19	0.94	0.035	0.54	0.28	1.04	0.065
Electrical cardioversion	0.67	0.49	0.93	0.015	0.62	0.45	0.85	0.003

COPD: chronic obstructive pulmonary disease; Household income categorized in national quartiles; LCL: 95% lower confidence limit; OR: odds ratio; UCL: 95% upper confidence limit; TIA: transient ischemic attack

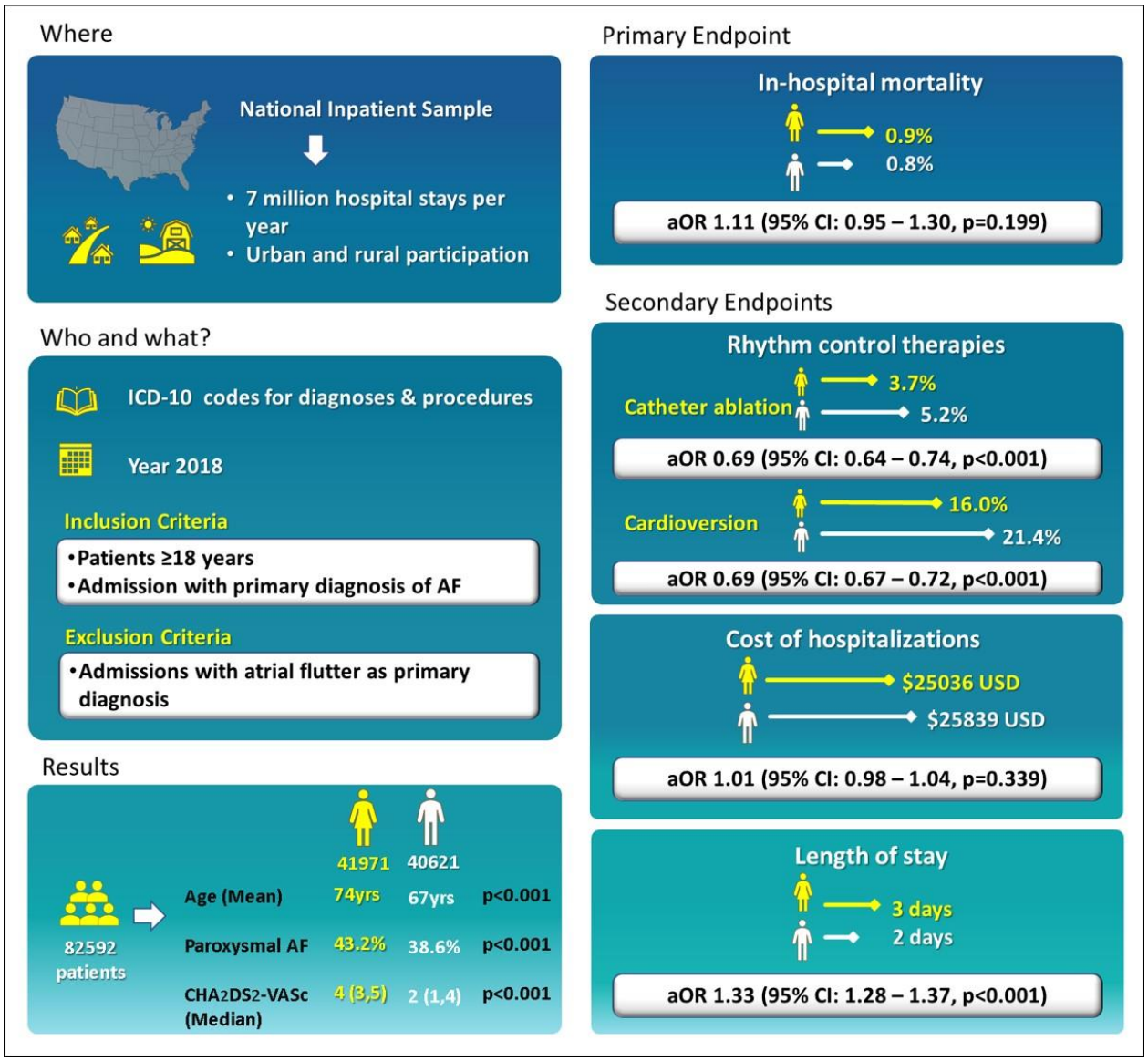
Table 6. Factors associated with in-hospital mortality among women and men in multivariable logistic regression analysis

