Effectiveness and safety of edoxaban compared with apixaban in elderly patients with nonvalvular atrial fibrillation: a real-world population-based cohort study

Richard Chiv

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Montreal

August 2023

A thesis submitted to McGill University in partial fulfilment of the requirements of the degree of Master of Science in Epidemiology

Abstract

Background: The very elderly (≥ 80 years) are at high risk of nonvalvular atrial fibrillation (NVAF) and thromboembolism, as older age represents the most prominent risk factor for both conditions. Direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban and edoxaban, are recommended over vitamin K antagonists for the prevention of stroke and systemic embolism for most patients with NVAF. While no trials with head-to-head DOAC comparisons have been conducted, observational studies in patients with NVAF have reported apixaban as holding the most favorable profile with similar effectiveness and a lower risk of major bleeding. In very elderly patients, two recent cohort studies comparing apixaban to dabigatran, rivaroxaban, and warfarin reported consistent findings. However, given its recent approval, the comparative effectiveness and safety of edoxaban in this population, relative to the commonly used apixaban, remain unknown.

Objectives: The two primary objectives of this manuscript-based thesis were to assess the effectiveness (prevention of ischemic stroke/transient ischemic attack/systemic embolism) and safety (risk of major bleeding, defined as any bleeding requiring a hospitalization) of edoxaban compared with apixaban in very elderly patients with NVAF aged 80 years and older.

Methods: This retrospective population-based cohort study was conducted using the United Kingdom Clinical Practice Research Datalink database, linked to the Hospital Episode Statistics and Office for National Statistics databases. We formed a cohort of all patients with incident NVAF aged 80 years and older newly treated with edoxaban or apixaban between July 1, 2015, and March 31, 2021. Cohort entry was defined as the first prescription for one of the two drugs after NVAF diagnosis. Patients were followed until the occurrence of the outcome of interest (depending on the studied outcome), treatment discontinuation or switching to another anticoagulant, death from any cause, end of the registration with the general practice, or end of the study period (March 31, 2021), whichever occurred first. Propensity score fine stratification and weighting was used for confounding adjustment. We fitted a weighted Cox proportional hazards model with robust sandwich variance to separately estimate the hazard ratio (HR) with 95% confidence interval (95% CI) of each primary outcome associated with edoxaban use compared with apixaban use. We also assessed the risk of all-cause mortality and a composite outcome of ischemic stroke/transient ischemic attack, systemic embolism, gastrointestinal bleeding, and

intracranial hemorrhage as secondary outcomes. We performed several sensitivity analyses to assess the robustness of our results.

Results: The cohort included 7,251 new users of edoxaban and 39,991 of apixaban. Edoxaban was as effective as apixaban in thromboembolism prevention (weighted incidence rates: 20.38 vs. 19.22 per 1,000 person-years; HR 1.06; 95% CI 0.89-1.26). However, compared with apixaban, edoxaban was associated with a higher risk of major bleeding (weighted incidence rates: 45.57 vs. 31.21 per 1,000 person-years; HR 1.42; 95% CI 1.26-1.61). The risk of the composite outcome was also 21% higher with edoxaban (weighted incidence rates: 44.34 vs. 36.12 per 1,000 person-years; HR 1.21; 95% CI 1.07-1.38). All-cause mortality was similar between edoxaban and apixaban (weighted incidence rates: 118.43 vs. 113.70 per 1,000 person-years; HR 1.04; 95% CI 0.96-1.12). Results from the sensitivity analyses were consistent with those of the primary analyses.

Discussion: In very elderly patients with NVAF, edoxaban was as effective as apixaban in thromboembolism prevention, although associated with a higher risk of major bleeding.

Conclusion: Results of this study may improve the management of NVAF by informing physicians on the choice of DOACs for this vulnerable population.

Abrégé

Contexte: Les personnes âgés de 80 ans et plus sont à haut risque de fibrillation auriculaire non-valvulaire (FANV) et de thromboembolies, l'âge avancé représentant un facteur de risque majeur pour ces conditions. Les anticoagulants oraux directs (AODs), plutôt que les antagonistes de la vitamine K, sont recommandés en prévention des thromboembolies chez la plupart des patients atteints de FANV. Malgré l'absence d'essais cliniques comparant les AODs, les études observationnelles suggèrent que l'apixaban présenterait le rapport bénéfice/risque le plus intéressant. En effet, il offre une efficacité similaire en prévention des événements thromboemboliques, mais avec un moindre risque de saignement majeur. Cependant, étant donné l'approbation récente de l'edoxaban, son efficacité (prévention thromboembolique) et son innocuité (risque de saignement majeur requérant une hospitalisation) comparées à l'apixaban chez les personnes de 80 ans et plus demeurent inconnues.

Objectifs : Les deux objectifs principaux de cette thèse avec manuscrit visaient à évaluer l'efficacité (prévention d'accident cérébrovasculaire/accident ischémique transitoire ou embolie systémique) et l'innocuité (risque de saignement majeur) de l'edoxaban comparativement à l'apixaban chez les patients de 80 ans et plus atteints de FANV.

Méthodes : Cette étude de cohorte rétrospective populationnelle a été conduite avec la base de données *Clinical Practice Research Datalink* du Royaume-Uni, couplée aux données hospitalières de l'*Hospital Episode Statistics* et au registre de décès de *l'Office for National Statistics*. Nous avons formé une cohorte de patients âgés de 80 ans et plus atteints de FANV nouvellement traités avec edoxaban ou apixaban entre le 1er juillet 2015 et le 31 mars 2021. La date de la première prescription pour l'un des deux AODs définissait l'entrée dans la cohorte. Les patients étaient suivis jusqu'à la première survenue de l'un des événements suivants : événement d'intérêt étudié, cessation ou changement de traitement anticoagulant, décès, fin de l'enregistrement avec la pratique ou fin de l'étude. La stratification fine selon le score de propension avec pondération a été utilisée pour contrôler les facteurs de confusion potentiels. Un modèle des risques proportionnels de Cox a permis d'estimer séparément le rapport de taux d'incidence (HR) avec intervalle de confiance à 95% (IC 95%) de chaque événement d'intérêt. En analyses secondaires, nous avons estimé le risque de décès ainsi que le risque d'un événement composite incluant accident cérébrovasculaire/accident ischémique transitoire, embolie systémique, saignement

gastrointestinal et hémorragie intracrânienne. Enfin, plusieurs analyses de sensibilité ont été effectuées pour évaluer la robustesse de nos résultats.

Résultats: La cohorte incluait 7 252 patients initiant edoxaban et 40 093 patients initiant apixaban. L'edoxaban était aussi efficace que l'apixaban (taux d'incidence pondérés 20,38 vs. 19,22 pour 1000 personnes-années; HR 1,06; IC 95% 0,89-1,26), malgré un risque accru de saignement majeur (taux d'incidence pondérés: 45,57 vs. 31,21 pour 1000 personnes-années; HR 1,42; IC 95% 1,26-1,61). Comparativement à l'apixaban, l'edoxaban était aussi associé à une augmentation de 21% du risque d'événement composite (taux d'incidence pondérés : 44,34 vs. 36,12 pour 1000 personnes-années; HR 1,21; IC 95% 1,07-1,38), tandis qu'aucune différence n'était observée sur le risque de décès (taux d'incidence pondérés: 118,43 vs. 113,70 pour 1000 personnes-années; HR 1,04; 95% CI 0,96-1,12). Les résultats des analyses de sensibilité concordaient avec ceux des analyses principales.

Discussion : Dans cette étude de cohorte de patients âgés de 80 ans et plus atteints de FANV, l'edoxaban offrait une protection thromboembolique comparable à celle de l'apixaban avec un risque accru de saignement majeur.

Conclusion: Les résultats de cette étude pourraient orienter les cliniciens sur le choix approprié d'un AOD pour cette population.

Preface

This manuscript-based thesis is organised in eight chapters. **Chapter 1** provides a brief introduction on atrial fibrillation and on the current available evidence regarding the use of direct oral anticoagulants for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation over the age of 80 to introduce the rationale and primary objectives of this thesis. **Chapter 2** presents a literature review on atrial fibrillation (epidemiology, pathophysiology, classification, screening/diagnosis, symptoms management, associated risk of thromboembolism, bleeding, mortality and morbidity). It then discusses the use of oral anticoagulants (vitamin K antagonists and direct oral anticoagulants) for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. This chapter subsequently discusses the current body of evidence (from clinical trials and observational studies) regarding the effectiveness and safety of direct oral anticoagulants compared with warfarin and between direct oral anticoagulants in patients with nonvalvular atrial fibrillation. The two following sections of Chapter 2 provide a specific review on patients with atrial fibrillation over the age of 80 (defined as very elderly), followed by a presentation of the challenges surrounding the management of their risk of thromboembolism. Chapter 2 ends with a section about the currently limited body of knowledge (from observational studies) regarding the comparative effectiveness and safety between direct oral anticoagulants in patients with nonvalvular atrial fibrillation over 80 to lay out the rationale and primary overall objectives of this thesis. **Chapter 3** describes the two primary and two secondary objectives of this thesis. **Chapter 4** supplements the Method section in the manuscript (**Chapter 5**) with further details about the methodology of the cohort study. **Chapter 5** contains the manuscript of the population-based cohort study, titled "Effectiveness and safety of edoxaban compared with apixaban in elderly patients with nonvalvular atrial fibrillation: a real-world population-based cohort study" and also included a section for the references and supplementary materials. **Chapter 6** summarizes the main objectives and primary findings, discusses the strengths/limitations and the implications of the findings (including future perspectives) of this thesis. The conclusion and all the references of this thesis can be found in **Chapter 7** and **Chapter 8**, respectively.

Contributions of the Authors

Authors	Contributions of the authors
Richard Chiv (Master student candidate)	**Drafted the thesis, contributed and drafted the protocol, conducted the statistical analyses, interpreted the data, and drafted the manuscript**
Sarah Beradid (Research assistant)	**Conducted the statistical analyses, interpreted the data, and provided statistical and analytical oversight**
Dr. Samy Suissa (Thesis Co-supervisor)	**Reviewed the thesis, protocol, and manuscript, and provided oversight, supervision, and funding**
Dr. Christel Renoux (Thesis Supervisor)	**Conceived and designed the study, reviewed the thesis, drafted and reviewed the protocol, interpreted the data, reviewed the manuscript, and provided oversight and supervision**

Acknowledgements

Je voudrais exprimer ma profonde reconnaissance envers le Dr. Samy Suissa et la Dre. Christel Renoux pour cette immense opportunité d'œuvrer pour vous au sein du Centre d'Épidémiologie Clinique à l'Institut Lady Davis de recherches médicales, situé à l'Hôpital général juif. Ce fut un honneur et je vous en serai à tout jamais redevable pour cette Maîtrise, mais surtout pour cette expérience de vie. Milles merci.

À la Dre. Christel Renoux, je souhaiterais vous remercier plus particulièrement pour votre temps, mentorat (expertise), rigueur, niveau d'exigence très élevé et j'en passe. Il est à mon avis impossible d'exprimer ma reconnaissance envers vous en si peu de mots. Cela ne vous traduirait nullement justice. Je ne fus pas toujours facile, mais j'aimerais également souligner votre grande patience et votre grande sagesse. Ce fut un privilège d'évoluer sous votre aile le temps de deux années (oh si vite écoulées). Sans vous, la contemplation de ma maîtrise aurait été probablement sans fin…un naufrage peut-être, qui sait… Je ressors aujourd'hui de cette longue aventure, changé, sans exagération. Sachez que j'ai apprécié notre collaboration, malgré parfois ma grande réserve émotionnelle.

J'aimerais également prendre ce temps pour remercier Sarah Beradid pour son temps, dur travail, ses analyses statistiques et précieux conseils statistiques et en programmation SAS.

Et finalement, pour conclure…mais surtout pour célébrer, des flûtes de champagne avec Guilhem Dubois, Annie Chiv et bien entendu, mes parents.

Table of Contents

List of Tables

List of Figures

List of abbreviations/acronyms

95% CI	95% confidence interval
AF	Atrial fibrillation
CPRD	Clinical Practice Research Datalink
DOACs	Direct oral anticoagulants
ECG.	Electrocardiogram
ESC	European Society of Cardiology
GI	Gastrointestinal
HES	Hospital Episode Statistics
HR	Hazard ratio
ICD 10	International Classification of Diseases version 10
ICH	Intracranial hemorrhage
IPCW	Inverse probability of censoring weights
ITT	Intention-to-treat
MB	Major bleeding
NVAF	Nonvalvular atrial fibrillation
OACs	Oral anticoagulants
ONS	Office for the National Statistics
PS	Propensity score
RCTs	Randomized controlled trials
SE	Systemic embolism
TIA	Transient ischemic attack

UK	United Kingdom
VKAs	Vitamin K antagonists

Chapter 1: Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, and its prevalence rises with advancing age [1-4]. Indeed, the prevalence of AF increases from 0.12-0.16% in the age group below 49 years old to almost 17% in individuals over the age of 80 (referred as the very elderly) [3, 5-6]. Thus, with ageing of the world population, AF is expected to prevail significantly in the very elderly [7-8]. Patients with AF face a five-fold increased risk of ischemic stroke compared with those without the disease, and older age represents a major independent risk factor for thromboembolic events [9-11]. International AF guidelines, such as the 2020 European Society of Cardiology (ESC), 2019 American Heart Association and 2020 Canadian Cardiovascular Society, recommend the chronic use of oral anticoagulants (OACs) for most patients with nonvalvular AF (NVAF) to prevent thromboembolic events [12-16]. These guidelines recommend direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban and edoxaban, over warfarin as first-line therapy for most patients with NVAF to prevent thromboembolism [17-21]. Pivotal randomized controlled trials (RCTs) and observational studies have indeed shown that DOACs are at least as effective as warfarin for the prevention of stroke or systemic embolism (SE) with lower risk of intracranial hemorrhage (ICH) [19-20, 22-34]. However, the main drawback to the use of some DOACs is the potential higher risk of gastrointestinal (GI) bleeding, notably in individuals with AF over the age of 75 compared to patients younger than 75 with AF [35-37].

DOAC initiation rates have now outranked vitamin K antagonists (VKAs), with apixaban being the most prescribed DOAC in several countries since 2017, followed by rivaroxaban and dabigatran [39-45]. Edoxaban is the latest approved DOAC in 2015 in most countries (e.g., United Kingdom and United States), and its prescription is increasing worldwide [40, 43, 46-51]. Although patients with AF over the age of 80 are likely to benefit from the use of DOACs, these medications are often under-prescribed to them in clinical practice, physicians citing older age and bleeding risk as common reasons [6, 9, 38, 52-53]. This issue may root in the lack of clear guidelines for this underrepresented population in RCTs, which may complicate AF clinical management [6, 31, 53-55]. Such problem is further exacerbated by the absence of RCTs with head-to-head DOACs comparisons to guide the choice of DOAC for this population [52-56]. The scarcity of observational studies in patients over 80 is also problematic, given that more than 40% of strokes occur in this population [57-58]. To our knowledge, only two cohort studies have conducted head-to-head DOAC

comparisons in patients with NVAF over 80 years old [61-62]. The first cohort study concluded that apixaban was at least as effective as dabigatran and rivaroxaban to prevent the risk of thromboembolism with a lower risk of major bleeding (MB) in patients with NVAF over 80 years old [61]. This finding is consistent with results from previous observational studies that suggested an overall more favorable effectiveness/safety profile of apixaban compared with dabigatran and/or rivaroxaban in younger populations with NVAF [33, 36, 57-58]. The second cohort study reported that rivaroxaban, compared with dabigatran, was associated with a higher risk of stroke/SE but similar risk of MB in patients with NVAF over 85 [62]. However, given the recent approval of edoxaban, its effectiveness and safety compared with apixaban in very elderly individuals with NVAF is unknown. Further real-world evidence studies that include edoxaban must be conducted [38, 47-48, 61-62] to inform physicians on the choice of DOAC and improve the management of very elderly patients with NVAF [63-64].

Therefore, the two primary objectives of this retrospective population-based cohort study were to assess the effectiveness (prevention of ischemic stroke/transient ischemic attack/systemic embolism) and safety (risk of MB) of edoxaban compared with apixaban in patients with NVAF aged 80 years and older.

Chapter 2: Literature review

Chapter 2 lays out the foundation, rationale and main objectives of this manuscript-based thesis. It reviews the literature on atrial fibrillation and the use of oral anticoagulants to prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation, supported with data from randomized controlled trials and/or observational studies.

The three last sections of this chapter are devoted to the population over the age of 80 with nonvalvular atrial fibrillation and highlights the challenges surrounding the use of direct oral anticoagulants in this population.

2.1 Atrial fibrillation

AF is a type of supraventricular tachyarrhythmia characterized by an ectopic disorganization of the atrial electric activation, which leads to inefficient systolic atrial contractions [13-14, 65]. Its distinctive electrocardiographic indicators consist of the presence of undistinguishable P waves, irregular R-R intervals or narrow QRS complex in the absence of an impairment of the atrioventricular conduction [13-14]. Disorganized atrial activations between QRS complexes may sometimes be observed on the electrocardiogram as erratic discharge of fibrillatory waves [13-14, 66-69].

2.1.1 Epidemiology of AF

AF is the most common type of cardiac arrhythmia with a global prevalence of 46.3 million individuals and poses as a major economic burden [5, 7, 70-83]. The United Kingdom (UK) National Health Service has for instance spent £459 millions on AF in 2000, and expenditures related to this disease are expected to reach 3851 million pounds by 2040 [4, 78]. In the US, the incremental cost of AF spans from 6 to 26 billion American dollars annually [7]. With ageing of the world population, in addition to increasing the economic burden of AF, AF is expected to significantly prevail in the elderly because of its increasing prevalence with advancing age [4, 7-8]. More specifically, beyond the age of 55, its prevalence increases by two-fold every decade [50, 88-89]. It is estimated that nearly 70 % of individuals with AF are in the 65-85 age group and 10-17% of them are over 80 years old [1, 6, 84-87]. The incidence of AF increases with age as well, being the highest in individuals over 85 [7, 90-91]. The incidence rates of AF were reported in a study to be 0.5, 1.1, 3.2, 6.2 and 7.7 per 1000 persons for the 45-54, 55-64, 65-74, 75-84 and $\geq$ 85 years old, respectively [90-91]. The very elderly represents therefore an important target population in the clinical management of AF.

There are also sex and ethnicity differences in AF [14, 92-94]. The Framingham Heart study reported that men face a 1.5 time higher risk of developing AF compared with women [7, 14, 95-97]. The age-adjusted incidence of AF in North American and European populations for example have been observed to be between 1.5 to 2 times higher in men than in women [86, 93]. However, because of the longer life expectancy in women, the lifetime risk of AF for both sexes are comparable [93, 98]. In men and women over the age of 60, their lifetime risk for AF were 25.8% and 23.4%, respectively [93, 98]. As for ethnicity, previous studies have pointed out the lower prevalence and incidence of AF in African Americans, Asians and Hispanics populations compared to those of European ancestry [14, 99-103]. For instance, the Multi-Ethnic Study of Atherosclerosis study found that the incidence of AF adjusted for age and sex in non-Hispanic Black, Hispanic, and Chinese individuals were respectively 49%, 46% and 65% lower than in non-Hispanic White individuals [104].

Although age represents the most prominent risk factor for AF, other predictors include sex, physical activity, obesity, diet, tobacco, moderate to heavy alcohol consumption, obstructive sleep apnea, hypertension, dyslipidemia, diabetes mellitus, myocardial infarction, congenital heart disease, valvular heart disease, heart failure and chronic kidney disease [69, 88, 96, 105, 101, 105-110]. AF has a genetic component as well, although its clinical implications remain unclear [69, 97, 108, 111-112, 141]. Based on the Framingham Offspring study, individuals with a family history of AF have a 1.8-fold increased risk in developing the disease [97].

2.1.2 Pathophysiology of AF

The complex pathogenesis of AF is worsened by age-related cardiovascular structural and electrical changes [6, 13-14]. It commonly occurs from the interplay between ectopic, arrhythmogenic foci, often located in the muscular sleeves of pulmonary veins, and abnormal atrial tissue substrates that are capable of sustaining an arrhythmia [6, 13-14, 108, 113-116].

More specifically, rapid ectopic arrhythmogenic foci cause successive and disseminating excitation wavelet re-entries in the atrial myocardium [13-14, 16, 113-114, 117]. The resulting reduced refractoriness and slowing of the electrical conductions lead to the continuous promotion of re-entries within the atrial myocardium [118-120]. Over time, repeating AF episodes may initiate atrial fibrosis due to their potential in inducing structural and electrical permanent remodeling of the atria in the form of decreased atrial action potentials for instance [13-14, 88, 113-114, 117, 121-124]. The electrophysiological and structural atrial

alterations contribute to suboptimal ventricular rate control and filling due to reduced cardiac output [13-14, 124-130].

The most regularly reported symptoms of AF are fatigue, shortness of breath upon physical exertion, palpitations, dizziness, *angina pectoris*, dyspnea, and syncope [127, 131]. Patients with AF must have their symptoms assessed, treated, and monitored since AF is associated with a higher risk of stroke, severe morbidity, and mortality, impaired functional status, lower quality of life and higher risk of all-cause hospitalization [107, 132]. However, a non-negligible 12 to 42.5% of individuals with AF are asymptomatic [135-136]. The first detection of AF may only occur during a clinical presentation related to its complications such as stroke, thromboembolism, or heart failure [13-14, 173]. Asymptomatic AF is not uncommon in the elderly, and this may represent a diagnostic challenge [5, 137, 138-142].

2.1.3 Classification of AF

Several classification frameworks of AF have been proposed, but most guidelines classify AF based on the temporality and pattern of AF episodes to gauge the severity of the disease and make therapeutic recommendations [13-16, 31, 113 143]. AF can be classified as paroxysmal, persistent, long-standing persistent and permanent [13-14]. Paroxysmal AF is characterized as a continuous AF episode that lasts more than 30 seconds, which either terminates spontaneously or resolves within 7 days of disease onset post-intervention [13]. Persistent AF is a continuous AF episode that last more than 7 days, including episodes terminated by cardioversion (pharmacological or non-pharmacological) after 7 days but less than 12 months. For continuous AF episodes lasting more than 12 months, AF is defined as long-standing persistent. Finally, AF is classified as permanent in the situation where AF is accepted by the patient and physician and both jointly decide to cease any treatment to sustain and/or restore sinus rhythm, irrespective of the pathophysiology of AF. The terms “valvular AF” and NVAF are also commonly encountered terminologies in the literature [131]. NVAF refers to AF of nonvalvular cardiac disease etiology such as moderate to severe rheumatic mitral stenosis, mechanical or bioprosthetic heart valve or mitral valve repair [13-14, 131, 135-136, 144]. NVAF accounts for approximately 50% to 80% of all AF cases.

2.1.4 Screening and diagnosis of AF

AF screening has been suggested for early initiation of OAC therapy and/or symptom management to prevent thromboembolism, mortality, and cardiovascular complications [5, 137, 133-134, 138, 141, 145]. Guidelines such as the 2020 ESC and Canadian Cardiovascular

Society only recommend opportunistic screenings (pulse taking or rhythm strip) in primary routine care settings over targeted screenings in patients over 65 years at higher risk of stroke due to insufficient evidence to support the latter populational scale implementation and its high costs [146-148]. The American Heart Association supports instead active screening in individuals aged over 65 by pulse taking followed by an electrocardiogram (ECG) in the event of an irregular pulse palpitation [149]. The ESC 2020 guideline does highlight the potential benefits of a systematic AF screening program in individuals over 75 or those at higher risk of stroke [146, 150-152]. This is because many patients are asymptomatic and around 70% of AF episodes systematically monitored by an ECG are effectively silent [146, 150-152]. The European guideline also recognizes the likely benefits regarding the use of wearable technological devices/tools integrated in certain smartphones or smart watches to detect and record AF episodes, conditionally on patients' awareness of the limits and significance imposed by such tools [14, 146, 153].

The gold standard for a definitive AF diagnosis is the standard 12-lead or one single-lead ECG showing the absence of repeating P waves and presence of irregular RR intervals with unimpaired atrioventricular conduction, in addition to documented minimal AF episode duration of 30 seconds [14, 153-154]. An inconclusive 12-lead ECG requires repetitive ECGs or a 12- or 48 hours-Holter ambulatory monitoring for long-term ECG signals recording to confirm an AF diagnosis [5, 14, 158-157]. Further examinations that include blood tests, physical examination, chest radiography, echocardiography can also be conducted [157].

2.1.5 Clinical management of AF symptoms

The management of AF symptoms englobes two main approaches, rate or rhythm control therapies, that can be achieved pharmacologically or with non-pharmacological interventions [158]. Symptoms relieving strategies can improve patients' quality of life and reduce the risk of cardiovascular complications, hospitalization, and mortality [5, 156, 163].

Atrial myocardial rapid reactivation leaves the atrial myocardium in a contractile standstill state, leading to irregular and rapid ventricular rates [156]. A rate control therapy approach can alleviate AF symptoms and allow physical exercise [152-153]. This approach slows the atrioventricular node conduction to prevent tachycardia-induced cardiomyopathy and heart failure by preserving the left ventricular function during an AF episode [152-153, 159]. It can be achieved pharmacologically with beta blockers (e.g., metoprolol, atenolol, and carvedilol), calcium channel blockers (e.g., verapamil and diltiazem) or digoxin [153, 159].

Non-pharmacological treatments (e.g., AV node ablation and pacemaker insertion) can be considered in case of symptoms persistence, drug failure or drug-related adverse events [160-161].

Rhythm control therapy aims at restoring and maintaining sinus rhythm and can be advised if the symptoms of AF persist despite adequate rate control treatment [153, 162]. The normalization of the sinus rhythm can be achieved as well with first-line anti-arrhythmic drugs such as amiodarone, dronedarone and flecainide [153, 156-163]. The delivery of an electrical shock to the heart with an electrical cardioversion can also be considered to restore the sinus rhythm [163-164]. In the event of drug failure, non-pharmacological approaches such as radiotherapy-based catheter AF ablation, cryoablation or surgical AF ablation (also known as MAZE surgery) can be considered to eliminate an arrhythmogenic focus [153, 163-164].

Most guidelines recommend rate control over rhythm control approach as first-line therapy for asymptomatic and elderly patients with AF unless the cause of AF is reversible, it is a new-onset AF or when rhythm control is clinically deemed more appropriate [5, 160-162, 165]. Further real-word studies on elderly patients diagnosed with AF should be conducted, though the current literature seems to point out the superiority of rate control in older patients [5].

2.2 Risk of thromboembolism, morbidity and mortality related to AF

Although the management of symptoms related to AF remains important, the most severe complication of AF is the elevated risk of thromboembolism, in particular ischemic stroke (~ 40% of stroke in patients older than 75 are related to NVAF) [18, 37, 94, 130, 166-169]. This is due to the stagnant pool of blood, often found in the left atrial appendage, that promotes the formation of thrombi [124-129]. Compared to individuals without AF across all age groups, the presence of AF is associated with a five- to six-fold increased risk of stroke [94, 128, 167, 169]. Not only does older age increase the risk of AF, but it also poses as a significant independent predictor of stroke [110, 170-172]. The Framingham study found that the attributable risk of stroke among individuals with AF increases progressively with older age, from 5.9% in individuals aged 55-59 years old to 22.3% in those aged 80-84 years among men and from 3.0% to 23.9% among women. [173-175].

AF is a leading cause of morbidity and mortality [86, 170]. AF-related strokes are associated with greater disability and fatality compared to those from other causes [124-130].

AF is also related to cognitive decline, chronic kidney disease, several other cardiovascular comorbidities such as heart failure, hypertension, valvular and coronary heart diseases, and associated with higher healthcare utilizations [176-179]. When adjusted for cardiovascular comorbidities, the presence of AF is associated with a two-fold increase in all-cause mortality, the risk being highest during the first year following AF symptoms [9, 18, 176, 180]. AF-related mortality also increases with age [170]. In the Framingham Heart study, the excess mortality caused by AF was three times higher in patients over 75 compared to those under 65 years old [173, 181]. It also showed that the risk of all-cause mortality in women and men with AF across all age groups were 90% and 50% higher, respectively, than their counterparts without AF [182]. However, some studies suggested lower mortality rates in women compared to men across all age groups or no sex differences [86, 92, 177].

2.3 Oral anticoagulation for the prevention of stroke and systemic embolism

2.3.1 Stroke and bleeding risk assessment schemes

Most international guidelines recommend the chronic use of OACs for most patients with AF to prevent thromboembolism [13-16,130, 183]. To guide clinical decisions regarding OAC initiation, the first step involves the assessment of patients' risk of stroke with a stroke risk stratification scheme [18, 170, 130]. Several stroke risk assessment scores have been developed, but most guidelines recommend the CHA_2DS_2-VASc score, which superseded the $CHADS_2$ score. The latter is still used by certain guidelines like the Japanese Circulation Society and Canadian guideline in its original or modified form [16, 183-184].

The $CHADS_2$ score (maximum score of 6 points) incorporates the following predictors of stroke: congestive heart failure (1 point), hypertension (1 point), age ≥75 years (1 point), diabetes mellitus (1 point), prior stroke, transient ischemic attack (TIA), or thromboembolism (2 points) [13]. Patients with a $CHADS_2$ score of 0, 1 and >1 are at low, moderate, and high risk of stroke, respectively [185]. The Canadian and Japanese guidelines do not recommend the use of OACs for patients with NVAF with a score of 0 [16, 183]. The Japanese guideline recommend OACs for patients with a score ≥ 2 but only dabigatran and apixaban are recommended for patients with a score of 1 (warfarin, rivaroxaban and edoxaban may be considered) [184]. The 2020 Canadian Cardiovascular Society guideline uses a slightly modified version of this score, the CHADS-65, with age over 65 and vascular disease (coronary and peripheral vascular diseases) added to its algorithm [15]. It supports the use of OACs for the prevention of stroke for most patients over the age of 65 or younger patients with a $CHADS_2$

score ≥ 1. Antiplatelet therapy (e.g., acetylsalicylic acid) is only recommended in patients with coronary or peripheral vascular disease and without any of the stroke risk factors assessed by the $CHADS_2$ score. The main limitation of this score is its low ability to discriminate between patients at low and moderate risk of stroke, with a high proportion of patients being categorized automatically as intermediate [13-15,186]. This could potentially complicate decisions regarding OAC initiation [37, 183, 186]. Another of its limitation is that it does not consider other significant stroke risk factors [13-14]. This could imply that some patients whose only stroke risk factor is a prior stroke event could be at much greater risk of stroke than what their $CHADS_2$ score of 2 might suggest [13].

The American Heart Association, 2020 ESC and the Asian Pacific Heart Rhythm Society recommend the use of a more comprehensive score, the CHA_2DS_2-VASc (maximum score of 9 points), which is a refined version of the $CHADS_2$ score [18, 170, 187-188]. The CHA_2DS_2-VASc essentially incorporates 3 additional stroke risk factors not considered in the previous score and attributes a higher weight to age over 75 : congestive heart failure (1 point), hypertension (1 point), age over at least 75 years old (2 points), diabetes mellitus (1 point), prior history of stroke, TIA or thromboembolism (2 points), vascular disease (peripheral artery disease, myocardial infarction or aortic plaque (1 point)), age between 65 and 74 years old (1 point) and female sex category (stroke risk modifier of 1 point) [13, 18, 170, 189-190]. Patients with a score of 0, 1, ≥ 2 on the CHA_2DS_2-VASc are considered at low, intermediate, and high risk of stroke, respectively [183]. The ESC and American Heart Association guidelines issued recommendations on OAC therapy based on patients' score and sex [13-14]. Both guidelines support the use of OACs in men and women with NVAF with a score greater than 2 and 3, respectively, while those with a score of 0 and 1 should not receive any [13-14]. OAC therapy may still be considered in men and women with NVAF with a score of 1 and 2, respectively [13-14]. Contrary to the $CHADS_2$, the CHA_2DS_2-VASc score can truly identify patients at low risk of stroke [191]. One other characteristic of the CHA_2DS_2-VASc is its emphasis on older age (over 75 years) as an important stroke risk factor by assigning a score of 2 by default instead of 1 in the $CHADS_2$ [172-173, 192]. The CHA_2DS_2-VASc has been shown to possess a slightly higher predictive value compared to the $CHADS_2$ in terms of stroke risk assessment [193-194].

One caveat associated with the use of OACs is the risk of MB (mainly GI bleeding and ICH), especially in the elderly, because older age increases the risk of bleeding [17-18]. Most guidelines, with the exception of the American Heart Association, recommend the HAS-BLED score (maximum of 9 points) to assess patients' risk of bleeding [152, 195-200]. It includes the

following bleeding risk factors: hypertension (1 point), abnormal renal/liver function (1 point each), prior history of stroke (1 point), prior history of major bleeding/predisposition to bleeding (1 point), labile international normalized ratio with a time in therapeutic range below 60% (1 point), age ≥ 65 years (1 point) and history of alcohol or use of drug like non-steroidal anti-inflammatory drugs or antiplatelet agents (1 point each) [18, 197-199]. Patients with a score of 0, 1-2 and ≥ 3 are at low, moderate, and high risk of bleeding, respectively [14]. In the absence of any contraindication for OACs, the clinical interpretation of a HAS-BLED score should not guide their prescription [197]. Patients with a score ≥3 should be closely monitored by their physician and have their modifiable bleeding risk factor(s) addressed [13-14]. Finally, the HAS-BLED score has been shown to hold a higher performance at predicting the risk of bleeding compared with other bleeding risk assessment scales [198].

Because the risk of stroke and bleeding may change as people age or develop new comorbidities, AF guidelines such as the ESC and the American Heart Association encourage periodic reassessment of these two risks in low-risk patients [13-14, 198]. For instance, the ESC recommends the reassessment of the risk of stroke every 4 to 6 months following the initial estimation to re-evaluate the need for OAC therapy [14]. Two OACs classes, VKAs and DOACs, can be prescribed to patients with NVAF at high risk of stroke to prevent thromboembolic events [12, 152]. These drug can also potentially reduce patients' risk of morbidity, mortality and improve their quality of life and autonomy. Antiplatelet agents like aspirin, are not effective treatment choices for the prevention of thromboembolism and are not recommended by AF guidelines[152].

2.3.2 Vitamin K antagonists

Vitamin K is a fat-soluble vitamin essential for human hemostasis and its deficiency has been tied to several hemorrhagic pathologies [201]. In the coagulation cascade, vitamin K acts as a co-factor for the enzyme carboxylase [201-204]. This binding results in the conversion of glutamic acid into gamma-carboxyl residues to allow the binding of calcium to vitamin K-dependent anticoagulation proteins C and S and the formation of activated clotting factors II, VII, IX, X [201-204]. During this process that occurs in the liver, the activated form of vitamin K, vitamin K_1 hydroquinone, is transformed by a carboxylase into vitamin K_1 epoxide, then to vitamin K_1 quinone by an epoxide reductase before its final reduction to its activated form [201-203]. VKAs can deplete the supply of activated vitamin K and decrease the synthesis of activated vitamin K-dependent clotting factors, proteins C and S [204-207].

Among VKA agents (e.g., warfarin, acenocoumarol, and phenprocoumon), warfarin is the most prescribed to prevent stroke in patients with AF [61, 206-210]. For instance, its prescription totalized more than 7 million in 2019 in the UK [211]. Warfarin has a half-life ranging from 20 to 60 hours, is mainly metabolized by the liver, and excreted by the kidneys [208]. Compared to antiplatelet agents like acetylsalicylic acid (aspirin), several studies have shown that warfarin is more effective at decreasing the risk of stroke in patients with AF [212]. Indeed, in patients with NVAF, warfarin has been shown to reduce the risk of stroke by 64% compared to 22% with aspirin, with similar risk of significant bleeding per year (~1.4-1.5%) [213-214]. In elderly patients with AF over the age of 75, the Birmingham Atrial Fibrillation Treatment of the Aged RCT has provided similar evidence for stroke risk reduction [212, 215].

Warfarin benefits come at the cost of an increased risk of MB such as ICH and GI bleeding. [209, 216]. One meta-analysis showed that major and fatal bleeding incidence rates in patients treated with warfarin were respectively 7.2 and 1.3 per 100 patient-years [217]. Compared to individuals below the age of 50, those over 80 treated with warfarin faced greater fatal bleeding risk [218]. In patients with NVAF, the use of warfarin, among other factors such as increasing age and congestive heart failure, was associated with an increased risk of MB [219]. Reversal agents, such as the administration of vitamin K or of coagulation factors in case of life-threatening bleeding situations, are available [216]. To ensure the effective and safe use of warfarin, frequent therapeutic monitoring, and potential dose adjustments with regular laboratory blood tests like prothrombin time and international normalized ratio are imperative [209, 220]. The former test assesses the required time for the blood to clot [221]. The latter one is preferentially used because of the standardization of the prothrombin time based on the thromboplastic reagent [218, 221-222]. Optimal anticoagulation requires the maintenance of an international normalized ratio between 2 and 3 at least 70% of the time in therapeutic range, which is a measure of the quality of the anticoagulation therapy [222-225]. A time in therapeutic range below 60% more than doubles the risk of ischemic stroke [226].

However, one disadvantage associated with the use of warfarin is that the optimal therapeutic window may be difficult to achieve for some individuals with AF [218, 223-224]. The use of warfarin may also be cumbersome for some patients because it requires frequent and tight monitoring and potential dose adjustment [223-224]. It also has several drug-drug and food interactions, which can potentially complicate the management of AF in elderly patients, given that they often have other comorbidities and polypharmacy [218, 224]. Other limitations of warfarin include its indirect anticoagulant mechanism that targets several clotting

factors, slow pharmacological onset/offset, and unpredictable pharmacokinetics, and pharmacodynamics [224]. These limitations prompted the development of novel oral anticoagulants to overcome them [227-228].

2.3.3 Direct oral anticoagulants

DOACs were developed as an alternative to VKAs in response to the aforementioned disadvantages of VKAs [21, 227]. Indeed, unlike VKAs, they have a wider therapeutic index, quicker onset and offset of action (crucial to the management of acute bleeding or presurgical procedures), shorter half-life, less drug-drug, and food interactions and do not require regular clinical monitoring and dose adjustments [21]. DOACs were initially approved for the treatment of venous thromboembolism, starting with dabigatran in 2008, and subsequently for NVAF. Four DOACs are currently recommended over warfarin by most guidelines as first-line OAC therapy for most patients with NVAF to prevent thromboembolism [8, 229, 231]. DOACs are not indicated for patients with mechanical cardiac valves as these patients were excluded from the 4 pivotal RCTs that assessed the efficacy and safety of each DOAC compared with warfarin in patients with NVAF [21]. Approved in the following order, DOACs include dabigatran (Pradaxa© by Boehringer Ingelheim), rivaroxaban (Xarelto© by Janssen Pharmaceuticals & Bayer HealthCare), apixaban (Eliquis© by Bristol Myers Squib & Pfizer) and edoxaban (Savaysa© in the US or Lixiana© in the UK by Daiichi Sankyo). In pivotal RCTs, DOACs were deemed either superior or non-inferior to warfarin with respect to the prevention of thromboembolism and/or the risk of MB, with the key advantage of being associated with a lower risk of ICH [8, 13-14]. The mechanism of action of dabigatran involves the direct inhibition of factor IIa (thrombin) while the three others DOACs directly inhibit factor Xa [229]. The pharmacology and posology for each DOAC in the treatment for NVAF are summarized below.

Dabigatran is administrated twice daily (standard dose 150 mg) as a pro-drug and is hydrolyzed into active dabigatran by plasmatic, hepatic, or GI esterases [21, 232]. Dabigatran has a very low bioavailability approximating 3-7%, a half-life between 12 and 17 hours and the time required to reach the maximum plasmatic concentration is between 1.5-2 hours (T_{max}) [21, 229]. It is at 20% conjugated with glucuronic acid and excreted as acyl glucuronides by the biliary system but is primarily cleared unchanged at 80% by the kidneys [229, 232]. Food intake prolongs the T_{max} to 2 hours and therefore, discouraged.

Rivaroxaban is administered once daily (standard dose 20 mg), has a high bioavailability (80-100%), a half-life of 7-11 hours and a T_{max} between 2-5 hours [8, 21]. Its metabolism mainly involves at 65% the cytochrome 3A4 and to some extent, the cytochrome 2J2. Rivaroxaban is eliminated through the hepatobiliary (66%) and renal (33%) pathways. A third of the drug is renally excreted unchanged. Food intake is mandatory because it increases the total systemic exposure to rivaroxaban (mean area under the curve) to around 40%.

Apixaban is administered twice daily (standard dose 5 mg) and unlike dabigatran and rivaroxaban, the bioavailability (50%) of apixaban is unaffected by food intake [21]. It has an approximate half-life of 12 hours and a T_{max} of 1-3 hours. Its metabolism engages the cytochrome 3A4 or 5 at 74% and to a lesser extent, the cytochromes 1A2, 2C8/9/19 and 2J2. It is eliminated through the hepatobiliary and renal pathways, at 75% and 25%, respectively [21].

Finally, edoxaban is administered once daily (standard dose 60 mg) and its bioavailability (62%) remains unaffected by food intake [21, 228, 233]. It has a half-life of 10-14 hours and a T_{max} between 1-2 hours. Metabolized at 50% by the cytochrome 3A4, edoxaban is eliminated at 50% via the hepatobiliary route, with the remaining half being renally excreted unchanged [21, 228, 233].

Idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban are available reversal agents in case of severe hemorrhages, emergency surgery or interventions with high bleeding risk [21, 232, 234]. A reversal agent is yet to be approved for edoxaban [235].

2.3.4 Prescription trends of DOACs

VKAs have been the treatment of choice for the prevention of thromboembolism in patients with NVAF for the past 60 years [38]. However, with the introduction of DOACs, their rate of initiation has steadily increased, and they have now outranked VKAs [38, 45, 236-239]. For instance, one retrospective cohort study analyzing an American large healthcare database showed that while the majority of OAC initiators with AF received VKAs (87.5%-99.8%) in 2010, most of them were prescribed DOACs by 2020 [45].

Among DOACs, the prescription of dabigatran gradually decreased over time, being eventually surpassed by rivaroxaban and apixaban [38, 43, 45, 64]. Since 2017, apixaban became the most prescribed DOAC in most countries [38-46, 240-241]. Prescription trend

studies that include edoxaban are still scarce given its recent approval in 2015, although its worldwide prescription is increasing [39, 43, 46-50].

Patients with NVAF over 85 are often not prescribed OACs, despite their guideline-based eligibility [55]. However, OACs uptake is increasing in this population, with DOACs initiation rates outranking those of VKAs in several parts of the world [38-39, 43, 236-237, 240-243]. Dabigatran is the least prescribed DOAC among OAC initiators aged 85 years and older [38, 240]. One possible explanation is its possible higher risk of GI bleeding due to its different pharmacology. An American cohort study observed that apixaban was the most prescribed OAC in patients with NVAF over the age of 80 from 2015 to 2020 [241].

2.3.5 Effectiveness and safety of DOACs versus VKAs in RCTs

Overall, the four DOACs were showed to have greater or similar efficacy in thromboembolism prevention with similar or lower risk of MB compared with warfarin in RCTs [228]. All DOACs were associated with a lower risk of ICH compared with warfarin. The main results from the 4 pivotal RCTs are summarized below.

The RE-LY trial compared two doses of dabigatran (110 mg and 150 mg) with warfarin and enrolled 18,113 patients with NVAF between December 2005, and December 2007 [21]. There were respectively 6,015, 6,076 and 6,022 patients on dabigatran 110 mg, dabigatran 150 mg and warfarin and the median duration of follow-up period was 2 years [21]. Dabigatran 110 mg and 150 mg administered twice daily were non-inferior to warfarin with respect to stroke/SE risk [21, 228-229, 244]. More specifically, dabigatran 150 mg (standard dose) was associated with a 34% lower risk of stroke/SE compared to warfarin (relative risk (RR) 0.66; 95 % confidence interval (CI) 0.53-0.82) while there was no difference with warfarin for dabigatran 110 mg ((RR 0.91; 95% CI 0.74- 1.11) [244]. In terms of safety, standard-dose dabigatran was associated with similar risk of MB compared with warfarin (RR 0.93; 95% CI 0.81-1.07), but dabigatran 110 mg was associated with a lower risk of MB compared with warfarin (RR 0.80; 95% CI 0.69-0.93). Dabigatran 150 mg and 110 mg were associated with a 60% (RR 0.40; 95 % CI 0.27-0.60) and 69% (RR 0.31; 95% CI 0.20-0.47) lower risk of ICH, respectively. The rate of GI bleeding was higher in patients treated with dabigatran 150 mg compared to warfarin (RR 1.50; 95% CI 1.19-1.89) but comparable for dabigatran 110 mg (RR 1.10; 95% CI 0.86-1.41). Finally, there was no statistically significant mortality risk reduction with dabigatran 150 mg (RR 0.88; 95% CI 0.77-1.00) and 110 mg (RR 0.91; 95% CI 0.80-1.03) compared to warfarin.

The ROCKET-AF was a non-inferiority trial that included per-protocol (main analysis) and ITT analyses [245]. The trial enrolled 14,264 patients with NVAF randomized to rivaroxaban or warfarin from December 2006 to June 2009 [245]. There were 7,131 and 7,133 patients treated with rivaroxaban and warfarin, respectively, and the median follow-up was 707 days. In the per-protocol analysis, rivaroxaban was associated with a lower risk of stroke/SE compared with warfarin (HR 0.79; 95% CI 0.66-0.96). In the ITT analysis, the risk reduction was less important and not statistically significant (HR 0.88; 95% CI 0.75-1.03). The risk of any MB (only the per-protocol analysis was performed) was similar between both treatment groups (HR 1.04; 95% CI 0.90-1.20), but the risk of ICH was lower with rivaroxaban (HR 0.67; 95% 0.47-0.93). Major GI bleeding events were slightly higher in patients treated with rivaroxaban compared to warfarin (3.1% vs. 2.16%). In the per-protocol analysis, the use of rivaroxaban was also associated with a numerically lower HR for all-cause mortality compared to warfarin (HR 0.85; 95% CI 0.70-1.02) and in the ITT analysis, the HR was 0.92 (95% CI 0.82-1.03).

The ARISTOTLE trial randomized a total of 18,201 patients to receive either apixaban 5 mg twice daily (9,120 patients) or warfarin (9,081 patients) from December 2006 to April 2010 with a median follow-up time of 1.8 years [246]. Compared with warfarin, apixaban was associated with a 21% lower risk of stroke/SE (HR 0.79; 95% CI 0.66-0.95). Patients treated with apixaban had a lower risk of MB (HR 0.69; 95% CI 0.60-0.80), ICH (HR 0.42; 95% CI 0.30-0.58) and a similar risk of GI bleeding (HR 0.89; 95% CI 0.70-1.15). All-cause mortality was lower in the apixaban group (HR 0.89; 95% CI 0.80-0.99).

The ENGAGE AF-TIMI 48 trial compared two doses of edoxaban (30 mg and 60 mg) with warfarin [247]. Patients were assigned to either low-dose edoxaban (n=7,034), high-dose edoxaban (n=7,035) or warfarin (n=7,036) and the median follow-up time was 1022 days [247]. Compared with warfarin, the risk of stroke/SE was comparable for edoxaban 60 mg (HR 0.87; 95% CI 0.73-1.04) and 30 mg (HR 1.13; 95% CI 0.96-1.34). A risk reduction in MB was observed for high dose edoxaban (HR 0.80; 95% CI .71-0.91) and low-dose (HR 0.47; 95% CI 0.41-0.55) . The risk of intracranial bleeding was also lower with high-dose edoxaban (HR 0.47; 95% CI 0.34-0.63) and low-dose edoxaban (HR 0.30; 95% CI 0.21-0.43). The risk of GI bleeding was higher in the high-dose edoxaban group (HR 1.23; 95% CI 1.02-1.50), but not for the low-dose edoxaban group (HR 0.67; 95% CI 0.53-0.83). The risk of mortality was similar between patients treated with edoxaban 60 mg (HR 0.92; 95% CI 0.83-1.01) and

warfarin, but lower in patients treated with edoxaban 30 mg (HR 0.87; 95% CI 0.79-0.96) compared to warfarin.

2.3.6 Effectiveness and safety of DOACs versus VKAs in observational studies

Several observational studies have shown an overall more favorable profile of DOACs over warfarin with respect to stroke and/or SE prevention and MB risk [248-261]. One Canadian cohort study reported similar risk of stroke/SE (pooled HR 1.02; 95% CI 0.87-1.19) and lower MB risk (pooled HR 0.81; 95% CI 0.69-0.97) in patients with NVAF treated with DOACs compared with patients treated with warfarin [261]. Conversely, another cohort study found a lower risk of ischemic stroke/hemorrhagic stroke/SE associated with the use of dabigatran (HR 0.82; 95% CI 0.71-0.95), rivaroxaban (HR 0.79; 95% CI 0.73-0.85) and apixaban (HR 0.64; 95%CI 0.58-0.70) compared with warfarin in patients with NVAF [249]. However, the magnitude of these risk estimates for the effectiveness composite outcome may have been affected by the inclusion of hemorrhagic stroke [249]. In this study, only dabigatran (HR 0.71; 95% CI 0.65-0.78) and apixaban (HR 0.60; 95% CI 0.56-0.63) were associated with lower MB events (including GI bleeding, ICH, and MB at other key sites) compared with warfarin [249]. The similar/lower risk of ICH, GI bleeding and all-cause mortality associated with the use of some DOACs compared with warfarin have also been documented in previous publications [231, 248-249, 251, 253, 262-265]. A meta-analysis of 25 cohort studies concluded that patients with NVAF treated with DOACs compared with those treated with warfarin had a lower risk of ICH (pooled HR 0.50; 95% CI 0.40-0.62), GI bleeding (pooled HR 0.66%; 95% CI 0.46-0.95) and all-cause mortality (pooled HR 0.62; 95% CI 0.56-0.69) [265]. One cohort study found that dabigatran (HR 0.38; 95%CI 0.31-0.47), rivaroxaban (HR 0.65; 95% CI 0.56-0.77) and apixaban (HR 0.54; 95% CI 0.43-0.68) were all associated with lower risk of ICH [248]. In this study, only apixaban was associated with lower GI bleeding risk (HR 0.52; 95% CI 0.45-0.60) [248].

Many observational studies have found that apixaban was more favorable than warfarin with respect to its effectiveness/safety profile [58, 250-251, 253, 256, 266-268]. One meta-analysis of 38 cohort studies showed that apixaban was associated with a decreased risk of stroke/SE (RR 0.77; 95% CI 0.64-0.93) and lower risk of MB (RR 0.58; 95% CI 0.52-0.65) compared with warfarin [269].

Given the recent approval of edoxaban, only a few observational studies have included edoxaban in their comparative analyses [58, 256, 259, 270]. Consistent with results from the

ENGAGE AF-TIMI 48 trial [247], one cohort study found that standard-dose edoxaban was associated with similar risk of ischemic stroke/SE (HR 0.65; 95% CI 0.40-1.06) and lower risk of MB (HR 0.37; 95% CI 0.19-0.74) compared with warfarin [256]. A Danish cohort study found that edoxaban 60 mg was associated with similar risk of ischemic stroke/unspecified stroke/SE (HR 1.00; 95% CI 0.59-1.71) and MB (HR 1.09; 95% CI 0.77-1.57) compared with warfarin [259].

2.3.7 Effectiveness and safety of DOACs vs. DOACs in observational studies

Several cohort studies with head-to-head DOAC comparisons have been conducted between dabigatran, rivaroxaban and apixaban and have generally shown that apixaban was at least as effective (stroke prevention) as dabigatran and/or rivaroxaban and associated with a lower risk of MB [33, 56, 58, 248, 250, 257, 271-276]. One meta-analysis of 38 cohort studies concluded that apixaban was associated with a reduction in the risk of stroke/SE (RR 0.84; 95% CI 0.74-0.95) and MB (RR 0.79; 95% CI 0.70-0.88) compared with dabigatran [269]. Compared with rivaroxaban, apixaban was associated with similar risk of stroke/SE (RR 0.90; 95% CI 95% CI 0.78-1.03) and lower risk of MB (RR 0.61; 95% CI 0.53-0.70) [269]. The mortality rate in patients treated with apixaban was also lower compared to those treated with rivaroxaban (RR 0.83; 95% CI 0.71-0.96), in addition to the lower risk of ICH (RR 0.71; 95% CI 0.61-0.84) [269]. Compared with other DOACs, the use of apixaban has been shown to be associated with lower risk GI bleeding [33, 57, 58, 277-278]. One meta-analysis of 19 cohort studies showed that apixaban was associated with a lower risk of GI bleeding compared with dabigatran (pooled HR 0.59; 95% CI 0.46–0.75) and rivaroxaban (pooled HR 0.56; 95% CI 0.36–0.86).

As previously stated, given edoxaban recent approval, few cohort studies have assessed the effectiveness and safety of edoxaban compared with other DOACs. One Belgian cohort study on OAC-naïve patients with NVAF (aged ≥ 45 years) assessed the effectiveness and safety of dabigatran versus edoxaban, edoxaban versus rivaroxaban and apixaban versus edoxaban [260]. Although all four DOACs were associated with similar effectiveness against stroke/SE in this study, differences in the risk of MB/clinically relevant non-major bleeding were observed [260]. Indeed, dabigatran (HR 0.91; 95% CI 0.83-0.99) and apixaban (HR 0.86; 95% CI 0.81-0.91) were associated with lower risk of the safety outcome compared with edoxaban, while the risk was similar between rivaroxaban and edoxaban users [260]. One German cohort study on OAC-naïve patients with NVAF (aged ≥ 18 years) reported that

edoxaban, compared with dabigatran and rivaroxaban, was associated with a reduced risk of ischemic stroke/SE and all MB (major GI bleeding, ICH and other MB) [255]. Compared with rivaroxaban, edoxaban was also associated with lower rate of major GI bleeding and ICH events [255]. In comparison with apixaban, the hazard ratio of all MB (HR 1.09; 95% CI 0.92-1.30), ICH (HR 1.27; 95% CI 0.82-1.98) and other MB (HR 1.17; 95% CI 0.79-1.72) associated with edoxaban were numerically greater, but the risk of ischemic stroke/SE was lower (HR 0.83; 95% CI 0.69-0.99) and the risk of major GI bleeding (HR 1.00; 95% CI 0.81-1.24), similar [255]. A network meta-analysis reported similar risk of stroke/SE associated with edoxaban compared with dabigatran 110 mg (RR 1.01; 95% CI 0.53-1.94), dabigatran 150 mg (RR 1.02; 95% CI 0.55-1.87), rivaroxaban (RR 1.04; 95% CI 0.54-2.00) and apixaban (RR 0.98; 95% CI 0.48-2.03) in patients with NVAF aged 65 years and older [279]. The risk of MB associated with edoxaban compared with dabigatran 110 mg (RR 0.85; 95% CI 0.43-1.69), dabigatran 150 mg (RR 0.85; 95% CI 0.44-1.64), rivaroxaban (RR 0.84; 95% CI 0.41-1.71) and apixaban (RR 1.05; 95% CI 0.47-2.31) were also similar although confidence intervals were wide [279]. However, the authors indirectly compared edoxaban with apixaban using warfarin as the common reference and their estimates were based on results from 4 RCTs that compared edoxaban with warfarin (two being phase 2 trials) and 2 RCTs that compared apixaban with warfarin [279]. Moreover, four of the six included RCTs had relatively small sample size, resulting in limited power [279].

In summary, despite the limited evidence regarding the effectiveness and safety of edoxaban compared with other DOACs, the current literature seems to suggest, in overall, similar effectiveness against thromboembolism, with possibly a lower risk of major bleeding associated with edoxaban compared with rivaroxaban.

2.4 AF in very elderly patients aged ≥ 80

As previously described, the risk of AF increases the risk of stroke and older age represents a significant risk factor for both conditions [13]. By 2050, the very elderly population over the age of 80 will approximately totalize 350 million of the world population and AF is commonly diagnosed in this population [5, 13, 20, 40, 70-78, 280-287]. By 2060, it is projected that the very elderly may represent nearly 70% of the population with AF [20, 49, 291]. This population will consequently significantly contribute to the global burden of stroke since both AF and advanced age are major independent risk factors for stroke. Indeed, approximately 24% of strokes that occurred in patients over the age of 80 were AF-related in

the Framingham Heart Study [6, 8, 288, 292-293]. Compared with individuals with AF aged 65 to 74 years, those over 75 years of age have also been shown to experience higher mortality and major adverse cardiac event rates [294-295]. Thus, the very elderly constitutes a critical target group for stroke prevention given their greater risk of stroke [55].

2.4.1 Challenges in the management of patients with NVAF aged ≥ 80 years

The clinical management of the very elderly with NVAF remains challenging as there are no specific guidelines tailored to this heterogeneous population [6, 285, 295-296]. This is partly owed to the limited evidence provided by the 4 pivotal RCTs on the efficacy and safety of DOACs versus warfarin in the very elderly population with NVAF [6, 55, 296]. These four RCTs were not powered enough to investigate these two primary outcomes in octogenarians and older, with evidence mainly from subsequent secondary analyses in patients over 75 [6, 23, 297]. The proportion of enrolled patients with NVAF over 80 was under-represented in the 4 pivotal trials [297]. Indeed, 13 to 17% of patients with NVAF were over the age of 80 and of them, only 4-7% were older than 85 [297]. The representativeness of those included was also questioned as elderly patients included in clinical trials are generally healthier and have a higher drug adherence than patients in clinical practice due to stringent inclusion and exclusion criteria [298]. Indeed, in clinical practice, patients with AF are generally older and have several comorbidities, polypharmacy, higher risk of frailty and fall, lower body weight, and a higher prevalence of reduced renal function, cognitive impairment, and lower drug adherence [26, 60, 294, 299-303]. These RCTs may have hence potentially excluded very old patients who may have been eligible to receive DOACs in real clinical context. In summary, data from these RCTs may not reflect the real-world effectiveness and safety of DOACs in the very elderly, who are more prone to thromboembolism and bleeding risk because of their more complex health characteristics [26, 49, 55, 286, 292, 297, 303-306].

While OACs are indicated in many elderly patients with NVAF, it has been reported that less than 50% of patients with AF aged 80-89 years are treated with OACs [241, 307]. One study showed that patients with AF over 80 were less likely to be prescribed OACs than those aged 75-79 years [40]. However, with the approval of DOACs, OAC initiation has improved since 2008 in several countries [38, 40, 241, 308-312]. For instance, one cohort study found an increase in DOAC initiation rate with age in the UK from 2009 to 2015, particularly in patients with AF older than 75 years[38]. However, DOACs are still often under-prescribed to patients over 80 [40, 313-318]. Physicians often cite older age and bleeding risk as common reasons

for withholding the prescription of DOACs [315-316]. However, there are several reports of DOACs being under-prescribed to very elderly patients with NVAF without any clear counterindication [6, 303, 316-317]. Such reluctance from clinicians goes against data that showed that the highest net clinical benefit of DOACs compared with antiplatelets, warfarin or non OAC therapy is found in patients with NVAF over 80 and 85 [286, 297, 305, 313, 319]. While it is reasonable to not prescribe OACs in some individuals, it has been shown that clinicians frequently underestimate the benefits of stroke prevention and overestimate the risk of bleeding in the elderly population [317-318].

Based on AF guidelines, the management of AF should undertake a holistic approach [11-13]. However, considerations in the selection of an antithrombotic therapy in older patients is more complex and should include comorbidities, cognitive function, predisposition to fall (higher risk of bleeding), frailty, polypharmacy (potential higher risk of drug-drug interactions), altered drug pharmacokinetics/pharmacodynamics due to ageing processes and drug adherence/compliance [49, 314, 320]. Patients' preferences, values and their overall quality of life should also be discussed when evaluating the net clinical benefits of OAC strategies to manage their risk of thromboembolism [11-13, 320]. The availability of a reversal agent may also potentially affect the decision to prescribe DOACs [314]. There should be a conversation about the benefit/risk ratio associated with each DOAC or any other OAC therapy between the clinician and their patients [314]. The 2014 American Heart Association suggested the individualization of antithrombotic therapy in patients with NVAF and recognized the importance of patients' values and preferences [314]

In summary, the lack of evidence-based guidance for the management of AF in the very elderly coupled with their older age, greater risk of thromboembolism, MB and their health characteristics add layers of complexity to the choice of DOAC for this population [6, 60]. The decision to initiate a DOAC should be discussed between clinicians and patients [314].

2.4.2 Effectiveness and safety of DOACs in very elderly patients with NVAF

Which DOAC is the most effective and safest to prescribe to very elderly patients with NVAF over 80 remains uncertain [6, 55]. There are currently no RCTs with DOAC head-to-head comparisons [42-45, 298]. Moreover, most available real-world evidence studies have compared DOACs with warfarin only and mostly in patients with NVAF over the age of 75 [22, 25, 244-247, 287, 321-323]. Previous observational studies that compared DOACs with warfarin in patients over 75 have shown the non-inferiority of DOACs compared with warfarin

in terms of thromboembolic and MB events [33, 59, 62, 271, 324-332]. One meta-analysis of RCTs and cohort studies that included 147,067 patients with NVAF over 80 years old concluded that DOACs were superior to warfarin with respect to the risk of stroke (RR 0.72; 95%CI 0.63-0.82), all-cause mortality (RR 0.82; 95%CI 0.70-0.96) and intracranial bleeding (RR 0.47; 95%CI 0.36-0.60) [297]. There was also no greater risk of MB (RR 0.85; 95% CI 0.69- 1.04) or GI bleeding (RR 1.08; 95% CI 0.76-1.53) associated with DOACs compared with warfarin. However, because studies have mainly compared individual DOACs with warfarin, determining which DOAC should be preferentially prescribed to the very elderly is not feasible.

To our knowledge, only two retrospective cohort studies performed DOAC head-to-head comparisons in patients with NVAF over 80 years old have been conducted [61-62]. The first cohort study investigated the comparative effectiveness and safety of dabigatran, rivaroxaban and apixaban in patients with NVAF over 80 from January 2013 to September 2015 [61]. Edoxaban was not assessed in this study. The authors analyzed data from the Centers for Medicare and Medicaid Services and 3 US commercial claims databases (Optum, PharMetrics and Humana) [61]. Using propensity score (PS)-matching, the study included 10,046 dabigatran-rivaroxaban, 9891 apixaban-dabigatran and 37,350 apixaban-rivaroxaban PS-matched pairs in the analyses. Patients were followed from the date of the first pharmacy claim for either one of the three DOACs (index date) until discontinuation or switch to another DOAC (as-treated exposure definition with a 30-day grace period), death, end of continuous medical/pharmacy enrolment or end of the study period (September 30, 2015), whichever occurred first. The two primary outcomes were stroke/SE and MB. Stroke/SE was defined as a composite of ischemic stroke, hemorrhagic stroke, and SE. All cause-mortality was also investigated as a secondary outcome. Apixaban was associated with a lower risk of stroke/SE compared to dabigatran (HR 0.68; 95% CI 0.51-0.89) and rivaroxaban (HR 0.77; 95% CI 0.67-0.88) [61]. Dabigatran was associated with a similar risk of stroke/SE compared with rivaroxaban (HR 1.19; 95% CI 0.93-1.52). The risk of MB was also lower with apixaban compared to dabigatran (HR 0.74; 95% CI 0.63-0.88) and rivaroxaban (HR 0.53; 95% CI 0.49-0.57) [60]. Apixaban was associated with significantly lower risk of GI bleeding compared with dabigatran (HR 0.59; 95% CI 0.47-0.74) and rivaroxaban (HR 0.44; 95% CI 0.39-0.49). Dabigatran was associated with lower risk of MB compared with rivaroxaban (HR 0.82; 95% CI 0.72-0.94). The risk of GI bleeding was similar between dabigatran (HR 0.85; 95% CI 0.71-1.01) and rivaroxaban. Finally, apixaban was associated with similar and lower risk of all-cause

mortality compared to dabigatran (HR 0.96; 95% CI 0.85-1.10) and rivaroxaban (HR 0.84; 95% CI 0.79 0.89), respectively. There was no difference in all-cause mortality between dabigatran (HR 0.98; 95% CI 0.87-1.10) and rivaroxaban. Results from this study suggested the superiority of apixaban over dabigatran and rivaroxaban in terms of stroke/SE and MB in patients with NVAF over 80 years.

The second cohort study assessed the effectiveness and safety of low-dose rivaroxaban 15 mg versus dabigatran 110 mg in very elderly patients with NVAF aged 85 years old and older, using French data from the Système National des Données de Santé [62]. Apixaban and edoxaban were not assessed in this study. Using high-dimensional PS matching, the study included 4 329 matched pairs of new users of rivaroxaban 15 mg and dabigatran 110 mg between 2013 or 2014. The first dispensed OAC between January 2013 and December 2014, was defined as the index date. Patients were followed until either treatment discontinuation (with a 60-day grace period), switching to another OAC, mortality or end of the study period, whichever occurs first. The risk of ischemic stroke/SE, MB (defined as ICH, critical organ bleeding, any clinically relevant bleeding requiring blood transfusion or acute post-hemorrhagic anemia, or death during hospitalization), clinically relevant bleeding (all hospitalizations with a main diagnosis of bleeding), ICH, GI bleeding, acute coronary syndrome (myocardial infarction or unstable angina) and all-cause mortality were individually assessed. All-cause mortality, MB, and stroke/SE were also assessed as a composite outcome. Rivaroxaban was associated with a higher risk of stroke/SE compared with dabigatran (HR 1.50; 95% CI 1.11-2.02). There was no difference in the risk of MB (HR 1.00; 95% CI 0.75-1.33) and all-cause mortality (HR 1.05; 95% CI 0.92-1.20) with the use of rivaroxaban versus dabigatran. The risk of ICH (HR 1.76; 95% CI 0.90-3.46) and GI bleeding (HR 0.80; 95% CI 0.58-1.09) were also similar between rivaroxaban and dabigatran use.

The superiority of apixaban over dabigatran and rivaroxaban reported in the cohort study described above is consistent with findings in younger populations with NVAF [61, 333, 297, 299, 316, 333-335]. Its more favorable benefits/safety profile compared with the other DOACs may explain why apixaban is the most prescribed DOAC in many countries [38-41, 43, 45, 334]. Edoxaban being the most recently approved DOAC, there is limited information on its effectiveness and safety compared with other DOACs, and no data in the very elderly population. Despite its introduction in the market, edoxaban is increasingly prescribed [38, 43, 47]. Additional real-world studies comparing edoxaban with other DOACs, in particular with apixaban, the most commonly prescribed DOAC are therefore needed. These studies could

improve AF guidelines, inform clinicians on the choice of DOACs for the very elderly with NVAF and overall, improve clinical cares and the management of AF in this vulnerable population.

In light of these knowledge gaps, the two primary objectives of this population-based cohort study were to separately assess the effectiveness (prevention of ischemic stroke/transient ischemic attack/SE) and safety (risk of major bleeding) of edoxaban compared with apixaban in elderly patients with NVAF aged 80 years and older in a primary care setting.

Chapter 3: Objectives and hypotheses

This chapter presents the two primary and two secondary objectives of this thesis.

3.1 Objectives

The overall objective of this thesis was to assess the effectiveness and safety of edoxaban compared with apixaban in patients with NVAF aged 80 years and older.

3.1.1 Primary objectives

This thesis had two primary objectives:

1) To assess whether edoxaban is associated with a decreased risk of ischemic stroke/TIA/SE compared with apixaban.

2) To assess whether edoxaban is associated with a decreased risk of major bleeding compared with apixaban.

3.1.2 Secondary objectives

This thesis has two secondary objectives:

1) To assess whether edoxaban is associated with a decreased risk of all-cause mortality compared with apixaban.

2) To assess whether edoxaban is associated with a decreased risk of a composite outcome including ischemic stroke/TIA, SE, GI bleeding, ICH and all-cause mortality, compared with apixaban.

3.2 Hypotheses

This thesis had two primary and two secondary hypotheses.

3.2.1 Primary hypotheses

1) Edoxaban is associated with a similar risk of ischemic stroke/TIA/SE compared with apixaban in patients with NVAF aged 80 years and older.

2) Edoxaban is associated with a similar risk of major bleeding compared with apixaban in patients with NVAF aged 80 years and older.

3.2.2 Secondary hypotheses

1) Edoxaban is associated with a similar risk of all-cause mortality compared with apixaban in patients with NVAF aged 80 years and older.

2) Edoxaban is associated with a similar of risk of the composite outcome that included ischemic stroke/TIA, SE, GI bleeding or ICH) compared with apixaban in patients with NVAF aged 80 years and older.

Chapter 4: Methods (supplemental material)

This chapter provides additional information on data source, data linkage and the statistical handling of confounding and missing data that may not have been discussed in the Methods section in the manuscript (Chapter 5).

4.1 Data source

This retrospective population-based cohort study was conducted using the UK Clinical Practice Research Datalink (CPRD), one of the largest and ongoing longitudinal primary care database in the world [336]. Its primary mission is to support public health and clinical studies and has been considerably used in observational studies, contributing to more than 3000 peer-reviewed articles. [336-337]. Funded in 1987 as the Value Added Medical Products, it evolved to become the general Practice Research Database in 1987 [336]. Since 2012, it is known as the CPRD [336]. As of November 2022, the CPRD database englobes approximately 60 millions of patients, including approximately 18 millions of currently registered patients in more than 2000 participating general practices across England, Wales, Scotland, and Northern Ireland [336-338]. Around 25% of these patients have at least 20 years of follow-up [337]. The CPRD embodies two databases of electronic health records that collect data from participating general practices/practitioners: the CPRD GOLD and CPRD Aurum [339]. The CPRD GOLD database has been collecting patient data through the Vision ® software for the past 30 years while the CPRD Aurum database has been collecting patient data with the EMIS Web® software since its launching in October 2017 [340]. The total number of acceptable patients for research in the CPRD GOLD database approximates 21 million with around 3 millions of currently registered patients [341]. AURUM database encompasses 41 millions of acceptable patients for research, of which, 13 millions of them are currently registered patients [341]. The CPRD database collects the following anonymized and coded information: demographic characteristics, lifestyle factors such as smoking status and alcohol abuse, signs, symptoms, medical diagnoses, automatically computerized prescriptions, hospital admissions, medical specialist or hospital referrals, immunizations, and laboratory test results [336, 342-343]. These data are recorded by participating general practitioners who have consented to monthly provide patient data from their routine general practice [336]. Data from non-participating general practitioners and long term care institutions are not included in the CPRD database [336, 340]. A patient also holds the right to make an individual request to be opted out of data sharing to

their general practitioner, who can then amend the patient's registration details on the system to disable the extraction of the patient's data [336].