Variables	Female				Male			
	OR	**LCL**	**UCL**	**P value**	**OR**	**LCL**	**UCL**	**P value**
Age	1.05	1.04	1.07	<0.001	1.05	1.04	1.06	<0.001
Race								
• White (reference)	1.00							
• Black	0.84	0.55	1.30	0.441	2.19	1.53	3.16	<0.001
• Hispanic	0.86	0.53	1.37	0.518	1.22	0.76	1.97	0.408
• Asian or Pacific Islander	0.53	0.17	1.66	0.276	3.37	1.89	6.00	<0.001
• Native American	2.58	0.80	8.37	0.113	2.94	0.91	9.48	0.071
• Other	1.07	0.53	2.20	0.844	0.93	0.38	2.28	0.879
Household income								
• Quartile 1	0.97	0.71	1.33	0.869	1.22	0.85	1.76	0.287
• Quartile 2	1.05	0.78	1.42	0.746	1.33	0.94	1.90	0.111
• Quartile 3	0.98	0.71	1.33	0.886	1.21	0.84	1.74	0.313
• Quartile 4 (reference)	1.00							
Tobacco smoking	1.12	0.72	1.75	0.602	1.01	0.70	1.47	0.947
Alcohol abuse	1.56	0.72	3.39	0.262	1.57	1.03	2.38	0.036
Obesity	0.92	0.67	1.28	0.638	0.89	0.63	1.26	0.518
Diabetes mellitus	1.04	0.82	1.33	0.745	0.98	0.76	1.27	0.908
Hypertension	0.96	0.70	1.32	0.822	0.77	0.56	1.07	0.121
Dyslipidemia	0.70	0.56	0.86	0.001	0.59	0.46	0.75	<0.001
Obstructive sleep apnea	0.47	0.27	0.80	0.005	0.83	0.57	1.19	0.307
COPD	1.44	1.13	1.85	0.003	1.64	1.26	2.12	<0.001
Previous stroke or TIA	5.17	3.52	7.61	<0.001	3.57	2.19	5.84	<0.001
Heart failure	2.04	1.53	2.71	<0.001	2.16	1.61	2.90	<0.001
Vascular disease	1.42	1.15	1.77	0.001	1.01	0.79	1.29	0.939
Chronic kidney disease	2.11	1.65	2.70	<0.001	2.15	1.63	2.83	<0.001
Atrial fibrillation type								

• Paroxysmal (reference)	1.00				1.00			
• Persistent	1.28	0.87	1.87	0.210	1.06	0.71	1.57	0.787
• Chronic	1.50	1.07	2.11	0.02	1.21	0.83	1.76	0.312
• Unspecified	1.85	1.45	2.37	<0.001	1.41	1.07	1.85	0.014
Catheter ablation	0.56	0.25	1.27	0.165	0.71	0.36	1.41	0.267
Electrical cardioversion	0.88	0.63	1.24	0.475	0.83	0.59	1.16	0.267

COPD: chronic obstructive pulmonary disease; Household income categorized in national quartiles; LCL: 95% lower confidence limit; OR: odds ratio; UCL: 95% upper confidence limit; TIA: transient ischemic attack