All medical history observations (diagnoses, symptoms, signs, hospital and clinical referrals, immunizations, and diagnostic tests results) contained in the CPRD GOLD database recorded by the general practitioner are coded using Read version (v) 2 codes along with their corresponding CPRD 'medcodes' (description of all medical codes) [344]. Data on drug and appliance prescriptions (brands and generic names) in the CPRD GOLD are coded using the Gemscript product code system with their corresponding 'prodcodes' (description of all product codes) [344].

The CPRD Aurum database uses a combination of Systematized Nomenclature of Medicine-Clinical Terms and Read/local EMIS® coding systems (with their corresponding 'medcodes') to code all medical history observations [345]. Data on drug and appliance prescriptions in the CPRD Aurum database are coded using the Dictionary of Medicines and Devices [345].

With more than 98% of the population in the UK being registered with a general practitioner, the CPRD database has been shown to be representative of the general UK population with respect to sex, age, and ethnicity [336]. Data quality assessment and validation in terms of their structure, format and integrity are ensured by the CPRD and concerns over the contents are addressed prior to their incorporation into the database during reviews [336, 346-348]. Although not an absolute gauge of data quality, the CPRD provides 2 criteria for the initial selection of research-quality patients and periods of quality data: the acceptability for patients and up to standard time for practices [336]. The first criterion is based on registration status, valid age/sex and recording of events in the patient's record [336]. The second criterion accounts for the continuity of recording and the number of recorded deaths [336]. The latter metric is computed for each participating general practice and represents the latest timestamp at which the practice reached the minimum criteria of quality [336]. At last, medical diagnoses recorded in the CPRD have also been shown to hold a high positive predictive value [336].

4.2 Data linkage

About 9 and 39 millions of patients from the CPRD GOLD and AURUM databases, respectively, are eligible for data linkage, as data are only available for patients in England [341]. The CPRD database can be linked to the Hospital Episode Statistics (HES) and the ONS [339, 346, 349-350]. The HES database encompasses the HES Admitted Patient Care, HES

Outpatient and HES Accident and Emergency dataset [340, 346, 349-350]. It contains data on all inpatient and day-case hospital admissions, outpatient appointments and attendances and Accident and Emergency attendances in England [349-350]. The ONS encodes mortality data (official date of death and cause of death) using the ICD 10 classification [351].

This study was conducted by linking the CPRD database to the HES Admitted Patient Care and to the ONS mortality database. Linkage to HES was required to obtain data on admission/discharge dates, primary diagnoses coded using the ICD 10 and performed medical procedures recorded with the UK Office of Population, Census and Surveys classification 4.6 [349-350]. This linkage was essential to accurately ascertain the two primary outcomes of interest (ischemic stroke/TIA/SE and MB) and to measure covariates prior to cohort entry. The ONS mortality database collects mortality data (patient's date of death and cause(s) of death) across England and Wales. Linkage to the ONS was therefore needed to identify all deaths related to the outcomes of interest.

4.3 Handling of confounding and missing data

This study used a PS-based fine stratification and weighting approach to address confounding (target of inference: average treatment effect among the treated population) [352-353]. The PS model included several relevant covariates such as demographic characteristics, lifestyle risk factors, comorbidities, co-medications, and healthcare utilization (number of hospitalizations). One hundred strata based on the computed PS distribution of the exposure of interest (edoxaban) were created and weights were then computed to account for stratum membership. For each stratum with at least 1 treated patient and 1 comparator patient, treated patients were given a weight of 1 while those in the reference group were given a weight that was computed with the following formula: (Number of exposed patients in PS stratum_i/Total number of exposed patients)/(Number of patients in the reference group in PS stratum_i/Total number of patients in the reference group). This method makes extreme weights due to PS near 0 or 1 unlikely and is appropriate when the prevalence of the exposure (edoxaban in this case) is low. The use of an active comparator (apixaban) may also help in the decrease of potential residual confounding. Comparisons were performed between patients with the same medical condition (NVAF) and initiating 2 different DOACs (edoxaban or apixaban). Primary analyses were reiterated using multiple imputations by chained equations for variables with missing values such as BMI and smoking status. An ordinal logistic regression model was used to impute variables with missing data with explanatory variables and cumulative hazard and one

of the exposure groups (at cohort entry), along with all relevant confounders mentioned below (see Chapter 5). We combined results from five imputed datasets to account for missing data on body mass index and smoking status [354-355].

Chapter 5: Effectiveness and safety of edoxaban compared with apixaban in elderly patients with nonvalvular atrial fibrillation : a real-world population-based cohort study

This chapter contains the manuscript of a population-based cohort study that compared the effectiveness (risk of thromboembolism) and safety (risk of major bleeding) of edoxaban with apixaban in patients with incident NVAF aged 80 years and older. The introduction of the manuscript provides the context, rationale and overall primary objectives of the cohort study (information on the very elderly population with NVAF, the current body of evidence regarding the effectiveness and safety of DOACs in this population and the gap of knowledge addressed by this study). The Methods section describes the data source, formation of the study cohort, defines the exposures, outcomes, covariates and describes the statistical analyses. The following section describes the results of the study, followed by a section to discuss the plausible interpretations of the results (contrasted with results from prior studies). The section Discussion also highlights the strengths and limitations of the study. The final section offers a conclusion of the study. This manuscript is currently under review in a peer-reviewed scientific journal. This version of the manuscript might differ from the one edited and accepted by the journal.

Effectiveness and safety of edoxaban compared with apixaban in elderly patients with nonvalvular atrial fibrillation: a real-world population-based cohort study

Richard Chiv, MSc.[1,2]; Sarah Beradid, MSc.[1]; Samy Suissa, PhD[1,2], Christel Renoux, MD, PhD[1,2,3]

[1]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada

[2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[3]Department of Neurology and Neurosurgery, McGill University, Montreal, Canada

5.1 Abstract

Background: The very elderly (≥ 80 years) are at high risk of nonvalvular atrial fibrillation (NVAF) and thromboembolism. Given its recent approval, the comparative effectiveness and safety of edoxaban in this population, relative to the commonly used apixaban, remain unknown.

Methods: Using the United Kingdom Clinical Practice Research Datalink database, we identified a cohort of patients with incident NVAF aged ≥ 80 newly treated with edoxaban or apixaban between 2015 and 2021. Cohort entry was defined as the first prescription for one of the two drugs. We used propensity score fine stratification and weighting for confounding adjustment. A weighted Cox proportional hazards model was used to estimate the hazard ratios (HR) with 95% confidence interval (95% CI) of ischemic stroke/TIA/systemic embolism and of major bleeding associated with edoxaban compared with apixaban. We also assessed the risk of all-cause mortality and a composite outcome of ischemic stroke/TIA, systemic embolism, gastrointestinal bleeding, and intracranial hemorrhage as secondary outcomes.

Results: The cohort included 7,251 new-users of edoxaban and 39,991 of apixaban. Edoxaban and apixaban had similar incidence rates of thromboembolism (20.38 vs. 19.22 per 1,000 person-years; HR 1.06; 95% CI 0.89-1.26), although the rate of major bleeding was higher with edoxaban (45.57 vs. 31.21 per 1,000 person-years; HR 1.42; 95% CI 1.26-1.61). The risk of the composite outcome was 21% higher with edoxaban (incidence rates: 44.3 vs. 36.1 per 1,000 person-years; HR 1.21; 95% CI 1.07-1.38). All-cause mortality was similar between edoxaban and apixaban (incidence rates: 118.4 vs. 113.7 per 1,000 person-years; HR 1.04; 95% CI 0.96-1.12).

Conclusions: In very elderly patients with NVAF, edoxaban resulted in similar thromboembolism prevention as apixaban, although it was associated with a higher risk of major bleeding. These findings may improve the management of NVAF by informing physicians on the choice of DOACs for this vulnerable population.

Keywords: nonvalvular atrial fibrillation, elderly, edoxaban, apixaban, stroke, bleeding

5.2 Introduction

Atrial fibrillation (AF) is a commonly diagnosed cardiac arrhythmia in the elderly and is associated with a five-fold increased risk of stroke [1-3]. Older age represents the most prominent independent risk factor for the development of AF and stroke [4-5]. Indeed, with AF affecting approximately 17% of patients over 80 years old, the attributable risk of stroke associated with AF increases from 1.5% in the 50-59 age group to 23.5% in the 80-89 age group [6-8]. Most AF guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) to prevent stroke and systemic embolism (SE) for most patients with nonvalvular AF (NVAF) [9-13]. However, DOACs are often under-prescribed to the elderly, with advanced age and higher bleeding risk frequently cited by physicians as common reasons for withholding their prescription [5-7].

Although the efficacy and safety of DOACs compared with warfarin have been established in the 4 pivotal randomized controlled trials (RCTs), very elderly individuals with NVAF were under-represented, constituting less than 7% of the overall trial study population [14-18]. Moreover, no RCT with head-to-head DOAC comparisons has been conducted [6]. Based on observational studies on younger populations with NVAF, apixaban, the most prescribed DOAC in several countries, has been suggested to be at least as effective as dabigatran and rivaroxaban while associated with a lower risk of major bleeding (MB) [19-24].

To our knowledge, only two retrospective cohort studies with head-to-head DOAC comparisons have been conducted in patients with NVAF over 80 [25-26]. The first study found that apixaban was superior to dabigatran and rivaroxaban with respect to the prevention of ischemic stroke/hemorrhagic stroke/SE with a reduced risk of MB and intracranial hemorrhage (ICH) [25]. The second cohort study, in patients with NVAF over 85, reported a higher risk of ischemic stroke/SE with similar MB risk associated with low-dose of rivaroxaban versus dabigatran [26]. Given edoxaban more recent approval, its benefit/harm profile compared with apixaban in the very elderly remain unknown. Therefore, the objective of this study was to assess the effectiveness and safety of edoxaban compared with apixaban in patients with NVAF aged 80 years and older, to better inform prescription choices in this vulnerable population.

5.3 Methods

5.3.1 Data source

We conducted a population-based cohort study using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), GOLD and Aurum databases. The CPRD is a large primary care database of anonymized electronic medical records of over 60 millions of patients enrolled in more than 2000 practices in the UK [27-28]. The CPRD has been shown to be representative of the general UK population in terms of sex, age, and ethnicity.[27] Collected data include demographic characteristics, lifestyle factors, medical diagnoses, laboratory results, prescriptions written by general practitioners, and medical specialist or hospital referrals [28]. Data quality control is performed regularly, and numerous studies have shown the validity and high quality of the recorded data [27,29]. CPRD was linked to the Hospital Episode Statistics (HES) Admitted Patient Care and to the Office for the National Statistics (ONS) [30-32]. The HES Admitted Patient Care is a UK National Health Service dataset that includes data on admission and discharge dates, primary diagnoses coded using the International Classification of Diseases tenth Revision codes (ICD 10), consulted medical specialists, and performed medical procedures coded with the UK Office of Population, Census and Surveys classification 4.6 framework [30-31]. The ONS dataset collects mortality data in England and Wales and includes patients' official date and cause(s) of death [32]. The study protocol was approved by the CPRD Research Data Governance (protocol no. 22_002346) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

5.3.2 Study population

We assembled a base cohort of all patients with a first diagnosis of AF between January 1, 2010, and March 31, 2021 (last date of HES data). We excluded patients with less than one year of medical history in the CPRD before AF diagnosis, and those with a prior AF diagnosis to only include patients with incident AF. Within this base cohort of patients with incident NVAF, we formed a study cohort of all patients with a first prescription for edoxaban or apixaban between July 1, 2015 (the date of edoxaban availability in the UK) and March 31, 2021, with cohort entry defined as the date of the first prescription. We excluded patients aged < 80 years at the time of their first edoxaban or apixaban prescription, those who were prescribed edoxaban or apixaban at any time before cohort entry and those who were prescribed two OACs at cohort entry. To only include patients with incident NVAF, those with a history of valvular surgery (valvular AF) or rheumatic valvular disease at any time before cohort entry

were excluded. We also excluded patients with a diagnosis of hyperthyroidism or dialysis in the 90 days prior to cohort entry, and those with a diagnosis of venous thromboembolism or joint surgery of the hip, femur, or knee in the 30 days prior to (and including) cohort entry date. All patients were followed until the occurrence of the outcome of interest (depending on the studied outcome), treatment discontinuation or switching to another anticoagulant, death from any cause, end of the registration with the general practice, or end of the study period (March 31, 2021), whichever occurred first.

5.3.3 Exposure definition

Patients were considered continuously exposed to the drug of interest from the date of the first prescription and censored upon treatment discontinuation or switching to another DOAC or to VKAs, with a 30-day grace period in the event of non-overlapping prescriptions.

5.3.4 Outcome definition

The primary effectiveness outcome was a composite of hospitalization with incident ischemic stroke, transient ischemic attack (TIA), or SE (referred as ischemic stroke/SE thereafter). The primary safety outcome was MB, defined as any bleeding requiring hospitalization. All outcomes were defined using relevant ICD 10 codes in HES (primary diagnosis in non-elective hospitalization). As secondary outcomes, we also investigated all-cause mortality and a composite outcome that included ischemic stroke/TIA, SE, gastrointestinal (GI) bleeding, and ICH.

5.3.5 Covariates

The covariates included demographic characteristics (age (modelled using cubic splines), sex, ethnicity), calendar year of cohort entry, lifestyle risk factors (most recent measures of alcohol abuse, body mass index and smoking status within 5 years before cohort entry), and the following comorbidities, measured at any time before cohort entry: hypertension, congestive heart failure, myocardial infarction, coronary artery disease, pacemaker or implantable cardioverter-defibrillator, coronary artery bypass surgery or percutaneous coronary intervention, prior ischemic stroke/TIA, SE, peripheral arterial disease, prior bleeding events, anemia or coagulation defects, depression, cancer (other than non-melanoma skin cancer), dementia or mild cognitive impairment, Parkinson's disease, history of falls, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, liver disease and diabetes mellitus. Time from NVAF diagnosis to apixaban or edoxaban

initiation was also included as a covariate. We also considered the following medications measured in the year before cohort entry: antidiabetic medications (metformin, sulfonylureas, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter-2, insulin, others), antihypertensive drugs (beta-blockers, thiazides, other diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers), antiarrhythmics, digoxin, antiplatelet agents, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, systemic corticosteroids, antidepressants, antipsychotics, benzodiazepines and hypnotics, antiepileptic drugs, proton pump inhibitors, H_2 blockers, and hormone replacement therapy. OAC drugs were also included for patients with previous use before cohort entry. Finally, we included the number of hospitalizations in the year before cohort entry as a surrogate marker for overall health. Scores commonly used to estimate the risk of ischemic stroke in NVAF (e.g., $CHADS_2$ and CHA_2DS_2-VASc scores) and the risk of bleeding (e.g., HAS-BLED score) were not adjusted for, given that the individual components of these scores were added in all models. Missing data were expected for body mass index and smoking status so that a separate category was created to classify missing information.

5.3.6 Statistical analysis

We used propensity score (PS)-based fine stratification and weighting to control for potential confounding [33-34]. The PS (the probability of receiving edoxaban, conditional on observed baseline covariates described above) was estimated using logistic regression, separately for patients without and with a history of OAC use before cohort entry. Following PS estimation, those in the non-overlapping regions of the PS distributions were excluded. Next, we computed fine-stratification weights using 100 strata based on the PS distribution of the edoxaban group. Inverse probability of censoring weighting (IPCW) was also used to account for potential informative censoring due to treatment termination or switching and to account for death as a competing risk. We described the baseline characteristics of each exposure group before and after fine stratification weighting, by prior OAC use strata. A standardized mean difference lower than 10% was considered a well-balanced covariate distribution. The crude and weighted incidence rates of ischemic stroke and major bleeding with their respective 95% confidence intervals (95% CIs) were estimated for each exposure group based on a Poisson distribution. We also plotted the weighted cumulative incidence curve for each primary outcome by exposure group. In the primary analyses, a weighted Cox proportional hazards regression model with robust sandwich variance with stratification by

prior OAC treatment was fitted to estimate the hazard ratio (HR) and 95% CI for each outcome associated with the use of edoxaban compared to the use of apixaban. All-cause mortality and a composite outcome of ischemic stroke/TIA, SE, GI bleeding, and ICH were individually assessed as secondary outcomes. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

5.3.7 Secondary analysis

To investigate potential effect measure modification, we performed stratified analyses according to age (< 90 versus ≥ 90 years old), sex, frailty status (frail versus non-frail), and CHA_2DS_2-VASc score (≤ 4 versus > 4) [35]. Frailty status was defined using relevant codes in the CPRD. We also investigated whether the risk of each primary outcome vary with prior use of other OACs and with dose prescribed at cohort entry (standard dose (5 mg apixaban/60 mg edoxaban) versus low dose (2.5 mg apixaban/30 mg edoxaban)). A stratified analysis by patients' modified HAS-BLED score assessed at cohort entry (≤ 2 versus > 2) was undertaken to evaluate potential effect measure modification on the risk of MB [36]. We used a modified HAS-BLED score that included hypertension, abnormal renal and/or liver function, ischemic stroke/TIA, bleeding, age ≥ 65 years, use of antiplatelets and/or NSAIDs drugs or alcohol abuse because of the unavailability of international normalized ratio values at cohort entry. Finally, we examined whether the risk varies by type of bleeding (GI bleeding, ICH and other bleeding).

5.3.8 Sensitivity analysis

We performed three sensitivity analyses to assess the robustness of the results. First, to assess potential exposure misclassification, the primary analyses were repeated using 15- and 60-day grace periods between successive prescriptions. Second, we used an intention-to-treat (ITT) exposure definition to further investigate potential informative censoring related to treatment discontinuation or switching with follow-up restricted to one year and a half. Lastly, we used multiple imputation by chained equations method and combined results from five imputed datasets to account for missing data on body mass index and smoking status [37].

5.4 Results

Following the applied inclusion and exclusion criteria, the study cohort included 7,251 new users of edoxaban and 39,991 new users of apixaban (**Figure 1**). Baseline characteristics of patients without and with prior use of OACs before and after fine stratification weighting are presented in **Table S1** and **Table S2**. Before fine stratification weighting, most

characteristics were similar in patients without prior OAC use, except for a higher number of hospitalizations in edoxaban users. Among patients with prior OAC use, before fine stratification weighting, edoxaban users were slightly healthier than apixaban users, with a lower prevalence of history of stroke/TIA, anemia, and chronic kidney disease. After weighting, both exposure groups from each sub-cohort were well-balanced with respect to all covariates. The median follow-up time varied from 255-262 days for patients treated with edoxaban and from 317-322 for patients treated with apixaban.

Table 1 presents the results of the primary analyses. The use of edoxaban was as effective as apixaban in the prevention of ischemic stroke/SE (weighted incidence rates: 20.38 vs. 19.22 per 1,000 person-years; HR 1.06; 95% CI 0.89-1.26). Edoxaban was associated with a higher risk of MB compared with apixaban (weighted incidence rates: 45.57 vs. 31.21 per 1,000 person-years; HR 1.42; 95% CI 1.26-1.61). There was no difference in all-cause mortality between edoxaban and apixaban use (weighted incidence rates: 118.43 vs. 113.70 per 1,000 person-years; HR 1.04; 95% CI 0.96-1.12). Compared with apixaban, the risk of the composite outcome was higher with edoxaban (weighted incidence rates: 44.34 vs. 36.12 per 1,000 person-years; HR 1.21; 95% CI 1.07-1.38). Weighted cumulative incidence curves for each primary outcome are presented in **Figure 2** and **Figure 3**.

Stratified analyses did not show any effect measure modification on the risk of the ischemic stroke/SE associated with edoxaban (**Figure 4** and **Table S3**). The risk of stroke did not vary by history of OAC use (**Table S4**) or by dose (**Table S5**). The risk of MB was not modified by age, frailty and CHA_2DS_2-VASc score (**Figure 4** and **Table S6**). However, the risk was numerically higher among men treated with edoxaban (HR 1.60; 95% CI 1.34-1.91) than among women (HR 1.25; 95% CI 1.04-1.52) (**Table S6)**. It was also greater in patients with a HAS-BLED ≤ 2 (HR 2.00; 95% CI 1.54-2.60) than in those with a HAS-BLED > 2 (HR 1.28; 95% CI 1.10-1.49). The risk did not vary by history of prior OAC use (**Table S7**) but was slightly higher with standard-dose of edoxaban vs. apixaban (HR 1.66; 95% CI 1.38-2.00) than with low-dose of edoxaban vs. apixaban (HR 1.28; 95% CI 1.06-1.54) (**Table S8**). Compared with apixaban, edoxaban was associated with a higher risk of GI bleeding (HR 1.53; 95% CI 1.27-1.85) and other bleeding (HR 1.45; 95% CI 1.21-1.74) with a similar risk of ICH (HR 0.95; 95% CI 0.63-1.42) (**Table S9**).

Results of the sensitivity analyses were overall consistent with those of the primary analyses (**Figure 5**, **Tables S10-S11**).

5.5 Discussion

In this population-based cohort study, edoxaban and apixaban had similar effectiveness against ischemic stroke. However, edoxaban was associated with a 42% greater MB risk. The risk of all-cause mortality was similar between the two DOACs. Compared with apixaban, the risk of the composite outcome was 21% higher with edoxaban. The results of the primary analyses remained robust across all sensitivity analyses.

Evidence regarding the comparative effectiveness/safety profile between the four DOACs to inform clinical practice in the very elderly with NVAF remains scarce [38-39]. Therefore, which DOAC should be preferentially prescribed to these patients is uncertain [38,40]. Two cohort studies compared the effectiveness and safety of apixaban, rivaroxaban and dabigatran in patients with NVAF older than 80 [25-26]. In line with previous findings from observational studies in younger populations, one of these studies suggested that while apixaban was at least as effective as dabigatran and rivaroxaban, it was associated with a lower risk of MB in patients with NVAF over 80 [19-22,25]. The other cohort study compared reduced dose of rivaroxaban and dabigatran in patients with NVAF over 85 and reported an increased risk of ischemic stroke/SE with similar risk of MB associated with low-dose rivaroxaban [26]. Our study is the first to examine the effectiveness and safety of edoxaban compared with apixaban in patients with NVAF over 80. Similar to evidence available in younger patients, our results suggest that edoxaban and apixaban offer similar effectiveness for the prevention of ischemic stroke in patients over 80, with no modification by age, sex, frailty, CHA_2DS_2-VASc score, history of OAC use and dose [41-45].

Edoxaban was however associated with a greater risk of MB compared with apixaban, mainly driven by GI bleeding and other bleeding. Our results are consistent with those from a previous cohort study in patients with NVAF (aged ≥ 45 years old), in which a lower risk of MB (HR 0.79; 95% CI 0.72-0.86) associated with apixaban compared with edoxaban was reported [41]. Conversely, another cohort study on patients with NVAF (aged ≥ 18 years) observed a similar risk of MB between both DOACs, but the exclusion of 8,838 patients with less than 180 days observability may have led to potential selection bias [42]. A network-meta-analysis reported a numerically higher MB risk estimate associated with edoxaban (HR 1.30; 95% CI 0.99-1.70) compared with apixaban in patients with NVAF aged ≥ 75 years, based on data pooled from *post hoc* sub-group analyses of 2 RCTs (edoxaban or apixaban versus warfarin) [43]. In clinical practice, some physicians are reluctant to prescribe OACs to the elderly due to the risk of bleeding [6]. Yet, the hazard ratio of MB in patients treated with

edoxaban with a HAS-BLED > 2 was numerically lower than in those with a HAS-BLED ≤ 2 in our study. Possible explanations include stricter monitoring or more regular reassessment of modifiable bleeding risk factor strategies in patients at higher risk of bleeding. Most AF guidelines recommend the use of the HAS-BLED score to identify and address potential bleeding risk factors, not to deny OAC therapy in eligible patients with AF [6,11-13].

Despite their guidelines-based eligibility for oral anticoagulation, frail and elderly individuals with NVAF are also frequently not treated with OACs, owing to clinicians' concerns over potential increased bleeding risk but also to the lack of observational evidence on their effectiveness/safety in these populations [46-49]. Two cohort studies examined the effectiveness/safety of DOACs in frail patients with NVAF [48-49]. One concluded that overall, all four DOACs had comparable effectiveness in the prevention of stroke/SE, but that apixaban was associated with a lower MB rate compared with dabigatran, rivaroxaban and edoxaban in frail patients with NVAF over 45 (even among frail patients over 85) [48]. However, the risk of all-cause mortality was increased among apixaban users compared with dabigatran and edoxaban users [48]. The other study compared the first three approved DOACs and found that their use was generally effective and safe in frail patients with NVAF (aged ≥ 65) [49]. Similarly, we found no effect measure modification on the risk of MB associated with edoxaban by age and frailty. Also, the risk of MB did not vary with CHA_2DS_2-VASc, history of OAC use and dose. However, the dosing of DOACs is still a challenge in the elderly or frail patients with NVAF [41,50]. Inappropriate dosing of DOACs, based on overestimation of the bleeding risk, is prevalent in these patients, which can possibly undermine the net clinical benefit of these treatments [41,50]. Overall, in the absence of any counterindication, most AF guidelines recommend the prescription of OACs to elderly and frail patients with NVAF as their benefits outweigh their risk of bleeding [10-13]. A shared-decision making approach is encouraged between physicians and patients to individualize and optimize OAC therapy strategies (including dosage regimen) based on their comorbidities, comedications, values and preferences [10-13,40,50].

This study had several strengths. The CPRD, shown to be representative of the general UK population, allowed us to assemble a large well-defined study population of 47,242 very elderly patients with incident NVAF. Moreover, linkage of the CPRD to the HES and ONS datasets to define the studied outcomes minimized potential outcome misclassification. All models were also adjusted for several potential confounders such as lifestyle risk factors that may not be captured in claims databases as smoking status and alcohol abuse. We also used

inverse probability of censoring weighting to account for treatment discontinuation or switching to another OAC and death as a competing risk in our primary analyses. Finally, our primary results remained robust across all sensitivity analyses.

Some limitations should also be considered. Due to the observational nature of this study, residual confounding is possible. This issue was mitigated by considering many comorbidities, comedications and markers of health that were well balanced between the two exposure groups. Exposure misclassification may have been present since the CPRD only records prescribed drugs issued by general practitioners, and not by specialists. However general practitioners play a central role in the management of patients with AF, so that most OAC prescriptions are likely to be captured. In addition, the definition of exposure was based solely on issued prescriptions and not on those filled or taken. This issue was explored in sensitivity analyses using two different exposure definitions (15- and 60-day grace period) and results were consistent with those of the primary analyses. Finally, outcome misclassification is possible, but likely to be non-differential between the two treatment groups and thus, may bias the estimates towards the null. This potential source of bias was minimized by using HES and ONS data to define the study outcomes.

In summary, while edoxaban and apixaban provided similar effectiveness for the prevention of ischemic stroke in very elderly patients with NVAF, the use of edoxaban was associated with an increased risk of major bleeding. Further population-based cohort studies with DOAC comparisons that include edoxaban in patients with NVAF over 80 should be undertaken to refine the current body of knowledge and inform AF guidelines on the choice of DOACs for this high-risk population.

5.6 Disclosures

The Authors declare that there is no conflict of interest.

5.7 Acknowledgements

Data Availability Statement: This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. The interpretation and conclusions contained in this

study are those of the author/s alone. Because electronic health records are classified as "sensitive data" by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

5.8 References

1. Renoux, C., Coulombe, J., & Suissa, S. (2017). Revisiting sex differences in outcomes in non-valvular atrial fibrillation: a population-based cohort study. *European heart journal*, *38*(19), 1473–1479. https://doi.org/10.1093/eurheartj/ehw613

2. Douros, A., Renoux, C., Coulombe, J., & Suissa, S. (2017). Patterns of long-term use of non-vitamin K antagonist oral anticoagulants for non-valvular atrial fibrillation: Quebec observational study. *Pharmacoepidemiology and drug safety*, *26*(12), 1546–1554. https://doi.org/10.1002/pds.4333

3. Díez-Villanueva, P., & Alfonso, F. (2019). Atrial fibrillation in the elderly. *Journal of geriatric cardiology : JGC*, *16*(1), 49–53. https://doi.org/10.11909/j.issn.1671-5411.2019.01.005

4. Kornej, J., Börschel, C. S., Benjamin, E. J., & Schnabel, R. B. (2020). Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. Circulation research, 127(1), 4–20. https://doi.org/10.1161/CIRCRESAHA.120.316340

5. Karamichalakis, N., Letsas, K. P., Vlachos, K., Georgopoulos, S., Bakalakos, A., Efremidis, M., & Sideris, A. (2015). Managing atrial fibrillation in the very elderly patient: challenges and solutions. Vascular health and risk management, 11, 555–562. https://doi.org/10.2147/VHRM.S83664

6. Zathar, Z., Karunatilleke, A., Fawzy, A. M., & Lip, G. (2019). Atrial Fibrillation in Older People: Concepts and Controversies. Frontiers in medicine, 6, 175. https://doi.org/10.3389/fmed.2019.00175

7. Botto, G., Ameri, P., Cappellari, M., Dentali, F., Ferri, N., Parrini, I., Porto, I., Squizzato, A., & Camporese, G. (2021). Unmet Clinical Needs in Elderly Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation. *Advances in therapy*, *38*(6), 2891–2907. https://doi.org/10.1007/s12325-021-01769-9

8. Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*, *22*(8), 983–988. https://doi.org/10.1161/01.str.22.8.983

9. Imberti, J. F., Mei, D. A., Vitolo, M., Bonini, N., Proietti, M., Potpara, T., Lip, G. Y. H., & Boriani, G. (2022). Comparing atrial fibrillation guidelines: Focus on stroke prevention, bleeding risk assessment and oral anticoagulant recommendations. *European journal of internal medicine*, *101*, 1–7. https://doi.org/10.1016/j.ejim.2022.04.023

10. January, C. T., Wann, L. S., Calkins, H., Chen, L. Y., Cigarroa, J. E., Cleveland, J. C., Jr, Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Furie, K. L., Heidenreich, P. A., Murray, K. T., Shea, J. B., Tracy, C. M., & Yancy, C. W. (2019). 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*, *74*(1), 104–132. https://doi.org/10.1016/j.jacc.2019.01.011

11. Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G. A., Dilaveris, P. E., Fauchier, L., Filippatos, G., Kalman, J. M., La Meir, M., Lane, D. A., Lebeau, J. P., Lettino, M., Lip, G. Y. H., Pinto, F. J., Thomas, G. N., … ESC Scientific Document Group (2021). 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European heart journal, 42(5), 373–498. https://doi.org/10.1093/eurheartj/ehaa612

12. Chao, T. F., Joung, B., Takahashi, Y., Lim, T. W., Choi, E. K., Chan, Y. H., Guo, Y., Sriratanasathavorn, C., Oh, S., Okumura, K., & Lip, G. Y. H. (2022). 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thrombosis and haemostasis*, *122*(1), 20–47. https://doi.org/10.1055/s-0041-1739411

13. Andrade, J. G., Aguilar, M., Atzema, C., Bell, A., Cairns, J. A., Cheung, C. C., Cox, J. L., Dorian, P., Gladstone, D. J., Healey, J. S., Khairy, P., Leblanc, K., McMurtry, M. S., Mitchell, L. B., Nair, G. M., Nattel, S., Parkash, R., Pilote, L., Sandhu, R. K., Sarrazin, J. F., … Members of the Secondary Panel (2020). The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. The Canadian journal of cardiology, 36(12), 1847–1948. https://doi.org/10.1016/j.cjca.2020.09.001

14. Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P. A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B. S., Darius, H., Diener, H. C., Joyner, C. D., Wallentin, L., … RE-LY Steering Committee and Investigators (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*, *361*(12), 1139–1151. https://doi.org/10.1056/NEJMoa0905561

15. Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., Breithardt, G., Halperin, J. L., Hankey, G. J., Piccini, J. P., Becker, R. C., Nessel, C. C., Paolini, J. F., Berkowitz, S. D., Fox, K. A., Califf, R. M., & ROCKET AF Investigators (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *The New England journal of medicine*, *365*(10), 883–891. https://doi.org/10.1056/NEJMoa1009638

16. Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., Al-Khalidi, H. R., Ansell, J., Atar, D., Avezum, A., Bahit, M. C., Diaz, R., Easton, J. D., Ezekowitz, J. A., Flaker, G., Garcia, D., Geraldes, M., Gersh, B. J., Golitsyn, S., Goto, S., … ARISTOTLE Committees and Investigators (2011). Apixaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*, *365*(11), 981–992. https://doi.org/10. 1056/NEJMoa1107039

17. Giugliano, R. P., Ruff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D., Halperin, J. L., Waldo, A. L., Ezekowitz, M. D., Weitz, J. I., Špinar, J., Ruzyllo, W., Ruda, M., Koretsune, Y., Betcher, J., Shi, M., Grip, L. T., Patel, S. P., Patel, I., Hanyok, J. J., Mercuri, M., … ENGAGE AF-TIMI 48 Investigators (2013). Edoxaban versus warfarin in patients with atrial fibrillation. *The New England journal of medicine*, *369*(22), 2093–2104. https://doi.org/10.105 6/NEJMoa1310907

18. Bonanad, C., García-Blas, S., Torres Llergo, J., Fernández-Olmo, R., Díez-Villanueva, P., Ariza-Solé, A., Martínez-Sellés, M., Raposeiras, S., Ayesta, A., Bertomeu-González, V., Tarazona Santabalbina, F., Facila, L., Vivas, D., Gabaldón-Pérez, A., Bodi, V., Nuñez, J., & Cordero, A. (2021). Direct Oral Anticoagulants versus Warfarin in Octogenarians with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Journal of clinical medicine*, *10*(22), 5268. https://doi.org/10.3390/jcm10225268

19. Durand, M., Schnitzer, M. E., Pang, M., Carney, G., Eltonsy, S., Filion, K. B., Fisher, A., Jun, M., Kuo, I. F., Matteau, A., Paterson, J. M., Quail, J., Renoux, C., & Canadian Network for Observational Drug Effect Studies (CNODES) Investigators (2021). Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: A multi-database cohort study with meta-analysis. *British journal of clinical pharmacology*, *87*(6), 2589–2601. https://doi.org/10.1111/bcp.14669

20. Perreault, S., Dragomir, A., Côté, R., Lenglet, A., White-Guay, B., de Denus, S., Schnitzer, M. E., Dubé, M. P., Brophy, J. M., Dorais, M., & Tardif, J. C. (2021). Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: A propensity score-matched cohort study. *Pharmacotherapy*, *41*(4), 379–393. https://doi.org/10. 1002/phar.2509

21. Buckley, B. J. R., Lane, D. A., Calvert, P., Zhang, J., Gent, D., Mullins, C. D., Dorian, P., Kohsaka, S., Hohnloser, S. H., & Lip, G. Y. H. (2022). Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Journal of clinical medicine*, *11*(13), 3788. https://doi.org/10.3390/jcm11133788

22. Li, G., Lip, G. Y. H., Holbrook, A., Chang, Y., Larsen, T. B., Sun, X., Tang, J., Mbuagbaw, L., Witt, D. M., Crowther, M., Thabane, L., & Levine, M. A. H. (2019). Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. *European journal of epidemiology*, *34*(2), 173–190. https://doi.org/10.1007/s10654-018-0415-7

23. Vora, P., Morgan Stewart, H., Russell, B., Asiimwe, A., & Brobert, G. (2022). Time Trends and Treatment Pathways in Prescribing Individual Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation: An Observational Study of More than Three Million Patients from Europe and the United States. *International journal of clinical practice*, *2022*, 6707985. https://doi.org/10.1155/2022/6707985

24. Alkhameys, S., & Barrett, R. (2022). Impact of the COVID-19 pandemic on England's national prescriptions of oral vitamin K antagonist (VKA) and direct-acting oral anticoagulants (DOACs): an interrupted time series analysis (January 2019-February 2021). *Current medical research and opinion*, *38*(7), 1081–1092. https://doi.org/10.1080/03007995.2022.2078100

25. Deitelzweig, S., Keshishian, A., Li, X., Kang, A., Dhamane, A. D., Luo, X., Balachander, N., Rosenblatt, L., Mardekian, J., Pan, X., Nadkarni, A., Di Fusco, M., Garcia Reeves, A. B., Yuce, H., & Lip, G. Y. H. (2019). Comparisons between Oral Anticoagulants among Older Nonvalvular Atrial Fibrillation Patients. *Journal of the American Geriatrics Society*, *67*(8), 1662–1671. https://doi.org/10.1111/jgs.15956

26. Fauchier, L., Blin, P., Sacher, F., Dureau-Pournin, C., Bernard, M. A., Lassalle, R., Droz-Perroteau, C., Dallongeville, J., & Moore, N. (2020). Reduced dose of rivaroxaban and dabigatran vs. vitamin K antagonists in very elderly patients with atrial fibrillation in a nationwide cohort study. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*, *22*(2), 205–215. https://doi.org/10.1093/europace/euz285

27. Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology*, *44*(3), 827–836. https://doi.org/10.1093/ije/dy

v098

28. Clinical Practice Research Datalink (2022, November 10). Data. https://cprd.com/data

29. Herrett, E., Thomas, S. L., Schoonen, W. M., Smeeth, L., & Hall, A. J. (2010). Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British journal of clinical pharmacology*, *69*(1), 4–14. https://doi.org/10.1111/j.1365-2125.2009.03537.x

30. Hospital Episode Statistics (HES) Admitted Patient Care and CPRD primary care data Documentation. Clinical Practice Research Datalink. https://cprd.com/sites/default/files/2022-02/Documentation_HES_APC_set22.pdf. Updated 2022. Accessed May 25, 2023.

31. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D., & Hardelid, P. (2017). Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *International journal of epidemiology*, *46*(4), 1093–1093i. https://doi.org/10.1093/ije/dyx015

32. Clinical Practice Research Datalink (2022, January 22). ONS death registration data and CPRD primary care data Documentation. https://cprd.com/sites/default/files/2022-02/Documentation_Death_set22_v2.6.pdf

33. Desai, R. J., & Franklin, J. M. (2019). Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ (Clinical research ed.)*, *367*, l5657. https://doi.org/10.1136/bmj.l5657

34. Desai, R. J., Rothman, K. J., Bateman, B. T., Hernandez-Diaz, S., & Huybrechts, K. F. (2017). A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. *Epidemiology (Cambridge, Mass.)*, *28*(2), 249–257. https://doi.org/10.1097/EDE.0000000000000595

35. Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A., & Crijns, H. J. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*, *137*(2), 263–272. https://doi.org/10.1378/chest.09-1584

36. Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*, *138*(5), 1093–1100. https://doi.org/10.1378/chest.10-0134

37. Azur, M. J., Stuart, E. A., Frangakis, C., & Leaf, P. J. (2011). Multiple imputation by chained equations: what is it and how does it work?. *International journal of methods in psychiatric research*, *20*(1), 40–49. https://doi.org/10.1002/mpr.329

38. Bonanad, C., Formiga, F., Anguita, M., Petidier, R., & Gullón, A. (2022). Oral Anticoagulant Use and Appropriateness in Elderly Patients with Atrial Fibrillation in Complex Clinical Conditions: ACONVENIENCE Study. *Journal of clinical medicine*, *11*(24), 7423. https://doi.org/10.3390/jcm11247423

39. Deng, K., Cheng, J., Rao, S., Xu, H., Li, L., & Gao, Y. (2020). Efficacy and Safety of Direct Oral Anticoagulants in Elderly Patients With Atrial Fibrillation: A Network Meta-Analysis. *Frontiers in medicine*, *7*, 107. https://doi.org/10.3389/fmed.2020.00107

40. Eikelboom, J. W., & Weitz, J. I. (2023). Direct Oral Anticoagulants in the Very Elderly. *Thrombosis and haemostasis*, *123*(4), 377–379. https://doi.org/10.1055/a-2021-8910

41. Grymonprez, M., De Backer, T. L., Bertels, X., Steurbaut, S., & Lahousse, L. (2023). Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: A nationwide cohort study. *Frontiers in pharmacology*, *14*, 1125576. https://doi.org/10.3389/fphar.2023.1125576

42. Marston, X. L., Wang, R., Yeh, Y. C., Zimmermann, L., Ye, X., Gao, X., Brüggenjürgen, B., & Unverdorben, M. (2022). Comparison of clinical outcomes of edoxaban versus apixaban, dabigatran, rivaroxaban, and vitamin K antagonists in patients with atrial fibrillation in Germany: A real-world cohort study. *International journal of cardiology*, *346*, 93–99. https://doi.org/10.1016/j.ijcard.2021.11.008

43. Malik, A. H., Yandrapalli, S., Aronow, W. S., Panza, J. A., & Cooper, H. A. (2019). Meta-Analysis of Direct-Acting Oral Anticoagulants Compared With Warfarin in Patients >75 Years of Age. *The American journal of cardiology*, *123*(12), 2051–2057. https://doi.org/10.1016/j.amjcard.2019.02.060

44. Lin, L., Lim, W. S., Zhou, H. J., Khoo, A. L., Tan, K. T., Chew, A. P., Foo, D., Chin, J. J., & Lim, B. P. (2015). Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis. Journal of the American Medical Directors Association, 16(12), . https://doi.org/10.1016/j.jamda.2015.09.008

45. Lee, S. R., Choi, E. K., Kwon, S., Han, K. D., Jung, J. H., Cha, M. J., Oh, S., & Lip, G. Y. H. (2019). Effectiveness and Safety of Contemporary Oral Anticoagulants Among Asians With Nonvalvular Atrial Fibrillation. Stroke, 50(8), 2245–2249. https://doi.org/10.1161/STROKEAHA.119.025536

46. Sanghai, S. R., Liu, W., Wang, W., Rongali, S., Orkaby, A. R., Saczynski, J. S., Rose, A. J., Kapoor, A., Li, W., Yu, H., & McManus, D. D. (2022). Prevalence of Frailty and

Associations with Oral Anticoagulant Prescribing in Atrial Fibrillation. Journal of general internal medicine, 37(4), 730–736. https://doi.org/10.1007/s11606-021-06834-1

47. Proietti, M., Camera, M., Gallieni, M., Gianturco, L., Gidaro, A., Piemontese, C., Pizzetti, G., Redaelli, F., Scimeca, B., Tadeo, C. S., Cesari, M., Bellelli, G., & Dalla Vecchia, L. A. (2022). Use and Prescription of Direct Oral Anticoagulants in Older and Frail Patients with Atrial Fibrillation: A Multidisciplinary Consensus Document. Journal of personalized medicine, 12(3), 469. https://doi.org/10.3390/jpm12030469

48. Grymonprez, M., Petrovic, M., De Backer, T. L., Steurbaut, S., & Lahousse, L. (2023). Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study. *European heart journal. Quality of care & clinical outcomes*, qcad019. Advance online publication. https://doi.org/10.1093/ehjqcco/qcad019

49. Lip, G. Y. H., Keshishian, A. V., Kang, A. L., Dhamane, A. D., Luo, X., Li, X., Balachander, N., Rosenblatt, L., Mardekian, J., Pan, X., Di Fusco, M., Garcia Reeves, A. B., Yuce, H., & Deitelzweig, S. (2021). Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study. *Journal of internal medicine*, *289*(1), 42–52. https://doi.org/10.1111/joim.13140

50. Fernández, C. S., Gullón, A., & Formiga, F. (2020). The problem of underdosing with direct-acting oral anticoagulants in elderly patients with nonvalvular atrial fibrillation. *Journal of comparative effectiveness research*, *9*(7), 509–523. https://doi.org/10.2217/cer-2019-0197

5.9 List of Figures and Table

Figure 1. Flowchart of cohort selection of edoxaban and apixaban new users with NVAF aged ≥ 80 years

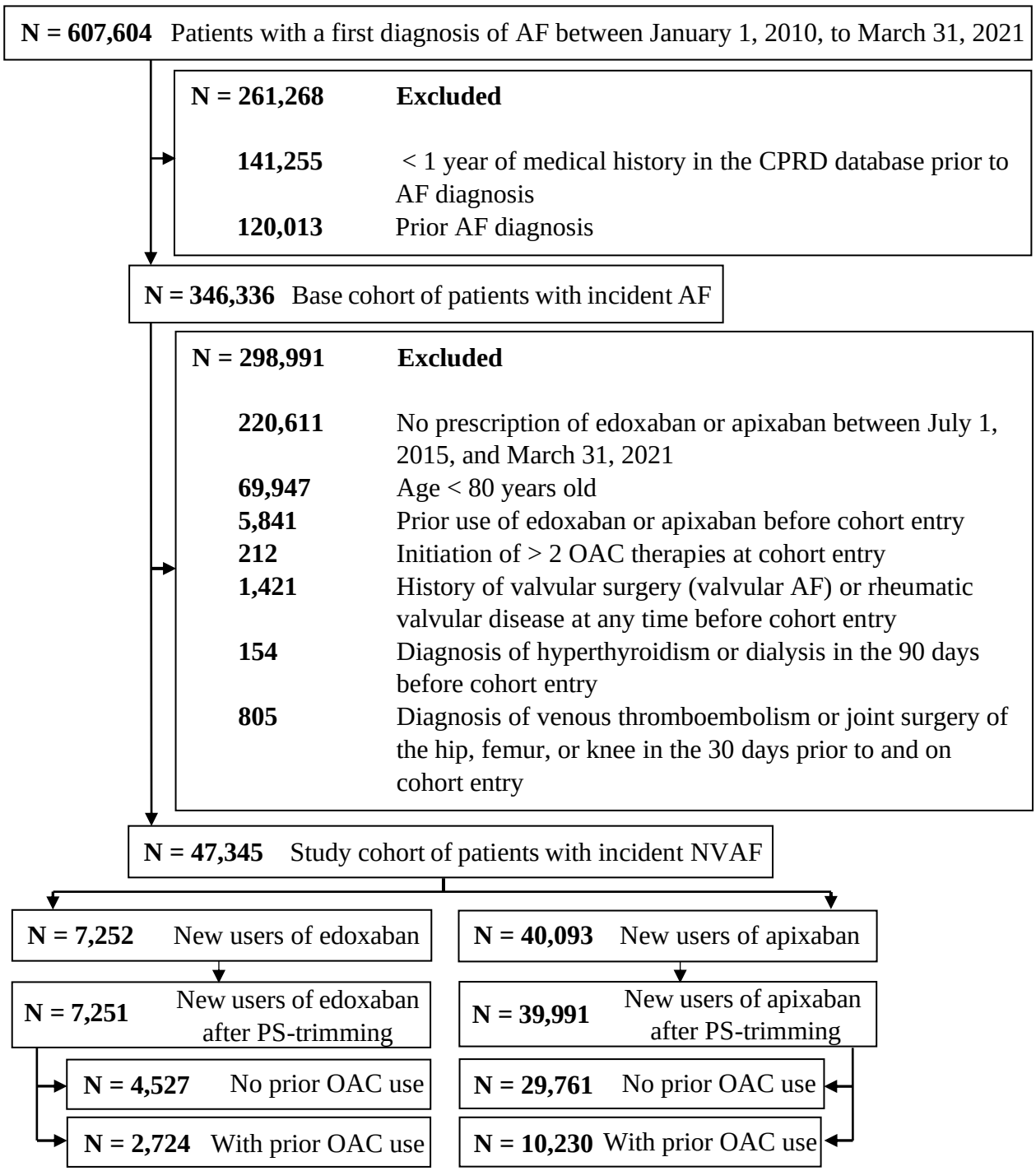
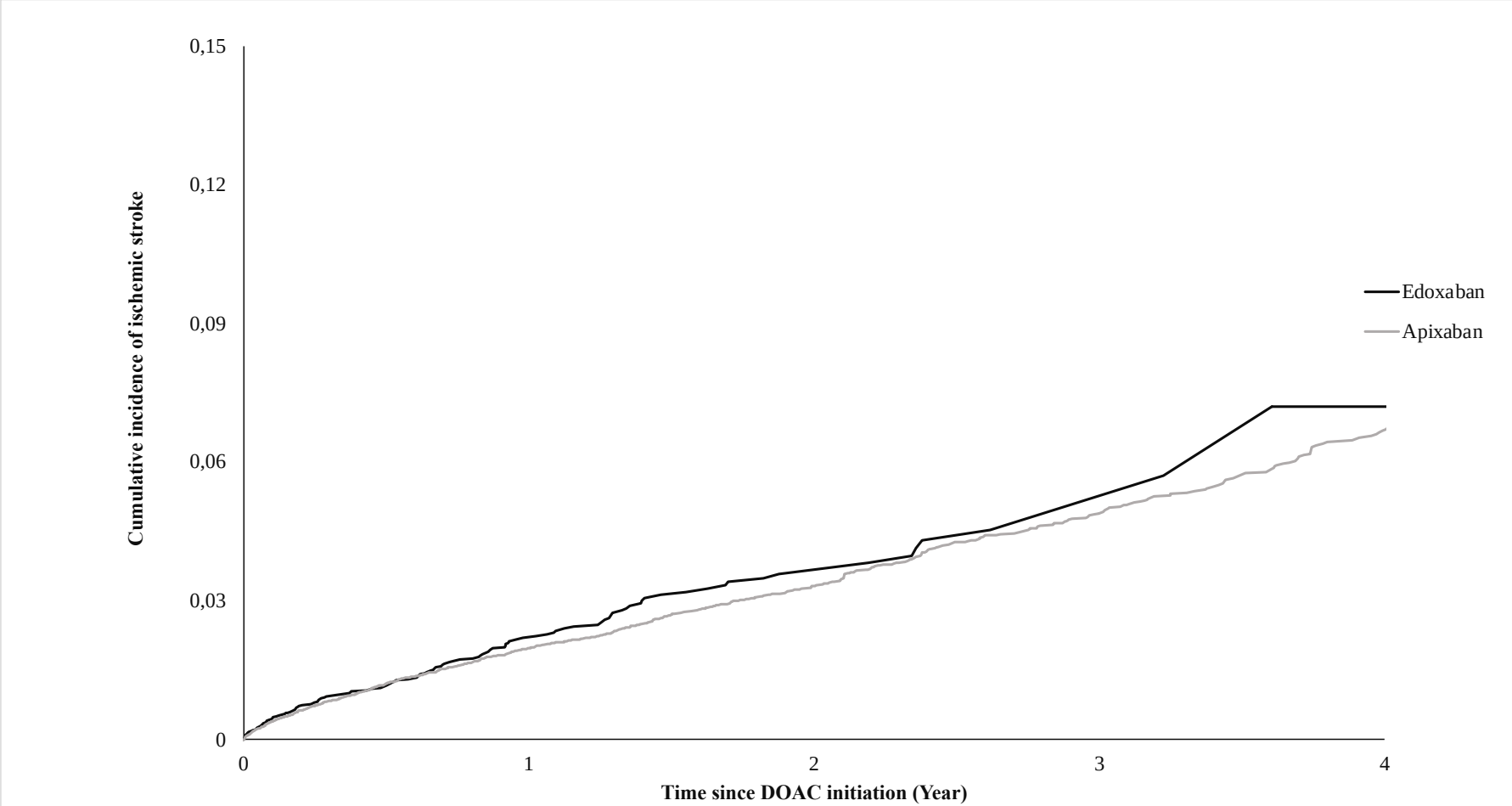


Figure 2. Weighted cumulative incidence curves of ischemic stroke for edoxaban and apixaban news users with NVAF



Number at risk

Edoxaban	7,251	2,678	922	241	27
Apixaban	39,991	15,612	5,530	2,207	797

Figure 3. Weighted cumulative incidence curves of major bleeding for edoxaban and apixaban news users with NVAF

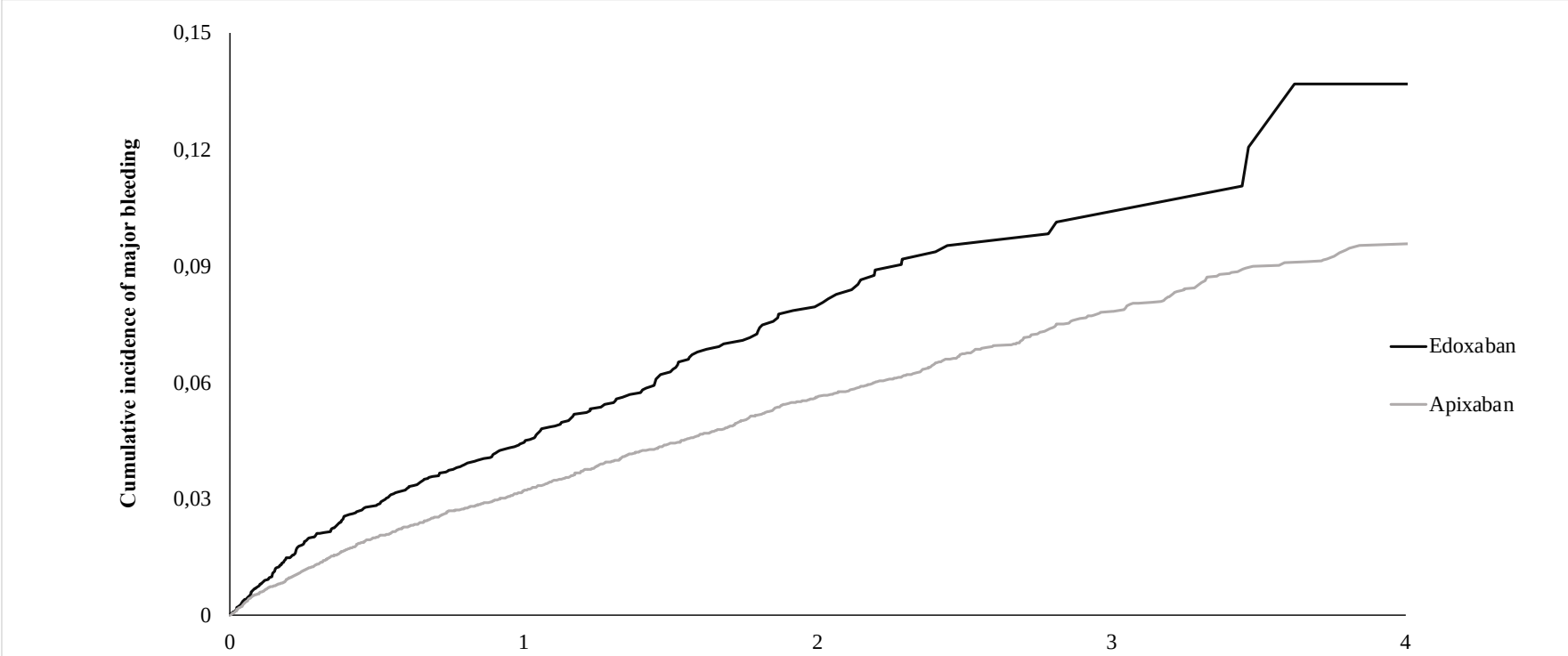


Figure 4. Forest plot summarizing the results of the stratified analyses for ischemic stroke/TIA/SE and major bleeding associated with edoxaban compared with apixaban

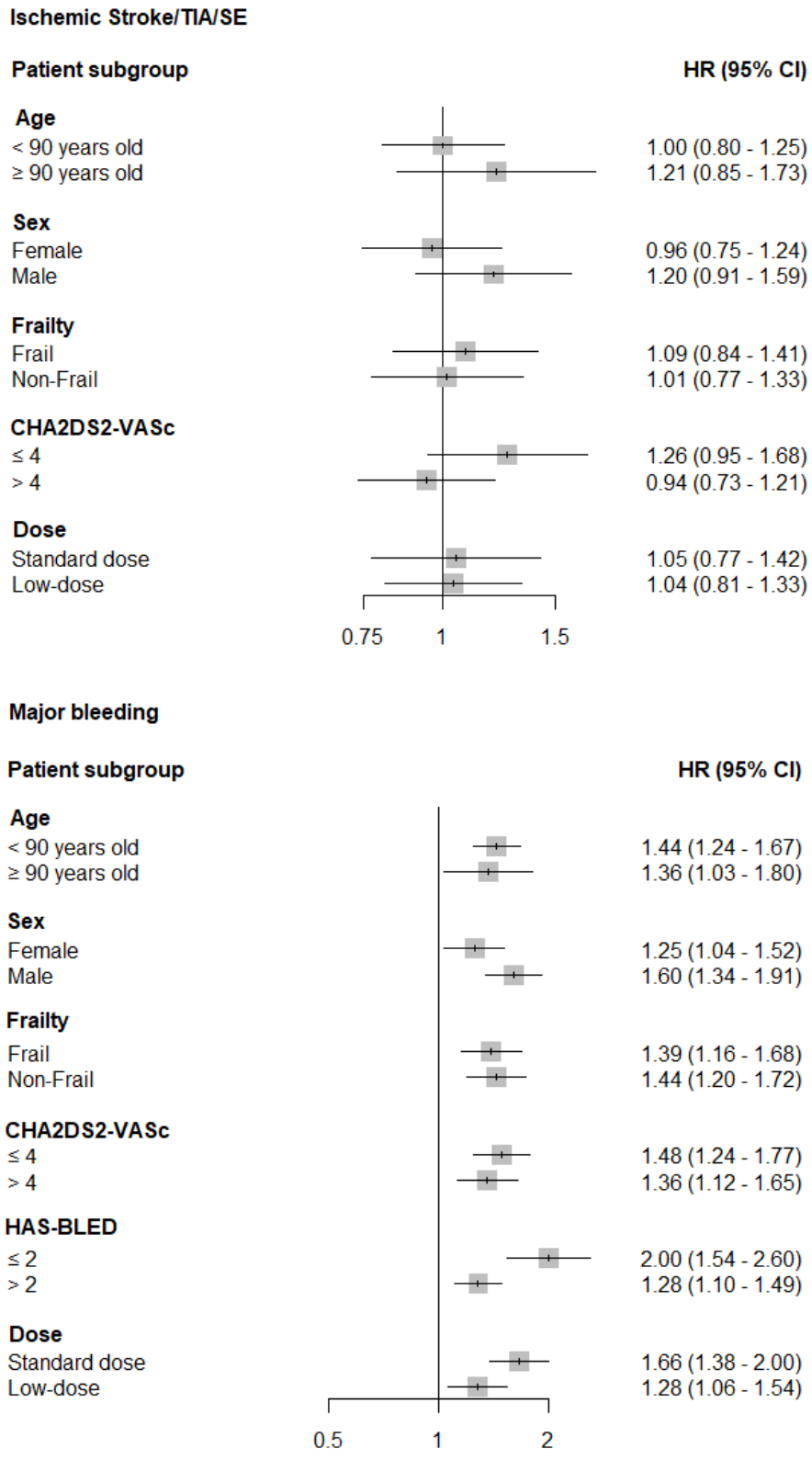


Figure 5. Forest plot summarizing the results of the primary and sensitivity analyses for ischemic stroke/TIA/SE and major bleeding associated with edoxaban compared with apixaban

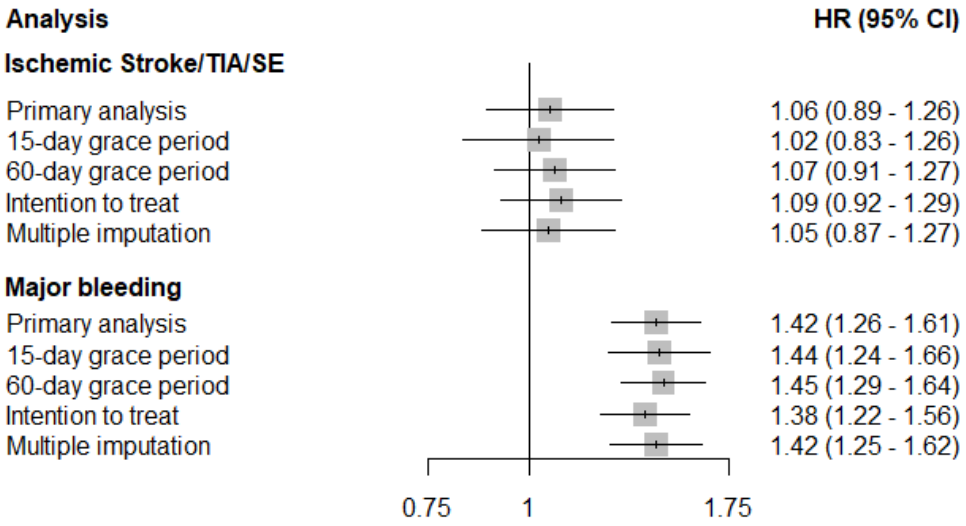


Table 1. Crude and adjusted hazard ratios of ischemic stroke, major bleeding, all-cause mortality, and composite outcome (ischemic stroke/TIA, SE, GI bleeding and ICH) associated with edoxaban compared with apixaban

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
Ischemic stroke					
Apixaban	1036	50265.40	19.22 (17.91-20.62)	1.00 [reference]	1.00 [reference]
Edoxaban	142	6859.10	20.38 (17.27-24.04)	0.92	1.06 (0.89-1.26)
Major bleeding					
Apixaban	1650	49735.88	31.21 (29.53-32.99)	1.00 [reference]	1.00 [reference]
Edoxaban	305	6731.26	45.57 (40.72-51.00)	1.26	1.42 (1.26-1.61)
All-Cause mortality					
Apixaban	6264	50849.59	113.70 (110.47-117.02)	1.00 [reference]	1.00 [reference]
Edoxaban	821	6897.39	118.43 (110.57-126.85)	0.9	1.04 (0.96-1.12)
Composite outcome					
Apixaban	1941	49815.20	36.12 (34.31-38.03)	1.00 [reference]	1.00 [reference]
Edoxaban	302	6784.57	44.34 (39.59-49.66)	1.05	1.21 (1.07-1.38)

***** Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: CI, confidence interval; GI, gastrointestinal; ICH, intracranial hemorrhage; HR, hazard ratio

5.10 Supplementary materials

SUPPLEMENTARY MATERIALS

Effectiveness and safety of edoxaban compared with apixaban in elderly patients with nonvalvular atrial fibrillation: a real-world population-based cohort study

Richard Chiv, MSc.; Sarah Beradid, MSc.; Samy Suissa, PhD, Christel Renoux, MD, PhD

TABLE OF CONTENTS

Table S1. Baseline characteristics of new edoxaban and apixaban users with NVAF (≥ 80 years) without prior OAC use before and after fine stratification weighting

Characteristics	Before fine stratification			After fine stratification		
	Edoxaban (4,527)	Apixaban (29,761)	Std. Diff.	Edoxaban (4,527)	Apixaban (29,761)	Std. Diff.
Age, years, mean (SD)	85.9 (4.3)	85.9 (4.4)	0.01	85.9 (4.3)	85.9 (4.3)	0.00
Sex, n (%)						
Females	2423 (53.5)	16652 (56.0)	0.05	2423 (53.5)	15873 (53.3)	0.00
Males	2104 (46.5)	13109 (44.0)	0.05	2104 (46.5)	13888 (46.7)	0.00
Ethnicity						
White	4133 (91.3)	27440 (92.2)	0.03	4133 (91.3)	27171 (91.3)	0.00
Others	155 (3.4)	1014 (3.4)	0.00	155 (3.4)	1019 (3.4)	0.00
Unknown	239 (5.3)	1307 (4.4)	0.04	239 (5.3)	1572 (5.3)	0.00
Calendar year of cohort entry						
2015-2018	1366 (30.2)	16970 (57.0)	0.56	1366 (30.2)	9008 (30.3)	0.00
2019	1379 (30.5)	6489 (21.8)	0.20	1379 (30.5)	8957 (30.1)	0.01
2020	1418 (31.3)	5068 (17.0)	0.34	1418 (31.3)	9378 (31.5)	0.00
2021	364 (8.0)	1234 (4.1)	0.16	364 (8.0)	2418 (8.1)	0.00
Alcohol abuse	126 (2.8)	908 (3.1)	0.02	126 (2.8)	820 (2.8)	0.00
Body mass index						
Underweight or Normal weight	1437 (31.7)	9223 (31.0)	0.02	1437 (31.7)	9390 (31.6)	0.00
Overweight	1415 (31.3)	9224 (31.0)	0.01	1415 (31.3)	9315 (31.3)	0.00
Obese	938 (20.7)	6166 (20.7)	0.00	938 (20.7)	6165 (20.7)	0.00
Unknown	737 (16.3)	5148 (17.3)	0.03	737 (16.3)	4892 (16.4)	0.00
Smoking status						
Never	1531 (33.8)	10316 (34.7)	0.02	1531 (33.8)	10021 (33.7)	0.00
Ever	2446 (54.0)	16506 (55.5)	0.03	2446 (54.0)	16123 (54.2)	0.00
Unknown	550 (12.1)	2939 (9.9)	0.07	550 (12.1)	3617 (12.2)	0.00
Comorbidities						
Hypertension	3336 (73.7)	22024 (74.0)	0.01	3336 (73.7)	21942 (73.7)	0.00
Congestive heart failure	761 (16.8)	5723 (19.2)	0.06	761 (16.8)	5048 (17.0)	0.00
Myocardial infarction	519 (11.5)	3790 (12.7)	0.04	519 (11.5)	3445 (11.6)	0.00
Coronary artery disease	1020 (22.5)	7146 (24.0)	0.04	1020 (22.5)	6741 (22.6)	0.00

Pacemaker/Implantable cardioverter defibrillator	508 (11.2)	2276 (7.6)	0.12	508 (11.2)	3355 (11.3)	0.00
CABG/Percutaneous coronary intervention	425 (9.4)	2616 (8.8)	0.02	425 (9.4)	2822 (9.5)	0.00
Ischemic stroke or transient ischemic attack	1111 (24.5)	7807 (26.2)	0.04	1111 (24.5)	7338 (24.7)	0.00
Systemic embolism	15 (0.3)	119 (0.4)	0.01	15 (0.3)	102 (0.3)	0.00
Peripheral arterial disease	228 (5.0)	1894 (6.4)	0.06	228 (5.0)	1525 (5.1)	0.00
Bleeding	1734 (38.3)	11361 (38.2)	0.00	1734 (38.3)	11385 (38.3)	0.00
Anemia or coagulation defects	1053 (23.3)	6921 (23.3)	0.00	1053 (23.3)	6968 (23.4)	0.00
Depression	871 (19.2)	5729 (19.3)	0.00	871 (19.2)	5695 (19.1)	0.00
Cancer (other than non-melanoma skin cancer)	1072 (23.7)	6858 (23.0)	0.02	1072 (23.7)	7062 (23.7)	0.00
Dementia or mild cognitive impairment	467 (10.3)	2756 (9.3)	0.04	467 (10.3)	3077 (10.3)	0.00
Parkinson’s disease	73 (1.6)	451 (1.5)	0.01	73 (1.6)	470 (1.6)	0.00
History of falls	1759 (38.9)	11330 (38.1)	0.02	1759 (38.9)	11516 (38.7)	0.00
Chronic obstructive pulmonary disease	1002 (22.1)	7094 (23.8)	0.04	1002 (22.1)	6596 (22.2)	0.00
Acute kidney injury	297 (6.6)	2227 (7.5)	0.04	297 (6.6)	1994 (6.7)	0.01
Chronic kidney disease	1637 (36.2)	11471 (38.5)	0.05	1637 (36.2)	10832 (36.4)	0.00
Liver disease	115 (2.5)	806 (2.7)	0.01	115 (2.5)	752 (2.5)	0.00
Diabetes mellitus	1283 (28.3)	8467 (28.4)	0.00	1283 (28.3)	8438 (28.4)	0.00
Time from NVAF diagnosis to DOAC initiation						
< 30 days	2912 (64.3)	19609 (65.9)	0.03	2912 (64.3)	19125 (64.3)	0.00
30-180 days	1009 (22.3)	5759 (19.4)	0.07	1009 (22.3)	6623 (22.3)	0.00
≥ 180 days	606 (13.4)	4393 (14.8)	0.04	606 (13.4)	4013 (13.5)	0.00
Comedications						
Metformin	428 (9.5)	3048 (10.2)	0.03	428 (9.5)	2792 (9.4)	0.00
Sulfonylureas	170 (3.8)	1293 (4.3)	0.03	170 (3.8)	1094 (3.7)	0.00
Glucagon-like peptide 1 receptor agonists[†]	S	41 (0.1)	0.01	S	25 (0.1)	0.00
Dipeptidyl peptidase 4 inhibitors	155 (3.4)	947 (3.2)	0.01	155 (3.4)	1019 (3.4)	0.00
Sodium-glucose cotransporter-2	11 (0.2)	43 (0.1)	0.02	11 (0.2)	67 (0.2)	0.00
Insulin	138 (3.0)	954 (3.2)	0.01	138 (3.0)	919 (3.1)	0.00
Other antidiabetic drugs[†]	10 (0.2)	121 (0.4)	0.03	10 (0.2)	63 (0.2)	0.00
Beta-blockers	1956 (43.2)	12669 (42.6)	0.01	1956 (43.2)	12830 (43.1)	0.00
Thiazides	744 (16.4)	5288 (17.8)	0.04	744 (16.4)	4852 (16.3)	0.00
Other diuretics	1268 (28.8)	9104 (30.6)	0.06	1268 (28.0)	8348 (28.1)	0.00
Angiotensin-converting enzyme inhibitors	1448 (32.0)	9994 (33.6)	0.03	1448 (32.0)	9493 (31.9)	0.00