Graphical abstract



9.7 Appendix

Supplementary Table 1. List of ICD-10 codes used for the study

Diagnoses	ICD-10
Heart Failure	I11.0, I13.0, I13.2, I09.81, I09.9, I25.5, I42.0, I425-I42.9, I43.x, I50.x
Heart Failure with Preserved Ejection Fraction	I50.3
Heart Failure with Reduced Ejection Fraction	I50.2, I50.4
Atrial fibrillation*	I48.0, I48.1, I48.11, I48.19, I48.2, I48.20, I48.21, I48.91
Atrial flutter*	I48.3, I48.4, I48.92
Vascular Disease (peripheral vascular disease, coronary artery disease/ischemic heart disease, carotid artery disease, or atherosclerotic aortic disease)	I20.x-I25.x, I70.x-I71.x, I73.1-I73.9, I77.1, I79.0, K55.1, K55.8-9, Z951, Z95.8-9
Diabetes mellitus	E10.x-E13.x
Hypertension	I10.x-I15.x, I67.4
Stroke, Transient Ischemic Attack (TIA) or Systemic Thromboembolism	I63.x, I69.3, I69.9, I74.x, I97.8, G45.x, G46.x, H34.0-H34.2, H34.9
History of stroke	Z86.7
Obstructive sleep apnea	G47.33
Chronic obstructive pulmonary disease	J44.x
Chronic kidney disease and end stage renal disease	N18.x
Obesity	E66.1, E66.01, E66.2, E66.8, E66.9, Z68.30, Z68.31, Z68.32, Z68.33, Z68.34, Z68.35, Z68.36, Z68.37, Z68.38, Z68.39, Z68.40, Z68.41, Z68.42, Z68.43, Z68.44, Z68.45
Dyslipidemia	E78.x
Tobacco smoking	Z72.0, F17.210, F17.200
Alcohol abuse	F10.x
Catheter ablation	02583ZZ, 02563ZZ, 02553ZZ, 02573ZZ, 025T3ZZ, 025S3ZZ
Electrical cardioversion	5A2204Z
Pacemaker implantation	Z95.0

Supplementary Table 2. CHA_2DS_2VASc Comorbidity Point Values

Condition	Score
Sex Category (female)	1
Age 65-74 years	1
Age ≥75 years	2
Stroke, transient ischemic attack, or systemic thromboembolism	2
Vascular disease	1
Congestive Heart Failure	1
Hypertension	1
Diabetes mellitus	1
Maximum Score	9

CHAPTER 10:

Conclusions of the thesis

This thesis provides contributions to important knowledge gaps related to the risk factors, screening, prognosis, risk stratification, and management of AF.

10.1 Risk factors and screening for atrial fibrillation

This work shows that reduced ventilatory function is associated with an increased risk of AF independent of age, sex, smoking, and several other known AF risk factors. This suggests that ventilatory parameters might improve AF risk prediction models. Furthermore, considering the high risk of AF associated with COPD and the frequent co-existence of these conditions, individuals with airway obstruction might represent an appropriate population for targeted AF screening. Future studies are needed to assess the added value of ventilatory function to AF prediction and the appropriate rhythm monitoring strategies for AF detection in patients with COPD.

Another group of individuals with high risk of AF are patients with cryptogenic stroke. Although landmark clinical trials revealed significantly increased AF detection with prolonged continuous cardiac monitoring with implantable cardiac monitors (ICM) over standard-of-care monitoring in patients with cryptogenic stroke, real-world data from various populations are still needed. This thesis provides further insight emphasizing that AF diagnostic yield in a real-world cohort of patients receiving prolonged cardiac monitoring with ICM have significantly lower AF detection rates to what has been previously reported.

These rates are even much lower when considering a cutoff duration (6 min) that is higher than the usual 2 min cutoff. A recent LOOP study which used a cutoff duration of 6 min to define an AF episode showed that in individuals with stroke risk factors, screening of AF with ICM resulted in higher AF detection and anticoagulation initiation but no significant reduction in the risk of stroke or systemic arterial embolism. This suggests that not all screen-detected AF merits anticoagulation. Furthermore, a meta-analysis of previous studies shows that about one in seven patients had AF detected within a month of mobile cardiac outpatient telemetry, suggesting that a non-invasive rhythm monitoring strategy should be considered before invasive monitoring.

10.2 Risk stratification

This thesis provides a couple of important contributions with respect to risk stratification. First, it shows that the weights of various risk factors included in risk stratification schemes such as the CHA_2DS_2-VASc score are not consistent with their attributable risk of stroke from cohort studies. Furthermore, it shows that female sex seems not to be universally associated with stroke or systemic embolism, suggesting that the decision to initiate anticoagulation should not be made on the sole basis of female sex as done according to recommendations by some scientific societies. To improve stroke risk stratification, future schemes should consider various non-clinical risk factors for stroke in patients with AF. This thesis shows an association between stroke and some anatomic and functional cardiac imaging parameters such as left atrial (LA) dimensions and ejection fraction, left atrial appendage (LAA) morphology, ejection fraction, flow velocities, and LA/LAA spontaneous echo-contrast and thrombus. Left atrial fibrosis, LA diameter index and LA reservoir strain are predictors of stroke in patients with AF. These imaging factors should be tested in large prospective cohort studies with established clinical risk factors and biomarkers to develop

and validate holistic stroke risk stratification schemes with better prognosis performance compared to the existing limited clinical scores.