Angiotensin II receptor blockers	864 (19.1)	5503 (18.5)	0.02	864 (19.1)	5721 (19.2)	0.00
Calcium channel blockers	1817 (40.1)	11624 (39.1)	0.02	1817 (40.1)	11907 (40.0)	0.00
Antiarrhythmics	97 (2.1)	745 (2.5)	0.02	97 (2.1)	642 (2.2)	0.00
Digoxin	141 (3.1)	1198 (4.0)	0.05	141 (3.1)	930 (3.1)	0.00
Antiplatelet agents	1953 (43.1)	13951 (46.9)	0.08	1953 (43.1)	12858 (43.2)	0.00
Lipid-lowering drugs	2370 (52.4)	16340 (54.9)	0.05	2370 (52.4)	15581 (52.4)	0.00
Non-steroidal anti-inflammatory drugs	1017 (22.5)	7536 (25.3)	0.07	1017 (22.5)	6658 (22.4)	0.00
Opioids	1397 (30.9)	9907 (33.3)	0.05	1397 (30.9)	9172 (30.8)	0.00
Systemic corticosteroids	621 (13.7)	4465 (15.0)	0.04	621 (13.7)	4104 (13.8)	0.00
Antidepressants	836 (18.5)	5757 (19.3)	0.02	836 (18.5)	5473 (18.4)	0.00
Antipsychotics	222 (4.9)	1595 (5.4)	0.02	222 (4.9)	1452 (4.9)	0.00
Benzodiazepines and hypnotics	402 (8.9)	2895 (9.7)	0.03	402 (8.9)	2617 (8.8)	0.00
Antiepileptic drugs	379 (8.4)	2518 (8.5)	0.00	379 (8.4)	2495 (8.4)	0.00
Proton pump inhibitors	2094 (46.3)	13993 (47.0)	0.02	2094 (46.3)	13759 (46.2)	0.00
H_2 blockers	238 (5.3)	1649 (5.5)	0.01	238 (5.3)	1586 (5.3)	0.00
Hormone replacement therapy‡	37 (0.8)	224 (0.8)	0.01	37 (0.8)	241 (0.8)	0.00
Oral anticoagulants						
Direct oral anticoagulants	-	-	-	-	-	-
Vitamin K antagonists	-	-	-	-	-	-
Number of hospitalizations						
0	2154 (47.6)	11101 (37.3)	0.21	2154 (47.6)	14187 (47.7)	0.00
1	1489 (32.9)	11677 (39.2)	0.13	1489 (32.9)	9767 (32.8)	0.00
≥ 2	884 (19.5)	6983 (23.5)	0.10	884 (19.5)	5807 (19.5)	0.00

*****Values are presented as number (%), unless otherwise specified

†Some values are supressed (S) due to small number (n < 5) as per confidentiality agreement with the data custodians

‡Percentage in women

Abbreviations: OAC,. oral anticoagulant; SD., standard deviation; Std. Diff., standardized difference; CABG., coronary artery bypass surgery

Table S2. Baseline characteristics of new edoxaban and apixaban users with NVAF (≥ 80 years) with prior OAC use before and after fine stratification weighting

Characteristics	Before fine stratification			After fine stratification		
	Edoxaban (2,724)	Apixaban (10,230)	Std. Diff.	Edoxaban (2,724)	Apixaban (10,230)	Std. Diff.
Age, years, mean (SD)	85.8 (4.3)	85.9 (4.2)	0.01	85.8 (4.3)	85.8 (4.3)	0.00
Sex, n (%)						
Females	1434 (52.6)	5602 (54.8)	0.04	1434 (52.6)	5370 (52.5)	0.00
Males	1290 (47.4)	4628 (45.2)	0.04	1290 (47.4)	4861 (47.5)	0.00
Ethnicity						
White	2559 (93.9)	9617 (94.0)	0.00	2559 (93.9)	9609 (93.9)	0.00
Others	72 (2.6)	312 (3.0)	0.02	72 (2.6)	265 (2.6)	0.00
Unknown	93 (3.4)	301 (2.9)	0.03	93 (3.4)	356 (3.5)	0.00
Calendar year of cohort entry						
2015-2018	731 (26.8)	5959 (58.3)	0.67	731 (26.8)	2803 (27.4)	0.01
2019	714 (26.2)	1919 (18.8)	0.18	714 (26.2)	2562 (25.0)	0.03
2020	1176 (43.2)	2058 (20.1)	0.51	1176 (43.2)	4495 (43.9)	0.02
2021	103 (3.8)	294 (2.9)	0.05	103 (3.8)	370 (3.6)	0.01
Alcohol abuse	56 (2.1)	292 (2.9)	0.05	56 (2.1)	210 (2.1)	0.00
Body mass index						
Underweight or Normal weight	912 (33.5)	3325 (32.5)	0.02	912 (33.5)	3504 (34.2)	0.02
Overweight	873 (32.0)	3302 (32.3)	0.00	873 (32.0)	3200 (31.3)	0.02
Obese	587 (21.5)	2280 (22.3)	0.02	587 (21.5)	2191 (21.4)	0.00
Unknown	352 (12.9)	1323 (12.9)	0.00	352 (12.9)	1336 (13.1)	0.00
Smoking status						
Never	884 (32.5)	3447 (33.7)	0.03	884 (32.5)	3305 (32.3)	0.00
Ever	1540 (56.5)	5929 (58.0)	0.03	1540 (56.5)	5780 (56.5)	0.00
Unknown	300 (11.0)	854 (8.3)	0.09	300 (11.0)	1145 (11.2)	0.01
Comorbidities						
Hypertension	2013 (73.9)	7784 (76.1)	0.05	2013 (73.9)	7552 (73.8)	0.00
Congestive heart failure	739 (27.1)	3138 (30.7)	0.08	739 (27.1)	2789 (27.3)	0.00
Myocardial infarction	309 (11.3)	1452 (14.2)	0.09	309 (11.3)	1161 (11.3)	0.00
Coronary artery disease	715 (26.2)	2958 (28.9)	0.06	715 (26.2)	2675 (26.2)	0.00

Pacemaker/Implantable cardioverter defibrillator	391 (14.4)	1399 (13.7)	0.02	391 (14.4)	1460 (14.3)	0.00
CABG/Percutaneous coronary intervention	283 (10.4)	1089 (10.6)	0.01	283 (10.4)	1066 (10.4)	0.00
Prior ischemic stroke or transient ischemic attack	726 (26.7)	3250 (31.8)	0.11	726 (26.7)	2676 (26.2)	0.01
Systemic embolism	17 (0.6)	83 (0.8)	0.02	17 (0.6)	69 (0.7)	0.01
Peripheral arterial disease	168 (6.2)	772 (7.5)	0.05	168 (6.2)	624 (6.1)	0.00
Prior bleeding events	1265 (46.4)	5003 (48.9)	0.05	1265 (46.4)	4728 (46.2)	0.00
Anemia or coagulation defects	641 (23.5)	2884 (28.2)	0.11	641 (23.5)	2381 (23.3)	0.01
Depression	545 (20.0)	2051 (20.0)	0.00	545 (20.0)	2031 (19.9)	0.00
Cancer (other than non-melanoma skin cancer)	660 (24.2)	2626 (25.7)	0.03	660 (24.2)	2485 (24.3)	0.00
Dementia and mild cognitive impairment	293 (10.8)	1046 (10.2)	0.02	293 (10.8)	1074 (10.5)	0.01
Parkinson’s disease	37 (1.4)	163 (1.6)	0.02	37 (1.4)	143 (1.4)	0.00
History of falls	1095 (40.2)	4481 (43.8)	0.07	1095 (40.2)	4122 (40.3)	0.00
Chronic obstructive pulmonary disease	648 (23.8)	2669 (26.1)	0.05	648 (23.8)	2439 (23.8)	0.00
Acute kidney injury	247 (9.1)	972 (9.5)	0.02	247 (9.1)	891 (8.7)	0.01
Chronic kidney disease	1163 (42.7)	4863 (47.5)	0.10	1163 (42.7)	4333 (42.4)	0.01
Liver disease	86 (3.2)	292 (2.9)	0.02	86 (3.2)	326 (3.2)	0.00
Diabetes mellitus	859 (31.5)	3358 (32.8)	0.03	859 (31.5)	3208 (31.4)	0.00
Time from NVAF diagnosis to DOAC initiation						
< 30 days	44 (1.6)	354 (3.5)	0.12	44 (1.6)	168 (1.6)	0.00
30-180 days	117 (4.3)	844 (8.3)	0.16	117 (4.3)	451 (4.4)	0.01
≥ 180 days	2563 (94.1)	9032 (88.3)	0.21	2563 (94.1)	9610 (93.9)	0.01
Comedications						
Metformin	263 (9.7)	1156 (11.3)	0.05	263 (9.7)	997 (9.7)	0.00
Sulfonylureas	116 (4.3)	494 (4.8)	0.03	116 (4.3)	426 (4.2)	0.00
Glucagon-like peptide 1 receptor agonists†	S	20 (0.2)	0.01	S	14 (0.1)	0.00
Dipeptidyl peptidase 4 inhibitors	104 (3.8)	431 (4.2)	0.02	104 (3.8)	364 (3.6)	0.01
Sodium-glucose cotransporter-2	8 (0.3)	19 (0.2)	0.02	8 (0.3)	29 (0.3)	0.00
Insulin	82 (3.0)	408 (4.0)	0.05	82 (3.0)	293 (2.9)	0.01
Other antidiabetic drugs†	S	24 (0.2)	0.03	S	11 (0.1)	0.00
Beta-blockers	1814 (66.6)	6792 (66.4)	0.00	1814 (66.6)	6819 (66.7)	0.00
Thiazides	358 (13.1)	1322 (12.9)	0.01	358 (13.1)	1315 (12.9)	0.01
Other diuretics	1158 (42.5)	5072 (49.6)	0.14	1158 (42.5)	4345 (42.5)	0.00
Angiotensin-converting enzyme inhibitors	1004 (36.9)	3960 (38.7)	0.04	1004 (36.9)	3778 (36.9)	0.00

Angiotensin II receptor blockers	545 (20.0)	2153 (21.0)	0.03	545 (20.0)	2061 (20.1)	0.00
Calcium channel blockers	881 (32.3)	3440 (33.6)	0.03	881 (32.3)	3323 (32.5)	0.00
Antiarrhythmics	192 (7.0)	707 (6.9)	0.01	192 (7.0)	718 (7.0)	0.00
Digoxin	459 (16.9)	1909 (18.7)	0.05	459 (16.9)	1710 (16.7)	0.00
Antiplatelet agents	264 (9.7)	1596 (15.6)	0.18	264 (9.7)	1001 (9.8)	0.00
Lipid-lowering drugs	1561 (57.3)	6007 (58.7)	0.03	1561 (57.3)	5832 (57.0)	0.01
Non-steroidal anti-inflammatory drugs	497 (18.2)	2333 (22.8)	0.11	497 (18.2)	1884 (18.4)	0.00
Opioids	877 (32.2)	3963 (38.7)	0.14	877 (32.2)	3290 (32.2)	0.00
Systemic corticosteroids	364 (13.4)	1624 (15.9)	0.07	364 (13.4)	1352 (13.2)	0.00
Antidepressants	467 (17.1)	2011 (19.7)	0.06	467 (17.1)	1772 (17.3)	0.00
Antipsychotics	109 (4.0)	580 (5.7)	0.08	109 (4.0)	408 (4.0)	0.00
Benzodiazepines and hypnotics	241 (8.8)	1095 (10.7)	0.06	241 (8.8)	937 (9.2)	0.01
Antiepileptic drugs	251 (9.2)	1051 (10.3)	0.04	251 (9.2)	925 (9.0)	0.01
Proton pump inhibitors	1178 (43.2)	5021 (49.1)	0.12	1178 (43.2)	4413 (43.1)	0.00
H_2 blockers	137 (5.0)	642 (6.3)	0.05	137 (5.0)	527 (5.2)	0.01
Hormone replacement therapy‡	15 (0.6)	78 (0.8)	0.03	15 (0.6)	52 (0.5)	0.01
Oral anticoagulants						
Direct oral anticoagulants	766 (28.1)	3289 (32.2)	0.09	766 (28.1)	2874 (28.1)	0.00
Vitamin K antagonists	2001 (73.5)	7233 (70.7)	0.06	2001 (73.5)	7519 (73.5)	0.00
Number of hospitalizations						
0	1664 (61.1)	4287 (41.9)	0.39	1664 (61.1)	6319 (61.8)	0.01
1	597 (21.9)	3001 (29.3)	0.17	597 (21.9)	2205 (21.6)	0.01
≥ 2	463 (17.0)	2942 (28.8)	0.28	463 (17.0)	1705 (16.7)	0.01

*Values are presented as number (%), unless otherwise specified

†Some values are supressed (S) due to small number (n < 5) as per confidentiality agreement with the data custodians

‡ Percentage in women

Abbreviations: OAC,. oral anticoagulant; SD., standard deviation; Std. Diff., standardized difference; CABG., coronary artery bypass surgery

Table S3. Crude and adjusted hazard ratios of ischemic stroke associated with edoxaban compared with apixaban in stratified analyses

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI)†
< 90 years old					
Apixaban	779	41467.28	17.32 (15.96-18.79)	1.00 [reference]	1.00 [reference]
Edoxaban	101	5592.24	17.64 (14.50-21.47)	0.87	1.00 (0.80-1.25)
≥ 90 years old					
Apixaban	257	8798.12	28.09 (24.45-32.27)	1.00 [reference]	1.00 [reference]
Edoxaban	41	1266.86	32.43 (23.85-44.10)	1.08	1.21 (0.85-1.73)
Female					
Apixaban	613	28373.61	20.71 (18.88-22.71)	1.00 [reference]	1.00 [reference]
Edoxaban	78	3712.62	20.44 (16.35-25.57)	0.89	0.96 (0.75-1.24)
Male					
Apixaban	423	21891.79	17.41 (15.61-19.42)	1.00 [reference]	1.00 [reference]
Edoxaban	64	3146.47	20.29 (15.86-25.95)	0.97	1.20 (0.91-1.59)
Frail					
Apixaban	380	16657.35	21.13 (19.02-23.48)	1.00 [reference]	1.00 [reference]
Edoxaban	78	3327.18	23.52 (18.82-29.39)	0.97	1.09 (0.84-1.41)
Non-frail					
Apixaban	656	33608.05	17.86 (16.25-19.64)	1.00 [reference]	1.00 [reference]
Edoxaban	64	3531.92	17.61 (13.76-22.53)	0.86	1.01 (0.77-1.33)
CHA_2DS_2-VASc ≤ 4					
Apixaban	353	27073.37	12.89 (11.51-14.43)	1.00 [reference]	1.00 [reference]
Edoxaban	64	4011.24	15.79 (12.34-20.21)	1.18	1.26 (0.95-1.68)
CHA_2DS_2-VASc > 4					

Apixaban	683	23192.03	27.94 (25.53-30.57)	1.00 [reference]	1.00 [reference]
Edoxaban	78	2847.85	27.07 (21.66-33.84)	0.84	0.94 (0.73-1.21)

***** Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: CI, confidence interval; HR, hazard ratio; CHA_2DS_2-VASc, congestive heart failure, arterial hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65-74 years, female sex

Table S4. Crude and adjusted hazard ratios of ischemic stroke associated with edoxaban compared with apixaban by history of OAC use

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
No history of OAC use					
Apixaban	721	38080.40	18.47 (17.01-20.06)	1.00 [reference]	1.00 [reference]
Edoxaban	85	4340.38	19.58 (15.83-24.22)	0.98	1.07 (0.86-1.34)
History of OAC use					
Apixaban	315	12185.00	21.34 (18.66-24.42)	1.00 [reference]	1.00 [reference]
Edoxaban	57	2518.72	22.63 (17.46-29.34)	0.84	1.03 (0.77-1.38)

***** Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: OACs, oral anticoagulants; CI, confidence interval; HR, hazard ratio

Table S5. Crude and adjusted hazard ratios of ischemic stroke associated with edoxaban compared with apixaban by dose

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
Standard dose					
Apixaban	432	24619.64	15.45 (13.82-17.26)	1.00 [reference]	1.00 [reference]
Edoxaban	53	3093.41	16.39 (12.49-21.52)	0.86	1.05 (0.77-1.42)
Low-dose					
Apixaban	603	25639.76	22.72 (20.75-24.89)	1.00 [reference]	1.00 [reference]
Edoxaban	89	3763.64	23.54 (19.11-29.00)	0.95	1.04 (0.81-1.33)

***** Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: CI, confidence interval; HR, hazard ratio

Table S6. Crude and adjusted hazard ratios of major bleeding associated with edoxaban compared with apixaban in stratified analyses

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
< 90 years old					
Apixaban	1309	40985.39	29.53 (27.73-31.45)	1.00 [reference]	1.00 [reference]
Edoxaban	238	5479.75	43.62 (38.40-49.55)	1.24	1.44 (1.24-1.67)
≥ 90 years old					
Apixaban	341	8750.49	39.04 (34.70-43.93)	1.00 [reference]	1.00 [reference]
Edoxaban	67	1251.51	54.13 (42.58-68.81)	1.31	1.36 (1.03-1.80)
Female					
Apixaban	840	28137.46	29.07 (26.88-31.43)	1.00 [reference]	1.00 [reference]
Edoxaban	137	3662.53	37.72 (31.89-44.62)	1.15	1.25 (1.04-1.52)
Male					
Apixaban	810	21598.42	33.72 (31.17-36.48)	1.00 [reference]	1.00 [reference]
Edoxaban	168	3068.73	54.92 (47.18-63.92)	1.35	1.60 (1.34-1.91)
Frail					
Apixaban	619	16497.79	34.61 (31.85-37.60)	1.00 [reference]	1.00 [reference]
Edoxaban	156	3277.80	48.19 (41.17-56.41)	1.21	1.39 (1.16-1.68)
Non-frail					
Apixaban	1031	33238.09	28.88 (26.80-31.12)	1.00 [reference]	1.00 [reference]
Edoxaban	149	3453.45	43.23 (36.80-50.78)	1.28	1.44 (1.20-1.72)
CHA_2DS_2-VASc ≤ 4					
Apixaban	830	26699.45	29.07 (26.96-31.35)	1.00 [reference]	1.00 [reference
Edoxaban	171	3935.06	43.61 (37.52-50.70)	1.29	1.48 (1.24-1.77)
CHA_2DS_2-VASc > 4					

Apixaban	820	23036.43	34.09 (31.41-37.00)	1.00 [reference]	1.00 [reference]
Edoxaban	134	2796.19	48.37 (40.82-57.32)	1.24	1.36 (1.12-1.65)
HAS-BLED ≤ 2					
Apixaban	308	11469.10	23.24 (20.52-26.33)	1.00 [reference]	1.00 [reference]
Edoxaban	83	1851.01	45.17 (36.38-56.09)	1.57	2.00 (1.54-2.60)
HAS-BLED > 2					
Apixaban	1342	38266.78	34.09 (32.04-36.27)	1.00 [reference]	1.00 [reference]
Edoxaban	222	4880.25	45.70 (40.05-52.14)	1.19	1.28 (1.10-1.49)

*****Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: CI, confidence interval; HR, hazard ratio; CHA_2DS_2-VASc, congestive heart failure, arterial hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65-74 years, female sex; HAS-BLED (modified), hypertension, abnormal renal/liver function, ischemic stroke, bleeding, elderly > 65 years, antiplatelet/non-steroidal anti-inflammatory drug use or alcohol abuse

Table S7. Crude and adjusted hazard ratios of major bleeding associated with edoxaban compared with apixaban by history of OAC use

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
No history of OAC use					
Apixaban	1195	37718.08	31.93 (29.98-34.00)	1.00 [reference]	1.00 [reference]
Edoxaban	193	4252.56	45.38 (39.41-52.26)	1.34	1.40 (1.20-1.63)
History of OAC use					
Apixaban	455	12017.79	29.30 (26.11-32.88)	1.00 [reference]	1.00 [reference]
Edoxaban	112	2478.70	45.18 (37.55-54.38)	1.12	1.48 (1.19-1.84)

***** Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: OACs, oral anticoagulants; CI, confidence interval; HR, hazard ratio

Table S8. Crude and adjusted hazard ratios of major bleeding associated with edoxaban compared with apixaban by dose

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
Standard dose					
Apixaban	825	24299.85	30.75 (28.40-33.30)	1.00 [reference]	1.00 [reference]
Edoxaban	154	3013.31	52.04 (44.42-60.96)	1.39	1.66 (1.38-2.00)
Low-dose					
Apixaban	826	25434.75	30.70 (28.38-33.20)	1.00 [reference]	1.00 [reference]
Edoxaban	151	3715.90	40.57 (34.57-47.61)	1.14	1.28 (1.06-1.54)

* Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: CI, confidence interval; HR, hazard ratio

Table S9. Crude and adjusted hazard ratios of major bleeding associated with edoxaban compared with apixaban by type of bleeding

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
GI bleeding					
Apixaban	694	50415.82	12.72 (11.67-13.87)	1.00 [reference]	1.00 [reference]
Edoxaban	135	6824.73	19.89 (16.80-23.56)	1.29	1.53 (1.27-1.85)
ICH					
Apixaban	233	50825.35	4.15 (3.57-4.82)	1.00 [reference]	1.00 [reference]
Edoxaban	29	6895.95	4.25 (2.95-6.12)	0.90	0.95 (0.63-1.42)
Other bleeding					
Apixaban	723	50193.89	14.02 (12.91-15.23)	1.00 [reference]	1.00 [reference]
Edoxaban	141	6805.36	20.81 (17.64-24.56)	1.32	1.45 (1.21-1.74)

* Per 1000 person-years

†Adjusted using fine stratification weighting and inverse probability of censoring weighting

Abbreviations: GI, gastrointestinal; ICH, intracranial hemorrhage; CI, confidence interval; HR, hazard ratio

Table S10. Crude and adjusted hazard ratios of ischemic stroke associated with edoxaban compared with apixaban in sensitivity analyses

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
15-day grace period					
Apixaban	758	35739.57	19.65 (18.13-21.29)	1.00 [reference]	1.00 [reference]
Edoxaban	110	5375.38	20.20 (16.74-24.38)	0.90	1.02 (0.83-1.26)
60-day grace period					
Apixaban	1267	60462.83	19.66 (18.44-20.97)	1.00 [reference]	1.00 [reference]
Edoxaban	170	7860.19	21.26 (18.28-24.74)	0.95	1.07 (0.91-1.27)
Intention-to-treat‡					
Apixaban	1082	43920.32	22.44 (21.01-23.98)	1.00 [reference]	1.00 [reference]
Edoxaban	175	7076.97	24.46 (21.07-28.39)	0.97	1.09 (0.92-1.29)
Multiple imputations					
Apixaban	1035	50272.28	19.27 (17.87-20.67)	1.00 [reference]	1.00 [reference]
Edoxaban	142	6852.62	20.37 (17.00-23.74)	0.92	1.05 (0.87-1.27)

* Per 1000 person-years
†Adjusted using fine stratification weighting
‡Follow-up restricted to 1.5 years
Abbreviations: CI, confidence interval; HR, hazard ratio

Table S11. Crude and adjusted hazard ratios of major bleeding associated with edoxaban compared with apixaban in sensitivity analyses

Exposure	Events	Person-years	Weighted incidence rate* (95% CI)	Crude HR	Adjusted HR (95% CI) †
15-day grace period					
Apixaban	1236	35440.00	32.72 (30.73-34.83)	1.00 [reference]	1.00 [reference]
Edoxaban	248	5298.81	47.24 (41.69-53.52)	1.26	1.44 (1.24-1.66)
60-day grace period					
Apixaban	1964	59743.97	31.06 (29.51-32.70)	1.00 [reference]	1.00 [reference]
Edoxaban	353	7709.08	46.07 (41.49-51.15)	1.28	1.45 (1.29-1.64)
Intention-to-treat‡					
Apixaban	1639	43466.77	34.51 (32.71-36.41)	1.00 [reference]	1.00 [reference]
Edoxaban	329	6948.44	47.70 (42.80-53.16)	1.21	1.38 (1.22-1.56)
Multiple imputations					
Apixaban	1649	49726.43	31.45 (29.70-33.20)	1.00 [reference]	1.00 [reference]
Edoxaban	305	6729.42	45.56 (40.43-50.69)	1.26	1.42 (1.25-1.62)

* Per 1000 person-years
†Adjusted using fine stratification weighting
‡Follow-up restricted to 1.5 years
Abbreviations: CI, confidence interval; HR, hazard ratio

Chapter 6: Discussion

Following the manuscript of the population-based cohort study presented in Chapter 5, this chapter summarizes the key findings of this thesis, offers a comprehensive evaluation of the strengths and limitations of this thesis, and expands further on the potential implications of the findings (including future perspectives).

6.1 Summary of the objectives and main results

This thesis evaluated the effectiveness (prevention of ischemic stroke/TIA/SE) and safety (risk of MB) of edoxaban compared with apixaban in very elderly patients aged 80 years and older with NVAF. As detailed in Chapter 2, OACs are still underprescribed in this population, despite the known net clinical benefit of OACs in older age groups [5-6]. In the absence of RCTs and of further observational studies with head-to-head DOAC comparisons in this population, clinical uncertainties regarding the optimal choice of DOACs for this population will remain [297, 299]. In view of the more recent approval of edoxaban, its effectiveness and safety compared with apixaban in the very elderly with NVAF remain a knowledge gap that must be addressed to inform clinicians on the prescription of DOAC for this vulnerable population. Thus, a large population-based cohort study on patients with NVAF over the age of 80 was conducted to evaluate the comparative effectiveness and safety of edoxaban with apixaban.

This population-based cohort study is the first to have assessed the effectiveness and safety of edoxaban compared with apixaban in very elderly patients with NVAF. Using the UK CPRD database, this study showed that the use of edoxaban was as effective as apixaban to prevent the risk of ischemic stroke/TIA/SE. However, edoxaban was associated with an increased risk of major bleeding compared with apixaban. The risk of the composite outcome was also higher in patients treated with edoxaban compared with those treated with apixaban, but the risk of all-cause mortality did not differ between exposure groups. The results of the sensitivity analyses were concordant with those of the primary analyses.

6.2 Strengths and limitations

This section provides a more thorough description of the strengths and limitations pertaining to the use of the UK CPRD database and to the cohort study that were discussed in Chapter 5.

Many strengths can be denoted in this study. First, the established high quality and validity of the data recorded in the CPRD database allowed us to assemble a large and clearly defined study population of 47,242 patients diagnosed with incident NVAF aged 80 years and older. Data from the CPRD have been shown to be representative of the general population with respect to age, sex and ethnicity. Among the potential list of relevant confounders that we adjusted for, the CPRD also collects data on lifestyle factors such as smoking status and alcohol consumption that are often unavailable in claims databases. This thesis was also able to consider frailty status, a relevant health measure in the very elderly, but rarely available in other databases. Linkage of the CPRD databases (Gold and Aurum) to the HES and ONS datasets to define the studied outcomes minimized potential outcome misclassification. Also, the use of a new user study design avoided biases related to the inclusion of prevalent users. The use of apixaban as an active comparator further decreased potential residual confounding. Next, inverse probability of censoring weighting was used to account for potential informative censoring related to treatment discontinuation or switching to another anticoagulant and for death as a competing risk in the primary analyses. This potential issue was also explored in a sensitivity analysis with exposure defined at cohort entry (analogous to an ITT) with a follow-up restricted to one year and a half.

This thesis was nevertheless affected by some limitations. First, the observational nature of this thesis makes it prone to potential residual confounding that was mitigated using propensity score fine stratification and weighting to balance covariate distribution between the two treatment groups. Second, exposure to edoxaban and apixaban were only based on prescriptions issued by general practitioners. It was also impossible to determine if these prescriptions were filled at the pharmacy and to verify the patient's level of treatment compliance. There was also no information on prescriptions issued by specialists. Nevertheless, this potential exposure misclassification is not expected to be differential between users of edoxaban and apixaban. Moreover, results from sensitivity analyses, where two different definitions of exposure (15- and 60-day grace periods) were used, were consistent with those of the primary analysis. Outcome misclassification may

have been present, but it is not likely to be differential between the two treatment groups and was minimized using the HES dataset to define the studied outcome. Also, we did not exclude patients with ischemic stroke, TIA, SE, or bleeding in the month before cohort entry, thus some outcomes may have been readmission for the same event. However, the outcome definition only included diagnoses in primary position in non-elective hospitalizations which mitigated this potential issue. Finally, there were missing data on BMI and smoking status, so that a separate category was created to classify these missing data. Multiple imputations by chained equations were then performed in the sensitivity analyses and results were concordant with those of the primary analyses.

6.3 Implications of the findings and future perspectives

Physicians are often hesitant to prescribe DOACs to very elderly patients with NVAF because of their advanced age, which predisposes them to several comorbidities (including cognitive impairment and frailty), a higher risk of fall (potential higher risk of bleeding) and to the use numerous comedications that can increase the risk of drug-drug interactions [315-316]. The pharmacokinetics or pharmacodynamics of DOACs may also be altered due to age-related biological changes [299]. This thesis adjusted for several relevant confounders and provided real-world evidence that edoxaban was as effective as apixaban to prevent ischemic stroke/TIA/SE in very elderly patients with NVAF. Moreover, the similar effectiveness of these drugs was maintained regardless of age (even in the oldest age group over 90 years), sex, frailty status, CHA_2DS_2-VASc score and dose. With reports that nearly 50% of very elderly patients with AF do not receive OACs despite their eligibility, these findings might potentially further encourage physicians to prescribe DOACs to prevent ischemic stroke and SE in this population [353].

However, this thesis found a higher risk of major bleeding associated with the use of edoxaban compared with the use of apixaban in very elderly patients with NVAF. A lower risk of MB associated with apixaban was also frequently observed compared with dabigatran and rivaroxaban in previous observational studies [17, 269, 272]. Concerns over the potential risk of bleeding are frequently raised by physicians as a reason to withhold the prescription of OACs to the elderly with NVAF, particularly to frail patients. [300, 315]. However, in this thesis, frailty and age did not modify the risk of MB. Given the limited information on the effectiveness and safety of DOACs in the elderly, especially on edoxaban [358-359], our results provide evidence

that frailty and age should not necessarily preclude older and frail patients from receiving OACs. Overall, guidelines recommend that physicians weight the benefits and harms associated with each DOAC and individualize treatment according to their patients' comorbidities and polypharmacy [13-17]. Values and preferences held by the patients should also be considered [13-16]. Because frailty is often an important component of elderly patients' health profile, further observational studies with DOAC comparisons stratified by frailty should be conducted to gather more real-world data and improve the management of NVAF [55]. Although we did not find any effect measure modification on the risk of MB by dose, the clinical factors affecting the dosing of DOACs in the elderly with NVAF should also be further investigated in observational studies to inform on the choice of DOAC dosage regimens in this population. Finally, the current prescription trend of OACs for NVAF should be re-examined given that edoxaban was often not included due to lack of power and limited sample size.

In summary, conclusions drawn from the results of this thesis may be generalizable to North American and European populations as DOACs are widely available across these two continents and recommendations are overall similar between most AF guidelines. Additional observational studies on very elderly patients with NVAF with head-to-head DOAC comparisons (including edoxaban) should be carried out to confirm our findings to provide actionable evidence-based recommendations to AF guidelines and medical professionals.

Chapter 7: Conclusion

In summary, this thesis assessed the effectiveness and safety of edoxaban compared with apixaban in patients with NVAF aged 80 years and older. Using the UK CPRD database, this thesis assembled a large population-based cohort of very elderly patients with incident NVAF treated with either edoxaban or apixaban. The results of this thesis showed that edoxaban was associated with a similar risk of ischemic stroke/TIA/SE compared with apixaban. However, edoxaban compared with apixaban was associated with an increased risk of major bleeding. The risk of all-cause mortality did not differ between the two DOACs. Compared with apixaban, the risk of the secondary composite outcome was however also greater with edoxaban compared with apixaban. The findings of this thesis provide valuable real-world evidence to inform physicians on the prescription of DOACs to very elderly patients with NVAF. This results might also offer actionable evidence to support recommendations in clinical practice guidelines. Future population-based cohort studies on this population that directly compared all four DOACs should be performed to provide additional data as to which DOAC should be preferentially (and safely) prescribed to elderly patients with NVAF over 80.

Chapter 8: References

1. He, N., Dell'Aniello, S., Zhai, S., Suissa, S., & Renoux, C. (2021). Risk of fracture in patients with non-valvular atrial fibrillation initiating direct oral anticoagulants vs. vitamin K antagonists. European heart journal. Cardiovascular pharmacotherapy, 7(5), 389–397. https://doi.org/10.1093/ehjcvp/pvaa094

2. Wodchis, W. P., Bhatia, R. S., Leblanc, K., Meshkat, N., & Morra, D. (2012). A review of the cost of atrial fibrillation. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research, 15(2), 240–248. https://doi.org/10.1016/j.jval.2011.09.009

3. Sheikh, A., Patel, N. J., Nalluri, N., Agnihotri, K., Spagnola, J., Patel, A., Asti, D., Kanotra, R., Khan, H., Savani, C., Arora, S., Patel, N., Thakkar, B., Patel, N., Pau, D., Badheka, A. O., Deshmukh, A., Kowalski, M., Viles-Gonzalez, J., & Paydak, H. (2015). Trends in hospitalization for atrial fibrillation: epidemiology, cost, and implications for the future. Progress In cardiovascular diseases, 58(2), 105–116. https://doi.org/10.1016/j.pcad.2015.07.002

4. Burdett, P., & Lip, G. (2022). Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. European heart journal. Quality of care & clinical outcomes, 8(2), 187–194. https://doi.org/10.1093/ehjqcco/qcaa093

5. Karamichalakis, N., Letsas, K. P., Vlachos, K., Georgopoulos, S., Bakalakos, A., Efremidis, M., & Sideris, A. (2015). Managing atrial fibrillation in the very elderly patient: challenges and solutions. Vascular health and risk management, 11, 555–562. https://doi.org/10.2147/VHRM.S83664

6. Zathar, Z., Karunatilleke, A., Fawzy, A. M., & Lip, G. (2019). Atrial Fibrillation in Older People: Concepts and Controversies. Frontiers in medicine, 6, 175. https://doi.org/10.3389/fmed.2019.00175

7. Rahman, F., Kwan, G. F., & Benjamin, E. J. (2014). Global epidemiology of atrial fibrillation. Nature reviews. Cardiology, 11(11), 639–654. https://doi.org/10.1038/nrcardio.2014.118

8. Ng, K. H., Hart, R. G., & Eikelboom, J. W. (2013). Anticoagulation in Patients Aged ≥75 years with Atrial Fibrillation: Role of Novel Oral Anticoagulants. Cardiology and therapy, 2(2), 135–149. https://doi.org/10.1007/s40119-013-0019-y

9. Douros, A., Renoux, C., Coulombe, J., & Suissa, S. (2017). Patterns of long-term use of non-vitamin K antagonist oral anticoagulants for non-valvular atrial fibrillation: Quebec observational study. Pharmacoepidemiology and drug safety, 26(12), 1546–1554. https://doi.org/10.1002/pds.4333

10. Renoux, C., Coulombe, J., & Suissa, S. (2017). Revisiting sex differences in outcomes in non-valvular atrial fibrillation: a population-based cohort study. European heart journal, 38(19), 1473–1479. https://doi.org/10.1093/eurheartj/ehw613

11. Kornej, J., Börschel, C. S., Benjamin, E. J., & Schnabel, R. B. (2020). Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. Circulation research, 127(1), 4–20. https://doi.org/10.1161/CIRCRESAHA.120.316340

12. Imberti, J. F., Mei, D. A., Vitolo, M., Bonini, N., Proietti, M., Potpara, T., Lip, G., & Boriani, G. (2022). Comparing atrial fibrillation guidelines: Focus on stroke prevention, bleeding risk assessment and oral anticoagulant recommendations. European journal of internal medicine, S0953-6205(22)00166-2. Advance online publication. https://doi.org/10.1016/j.ejim.2022.04.023

13. January, C. T., Wann, L. S., Calkins, H., Chen, L. Y., Cigarroa, J. E., Cleveland, J. C., Jr, Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Furie, K. L., Heidenreich, P. A., Murray, K. T., Shea, J. B., Tracy, C. M., & Yancy, C. W. (2019). 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology, 74(1), 104–132. https://doi.org/10.1016/j.jacc.2019.01.011

14. Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G. A., Dilaveris, P. E., Fauchier, L., Filippatos, G., Kalman, J. M., La Meir, M., Lane, D. A., Lebeau, J. P., Lettino, M., Lip, G., Pinto, F. J., Thomas, G. N., … ESC Scientific Document Group (2021). 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European heart journal, 42(5), 373–498. https://doi.org/10.1093/eurheartj/ehaa612

15. Chao, T. F., Joung, B., Takahashi, Y., Lim, T. W., Choi, E. K., Chan, Y. H., ... & Lip, G. Y. (2022). 2021 focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation: executive summary. Thrombosis and haemostasis, 122(01), 020-047.

16. Andrade, J. G., Aguilar, M., Atzema, C., Bell, A., Cairns, J. A., Cheung, C. C., Cox, J. L., Dorian, P., Gladstone, D. J., Healey, J. S., Khairy, P., Leblanc, K., McMurtry, M. S., Mitchell, L. B., Nair, G. M., Nattel, S., Parkash, R., Pilote, L., Sandhu, R. K., Sarrazin, J. F., … Members of the Secondary Panel (2020). The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. The Canadian journal of cardiology, 36(12), 1847–1948. https://doi.org/10.1016/j.cjca.2020.09.001

17. Durand, M., Schnitzer, M. E., Pang, M., Carney, G., Eltonsy, S., Filion, K. B., Fisher, A., Jun, M., Kuo, I. F., Matteau, A., Paterson, J. M., Quail, J., Renoux, C., & Canadian Network for Observational Drug Effect Studies (CNODES) Investigators (2021). Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: A multi-database cohort study with meta-analysis. British journal of clinical pharmacology, 87(6), 2589–2601. https://doi.org/10.1111/bcp.14669

18. Roy Chowdhury, K., Michaud, J., Yu, O., Yin, H., Azoulay, L., & Renoux, C. (2022). Effectiveness and safety of apixaban vs. rivaroxaban in patients with atrial fibrillation and type 2 diabetes mellitus. Thrombosis and haemostasis, 10.1055/a-1798-2116. Advance online publication. https://doi.org/10.1055/a-1798-2116

19. Poli, D., Antonucci, E., Ageno, W., Bertù, L., Migliaccio, L., Martinese, L., Pilato, G., Testa, S., & Palareti, G. (2019). Oral anticoagulation in very elderly patients with atrial fibrillation: Results from the prospective multicenter START2-REGISTER study. PloS one, 14(5), e0216831. https://doi.org/10.1371/journal.pone.0216831

20. Sharma, M., Cornelius, V. R., Patel, J. P., Davies, J. G., & Molokhia, M. (2015). Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis. Circulation, 132(3), 194–204. https ://doi.org/10.1161/CIRCULATIONAHA.114.013267

21. Roberti, R., Iannone, L. F., Palleria, C., Curcio, A., Rossi, M., Sciacqua, A., Armentaro, G., Vero, A., Manti, A., Cassano, V., Russo, E., De Sarro, G., & Citraro, R. (2021). Direct Oral

Anticoagulants: From Randomized Clinical Trials to Real-World Clinical Practice. Frontiers in pharmacology, 12, 684638. https://doi.org/10.3389/fphar.2021.684638

22. Eikelboom, J. W., Wallentin, L., Connolly, S. J., Ezekowitz, M., Healey, J. S., Oldgren, J., Yang, S., Alings, M., Kaatz, S., Hohnloser, S. H., Diener, H. C., Franzosi, M. G., Huber, K., Reilly, P., Varrone, J., & Yusuf, S. (2011). Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation, 123(21), 2363–2372. https://doi.org/10.1161/CIRCULATIONAHA.110.004747

23. Halperin, J. L., Hankey, G. J., Wojdyla, D. M., Piccini, J. P., Lokhnygina, Y., Patel, M. R., Breithardt, G., Singer, D. E., Becker, R. C., Hacke, W., Paolini, J. F., Nessel, C. C., Mahaffey, K. W., Califf, R. M., Fox, K. A., & ROCKET AF Steering Committee and Investigators (2014). Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Circulation, 130(2), 138–146. https://doi.org/10.1161/CIRCULATIONAHA.113.005008

24. Halvorsen, S., Atar, D., Yang, H., De Caterina, R., Erol, C., Garcia, D., Granger, C. B., Hanna, M., Held, C., Husted, S., Hylek, E. M., Jansky, P., Lopes, R. D., Ruzyllo, W., Thomas, L., & Wallentin, L. (2014). Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. European heart journal, 35(28), 1864–1872. https://doi.org/10.1093/eurheartj/ehu046

25. Kato, E. T., Giugliano, R. P., Ruff, C. T., Koretsune, Y., Yamashita, T., Kiss, R. G., Nordio, F., Murphy, S. A., Kimura, T., Jin, J., Lanz, H., Mercuri, M., Braunwald, E., & Antman, E. M. (2016). Efficacy and Safety of Edoxaban in Elderly Patients with Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial. Journal of the American Heart Association, 5(5), e003432. https://doi.org/10.1161/JAHA.116.003432

26. Cavallari, I., & Patti, G. (2018). Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. Anatolian journal of cardiology, 19(1), 67–71. https://doi.org/10.14744/AnatolJCardiol.2017.8256

27. Tsai, C. T., Liao, J. N., Chen, S. J., Jiang, Y. R., Chen, T. J., & Chao, T. F. (2021). Non-vitamin K antagonist oral anticoagulants versus warfarin in AF patients ≥ 85 years. European journal of clinical investigation, 51(6), e13488. https://doi.org/10.1111/eci.13488

28. Russo, V., Attena, E., Di Maio, M., Mazzone, C., Carbone, A., Parisi, V., Rago, A., D'Onofrio, A., Golino, P., & Nigro, G. (2020). Clinical profile of direct oral anticoagulants versus vitamin K anticoagulants in octogenarians with atrial fibrillation: a multicentre propensity score matched real-world cohort study. Journal of thrombosis and thrombolysis, 49(1), 42–53. https://doi.org/10.1007/s11239-019-01923-9

29. Ortiz, M. R., Muñiz, J., Esteve-Pastor, M. A., Marín, F., Roldán, I., Cequier, A., Martínez-Sellés, M., Saldivar, H. G., Bertomeu, V., & Anguita, M. (2020). Direct Anticoagulants Versus Vitamin K Antagonists in Patients Aged 80 Years or Older with Atrial Fibrillation in a "Real-world" Nationwide Registry: Insights from the FANTASIIA Study. Journal of cardiovascular pharmacology and therapeutics, 25(4), 316–323. https://doi.org/10.1177/1074248420916316

30. Naganuma, M., Shiga, T., & Hagiwara, N. (2020). Clinical Outcomes of Direct Oral Anticoagulants and Warfarin in Japanese Patients with Atrial Fibrillation Aged ≥ 85 Years: A Single-Center Observational Study. Drugs-real world outcomes, 7(4), 325–335. https://doi.org/10.1007/s40801-020-00209-4

31. Polymeris, A. A., Macha, K., Paciaroni, M., Wilson, D., Koga, M., Cappellari, M., Schaedelin, S., Zietz, A., Peters, N., Seiffge, D. J., Haupenthal, D., Gassmann, L., De Marchis, G. M., Wang, R., Gensicke, H., Stoll, S., Thilemann, S., Avramiotis, N. S., Bonetti, B., Tsivgoulis, G., … NOACISP-LONGTERM, Erlangen Registry, CROMIS-2, RAF, RAF-DOAC, SAMURAI-NVAF and Verona Registry Collaborators (2022). Oral Anticoagulants in the Oldest Old with Recent Stroke and Atrial Fibrillation. Annals of neurology, 91(1), 78–88. https://doi.org/10.1002/ana.26267

32. Akgün, A. N., Karaçağlar, E., Bal, U. A., & Özin, M. B. (2021). Comparison of non-vitamin K antagonist oral anticoagulants and well-controlled warfarin in octogenarians with non-valvular atrial fibrillation: Real-world data from a single tertiary center. Anatolian journal of cardiology, 25(7), 462–467. https://doi.org/10.5152/AnatolJCardiol.2021.25058

33. Abraham, N. S., Noseworthy, P. A., Yao, X., Sangaralingham, L. R., & Shah, N. D. (2017). Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology, 152(5), 1014–1022.e1. https://doi.org/10.1053/j.gastro.2016.12.018

34. Benamouzig, R., Guenoun, M., Deutsch, D., & Fauchier, L. (2021). Review Article: Gastrointestinal Bleeding Risk with Direct Oral Anticoagulants. Cardiovascular drugs and therapy, 10.1007/s10557-021-07211-0. Advance online publication. https://doi.org/10.1007/s10557-021-07211-0

35. Diener H. C. (2017). Preventing major gastrointestinal bleeding in elderly patients. Lancet (London, England), 390(10093), 435–437. https://doi.org/10.1016/S0140-6736 (17)31507-6

36. Shah, S. J., Singer, D. E., Fang, M. C., Reynolds, K., Go, A. S., & Eckman, M. H. (2019). Net Clinical Benefit of Oral Anticoagulation among Older Adults with Atrial Fibrillation. Circulation. Cardiovascular quality and outcomes, 12(11), e006212. https://doi.org/10.1161/CIRCOUTCOMES.119.006212

37. Lane, D. A., & Lip, G. Y. (2012). Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation, 126(7),860–865. https ://doi.org/10.1161/CIRCULATIONAHA.111.060061

38. Loo, S. Y., Dell'Aniello, S., Huiart, L., & Renoux, C. (2017). Trends in the prescription of novel oral anticoagulants in UK primary care. British journal of clinical pharmacology, 83(9), 2096–2106. https://doi.org/10.1111/bcp.13299

39. Harskamp, R. E., Himmelreich, J., Wong, G., & Teichert, M. (2021). Prescription patterns of direct oral anticoagulants and concomitant use of interacting medications in the Netherlands. Netherlands heart journal: monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, 29(9), 451–459. https://doi.org/10.1007/s12471-021-01612-4

40. Mitchell, A., Snowball, J., Welsh, T. J., Watson, M. C., & McGrogan, A. (2021). Prescribing of direct oral anticoagulants and warfarin to older people with atrial fibrillation in UK general practice: a cohort study. BMC medicine, 19(1), 189. https://doi.org/10.1186/s12916-021-02067-5

41. Rose, A. J., Goldberg, R., McManus, D. D., Kapoor, A., Wang, V., Liu, W., & Yu, H. (2019). Anticoagulant Prescribing for Non-Valvular Atrial Fibrillation in the Veterans Health Administration. Journal of the American Heart Association, 8(17), e012646. https://doi.org/10.1161/JAHA.119.012646

42. Kuroda, M., Tamiya, E., Nose, T., Ogimoto, A., Taura, J., Imamura, Y., Fukuzawa, M., Hayashi, T., Akao, M., Yamashita, T., Lip, G., & Okumura, K. (2022). Effect of 15-mg Edoxaban on Clinical Outcomes in 3 Age Strata in Older Patients With Atrial Fibrillation: A Prespecified

Subanalysis of the ELDERCARE-AF Randomized Clinical Trial. JAMA cardiology, 7(6), 583–590. https://doi.org/10.1001/jamacardio.2022.0480

43. Alkhameys, S., & Barrett, R. (2022). Impact of the COVID-19 pandemic on England's national prescriptions of oral vitamin K antagonist (VKA) and direct-acting oral anticoagulants (DOACs): an interrupted time series analysis (January 2019-February 2021). Current medical research and opinion, 1–12. Advance online publication. https://doi.org/10.1080/03007995.2022.2078100

44. Wheelock, K. M., Ross, J. S., Murugiah, K., Lin, Z., Krumholz, H. M., & Khera, R. (2021). Clinician Trends in Prescribing Direct Oral Anticoagulants for US Medicare Beneficiaries. JAMA network open, 4(12), e2137288. https://doi.org/10.1001/jamanetworkopen.2021.37288

45. Vora, P., Morgan Stewart, H., Russell, B., Asiimwe, A., & Brobert, G. (2022). Time Trends and Treatment Pathways in Prescribing Individual Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation: An Observational Study of More than Three Million Patients from Europe and the United States. International journal of clinical practice, 2022, 6707985. https://doi.org/10.1155/2022/6707985

46. Patel, R., Czuprynska, J., Roberts, L. N., Vadher, B., Rea, C., Patel, R., Gee, E., Saul, G., Coles, E., Brown, A., Byrne, R., Speed, V., Patel, J. P., & Arya, R. (2021). Switching warfarin patients to a direct oral anticoagulant during the Coronavirus Disease-19 pandemic. Thrombosis research, 197, 192–194. https://doi.org/10.1016/j.thromres.2020.11.004

47. De Caterina, R., Kelly, P., Monteiro, P., Deharo, J. C., de Asmundis, C., López-de-Sá, E., Weiss, T. W., Waltenberger, J., Steffel, J., de Groot, J. R., Levy, P., Bakhai, A., Zierhut, W., Laeis, P., Kerschnitzki, M., Reimitz, P. E., Kirchhof, P., & ETNA-AF-Europe investigators (2019). Characteristics of patients initiated on edoxaban in Europe: baseline data from edoxaban treatment in routine clinical practice for patients with atrial fibrillation (AF) in Europe (ETNA-AF-Europe). BMC cardiovascular disorders, 19(1), 165. https://doi.org/10.1186/s12872-019-1144-x

48. Pottegård, A., Grove, E. L., & Hellfritzsch, M. (2018). Use of direct oral anticoagulants in the first year after market entry of edoxaban: A Danish nationwide drug utilization study. Pharmacoepidemiology and drug safety, 27(2), 174–181. https://doi.org/10.1002/pds.4350

49. Polidori, M. C., Alves, M., Bahat, G., Boureau, A. S., Ozkok, S., Pfister, R., Pilotto, A., Veronese, N., Bo, M., & Special Interest Group "Cardiovascular Diseases" of the EuGMS (2022). Atrial fibrillation: a geriatric perspective on the 2020 ESC guidelines. European geriatric medicine, 13(1), 5–18. https://doi.org/10.1007/s41999-021-00537-w

50. Ho, K. H., van Hove, M., & Leng, G. (2020). Trends in anticoagulant prescribing: a review of local policies in English primary care. BMC health services research, 20(1), 279. https://doi.org/10.1186/s12913-020-5058-1

51. European Medicines Agency. (2015). Lixiana: EPAR-Medicine overview. Available from: https://www.ema.europa.eu/en/documents/overview/lixiana88ixiana-epar-medicineoverview_en.pdf

52. Food and Drug Administration. (2015). Center for drug evaluation and research. Application number: 206316Orig1Orig2s000. Summary review. Available from: https://www.Accessdata.fda.gov/drugsatfda_docs/nda/2015/206316Orig1Orig2s000SumR.pdf

53. Fernández, C. S., Gullón, A., & Formiga, F. (2020). The problem of underdosing with direct-acting oral anticoagulants in elderly patients with nonvalvular atrial fibrillation. Journal of comparative effectiveness research, 9(7), 509–523. https://doi.org/10.2217/cer-2019-0197

54. Xia, X., Wang, L., Lin, T., Yue, J., Yang, Z., Mi, C., Liao, Z., Chen, Y., Ge, N., & Wu, C. (2022). Barriers to prescribing oral anticoagulants to inpatients aged 80 years and older with nonvalvular atrial fibrillation: a cross-sectional study. BMC geriatrics, 22(1), 263.https://doi.org/10.1186/s12877-022-029650

55. Botto, G., Ameri, P., Cappellari, M., Dentali, F., Ferri, N., Parrini, I., Porto, I., Squizzato, A., & Camporese, G. (2021). Unmet Clinical Needs in Elderly Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation. Advances in therapy, 38(6), 2891–2907. https://doi.org/10.1007/s12325-021-01769-9

56. Grymonprez, M., Steurbaut, S., De Backer, T. L., Petrovic, M., & Lahousse, L. (2020). Effectiveness and Safety of Oral Anticoagulants in Older Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis. Frontiers in pharmacology, 11, 583311. https://doi.org/10.3389/fphar.2020.583311

57. Van Ganse, E., Danchin, N., Mahé, I., Hanon, O., Jacoud, F., Nolin, M., Dalon, F., Lefevre, C., Cotté, F. E., Gollety, S., Falissard, B., Belhassen, M., & Steg, P. G. (2020). Comparative Safety and Effectiveness of Oral Anticoagulants in Nonvalvular Atrial Fibrillation: The NAXOS Study. Stroke, 51(7), 2066–2075. https://doi.org/10.1161/STROKEAHA.120.028825

58. Douros, A., Durand, M., Doyle, C. M., Yoon, S., Reynier, P., & Filion, K. B. (2019). Comparative Effectiveness and Safety of Direct Oral Anticoagulants in Patients with Atrial

Fibrillation: A Systematic Review and Meta-Analysis of Observational Studies. Drug safety, 42(10), 1135–1148. https://doi.org/10.1007/s40264-019-00842-1

59. Sadlon, A. H., & Tsakiris, D. A. (2016). Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. Swiss medical weekly, 146, w14356. https://doi.org/10.4414/smw.2016.14356

60. Vannucchi, V., Moroni, F., Grifoni, E., Marcucci, R., Landini, G., Prisco, D., & Masotti, L. (2020). Management of oral anticoagulation in very old patients with non-valvular atrial fibrillation related acute ischemic stroke. Journal of thrombosis and thrombolysis, 49(1), 8693. ht tps://doi.org/10.1007/s11239-019-01972-0

61. Deitelzweig, S., Keshishian, A., Li, X., Kang, A., Dhamane, A. D., Luo, X., Balachander, N., Rosenblatt, L., Mardekian, J., Pan, X., Nadkarni, A., Di Fusco, M., Garcia Reeves, A. B., Yuce, H., & Lip, G. (2019). Comparisons between Oral Anticoagulants among Older Nonvalvular Atrial Fibrillation Patients. Journal of the American Geriatrics Society, 67(8), 1662–1671. https://doi.or g/10.1111/jgs.15956

62. Fauchier, L., Blin, P., Sacher, F., Dureau-Pournin, C., Bernard, M. A., Lassalle, R., Droz-Perroteau, C., Dallongeville, J., & Moore, N. (2020). Reduced dose of rivaroxaban and dabigatran vs. vitamin K antagonists in very elderly patients with atrial fibrillation in a nationwide cohort study. Europace: European pacing, arrhythmias, and cardiac
electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 22(2), 205–215. https://doi.org /10.1093/europace/euz285

63. Lee, S. R., Choi, E. K., Kwon, S., Han, K. D., Jung, J. H., Cha, M. J., Oh, S., & Lip, G. (2019). Effectiveness and Safety of Contemporary Oral Anticoagulants among Asians with Nonvalvular Atrial Fibrillation. Stroke, 50(8), 2245–2249. https://doi.org/10.1161/STROKEAHA.119.025536

64. Afzal, S., Zaidi, S., Merchant, H. A., Babar, Z. U., & Hasan, S. S. (2021). Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. Journal of thrombosis and thrombolysis, 52(2), 646–653. https://doi.org/10.1007 /s11239-02102416-4

65. Cintra, F. D., & Figueiredo, M. (2021). Atrial Fibrillation (Part 1): Pathophysiology, Risk Factors, and Therapeutic Basis. Fibrilação Atrial (Parte 1): Fisiopatologia, Fatores de Risco e Bases Terapêuticas. Arquivos brasileiros de cardiologia, 116(1), 129–139. https://doi.org/10.3666

0/abc.20200485

66. Bibas, L., Levi, M., & Essebag, V. (2016). Diagnosis and management of supraventricular tachycardias. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 188(17-18), E466–E473. https://doi.org/10.1503/cmaj.160079

67. Goodacre, S., & Irons, R. (2002). ABC of clinical electrocardiography: Atrial arrhythmias. BMJ (Clinical research ed.), 324(7337), 594–597. https://doi.org/10.1136/bmj.324.7337.594

68. Bibas, L., Levi, M., & Essebag, V. (2016). Diagnosis and management of supraventricular tachycardias. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 188(17-18), E466–E473. https://doi.org/10.1503/cmaj.160079

69. Wasmer, K., Eckardt, L., & Breithardt, G. (2017). Predisposing factors for atrial fibrillation in the elderly. Journal of geriatric cardiology: JGC, 14(3), 179–184. https://doi.org/10.11909/j.issn.1671-5411.2017.03.010

70. Aggarwal, P., Woolford, S. J., & Patel, H. P. (2020). Multi-Morbidity and Polypharmacy in Older People: Challenges and Opportunities for Clinical Practice. Geriatrics (Basel, Switzerland), 5(4), 85. https://doi.org/10.3390/geriatrics5040085Yabluchanskiy, A., Ungvari, Z., Csiszar, A., & Tarantini, S. (2018). Advances and challenges in geroscience research: An update. Physiology international, 105(4), 298–308. https://doi.org/10.1556/2060.105.2018.4.32

71. Dovjak P. (2022). Polypharmacy in elderly people. Wiener medizinische Wochenschrift (1946), 172(5-6), 109–113. https://doi.org/10.1007/s10354-021-00903-0

72. Martinez-Lacoba, R., Pardo-Garcia, I., & Escribano-Sotos, F. (2021). Aging, Dependence, and Long-Term Care: A Systematic Review of Employment Creation. Inquiry : a journal of medical care organization, provision, and financing, 58, 469580211062426. https://doi.org/10.1177/00469580211062426

73. DeVito, L. M., Barzilai, N., Cuervo, A. M., Niedernhofer, L. J., Milman, S., Levine, M., Promislow, D., Ferrucci, L., Kuchel, G. A., Mannick, J., Justice, J., Gonzales, M. M., Kirkland, J. L., Cohen, P., & Campisi, J. (2022). Extending human healthspan and longevity: a symposium report. Annals of the New York Academy of Sciences, 1507(1), 70–83. https://doi.org/10.1111/nyas.14681

74. Chugh, S. S., Havmoeller, R., Narayanan, K., Singh, D., Rienstra, M., Benjamin, E. J., Gillum, R. F., Kim, Y. H., McAnulty, J. H., Jr, Zheng, Z. J., Forouzanfar, M. H., Naghavi, M., Mensah, G.

A., Ezzati, M., & Murray, C. J. (2014). Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation, 129(8), 837–847. https://doi.org/10.1161/CIRCULATIONAHA.113.005119

75. Rodgers, J. L., Jones, J., Bolleddu, S. I., Vanthenapalli, S., Rodgers, L. E., Shah, K., Karia, K., & Panguluri, S. K. (2019). Cardiovascular Risks Associated with Gender and Aging. Journal of cardiovascular development and disease, 6(2), 19. https://doi.org/10.3390/Jcdd6020019

76. GBD 2019 Stroke Collaborators (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. Neurology, 20(10), 795–820. https://doi.org/10.1016/S1474-4422(21)00252-0

77. Lip, G. Y., Kakar, P., & Watson, T. (2007). Atrial fibrillation--the growing epidemic. Heart (British Cardiac Society), 93(5), 542–543. https://doi.org/10.1136/hrt.2006.110791

78. Stewart, S., Murphy, N. F., Walker, A., McGuire, A., & McMurray, J. J. (2004). Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart (British Cardiac Society), 90(3), 286–292. https://doi.org/10.1136/hrt.2002.008748

79. Lip, G. Y., Clementy, N., Pericart, L., Banerjee, A., & Fauchier, L. (2015). Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. Stroke, 46(1), 143–150. https://doi.org/10.1161/STROKEAHA.114.007199

80. Florisson, S., Aagesen, E. K., Bertelsen, A. S., Nielsen, L. P., & Rosholm, J. U. (2021). Are older adults insufficiently included in clinical trials? -An umbrella reviews Basic & clinical pharmacology & toxicology, 128(2), 213–223. https://doi.org/10.1111/bcpt.13536

81. Chen, L. Y., Chung, M. K., Allen, L. A., Ezekowitz, M., Furie, K. L., McCabe, P., Noseworthy, P. A., Perez, M. V., Turakhia, M. P., & American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council (2018). Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. Circulation, 137(20), e623–e644. https://doi.org/10.1161/CIR.0000000000000568

82. Colilla, S., Crow, A., Petkun, W., Singer, D. E., Simon, T., & Liu, X. (2013). Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. The American journal of cardiology, 112(8), 1142–1147. https://doi.org/10.1016/j.amjcard.2013.05.063

83. Wolowacz, S. E., Samuel, M., Brennan, V. K., Jasso-Mosqueda, J. G., & Van Gelder, I. C. (2011). The cost of illness of atrial fibrillation: a systematic review of the recent literature. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 13(10), 1375–1385. https://doi.org/10.1093/europace/eur194

84. Zoni-Berisso, M., Lercari, F., Carazza, T., & Domenicucci, S. (2014). Epidemiology of atrial fibrillation: European perspective. Clinical epidemiology, 6, 213–220. https://doi.org/10.2147/CLEP.S47385

85. Lernfelt, G., Mandalenakis, Z., Hornestam, B., Lernfelt, B., Rosengren, A., Sundh, V., & Hansson, P. O. (2020). Atrial fibrillation in the elderly general population: a 30-year follow-up from 70 to 100 years of age. Scandinavian cardiovascular journal : SCJ, 54(4), 232–238. https://doi.org/10.1080/14017431.2020.1729399

86. Renoux, C., Patenaude, V., & Suissa, S. (2014). Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. Journal of the American Heart Association, 3(6), e001402. https://doi.org/10.1161/JAHA.114.001402

87. Morseth, B., Geelhoed, B., Linneberg, A., Johansson, L., Kuulasmaa, K., Salomaa, V., Iacoviello, L., Costanzo, S., Söderberg, S., Niiranen, T. J., Vishram-Nielsen, J., Njølstad, I., Wilsgaard, T., Mathiesen, E. B., Løchen, M. L., Zeller, T., Blankenberg, S., Ojeda, F. M., Schnabel, R. B., & MORGAM consortium (2021). Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. Open heart, 8(2), e001624. https://doi.org/10.1136/openhrt-2021-001624

88. Staerk, L., Sherer, J. A., Ko, D., Benjamin, E. J., & Helm, R. H. (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circulation research, 120(9), 1501–1517. https://doi.org/10.1161/CIRCRESAHA.117.309732

89. Subramanya, V., Claxton, J. S., Lutsey, P. L., MacLehose, R. F., Chen, L. Y., Chamberlain, A. M., Norby, F. L., & Alonso, A. (2021). Sex differences in treatment strategy and adverse outcomes among patients 75 and older with atrial fibrillation in the MarketScan database. BMC cardiovascular disorders, 21(1), 598. https://doi.org/10.1186/s12872-021-02419-2

90. Murphy, N. F., Simpson, C. R., Jhund, P. S., Stewart, S., Kirkpatrick, M., Chalmers, J., MacIntyre, K., & McMurray, J. J. (2007). A national survey of the prevalence, incidence, primary

care burden and treatment of atrial fibrillation in Scotland. Heart (British Cardiac Society), 93(5), 606–612. https://doi.org/10.1136/hrt.2006.107573

91. Williams, B. A., Chamberlain, A. M., Blankenship, J. C., Hylek, E. M., & Voyce, S. (2020). Trends in Atrial Fibrillation Incidence Rates Within an Integrated Health Care Delivery System, 2006 to 2018. JAMA network open, 3(8), e2014874. https://doi.org/10.1001/Jamanetworkopen.2020.14874

92. Westerman, S., & Wenger, N. (2019). Gender Differences in Atrial Fibrillation: A Review of Epidemiology, Management, and Outcomes. Current cardiology reviews, 15(2), 136–144. https://doi.org/10.2174/1573403X15666181205110624

93. Ko, D., Rahman, F., Schnabel, R. B., Yin, X., Benjamin, E. J., & Christophersen, I. E. (2016). Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nature reviews. Cardiology, 13(6), 321–332. https://doi.org/10.1038/nrcardio.2016.45

94. Frost, L., Engholm, G., Johnsen, S., Møller, H., & Husted, S. (2000). Incident stroke after discharge from the hospital with a diagnosis of atrial fibrillation. The American journal of medicine, 108(1), 36–40. https://doi.org/10.1016/s0002-9343(99)00415-5

95. Benjamin, E. J., Levy, D., Vaziri, S. M., D'Agostino, R. B., Belanger, A. J., & Wolf, P. A. (1994). Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA, 271(11), 840–844.

96. Andrade, J., Khairy, P., Dobrev, D., & Nattel, S. (2014). The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circulation research, 114(9), 1453–1468. https://doi.org/10.1161/CIRCRESAHA.114.303211

97. Ragab, A. A. Y., Sitorus, G. D. S., Brundel, B. B. J. J. M., & de Groot, N. M. S. (2020). The Genetic Puzzle of Familial Atrial Fibrillation. Frontiers in cardiovascular medicine, 7, 14. https://doi.org/10.3389/fcvm.2020.00014

98. Heeringa, J., van der Kuip, D. A., Hofman, A., Kors, J. A., van Herpen, G., Stricker, B. H., Stijnen, T., Lip, G. Y., & Witteman, J. C. (2006). Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European heart journal, 27(8), 949–953. https://doi.org/10.1093/eurheartj/ehi825

99. Heckbert, S. R., Austin, T. R., Jensen, P. N., Chen, L. Y., Post, W. S., Floyd, J. S., Soliman, E. Z., Kronmal, R. A., & Psaty, B. M. (2020). Differences by Race/Ethnicity in the Prevalence of

Clinically Detected and Monitor-Detected Atrial Fibrillation: MESA. Circulation. Arrhythmia and electrophysiology, 13(1), e007698.https://doi.org/10.1161/CIRCEP.119.007698

100. Volgman, A. S., Bairey Merz, C. N., Benjamin, E. J., Curtis, A. B., Fang, M. C., Lindley, K. J., Pepine, C. J., Vaseghi, M., Waldo, A. L., Wenger, N. K., & Russo, A. M. (2019). Sex and Race/Ethnicity Differences in Atrial Fibrillation. Journal of the American College of Cardiology, 74(22), 2812–2815. https://doi.org/10.1016/j.jacc.2019.09.045

101. Chung, M. K., Eckhardt, L. L., Chen, L. Y., Ahmed, H. M., Gopinathannair, R., Joglar, J. A., Noseworthy, P. A., Pack, Q. R., Sanders, P., Trulock, K. M., & American Heart Association Electrocardiography and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health (2020). Lifestyle and Risk Factor Modification for Reduction of Atrial Fibrillation: A Scientific Statement From the American Heart Association. Circulation, 141(16), e750–e772. https://doi.org/10.1161/CIR.0000000000000748

102. Alonso, A., Agarwal, S. K., Soliman, E. Z., Ambrose, M., Chamberlain, A. M., Prineas, R. J., & Folsom, A. R. (2009). Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. American heart journal, 158(1), 111–117. https://doi.org/10.1016/j.ahj.2009.05.010

103. Dewland, T. A., Olgin, J. E., Vittinghoff, E., & Marcus, G. M. (2013). Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation*, *128*(23), 2470–2477. https://doi.org/10.1161/CIRCULATIONAHA.113.002449

104. Tamirisa, K. P., Al-Khatib, S. M., Mohanty, S., Han, J. K., Natale, A., Gupta, D., Russo, A. M., Al-Ahmad, A., Gillis, A. M., & Thomas, K. L. (2021). Racial and Ethnic Differences in the Management of Atrial Fibrillation. CJC open, 3(12 Suppl), S137–S148. https://doi.org/10.1016/j.cjco.2021.09.004

105. Nanda, A., & Kabra, R. (2019). Racial Differences in Atrial Fibrillation Epidemiology, Management, and Outcomes. Current treatment options in cardiovascular medicine, 21(12), 85. https://doi.org/10.1007/s11936-019-0793-5

105. Marulanda-Londoño, E., & Chaturvedi, S. (2017). The Interplay between Obstructive Sleep Apnea and Atrial Fibrillation. Frontiers in neurology, 8, 668. https://doi.org/10.3389/fnur.2017.00668

106. Shamloo, A. S., Dagres, N., Arya, A., & Hindricks, G. (2019). Atrial fibrillation: A review of modifiable risk factors and preventive strategies. Romanian journal of internal medicine = Revue roumaine de medecine interne, 57(2), 99–109. https://doi.org/10.2478/rjim-2018-0045

107. Streur M. (2019). Atrial Fibrillation Symptom Perception. The journal for nurse practitioners: JNP, 15(1), 60–64. https://doi.org/10.1016/j.nurpra.2018.08.015

108. Kalstø, S. M., Siland, J. E., Rienstra, M., & Christophersen, I. E. (2019). Atrial Fibrillation Genetics Update: Toward Clinical Implementation. Frontiers in cardiovascular medicine, 6, 127. https://doi.org/10.3389/fcvm.2019.00127

109. Laredo, M., Waldmann, V., Khairy, P., & Nattel, S. (2018). Age as a Critical Determinant of Atrial Fibrillation: A Two-sided Relationship. The Canadian journal of cardiology, 34(11), 1396–1406. https://doi.org/10.1016/j.cjca.2018.08.007

110. Zhang, J., Johnsen, S. P., Guo, Y., & Lip, G. (2021). Epidemiology of Atrial Fibrillation: Geographic/Ecological Risk Factors, Age, Sex, Genetics. Cardiac electrophysiology clinics, 13(1), 1–23. https://doi.org/10.1016/j.ccep.2020.10.010

111. Kirchhof, P., Breithardt, G., Aliot, E., Al Khatib, S., Apostolakis, S., Auricchio, A., Bailleul, C., Bax, J., Benninger, G., Blomstrom-Lundqvist, C., Boersma, L., Boriani, G., Brandes, A., Brown, H., Brueckmann, M., Calkins, H., Casadei, B., Clemens, A., Crijns, H., Derwand, R., … Camm, A. J. (2013). Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 15(11), 1540–1556. https://doi.org/10.1093/europace/eut232

112. Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., Atar, D., Casadei, B., Castella, M., Diener, H. C., Heidbuchel, H., Hendriks, J., Hindricks, G., Manolis, A. S., Oldgren, J., Popescu, B. A., Schotten, U., Van Putte, B., Vardas, P., Agewall, S., Camm, J., Baron Esquivias, G., … Zeppenfeld, K. (2016). 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 18(11), 1609–1678. https://doi.org/10.1093/europace/euw295