Carotid disease is an overlooked risk factor for stroke in patients with AF. It is not considered in most risk stratification schemes including the CHA_2DS_2-VASc score. However, AF and carotid artery disease frequently co-exist, with about one in ten patients with AF who has carotid stenosis, and vice versa; and non-stenotic carotid disease being much more frequent. Moreover, there is an association between carotid atherosclerosis and the risk of stroke in patients with AF, suggesting that the incorporation of carotid atherosclerosis and characteristics of carotid plaques into scoring systems might improve stroke prediction in patients with AF. This hypothesis was tested using data from the Cardiovascular Health Study, a prospective cohort study. Moderate to severe carotid stenosis (≥ 50%) was uncommon, affecting only 5.5% of participants, whereas a third of patients had carotid plaques considered vulnerable or high-risk. Neither the degree of carotid stenosis nor the presence of vulnerable plaques was associated with incident ischemic stroke. This suggests that carotid disease was probably not an important cause of ischemic stroke in this population of patients with AF and therefore, vulnerable carotid plaques might not improve stroke risk stratification in patients with AF.

10.3 Prognostic impact of atrial fibrillation on acute cardiovascular events

This thesis demonstrates that AF is common in patients with acute coronary syndromes (one in nine) and acute pulmonary embolism (one in eight), and that AF is associated with poor short-term and long-term outcomes including re-infarction, heart failure, stroke, acute kidney injury, heart failure, major bleeding, and death. These findings have important implications.

Considering this strong prognostic impact of AF in patients with acute coronary syndrome and acute pulmonary embolism, its incorporation into risk stratification schemes for these patients should be considered. Furthermore, considering the significant incidence of AF in these patients, appropriate rhythm monitoring strategies are needed. Such strategies should be investigated in future studies.

10.4 Sex differences in atrial fibrillation management and outcomes

This thesis also makes important contributions to knowledge on sex differences in the management and outcomes of AF. First, by analysing data from 142 randomized controlled trials (RCTs) of AF published in top tiers cardiovascular journals, it shows that despite recent progress, females remain substantially less represented in RCTs of AF management. This calls into question the generalizability of these trials and the validity of the evidence guiding the treatment of females. More efforts are needed to increase female enrolment, with a special attention in trials conducted in Northern America and those with lower sample size. Avoiding the exclusion of older individuals may also improve female representation. Furthermore, sex-stratified reporting of primary outcomes infrequently occurs in RCTs of AF. Reporting by sex should become a requirement in journals' reporting guidelines in a bid to reduce the sex disparity observed in enrolment and reporting of major trials in AF.

Second, although several studies showed sex differences in the pathophysiology and clinical patterns of AF, the impact of sex on the response to various treatments in patients with AF remained largely unknown. This thesis assessed sex differences in weight-loss, cardiorespiratory fitness gain, and progression and recurrence of AF in patients undergoing aggressive risk factor modification. It shows that despite sex differences at baseline with regards to age, AF type, BMI, and cardiorespiratory fitness, the benefits of weight-loss and

fitness gain were favorable for both males and females. However, improvement in fitness had a much greater benefit for total arrhythmia freedom for females, whereas there was a trend towards more common regression from persistent to paroxysmal AF in males. These findings reinforce the need to address lifestyle risk factors to minimize arrhythmia recurrence and reduce symptom severity for all individuals.

Finally, this work also investigated the impact of sex on the clinical profile, utilization of rhythm control therapies, in-hospital mortality, length of stay (LOS), and cost of hospitalization in patients admitted for AF in the United States. Women were older, with a higher comorbidity burden, and were less likely to undergo catheter ablation or electrical cardioversion. There were similarities and disparities in risk factors for mortality between males and females. Women had a relatively higher mortality rate, although after risk adjustment, female sex was not a predictor of mortality. Women also had significantly longer hospital stay. This shows that sex specificities need more consideration in research in the AF population.

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