113. Markides, V., & Schilling, R. J. (2003). Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. Heart (British Cardiac Society), 89(8), 939–943. https://doi.org/10.1136/heart.89.8.939

114. Haïssaguerre, M., Jaïs, P., Shah, D. C., Takahashi, A., Hocini, M., Quiniou, G., Garrigue, S., Le Mouroux, A., Le Métayer, P., & Clémenty, J. (1998). Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. The New England journal of medicine, 339(10), 659–666. https://doi.org/10.1056/NEJM199809033391003

115. Chen, Q., Yi, Z., & Cheng, J. (2018). Atrial fibrillation in aging population. Aging medicine (Milton (N.S.W)), 1(1), 67–74. https://doi.org/10.1002/agm2.12015

116. North, B. J., & Sinclair, D. A. (2012). The intersection between aging and cardiovascular disease. Circulation research, 110(8), 1097–1108. https://doi.org/10.1161/CIRCRESAHA.111.246876

117. Iwasaki, Y. K., Nishida, K., Kato, T., & Nattel, S. (2011). Atrial fibrillation pathophysiology: implications for management. Circulation, 124(20), 2264–2274. https://doi.org/10.1161/CIRCULATIONAHA.111.019893

118. Veenhuyzen, G. D., Simpson, C. S., & Abdollah, H. (2004). Atrial fibrillation. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne, 171(7), 755–760. https://doi.org/10.1503/cmaj.1031364

119. Wijffels, M. C., Kirchhof, C. J., Dorland, R., & Allessie, M. A. (1995). Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation, 92(7), 1954–1968. https://doi.org/10.1161/01.cir.92.7.1954

120. Rostock, T., Steven, D., Lutomsky, B., Servatius, H., Drewitz, I., Klemm, H., Müllerleile, K., Ventura, R., Meinertz, T., & Willems, S. (2008). Atrial fibrillation begets atrial fibrillation in the pulmonary veins on the impact of atrial fibrillation on the electrophysiological properties of the pulmonary veins in humans. Journal of the American College of Cardiology, 51(22), 2153–2160. https://doi.org/10.1016/j.jacc.2008.02.059

121. Pellman, J., & Sheikh, F. (2015). Atrial fibrillation: mechanisms, therapeutics, and future directions. Comprehensive Physiology, 5(2), 649–665. https://doi.org/10.1002/cphy.c140047

122. He, J., Li, S., Ding, Y., Tong, Y., & Li, X. (2022). Research Progress on Natural Products' Therapeutic Effects on Atrial Fibrillation by Regulating Ion Channels. Cardiovascular therapeutics, 2022, 4559809. https://doi.org/10.1155/2022/4559809

123. Bai D. (2014). Atrial fibrillation-linked GJA5/connexin40 mutants impaired gap junctions via different mechanisms. FEBS letters, 588(8), 1238–1243. https://doi.org/10.1016/j.febslet.2014.02.064

124. Nattel, S., Burstein, B., & Dobrev, D. (2008). Atrial remodeling and atrial fibrillation: mechanisms and implications. Circulation. Arrhythmia and electrophysiology, 1(1), 62–73. https://doi.org/10.1161/CIRCEP.107.754564

125. Melillo, E., Palmiero, G., Ferro, A., Mocavero, P. E., Monda, V., & Ascione, L. (2019). Diagnosis and Management of Left Atrium Appendage Thrombosis in Atrial Fibrillation Patients Undergoing Cardioversion. Medicina (Kaunas, Lithuania), 55(9), 511. https://doi.org/10.3390/medicina55090511

126. Schotten, U., Verheule, S., Kirchhof, P., & Goette, A. (2011). Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiological reviews, 91(1), 265–325. https://doi.org/10.1152/physrev.00031.2009

127. Alpert, J. S., Petersen, P., & Godtfredsen, J. (1988). Atrial fibrillation: natural history, complications, and management. Annual review of medicine, 39, 41–52. https://doi.org/10.1146/annurev.me.39.020188.000353

128. D'Souza, A., Butcher, K. S., & Buck, B. H. (2018). The Multiple Causes of Stroke in Atrial Fibrillation: Thinking Broadly. The Canadian journal of cardiology, 34(11), 1503–1511. https://doi.org/10.1016/j.cjca.2018.08.036

129. Masci, A., Barone, L., Dedè, L., Fedele, M., Tomasi, C., Quarteroni, A., & Corsi, C. (2019). The Impact of Left Atrium Appendage Morphology on Stroke Risk Assessment in Atrial Fibrillation: A Computational Fluid Dynamics Study. Frontiers in physiology, 9, 1938. https://doi.org/10.3389/fphys.2018.01938

130. Freedman, B., Potpara, T. S., & Lip, G. Y. (2016). Stroke prevention in atrial fibrillation. *Lancet (London, England)*, *388*(10046), 806–817. https://doi.org/10.1016/S0140-6736(16)31257-0

131. Martins, R. P., Galand, V., Colette, E., Behar, N., Pavin, D., Leclercq, C., Daubert, J. C., & Mabo, P. (2016). Defining nonvalvular atrial fibrillation: A quest for clarification. American heart journal, 178, 161–167. https://doi.org/10.1016/j.ahj.2016.05.014

132. Heo, R., Cha, MJ., Kim, TH. *et al.* Characteristics of symptom burden in atrial fibrillation with concomitant heart failure. *Int J Arrhythm* **21,** 1 (2020). https://doi.org/10.1186/s42444-019-0009-9

133. Heidt, S. T., Kratz, A., Najarian, K., Hassett, A. L., Oral, H., Gonzalez, R., Nallamothu, B. K., Clauw, D., & Ghanbari, H. (2016). Symptoms In Atrial Fibrillation: A Contemporary Review And Future Directions. *Journal of atrial fibrillation*, *9*(1), 1422. https://doi.org/10.4022/jafib.1422

134. Dewar, R. I., Lip, G. Y., & Guidelines Development Group for the NICE clinical guideline for the management of atrial fibrillation (2007). Identification, diagnosis and assessment of atrial fibrillation. *Heart (British Cardiac Society)*, *93*(1), 25–28. https://doi.org/10.1136/hrt.2006.099861

135. Fauchier, L., Philippart, R., Clementy, N., Bourguignon, T., Angoulvant, D., Ivanes, F., Babuty, D., & Bernard, A. (2015). How to define valvular atrial fibrillation? Archives of cardiovascular diseases, 108(10), 530–539. https://doi.org/10.1016/j.acvd.2015.06.002

136. Vo, N. M., Leung, M., van Rosendael, P. J., Goedemans, L., van Wijngaarden, S. E., Prihadi, E. A., van der Bijl, P., Ajmone Marsan, N., Delgado, V., & Bax, J. J. (2020). Characteristics and Prognosis of Patients with Nonvalvular Atrial Fibrillation and Significant Valvular Heart Disease Referred for Electrical Cardioversion. The American journal of cardiology, 128, 84–91. https://doi.org/10.1016/j.amjcard.2020.04.035

137. Morillo, C. A., Banerjee, A., Perel, P., Wood, D., & Jouven, X. (2017). Atrial fibrillation: the current epidemic. Journal of geriatric cardiology: JGC, 14

138. Hakim, F. A., & Shen, W. K. (2014). Atrial fibrillation in the elderly: a review. *Future cardiology*, *10*(6), 745–758. https://doi.org/10.2217/fca.14.32

139. Rienstra, M., Lubitz, S. A., Mahida, S., Magnani, J. W., Fontes, J. D., Sinner, M. F., Van Gelder, I. C., Ellinor, P. T., & Benjamin, E. J. (2012). Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation*, *125*(23), 2933–2943. https://doi.org/10.1161/CIRCULATIONAHA.111.069450

140. Rho, R. W., & Page, R. L. (2005). Asymptomatic atrial fibrillation. *Progress in cardiovascular diseases*, *48*(2), 79–87. https://doi.org/10.1016/j.pcad.2005.06.005

141. Resnick B. (1999). Atrial fibrillation in the older adult. Presentation and management issues. *Geriatric nursing (New York, N.Y.)*, *20*(4), 188–194. https://doi.org/10.1053/gn.1999.v20.101045001

142. Camm, A. J. (2011). Stroke Prevention in Atrial Fibrillation-The Unmet Need and Morbidity Burden, European Cardiology 2011;7(3):187–95https://doi.org/10.15420/ecr.2011.7.3.187

143. Lubitz, S. A., Benjamin, E. J., Ruskin, J. N., Fuster, V., & Ellinor, P. T. (2010). Challenges in the classification of atrial fibrillation. *Nature reviews. Cardiology*, *7*(8), 451–460. https://doi.org/10.1038/nrcardio.2010.86

144. Chatap, G., Giraud, K., & Vincent, J. P. (2002). Atrial fibrillation in the elderly: facts and management. Drugs & aging, 19(11), 819–846. https://doi.org/10.2165/00002512-200219110-00002

145. Jones, N. R., Taylor, C. J., Hobbs, F., Bowman, L., & Casadei, B. (2020). Screening for atrial fibrillation: a call for evidence. European heart journal, 41(10), 1075–1085.https://doi.org/10.1093/eurheartj/ehz834

146. Tonko, J. B., & Wright, M. J. (2021). Review of the 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation-What Has Changed and How Does This Affect Daily Practice. Journal of clinical medicine, 10(17), 3922. https://doi.org/10.3390/jcm10173922

147. Ponamgi, S. P., Siontis, K. C., Rushlow, D. R., Graff-Radford, J., Montori, V., & Noseworthy, P. A. (2021). Screening and management of atrial fibrillation in primary care. BMJ (Clinical research ed.), 373, n379. https://doi.org/10.1136/bmj.n379

148. Pothineni, N., & Deo, R. (2020). Screening for Atrial Fibrillation: Closing the "LOOP". Circulation, 141(19), 1523–1526. https://doi.org/10.1161/CIRCULATIONAHA.120.046298

149. Bañeras, J., Pariggiano, I., Ródenas-Alesina, E., Oristrell, G., Escalona, R., Miranda, B., Rello, P., Soriano, T., Gordon, B., Belahnech, Y., Calabrò, P., García-Dorado, D., Ferreira-González, I., & Radua, J. (2022). Optimal opportunistic screening of atrial fibrillation using pulse palpation in cardiology outpatient clinics: Who and how. PloS one, 17(4), e0266955. https://doi.org/10.1371/journal.pone.0266955

150. Mairesse, G. H., Moran, P., Van Gelder, I. C., Elsner, C., Rosenqvist, M., Mant, J., Banerjee, A., Gorenek, B., Brachmann, J., Varma, N., Glotz de Lima, G., Kalman, J., Claes, N., Lobban, T., Lane, D., Lip, G., Boriani, G., & ESC Scientific Document Group (2017). Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac

pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 19(10), 1589–1623. https://doi.org/10.1093/europace/eux177

151. Cheung, C. C., Nattel, S., Macle, L., & Andrade, J. G. (2021). Management of Atrial Fibrillation in 2021: An Updated Comparison of the Current CCS/CHRS, ESC, and AHA/ACC/HRS Guidelines. The Canadian journal of cardiology, 37(10), 1607–1618. https://doi.org/10.1016/j.cjca.2021.06.011

152. Kirchhof P. (2017). The future of atrial fibrillation management: integrated care and stratified therapy. Lancet (London, England), 390(10105), 1873–1887. https://doi.org/10.1016/S0140-6736(17)31072-3

153. Kotalczyk, A., Lip, G. Y., & Calkins, H. (2021). The 2020 ESC Guidelines on the Diagnosis and Management of Atrial Fibrillation. Arrhythmia & electrophysiology review, 10(2), 65–67. https://doi.org/10.15420/aer.2021.07

154. Brundel, B., Ai, X., Hills, M. T., Kuipers, M. F., Lip, G., & de Groot, N. (2022). Atrial fibrillation. Nature reviews. Disease primers, 8(1), 21. https://doi.org/10.1038/s41572-022-003479

155. Rosero, S. Z., Kutyifa, V., Olshansky, B., & Zareba, W. (2013). Ambulatory ECG monitoring in atrial fibrillation management. Progress in cardiovascular diseases, 56(2), 143–152. https://doi.org/10.1016/j.pcad.2013.10.001

156. Salih, M., Abdel-Hafez, O., Ibrahim, R., & Nair, R. (2021). Atrial fibrillation in the elderly population: Challenges and management considerations. Journal of arrhythmia, 37(4), 912–921. https://doi.org/10.1002/joa3.12580

157. Romero, I., Nedios, S., & Kriatselis, C. (2014). Diagnosis and management of atrial fibrillation: an overview. Cardiovascular therapeutics, 32(5), 242–252. https://doi.org/10.1111/1755-5922.12090

158. Dahya, V., & Taigen, T. L. (2019). Pharmacologic and Nonpharmacologic Management of Atrial Fibrillation. The Medical clinics of North America, 103(5), 835–846. https://doi.org/10.1016/j.mcna.2019.04.004

159. Kistler, P. M., & Habersberger, J. (2007). Management of atrial fibrillation. Australian family physician, 36(7), 506–511.

160. Kraft, M., Büscher, A., Wiedmann, F., L'hoste, Y., Haefeli, W. E., Frey, N., Katus, H. A., & Schmidt, C. (2021). Current Drug Treatment Strategies for Atrial Fibrillation and TASK-1

Inhibition as an Emerging Novel Therapy Option. Frontiers in pharmacology, 12, 638445. https://doi.org/10.3389/fphar.2021.638445

161. Van Gelder, I. C., Hagens, V. E., Bosker, H. A., Kingma, J. H., Kamp, O., Kingma, T., Said, S. A., Darmanata, J. I., Timmermans, A. J., Tijssen, J. G., Crijns, H. J., & Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group (2002). A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. The New England journal of medicine, 347(23), 1834–1840. https://doi.org/10.1056/NEJMoa021375

162. Díez-Villanueva, P., & Alfonso, F. (2019). Atrial fibrillation in the elderly. Journal of geriatric cardiology: JGC, 16(1), 49–53. https://doi.org/10.11909/j.issn.1671-5411.2019.01.005

163. Piccini, J. P., & Fauchier, L. (2016). Rhythm control in atrial fibrillation. Lancet (London, England), 388(10046), 829–840. https://doi.org/10.1016/S0140-6736(16)31277-6

164. Medical Advisory Secretariat (2006). Ablation for atrial fibrillation: an evidence-based analysis. Ontario health technology assessment series, 6(7), 1–63.

165. Camm, A. J., Naccarelli, G. V., Mittal, S., Crijns, H. J. G. M., Hohnloser, S. H., Ma, C. S., Natale, A., Turakhia, M. P., & Kirchhof, P. (2022). The Increasing Role of Rhythm Control in Patients With Atrial Fibrillation: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, *79*(19), 1932–1948. https://doi.org/10.1016/j.jacc.2022.03.337

167. Boursier-Bossy, V., Zuber, M., & Emmerich, J. (2020). Ischemic stroke and non-valvular atrial fibrillation: When to introduce anticoagulant therapy? Journal de medecine vasculaire, 45(2), 72–80. https://doi.org/10.1016/j.jdmv.2020.01.153

168. Yang, P. S., Pak, H. N., Park, D. H., Yoo, J., Kim, T. H., Uhm, J. S., Kim, Y. D., Nam, H. S., Joung, B., Lee, M. H., & Heo, J. H. (2018). Non-cardioembolic risk factors in atrial fibrillation-associated ischemic stroke. PloS one, 13(7), e0201062. https://doi.org/10.1371/journal.pone.0201062

169. Topcuoglu, M. A., Liu, L., Kim, D. E., & Gurol, M. E. (2018). Updates on Prevention of Cardioembolic Strokes. Journal of stroke, 20(2), 180–196. https://doi.org/10.5853/jos.2018.00780

170. Mitrousi, K., Lip, G., & Apostolakis, S. (2013). Age as a Risk Factor for Stroke in Atrial Fibrillation Patients: Implications in Thromboprophylaxis in the Era of Novel Oral Anticoagulants. Journal of atrial fibrillation, 6(1), 783. https://doi.org/10.4022/jafib.783

171. Kelly-Hayes M. (2010). Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. Journal of the American Geriatrics Society, 58 Suppl 2(Suppl 2), S325–S328. https://doi.org/10.1111/j.1532-5415.2010.02915.x

172. Fohtung, R. B. (2016). Washington University School of Medicine, St Louis, MO, Rich, MW, & Washington University School of Medicine, St Louis, MO. Identification of Patients at Risk of Stroke From Atrial Fibrillation. US Cardiology Review, 10(2), 1.

173. Marinigh, R., Lip, G. Y., Fiotti, N., Giansante, C., & Lane, D. A. (2010). Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. Journal of the American College of Cardiology, 56(11), 827–837. https://doi.org/10.1016/j.jacc.2010.05.028

174. Wagstaff, A. J., Overvad, T. F., Lip, G. Y., & Lane, D. A. (2014). Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM : monthly journal of the Association of Physicians*, *107*(12), 955–967. https://doi.org/10.1093/qjmed/hcu054

175. Lubitz, S. A., Bauer, K. A., Benjamin, E. J., Besdine, R. W., Forman, D. E., Gurol, M. E., Reddy, V. Y., & Singer, D. E. (2013). Stroke prevention in atrial fibrillation in older adults: existing knowledge gaps and areas for innovation: a summary of an American Federation for Aging research seminar. *Journal of the American Geriatrics Society*, *61*(10), 1798–1803. Https://doi.org/10.1111/jgs.12456

176. Odutayo, A., Wong, C. X., Hsiao, A. J., Hopewell, S., Altman, D. G., & Emdin, C. A. (2016). Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ (Clinical research ed.), 354, i4482. https://doi.org/10.1136/bmj.i4482

177. Sankaranarayanan, R., Kirkwood, G., Visweswariah, R., & Fox, D. J. (2015). How does Chronic Atrial Fibrillation Influence Mortality in the Modern Treatment Era?. Current cardiology reviews, 11(3), 190–198. https://doi.org/10.2174/1573403x10666140902143020

178. Jani, B. D., Nicholl, B. I., McQueenie, R., Connelly, D. T., Hanlon, P., Gallacher, K. I., Lee, D., & Mair, F. S. (2018). Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 20(FI_3), f329–f336. https://doi.org/10.1093/europace/eux322

179. Thacker, E. L., McKnight, B., Psaty, B. M., Longstreth, W. T., Jr, Sitlani, C. M., Dublin, S., Arnold, A. M., Fitzpatrick, A. L., Gottesman, R. F., & Heckbert, S. R. (2013). Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology, 81(2), 119–125. https://doi.org/10.1212/WNL.0b013e31829a33d1

180. Lee, E., Choi, E. K., Han, K. D., Lee, H., Choe, W. S., Lee, S. R., Cha, M. J., Lim, W. H., Kim, Y. J., & Oh, S. (2018). Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study. PloS one, 13(12), e0209687. https://doi.org/10.1371/Journal.pone.0209687

181. Kim, T. H., Yang, P. S., Yu, H. T., Jang, E., Uhm, J. S., Kim, J. Y., Pak, H. N., Lee, M. H., Joung, B., & Lip, G. (2018). Age Threshold for Ischemic Stroke Risk in Atrial Fibrillation. Stroke, 49(8), 1872–1879. https://doi.org/10.1161/STROKEAHA.118.021047

182. Benjamin, E. J., Wolf, P. A., D'Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*, *98*(10), 946–952. https://doi.org/10.1161/01.cir.98.10.946

183. Chen, J. Y., Zhang, A. D., Lu, H. Y., Guo, J., Wang, F. F., & Li, Z. C. (2013). CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *Journal of geriatric cardiology : JGC*, *10*(3), 258–266. https://doi.org/10.3969/j.issn.1671-5411.2013.03.004

184. JCS Joint Working Group (2014). Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). Circulation journal : official journal of the Japanese Circulation Society, 78(8), 1997–2021. https://doi.org/10.1253/circj.cj-66-0092

185. Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*, *285*(22), 2864–2870. https://doi.org/10.1001/jama.285.22.2864

186. Karthikeyan, G., & Eikelboom, J. W. (2010). The CHADS2 score for stroke risk stratification in atrial fibrillation--friend or foe?. *Thrombosis and haemostasis*, *104*(1), 45–48. https://doi.org/10.1160/TH09-11-0757

187. Coppens, M., Eikelboom, J. W., Hart, R. G., Yusuf, S., Lip, G. Y., Dorian, P., Shestakovska, O., & Connolly, S. J. (2013). The CHA2DS2-VASc score identifies those patients with atrial

fibrillation and a CHADS2 score of 1 who are unlikely to benefit from oral anticoagulant therapy. *European heart journal*, *34*(3), 170–176. https://doi.org/10.1093/eurheartj/ehs314

188. Jia, X., Levine, G. N., & Birnbaum, Y. (2018). The CHA_2DS_2-VASc score: Not as simple as it seems. *International journal of cardiology*, *257*, 92–96. https://doi.org/10.1016/j.ijcard.2017.12.027

189. Ding, W. Y., Harrison, S., Gupta, D., Lip, G. Y. H., & Lane, D. A. (2020). Stroke and Bleeding Risk Assessments in Patients With Atrial Fibrillation: Concepts and Controversies. *Frontiers in medicine*, *7*, 54. https://doi.org/10.3389/fmed.2020.00054

190. Odum, L. E., Cochran, K. A., Aistrope, D. S., & Snella, K. A. (2012). The $CHADS_2$versus the new CHA2DS2-VASc scoring systems for guiding antithrombotic treatment of patients with atrial fibrillation: review of the literature and recommendations for use. *Pharmacotherapy*, *32*(3), 285–296. https://doi.org/10.1002/j.1875-9114.2012.01023.x

191. Al-Turaiki, A. M., Al-Ammari, M. A., Al-Harbi, S. A., Khalidi, N. S., Alkatheri, A. M., Aldebasi, T. M., AbuRuz, S. M., & Albekairy, A. M. (2016). Assessment and comparison of CHADS2, CHA2DS2-VASc, and HAS-BLED scores in patients with atrial fibrillation in Saudi Arabia. *Annals of thoracic medicine*, *11*(2), 146–150. https://doi.org/10.4103/1817-1737.180026

192. Mant, J., Hobbs, F. R., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G. Y., ... & Midland Research Practices Network (MidReC. (2007). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. The Lancet, 370(9586), 493-503.

193. Xiong, Q., Chen, S., Senoo, K., Proietti, M., Hong, K., & Lip, G. Y. (2015). The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: A systemic review and meta-analysis. *International journal of cardiology*, *195*, 237–242. https://doi.org/10.1016/j.ijcard.2015.05.115

194. Olesen, J. B., Torp-Pedersen, C., Hansen, M. L., & Lip, G. Y. (2012). The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thrombosis and haemostasis*, *107*(6), 1172–1179. https://doi.org/10.1160/TH12-03-0175

195. Katritsis, D. G., Gersh, B. J., & Camm, A. J. (2015). Anticoagulation in Atrial Fibrillation - Current Concepts. Arrhythmia & electrophysiology review, 4(2), 100–107. https://doi.org/10.154

20/aer.2015.04.02.100

196. Chao, T. F., Nedeljkovic, M. A., Lip, G., & Potpara, T. S. (2020). Stroke prevention in atrial fibrillation: comparison of recent international guidelines. European heart journal supplements : journal of the European Society of Cardiology, 22(Suppl O), O53–O60. https://doi.org/10.1093/eurheartj/suaa180

197. Proietti, M., Romiti, G. F., Vitolo, M., Potpara, T. S., Boriani, G., & Lip, G. (2021). Comparison of HAS-BLED and ORBIT Bleeding Risk Scores in AF Patients treated with NOACs: A Report from the ESC-EHRA EORP-AF General Long-Term Registry. European heart journal. Quality of care & clinical outcomes, qcab069. Advance online publication. https://doi.org/10.1093/ehjqcco/qcab069

198. Zhu, W., He, W., Guo, L., Wang, X., & Hong, K. (2015). The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. Clinical cardiology, 38(9), 555–561. https://doi.org/10.1002/clc.22435

199. Pisters, R., Lane, D. A., Nieuwlaat, R., de Vos, C. B., Crijns, H. J., & Lip, G. Y. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest, 138(5), 1093–1100. https://doi.org/10.1378/chest.10-0134

200. Okutucu, S., & Gorenek, B. (2022). Current Recommendations on Atrial Fibrillation: A Comparison of the Recent European and Canadian Guidelines. Cardiology, 147(1), 81–89. https://doi.org/10.1159/000519465

201. Merli, G. J., & Fink, J. (2008). Vitamin K and thrombosis. Vitamins and hormones, 78, 265–279. https://doi.org/10.1016/S0083-6729(07)00013-1

202. Dowd, P., Ham, S. W., Naganathan, S., & Hershline, R. (1995). The mechanism of action of vitamin K. *Annual review of nutrition*, *15*, 419–440. https://doi.org/10.1146/annurev.nu.15.070195.002223

203. Lapostolle, F., Siguret, V., Martin, A. C., Pailleret, C., Vigué, B., Zerbib, Y., & Tazarourte, K. (2018). Vitamin K antagonists and emergencies. *European journal of emergency medicine : official journal of the European Society for Emergency Medicine*, *25*(6), 378–386. https://doi.org/10.1097/MEJ.0000000000000541

204. Sohara, H., Amitani, S., Kurose, M., & Miyahara, K. (1997). Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. Journal of the American College of Cardiology, 29(1), 106–112. https://doi.org/10.1016/s0735-1097(96)00427-5

205. Gustafsson, C., Blombäck, M., Britton, M., Hamsten, A., & Svensson, J. (1990). Coagulation factors and the increased risk of stroke in nonvalvular atrial fibrillation. Stroke, 21(1), 47–51. https://doi.org/10.1161/01.str.21.1.47

206. Riva, N., & Ageno, W. (2015). Pros and cons of vitamin K antagonists and non-vitamin K antagonist oral anticoagulants. *Seminars in thrombosis and hemostasis*, *41*(2), 178–187. https://doi.org/10.1055/s-0035-1544231

207. Van Gorp, R. H., & Schurgers, L. J. (2015). New Insights into the Pros and Cons of the Clinical Use of Vitamin K Antagonists (VKAs) Versus Direct Oral Anticoagulants (DOACs). Nutrients, 7(11), 9538–9557. https://doi.org/10.3390/nu7115479

208. Schein, J. R., White, C. M., Nelson, W. W., Kluger, J., Mearns, E. S., & Coleman, C. I. (2016). Vitamin K antagonist use: evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. Thrombosis journal, 14, 14. https://doi.org/10.1186/s12959-016-0088-y

209. Patel S, Singh R, Preuss CV, et al. Warfarin. [Updated 2022 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470313/

210. Harter, K., Levine, M., & Henderson, S. O. (2015). Anticoagulation drug therapy: a review. The western journal of emergency medicine, 16(1), 11–17.https://doi.org/10.5811/westjem.2014.12.22933

211. Asiimwe, I. G., & Pirmohamed, M. (2022). Ethnic Diversity and Warfarin Pharmacogenomics. Frontiers in pharmacology, 13, 866058. https://doi.org/10.3389/fphar.2022.866058

212. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503. doi: 10.1016/S0140-6736(07)61233-1. PMID: 17693178.

213. Zirlik, A., & Bode, C. (2017). Vitamin K antagonists: relative strengths and weaknesses vs. direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. Journal of thrombosis and thrombolysis, 43(3), 365–379. https://doi.org/10.1007/s11239-016-1446-0

214. Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine, 146(12), 857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007

215. Jowett, S., Bryan, S., Mant, J., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G. Y., & Hobbs, F. D. (2011). Cost effectiveness of warfarin versus aspirin in patients older than 75 years with atrial fibrillation. Stroke, 42(6), 1717–1721. https://doi.org/10.1161/STROKEAHA.110.600767

216. Hanley J. P. (2004). Warfarin reversal. Journal of clinical pathology, 57(11), 1132–1139. https://doi.org/10.1136/jcp.2003.008904

217. Pirmohamed M. (2006). Warfarin: almost 60 years old and still causing problems. British journal of clinical pharmacology, 62(5), 509–511. https://doi.org/10.1111/j.1365-2125.2006.02806.x

218. Wong C. W. (2016). Anticoagulation for stroke prevention in elderly patients with non-valvular atrial fibrillation: what are the obstacles?. Hong Kong medical journal = Xianggang yi xue za zhi, 22(6), 608–615. https://doi.org/10.12809/hkmj154803

219. DiMarco, J. P., Flaker, G., Waldo, A. L., Corley, S. D., Greene, H. L., Safford, R. E., Rosenfeld, L. E., Mitrani, G., Nemeth, M., & AFFIRM Investigators (2005). Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. American heart journal, 149(4), 650–656. https://doi.org/10.1016/j.ahj.2004.11.015

220. Sterne JAC, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Southampton (UK): NIHR Journals Library; 2017 Mar. (Health Technology Assessment, No. 21.9.) Chapter 1, Background. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425026/

221. Barmore W, Bajwa T, Burns B. Biochemistry, Clotting Factors. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507850/

222. Urbonas, G., Valius, L., Šakalytė, G., Petniūnas, K., & Petniūnienė, I. (2019). The Quality of Anticoagulation Therapy among Warfarin-Treated Patients with Atrial Fibrillation in a Primary Health Care Setting. Medicina (Kaunas, Lithuania), 55(1), 15. https://doi.org/10.3390/medicina55010015

223. Emren, Z. Y., Şenöz, O., Erseçgin, A., & Emren, S. V. (2021). Evaluation of Bleeding Rate and Time in Therapeutic Range in Patients Using Warfarin Before and During the COVID-19 Pandemic-Warfarin Treatment in COVID-19. Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis, 27, 10760296211021495. https://doi.org/10.1177/10760296211021495

224. Liyew, Z., Tadesse, A., Bekele, N., & Tsegaye, T. (2021). Evaluation of Anticoagulation Control among Patients Taking Warfarin in University of Gondar Hospital, Northwest Ethiopia. Advances in hematology, 2021, 7530997. https://doi.org/10.1155/2021/7530997

225. Shameem, R., & Ansell, J. (2013). Disadvantages of VKA and requirements for novel anticoagulants. Best practice & research. Clinical haematology, 26(2), 103–114. https://doi.org/10.1016/j.beha.2013.07.009

226. Wan, D., Healey, J. S., & Simpson, C. S. (2018). The Guideline-Policy Gap in Direct-Acting Oral Anticoagulants Usage in Atrial Fibrillation: Evidence, Practice, and Public Policy Considerations. The Canadian journal of cardiology, 34(11), 1412–1425. https://doi.org/10.1016/j.cjca.2018.07.476

227. Shameem, R., & Ansell, J. (2013). Disadvantages of VKA and requirements for novel anticoagulants. Best practice & research. Clinical haematology, 26(2), 103–114. https://doi.org/10.1016/j.beha.2013.07.009

228. Schwarb, H., & Tsakiris, D. A. (2016). New Direct Oral Anticoagulants (DOAC) and Their Use Today. Dentistry journal, 4(1), 5. https://doi.org/10.3390/dj4010005

229. Wan, D., Healey, J. S., & Simpson, C. S. (2018). The Guideline-Policy Gap in Direct-Acting Oral Anticoagulants Usage in Atrial Fibrillation: Evidence, Practice, and Public Policy Considerations. The Canadian journal of cardiology, 34(11), 1412–1425. https://doi.org/10.1016/j.cjca.2018.07.476

230. Maruhashi, T., & Higashi, Y. (2020). Antithrombotic therapy for stroke prevention in patients with atrial fibrillation in Japan. Expert opinion on pharmacotherapy, 21(17), 2115–2124. https://doi.org/10.1080/14656566.2020.1799976

231. Xian, Y., Xu, H., O'Brien, E. C., Shah, S., Thomas, L., Pencina, M. J., Fonarow, G. C., Olson, D. M., Schwamm, L. H., Bhatt, D. L., Smith, E. E., Hannah, D., Maisch, L., Lytle, B. L., Peterson, E. D., & Hernandez, A. F. (2019). Clinical Effectiveness of Direct Oral Anticoagulants vs Warfarin in Older Patients With Atrial Fibrillation and Ischemic Stroke: Findings From the Patient-Centered Research Into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study. JAMA neurology, 76(10), 1192–1202. https://doi.org/10.1001/jamaneurol.2019.2099

232. Hankey, G. J., & Eikelboom, J. W. (2011). Dabigatran etexilate: a new oral thrombin inhibitor. Circulation, 123(13), 1436–1450.https://doi.org/10.1161/CIRCULATIONAHA.110.004424

233. Bounameaux, H., & Camm, A. J. (2014). Edoxaban: an update on the new oral direct factor Xa inhibitor. Drugs, 74(11), 1209–1231. https://doi.org/10.1007/s40265-014-0261-1

234. Chaudhary, R., Sharma, T., Garg, J., Sukhi, A., Bliden, K., Tantry, U., Turagam, M., Lakkireddy, D., & Gurbel, P. (2020). Direct oral anticoagulants: a review on the current role and scope of reversal agents. Journal of thrombosis and thrombolysis, 49(2), 271–286. https://doi.org/10.1007/s11239-019-01954-2

235. White, K., Faruqi, U., & Cohen, A. (2022). New agents for DOAC reversal: a practical management review. The British journal of cardiology, 29(1), 1. https://doi.org/10.5837/bjc.2022.001

236. Huiart, L., Ferdynus, C., Renoux, C., Beaugrand, A., Lafarge, S., Bruneau, L., Suissa, S., Maillard, O., & Ranouil, X. (2018). Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross-sectional study in the French health insurance databases. BMJ open, 8(3), e018180. https://doi.org/10.1136/bmjopen-2017-018180

237. Cheng, W. H., Chiang, C. E., Lin, Y. J., Chang, S. L., Lo, L. W., Hu, Y. F., Tuan, T. C., Liao, J. N., Chung, F. P., Chen, T. J., Lip, G. Y. H., Chen, S. A., & Chao, T. F. (2021). Non-Vitamin K Antagonist Oral Anticoagulants in Elderly (≥85 years) Patients With Newly Diagnosed Atrial Fibrillation: Changing Clinical Practice and Outcomes for Stroke Prevention in a Nationwide Cohort Study. *Mayo Clinic proceedings*,*96*(1), 52–65. https://doi.org/10.1016/j.mayocp.2020.08.042

238. Schuh, T., Reichardt, B., Finsterer, J., & Stöllberger, C. (2016). Age-dependency of prescribing patterns of oral anticoagulant drugs in Austria during 2011-2014. *Journal of thrombosis and thrombolysis*, *42*(3), 447–451. https://doi.org/10.1007/s11239-016-1380-1

239. Kager, C. C., Horsselenberg, M., Korevaar, J. C., Wagner, C., & Hek, K. (2023). Pattern of oral anticoagulant prescribing for atrial fibrillation in general practice: an observational study in The Netherlands. *BJGP open*, BJGPO.2022.0179. Advance online publication. https://doi.org/10.3399/BJGPO.2022.0179

240. Staerk, L., Fosbøl, E., Gadsbøll, K. et al (2016). Non-vitamin K antagonist oral anticoagulation usage according to age among patients with atrial fibrillation: Temporal trends 2011–2015 in Denmark. Sci Rep 6, 31477. https://doi.org/10.1038/srep31477

241. Ko, D., Lin, K. J., Bessette, L. G., Lee, S. B., Walkey, A. J., Cheng, S., Kim, E., Glynn, R. J., & Kim, D. H. (2022). Trends in Use of Oral Anticoagulants in Older Adults With Newly Diagnosed Atrial Fibrillation, 2010-2020. *JAMA network open*, *5*(11), e2242964. https://doi.org/10.1001/jamanetworkopen.2022.42964

242. Douros, A., Cui, Y., Platt, R. W., Filion, K. B., Sebastiani, G., & Renoux, C. (2022). Utilization and long-term persistence of direct oral anticoagulants among patients with nonvalvular atrial fibrillation and liver disease. British journal of clinical pharmacology, 88(3), 994–1009. https://doi.org/10.1111/bcp.15046

243. Kattoor, A. J., Pothineni, N. V., Goel, A., Syed, M., Syed, S., Paydak, H., & Mehta, J. L. (2019). Prescription Patterns and Outcomes of Patients With Atrial Fibrillation Treated With Direct Oral Anticoagulants and Warfarin: A Real-World Analysis. Journal of cardiovascular pharmacology and therapeutics, 24(5), 428–434. https://doi.org/10.1177/1074248419841634

244. Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P. A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B. S., Darius, H., Diener, H. C., Joyner, C. D., Wallentin, L., … RE-LY Steering Committee and Investigators (2009). Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine, 361(12), 1139–1151. https://doi.org/10.1056/NEJMoa0905561

245. Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., Breithardt, G., Halperin, J. L., Hankey, G. J., Piccini, J. P., Becker, R. C., Nessel, C. C., Paolini, J. F., Berkowitz, S. D., Fox, K. A., Califf, R. M., & ROCKET AF Investigators (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine, 365(10), 883–891. https://doi.org/10.1056/NEJMoa1009638

246. Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., Al-Khalidi, H. R., Ansell, J., Atar, D., Avezum, A., Bahit, M. C., Diaz, R., Easton, J. D.,

Ezekowitz, J. A., Flaker, G., Garcia, D., Geraldes, M., Gersh, B. J., Golitsyn, S., Goto, S., … ARISTOTLE Committees and Investigators (2011). Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine, 365(11), 981–992. https://doi.org/10.1056/NEJMoa1107039

247. Giugliano, R. P., Ruff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D., Halperin, J. L., Waldo, A. L., Ezekowitz, M. D., Weitz, J. I., Špinar, J., Ruzyllo, W., Ruda, M., Koretsune, Y., Betcher, J., Shi, M., Grip, L. T., Patel, S. P., Patel, I., Hanyok, J. J., Mercuri, M., … ENGAGE AF-TIMI 48 Investigators (2013). Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine, 369(22), 2093–2104. https://doi.org/10.1056/NEJMoa1310907

248. Graham, D. J., Baro, E., Zhang, R., Liao, J., Wernecke, M., Reichman, M. E., Hu, M., Illoh, O., Wei, Y., Goulding, M. R., Chillarige, Y., Southworth, M. R., MaCurdy, T. E., & Kelman, J. A. (2019). Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. The American journal of medicine, 132(5), 596–604.e11. https://doi.org/10.1016/j.amjmed.2018.12.023

249. Lip, G. Y. H., Keshishian, A., Li, X., Hamilton, M., Masseria, C., Gupta, K., Luo, X., Mardekian, J., Friend, K., Nadkarni, A., Pan, X., Baser, O., & Deitelzweig, S. (2018). Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. Stroke, 49(12), 2933–2944. https://doi.org/10.1161/STROKEAHA.118.020232

250. Gupta, K., Trocio, J., Keshishian, A., Zhang, Q., Dina, O., Mardekian, J., Nadkarni, A., & Shank, T. C. (2019). Effectiveness and safety of direct oral anticoagulants compared to warfarin in treatment naïve non-valvular atrial fibrillation patients in the US Department of defense population. BMC cardiovascular disorders, 19(1), 142. https://doi.org/10.1186/s12872-019-11161

251. Yao, X., Abraham, N. S., Sangaralingham, L. R., Bellolio, M. F., McBane, R. D., Shah, N. D., & Noseworthy, P. A. (2016). Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. Journal of the American Heart Association, 5(6), e003725. Chicago

252. Lip, G. Y., Pan, X., Kamble, S., Kawabata, H., Mardekian, J., Masseria, C., Bruno, A., & Phatak, H. (2016). Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. International journal of clinical practice, 70(9), 752–763. https://doi.org/10.1111/ijcp.12863

253. Larsen, T. B., Skjøth, F., Nielsen, P. B., Kjældgaard, J. N., & Lip, G. Y. (2016). Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. bmj, 353.

254. Halvorsen, S., Ghanima, W., Fride Tvete, I., Hoxmark, C., Falck, P., Solli, O., & Jonasson, C. (2017). A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. European heart journal. Cardiovascular pharmacotherapy, 3(1), 28–36. https://doi.org/10.1093/ehjcvp/pvw031

255. Marston, X. L., Wang, R., Yeh, Y. C., Zimmermann, L., Ye, X., Gao, X., Brüggenjürgen, B., & Unverdorben, M. (2022). Comparison of clinical outcomes of edoxaban versus apixaban, dabigatran, rivaroxaban, and vitamin K antagonists in patients with atrial fibrillation in Germany: A real-world cohort study. *International journal of cardiology*, *346*, 93–99. https://doi.org/10.1016/j.ijcard.2021.11.008

256. Chan, Y. H., Lee, H. F., See, L. C., Tu, H. T., Chao, T. F., Yeh, Y. H., Wu, L. S., Kuo, C. T., Chang, S. H., & Lip, G. Y. H. (2019). Effectiveness and Safety of Four Direct Oral Anticoagulants in Asian Patients with Nonvalvular Atrial Fibrillation. Chest, 156(3), 529–543. https://doi.org/10.1016/j.chest.2019.04.108

257. Hernandez, I., Zhang, Y., & Saba, S. (2017). Comparison of the Effectiveness and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Newly Diagnosed Atrial Fibrillation. The American journal of cardiology, 120(10), 1813–1819. https://doi.org/10.1016/j.amjcard.2017.07.092

258. Rutherford, O. W., Jonasson, C., Ghanima, W., Söderdahl, F., & Halvorsen, S. (2020). Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. European heart journal. Cardiovascular pharmacothera
py, 6(2), 75–85.https://doi.org/10.1093/ehjcvp/pvz086

259. Nielsen, P. B., Søgaard, M., Jensen, M., Ording, A. G., & Lip, G. Y. (2022). Comparative effectiveness and safety of edoxaban versus warfarin in patients with atrial fibrillation: A nationwide cohort study. International journal of stroke : official journal of the International Stroke Society, 17(5), 536–544. https://doi.org/10.1177/17474930211029441

260. Grymonprez M, De Backer TL, Bertels X, Steurbaut S, Lahousse L. Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial

fibrillation: A nationwide cohort study. *Front Pharmacol*. 2023;14:1125576. Published 2023 Feb 2. doi:10.3389/fphar.2023.1125576

261. Durand, M., Schnitzer, M. E., Pang, M., Carney, G., Eltonsy, S., Filion, K. B., Fisher, A., Jun, M., Kuo, I. F., Renoux, C., Paterson, J. M., Quail, J., Matteau, A., & Canadian Network for Observational Drug Effect Studies Investigators (2020). Comparative effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists in nonvalvular atrial fibrillation: a Canadian multicentre observational cohort study. *CMAJ open*, *8*(4), E877–E886. https://doi.org/10.9778/cmajo.20200055

262. Liew, A., O'Donnell, M., & Douketis, J. (2014). Comparing mortality in patients with atrial fibrillation who are receiving a direct-acting oral anticoagulant or warfarin: a meta-analysis of randomized trials. *Journal of thrombosis and haemostasis : JTH*, *12*(9), 1419–1424. https://doi.org/10.1111/jth.12651

263. Alberts, M., Chen, Y. W., Lin, J. H., Kogan, E., Twyman, K., & Milentijevic, D. (2020). Risks of Stroke and Mortality in Atrial Fibrillation Patients Treated With Rivaroxaban and Warfarin. *Stroke*, *51*(2), 549–555. https://doi.org/10.1161/STROKEAHA.119.025554

264. de Lusignan, S., Hobbs, F. D. R., Liyanage, H., Sherlock, J., Ferreira, F., Tripathy, M., Heiss, C., Feher, M., & Joy, M. P. (2022). Long term follow up of direct oral anticoagulants and warfarin therapy on stroke, with all-cause mortality as a competing risk, in people with atrial fibrillation: Sentinel network database study. *PloS one*, *17*(9), e0265998. https://doi.org/10.1371/journal.pone.0265998

265. Chan, Y. H., Lee, H. F., Chao, T. F., Wu, C. T., Chang, S. H., Yeh, Y. H., See, L. C., Kuo, C. T., Chu, P. H., Wang, C. L., & Lip, G. Y. H. (2019). Real-world Comparisons of Direct Oral Anticoagulants for Stroke Prevention in Asian Patients with Non-valvular Atrial Fibrillation: a Systematic Review and Meta-analysis. *Cardiovascular drugs and therapy*, *33*(6), 701–710. https://doi.org/10.1007/s10557-019-06910-z

266. Ramagopalan, S. V., Sicras-Mainar, A., Polanco-Sanchez, C., Carroll, R., & de Bobadilla, J. F. (2019). Patient characteristics and stroke and bleeding events in nonvalvular atrial fibrillation patients treated with apixaban and vitamin K antagonists: a Spanish real-world study. Journal of comparative effectiveness research, 8(14), 1201–1212. https://doi.org/10.2217/cer-2019-0079

267. Deitelzweig, S., Luo, X., Gupta, K., Trocio, J., Mardekian, J., Curtice, T., Lingohr-Smith, M., Menges, B., & Lin, J. (2017). Comparison of effectiveness and safety of treatment with apixaban

vs. other oral anticoagulants among elderly nonvalvular atrial fibrillation patients. *Current medical research and opinion*, *33*(10), 1745–1754. https://doi.org/10.1080/03007995.2017.1334638

268. Amin, A., Keshishian, A., Trocio, J., Dina, O., Le, H., Rosenblatt, L., Liu, X., Mardekian, J., Zhang, Q., Baser, O., Nadkarni, A., & Vo, L. (2020). A Real-World Observational Study of Hospitalization and Health Care Costs Among Nonvalvular Atrial Fibrillation Patients Prescribed Oral Anticoagulants in the U.S. Medicare Population. *Journal of managed care & specialty pharmacy*, *26*(5), 639–651. https://doi.org/10.18553/jmcp.2020.26.5.639

269. Buckley, B. J. R., Lane, D. A., Calvert, P., Zhang, J., Gent, D., Mullins, C. D., Dorian, P., Kohsaka, S., Hohnloser, S. H., & Lip, G. Y. H. (2022). Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 11(13), 3788. https://doi.org/10.3390/jcm11133788

270. Kong CHD, Zhou J, Lee S, et al 193 Edoxaban versus warfarin on stroke risk in patients with atrial fibrillation: a territory-wide cohort study Heart 2021;107:A149-A150.

271. Noseworthy, P. A., Yao, X., Abraham, N. S., Sangaralingham, L. R., McBane, R. D., & Shah, N. D. (2016). Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation. Chest, 150(6), 1302–1312. https://doi.org/10.1016/j.chest.2016.07.013

272. Perreault, S., Dragomir, A., Côté, R., Lenglet, A., White-Guay, B., de Denus, S., Schnitzer, M. E., Dubé, M. P., Brophy, J. M., Dorais, M., & Tardif, J. C. (2021). Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: A propensity score-matched cohort study. Pharmacotherapy, 41(4), 379–393. https://doi.org/10.1002/phar.2509

273. Andersson, N. W., Svanström, H., Lund, M., Pasternak, B., & Melbye, M. (2018). Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation. International journal of cardiology, 268, 113–119. https://doi.org/10.1016/j.ijcard.2018.03.047

274. Adeboyeje, G., Sylwestrzak, G., Barron, J. J., White, J., Rosenberg, A., Abarca, J., Crawford, G., & Redberg, R. (2017). Major Bleeding Risk During Anticoagulation with Warfarin, Dabigatran, Apixaban, or Rivaroxaban in Patients with Nonvalvular Atrial Fibrillation. Journal of managed care & specialty pharmacy, 23(9), 968–978. https://doi.org/10.18553/jmcp.2017.23.9.968

275. Mueller, T., Alvarez-Madrazo, S., Robertson, C., Wu, O., & Bennie, M. (2019). Comparative safety and effectiveness of direct oral anticoagulants in patients with atrial fibrillation in clinical practice in Scotland. *British journal of clinical pharmacology*, *85*(2), 422–431. https://doi.org/10.1111/bcp.13814

276. Rodríguez-Bernal, C. L., Santa-Ana-Téllez, Y., García-Sempere, A., Hurtado, I., Peiró, S., & Sanfélix-Gimeno, G. (2021). Clinical outcomes of nonvitamin K oral anticoagulants and acenocoumarol for stroke prevention in contemporary practice: A population-based propensity-weighted cohort study. *British journal of clinical pharmacology*, *87*(2), 632–643. https://doi.org/10.1111/bcp.14430

277. Lip, G. Y. H., Keshishian, A. V., Zhang, Y., Kang, A., Dhamane, A. D., Luo, X., Klem, C., Ferri, M., Jiang, J., Yuce, H., & Deitelzweig, S. (2021). Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With High Risk of Gastrointestinal Bleeding. *JAMA network open*, *4*(8), e2120064. https://doi.org/10.1001/jamanetworkopen.2021.20064

278. Lau, W. C. Y., Torre, C. O., Man, K. K. C., Stewart, H. M., Seager, S., Van Zandt, M., Reich, C., Li, J., Brewster, J., Lip, G. Y. H., Hingorani, A. D., Wei, L., & Wong, I. C. K. (2022). Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation : A Multinational Population-Based Cohort Study. *Annals of internal medicine*, *175*(11), 1515–1524. https://doi.org/10.7326/M22-0511

279. Lin, L., Lim, W. S., Zhou, H. J., Khoo, A. L., Tan, K. T., Chew, A. P., Foo, D., Chin, J. J., & Lim, B. P. (2015). Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis. *Journal of the American Medical Directors Association*, *16*(12), . https://doi.org/10.1016/j.jamda.2015.09.008

280. Malik, A. H., Yandrapalli, S., Aronow, W. S., Panza, J. A., & Cooper, H. A. (2019). Meta-Analysis of Direct-Acting Oral Anticoagulants Compared With Warfarin in Patients >75 Years of Age. *The American journal of cardiology*, *123*(12), 2051–2057. https://doi.org/10.1016/j.amjcard.2019.02.060

281. Waite L. J. (2004). The Demographic Faces of the Elderly. Population and development review, 30(Supplement), 3–16.

282. Kalache, A., & Keller, I. (2000). The greying world: a challenge for the twenty-first century. Science progress, 83 (Pt 1), 33–54.

283. Christensen, K., Doblhammer, G., Rau, R., & Vaupel, J. W. (2009). Ageing populations: the challenges ahead. Lancet (London, England), 374(9696), 1196–1208. https://doi.org/10.1016/S0140-6736(09)61460-4

284. Beard, J. R., Officer, A., de Carvalho, I. A., Sadana, R., Pot, A. M., Michel, J. P., Lloyd-Sherlock, P., Epping-Jordan, J. E., Peeters, G., Mahanani, W. R., Thiyagarajan, J. A., & Chatterji, S. (2016). The World report on ageing and health: a policy framework for healthy ageing. Lancet (London, England), 387(10033), 2145–2154. https://doi.org/10.1016/S0140-6736(15)00516-4

285. Steffel, J., Collins, R., Antz, M., Cornu, P., Desteghe, L., Haeusler, K. G., Oldgren, J., Reinecke, H., Roldan-Schilling, V., Rowell, N., Sinnaeve, P., Vanassche, T., Potpara, T., Camm, A. J., Heidbüchel, H., & External reviewers (2021). 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*, *23*(10), 1612–1676. https://doi.org/10.1093/europace/euab065

286. Patti, G., Lucerna, M., Pecen, L., Siller-Matula, J. M., Cavallari, I., Kirchhof, P., & De Caterina, R. (2017). Thromboembolic Risk, Bleeding Outcomes and Effect of Different Antithrombotic Strategies in Very Elderly Patients With Atrial Fibrillation: A Sub-Analysis From the PREFER in AF (*PRE*vention o*F*Thromboembolic Events-*E*uropean *R*egistry in *A*trial *F*ibrillation). *Journal of the American Heart Association*, *6*(7), e005657. https://doi.org/10.1161/JAHA.117.005657

287. Dominguez, L. J., Galioto, A., Ferlisi, A., Pineo, A., Putignano, E., Belvedere, M., Costanza, G., & Barbagallo, M. (2006). Ageing, lifestyle modifications, and cardiovascular disease in developing countries. The journal of nutrition, health & aging, 10(2), 143–149.

288. Fang, M. C., Chen, J., & Rich, M. W. (2007). Atrial fibrillation in the elderly. The American journal of medicine, 120(6), 481–487. https://doi.org/10.1016/j.amjmed.2007.01.026

289. Zoni-Berisso, M., Lercari, F., Carazza, T., & Domenicucci, S. (2014). Epidemiology of atrial fibrillation: European perspective. *Clinical epidemiology*, *6*, 213–220. https://doi.org/10.2147/CLEP.S47385

290. Lloyd-Jones, D. M., Wang, T. J., Leip, E. P., Larson, M. G., Levy, D., Vasan, R. S., D'Agostino, R. B., Massaro, J. M., Beiser, A., Wolf, P. A., & Benjamin, E. J. (2004). Lifetime risk

for development of atrial fibrillation: the Framingham Heart Study. *Circulation*, *110*(9), 1042–1046. https://doi.org/10.1161/01.CIR.0000140263.20897.42

291. Russo, T., Felzani, G., & Marini, C. (2011). Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. *Journal of aging research*, *2011*, 108785. https://doi.org/10.4061/2011/108785

292. Abumuaileq RR. (2019). Atrial fibrillation in the old/very old: prevalence and burden, predisposing factors and complications. European Society of Cardiology, 22(1). Available from: https://www.escardio.org/Journals/E-Journal-of-CardiologyPractice/Volume-17/Atrial-fibrillation-in-the-old-very-old-prevalence-and-burden-predisposing-factors-and complications

293. Lindley R. I. (2018). Stroke Prevention in the Very Elderly. Stroke, 49(3), 796–802. https://doi.org/10.1161/STROKEAHA.117.017952

294. Suárez Fernández, C., Formiga, F., Camafort, M., Cepeda Rodrigo, M., Díez-Manglano, J., Pose Reino, A., Tiberio, G., Mostaza, J. M., & Grupo de trabajo de Riesgo vascular de la SEMI (2015). Antithrombotic treatment in elderly patients with atrial fibrillation: a practical approach. *BMC cardiovascular disorders*, *15*, 143. https://doi.org/10.1186/s12872-015-0137-7

295. Zappulla, P., & Calvi, V. (2021). Gastrointestinal Bleeding and Direct Oral Anticoagulants among Patients with Atrial Fibrillation: Risk, Prevention, Management, and Quality of Life. *TH open : companion journal to thrombosis and haemostasis*, *5*(2), e200–e210. https://doi.org/10.1055/s-0041-1730035

296. Carbone, A., Bottino, R., D'Andrea, A., & Russo, V. (2023). Direct Oral Anticoagulants for Stroke Prevention in Special Populations: Beyond the Clinical Trials. *Biomedicines*, *11*(1), 131. https://doi.org/10.3390/biomedicines11010131

297. Bonanad, C., García-Blas, S., Torres Llergo, J., Fernández-Olmo, R., Díez-Villanueva, P., Ariza-Solé, A., Martínez-Sellés, M., Raposeiras, S., Ayesta, A., Bertomeu-González, V., Tarazona Santabalbina, F., Facila, L., Vivas, D., Gabaldón-Pérez, A., Bodi, V., Nuñez, J., & Cordero, A. (2021). Direct Oral Anticoagulants versus Warfarin in Octogenarians with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Journal of clinical medicine*, *10*(22), 5268. https://doi.org/10.3390/jcm10225268

298. Ingrasciotta, Y., Fontana, A., Mancuso, A., Ientile, V., Sultana, J., Uomo, I., Pastorello, M., Calabrò, P., Andò, G., & Trifirò, G. (2021). Comparison of Direct Oral Anticoagulant Use for the Treatment of Non-Valvular Atrial Fibrillation in Pivotal Clinical Trials vs. the Real-World Setting:

A Population-Based Study from Southern Italy. *Pharmaceuticals (Basel, Switzerland)*, *14*(4), 290. https://doi.org/10.3390/ph14040290

299. Toader D. (2019). Treating atrial fibrillation in very old patients with new oral anticoagulation drugs: arguments pro and contra. European Society of Cardiology, 17(5). Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-17/treating-atrial-fibrillation-in-very-old-patients-with-new-oral-anticoagulation

300. Oqab, Z., Pournazari, P., & Sheldon, R. S. (2018). What is the Impact of Frailty on Prescription of Anticoagulation in Elderly Patients with Atrial Fibrillation? A Systematic Review and Meta-Analysis. *Journal of atrial fibrillation*, *10*(6), 1870. https://doi.org/10.4022/jafib.1870

301. Lee, J. Y., Oh, I. Y., Lee, J. H., Kim, S., Cho, J., Park, C. H., Yoo, S., & Bang, S. M. (2021). Drug-drug interactions in atrial fibrillation patients receiving direct oral anticoagulants. *Scientific reports*, *11*(1), 22403. https://doi.org/10.1038/s41598-021-01786-2

302. Foulon-Pinto, G., Lafuente-Lafuente, C., Jourdi, G., Guen, J. L., Tall, F., Puymirat, E., Delrue, M., Rivière, L., Ketz, F., Gouin-Thibault, I., Mullier, F., Gaussem, P., Pautas, E., Lecompte, T., Curis, E., & Siguret, V. (2023). Assessment of DOAC in GEriatrics (Adage Study): Rivaroxaban/Apixaban Concentrations and Thrombin Generation Profiles in NVAF Very Elderly Patients. *Thrombosis and haemostasis*, 10.1055/a-1981-1763. Advance online publication.https://doi.org/10.1055/a-1981-1763

303. Deng, K., Cheng, J., Rao, S., Xu, H., Li, L., & Gao, Y. (2020). Efficacy and Safety of Direct Oral Anticoagulants in Elderly Patients With Atrial Fibrillation: A Network Meta-Analysis. *Frontiers in medicine*, *7*, 107. https://doi.org/10.3389/fmed.2020.00107

304. Potpara, T. S., Mujovic, N., & Lip, G. Y. H. (2020). Challenges in stroke prevention among very elderly patients with atrial fibrillation: discerning facts from prejudices. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*, *22*(2), 173–176. https://doi.org/10.1093/europace/euz344

305. Alnsasra, H., Haim, M., Senderey, A. B., Reges, O., Leventer-Roberts, M., Arnson, Y., Leibowitz, M., Hoshen, M., & Avgil-Tsadok, M. (2019). Net clinical benefit of anticoagulant treatments in elderly patients with nonvalvular atrial fibrillation: Experience from the real world. *Heart rhythm*, *16*(1), 31–37. https://doi.org/10.1016/j.hrthm.2018.08.016

306. Liao, J. N., Chan, Y. H., Kuo, L., Tsai, C. T., Lim, S. S., & Chao, T. F. (2022). Optimal anticoagulation in elderly patients with atrial fibrillation: Which drug at which dose?. *Kardiologia polska*, *80*(2), 128–136. https://doi.org/10.33963/KP.a2022.0046

307. Desai, N. R., Krumme, A. A., Schneeweiss, S., Shrank, W. H., Brill, G., Pezalla, E. J., Spettell, C. M., Brennan, T. A., Matlin, O. S., Avorn, J., & Choudhry, N. K. (2014). Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *The American journal of medicine*, *127*(11), 1075–1082.e1. https://doi.org/10.1016/j.amjmed.2014.05.013

308. Weitz, J. I., Semchuk, W., Turpie, A. G., Fisher, W. D., Kong, C., Ciaccia, A., & Cairns, J. A. (2015). Trends in Prescribing Oral Anticoagulants in Canada, 2008-2014. *Clinical therapeutics*, *37*(11), 2506–2514.e4. https://doi.org/10.1016/j.clinthera.2015.09.008

309. Tsuji, N., Takahashi, Y., Sakai, M., Ohtera, S., Kaneyama, J., Cho, K., Kato, G., Ohtsuru, S., & Nakayama, T. (2023). Trend of anticoagulant therapy in elderly patients with atrial fibrillation considering risks of cerebral infarction and bleeding. *Scientific reports*, *13*(1), 192. https://doi.org/10.1038/s41598-022-26741-7

310. Alalwan, A. A., Voils, S. A., & Hartzema, A. G. (2017). Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*, *74*(16), 1237–1244. https://doi.org/10.2146/ajhp160756

311. Olesen, J. B., Sørensen, R., Hansen, M. L., Lamberts, M., Weeke, P., Mikkelsen, A. P., Køber, L., Gislason, G. H., Torp-Pedersen, C., & Fosbøl, E. L. (2015). Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace : European pacing, arrhythmias, and cardiac electrophsiol ogy : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellularel ectrophysiology of the European Society of Cardiology*, *17*(2), 187–193. https://doi.org/10.1093/europace/euu225

312. Navar, A. M., Kolkailah, A. A., Overton, R., Shah, N. P., Rousseau, J. F., Flaker, G. C., Pignone, M. P., & Peterson, E. D. (2022). Trends in Oral Anticoagulant Use Among 436 864 Patients With Atrial Fibrillation in Community Practice, 2011 to 2020. *Journal of the American Heart Association*, *11*(22), e026723. https://doi.org/10.1161/JAHA.122.026723

313. Gorczyca, I., Jelonek, O., Michalska, A., Chrapek, M., Wałek, P., & Wożakowska-Kapłon, B. (2020). Stroke prevention and guideline adherent antithrombotic treatment in elderly patients with atrial fibrillation: A real-world experience. *Medicine*, *99*(29), e21209. https://doi.org/10.1097/MD.0000000000021209

314. Bo, M., Grisoglio, E., Brunetti, E., Falcone, Y., & Marchionni, N. (2017). Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence. *European journal of internal medicine*, *41*, 18–27. https://doi.org/10.1016/j.ejim.2017.03.012

315. Vedovati, M. C., & Agnelli, G. (2022). Direct Oral Anticoagulants in Old and Frail Patients with Atrial Fibrillation: The Advantages of an Anticoagulation Service. *Journal of personalized medicine*, *12*(8), 1339. https://doi.org/10.3390/jpm12081339

316. Bonanad, C., Formiga, F., Anguita, M., Petidier, R., & Gullón, A. (2022). Oral Anticoagulant Use and Appropriateness in Elderly Patients with Atrial Fibrillation in Complex Clinical Conditions: ACONVENIENCE Study. *Journal of clinical medicine*, *11*(24), 7423. https://doi.org/10.3390/jcm11247423

317. Munir, M. B., Hlavacek, P., Keshishian, A., Guo, J. D., Mallampati, R., Ferri, M., Russ, C., Emir, B., Cato, M., Yuce, H., & Hsu, J. C. (2022). Oral anticoagulant underutilization among elderly patients with atrial fibrillation: insights from the United States Medicare database. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*, 10.1007/s10840-022-01274-1. Advance online publication. https://doi.org/10.1007/s10840-022-01274-1

318. Dalgaard, F., Xu, H., Matsouaka, R. A., Russo, A. M., Curtis, A. B., Rasmussen, P. V., Ruwald, M. H., Fonarow, G. C., Lowenstern, A., Hansen, M. L., Pallisgaard, J. L., Alexander, K. P., Alexander, J. H., Lopes, R. D., Granger, C. B., Lewis, W. R., Piccini, J. P., & Al-Khatib, S. M. (2020). Management of Atrial Fibrillation in Older Patients by Morbidity Burden: Insights From Get With The Guidelines-Atrial Fibrillation. *Journal of the American Heart Association*, *9*(23), e017024. https://doi.org/10.1161/JAHA.120.017024

319. Chao, T. F., Chan, Y. H., Chiang, C. E., Tuan, T. C., Liao, J. N., Chen, T. J., Lip, G. Y. H., & Chen, S. A. (2022). Stroke prevention with direct oral anticoagulants in high-risk elderly atrial fibrillation patients at increased bleeding risk. *European heart journal. Quality of care & clinical outcomes*, *8*(7), 730–738. https://doi.org/10.1093/ehjqcco/qcab076

320. Cavallari, I., & Patti, G. (2020). Primum non nocere does not justify clinical inertia for stroke prevention in elderly patients with atrial fibrillation in the era of direct oral anticoagulants. *European journal of internal medicine*, *71*, 11–12. https://doi.org/10.1016/j.ejim.2019.12.013

321. Ruff, C. T., Giugliano, R. P., Braunwald, E., Hoffman, E. B., Deenadayalu, N., Ezekowitz, M. D., Camm, A. J., Weitz, J. I., Lewis, B. S., Parkhomenko, A., Yamashita, T., & Antman, E. M. (2014). Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)*, *383*(9921),955–962. https://doi.org/10.1016/S0140-6736(13)62343-0

322. Turagam, M. K., Velagapudi, P., & Flaker, G. C. (2015). Stroke prevention in the elderly atrial fibrillation patient with comorbid conditions: focus on non-vitamin K antagonist oral anticoagulants. *Clinical interventions in aging*, *10*, 1431–1444. https://doi.org/10.2147/CIA.S80641

323. Lopes, R. D., Al-Khatib, S. M., Wallentin, L., Yang, H., Ansell, J., Bahit, M. C., De Caterina, R., Dorian, P., Easton, J. D., Erol, C., Ezekowitz, J. A., Gersh, B. J., Granger, C. B., Hohnloser, S. H., Horowitz, J., Hylek, E. M., McMurray, J. J., Mohan, P., Vinereanu, D., & Alexander, J. H. (2012). Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet (London, England)*, *380*(9855), 1749–1758. https://doi.org/10.1016/S0140-6736(12)60986-6

324. Cohen, A. T., Hill, N. R., Luo, X., Masseria, C., Abariga, S. A., & Ashaye, A. O. (2018). A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: A comparison of efficacy and safety following treatment with direct oral anticoagulants. *International journal of cardiology*, *269*, 174–181. https://doi.org/10.1016/j.ijcard.2018.06.114

325. Schaefer, J. K., McBane, R. D., & Wysokinski, W. E. (2016). How to choose appropriate direct oral anticoagulant for patient with nonvalvular atrial fibrillation. *Annals of hematology*, *95*(3), 437–449. https://doi.org/10.1007/s00277-015-2566-x

326. Nielsen, P. B., Skjøth, F., Søgaard, M., Kjældgaard, J. N., Lip, G. Y., & Larsen, T. B. (2017). Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ (Clinical research ed.)*, *356*, j510. https://doi.org/10.1136/bmj.j510

327. Chan, Y. H., Kuo, C. T., Yeh, Y. H., Chang, S. H., Wu, L. S., Lee, H. F., Tu, H. T., & See, L. C. (2016). Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation. *Journal of the American College of Cardiology*, *68*(13), 1389–1401. https://doi.org/10.1016/j.jacc.2016.06.062

328. Hernandez, I., Baik, S. H., Piñera, A., & Zhang, Y. (2015). Risk of bleeding with dabigatran in atrial fibrillation. *JAMA internal medicine*, *175*(1), 18–24. https://doi.org/10.1001/jamainternmed.2014.5398

329. Caldeira, D., Nunes-Ferreira, A., Rodrigues, R., Vicente, E., Pinto, F. J., & Ferreira, J. J. (2019). Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis. *Archives of gerontology and geriatrics*, *81*, 209–214. https://doi.org/10.1016/j.archger.2018.12.013

330. Silverio, A., Di Maio, M., Prota, C., De Angelis, E., Radano, I., Citro, R., Carrizzo, A., Ciccarelli, M., Vecchione, C., Capodanno, D., & Galasso, G. (2021). Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *European heart journal. Cardiovascular pharmacotherapy*, *7*(FI1), f20–f29. https://doi.org/10.1093/ehjcvp/pvz073

331. Silverio, A., Di Maio, M., Prota, C., De Angelis, E., Radano, I., Citro, R., Carrizzo, A., Ciccarelli, M., Vecchione, C., Capodanno, D., & Galasso, G. (2021). Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *European heart journal. Cardiovascular pharmacotherapy*, *7*(FI1), f20–f29. https://doi.org/10.1093/ehjcvp/pvz073

332. Rutherford, O. W., Jonasson, C., Ghanima, W., Söderdahl, F., & Halvorsen, S. (2022). Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. *Heart (British Cardiac Society)*, *108*(5), 345–352. https://doi.org/10.1136/heartjnl-2020-318753

333. Fralick, M., Colacci, M., Schneeweiss, S., Huybrechts, K. F., Lin, K. J., & Gagne, J. J. (2020). Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice: A Cohort Study. *Annals of internal medicine*, *172*(7), 463–473. https://doi.org/10.7326/M19-2522

334. Daniel Víctor, O. (2022). Use of Non-Vitamin K-Dependent Oral Anticoagulants in Elderly and Fragile Patients with Atrial Fibrillation. Anticoagulation-Current Perspectives. doi:10.5772/intechopen.103033

335. Li, G., Lip, G., Holbrook, A., Chang, Y., Larsen, T. B., Sun, X., Tang, J., Mbuagbaw, L., Witt, D. M., Crowther, M., Thabane, L., & Levine, M. (2019). Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. European journal of epidemiology, 34(2), 173–190. https://doi.org/10.1007/s10654-018-0415-7

336. Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology*, *44*(3), 827–836. https://doi.org/10.1093/ije/dyv098

337. Clinical Practice Research Datalink (2022, November 10). Data. Available from: https://cprd .com/data

338. Clinical Practice Research Datalink (2022, January 17). Join the growing network of practices contributing to CPRD. Available from: https://cprd.com/join-growing-network-practices-contribu ting-cprd

339. Clinical Practice Research Datalink (2023, February 16). CPRD linked data. Available from: https://cprd.com/cprd-linked-data

340. Padmanabhan, S., Carty, L., Cameron, E., Ghosh, R. E., Williams, R., & Strongman, H. (2019). Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. *European journal of epidemiology*, *34*(1), 91–99. https://doi.org/10.1007/s10654-018-0442-4

341. Clinical Practice Research Datalink (2023, April 5).Data highlights. Available from: https://c prd.com/data-highlights

342. Clinical Practice Research Datalink (2022, September 26). Using CPRD Primary care data. Available from: https://cprd.com/using-cprd-primary-care-data

343. Clinical Practice Research Datalink (2023, February 3). Defining your study population. Available from: https://cprd.com/defining-your-study-population

344. Clinical Practice Research Datalink (2022, January 5). CPRD GOLD Data Specification. Available from: https://cprd.com/sites/default/files/202210/CPRD%20GOLD%20Full%20Data %20Specification%20v2.5%20update.pdf

345. Clinical Practice Research Datalink (2022, August 10). CPRD Aurum Data Specification. Available from: htt ps://cprd.com/sites/default/files/202208/CPRD%20Aurum%20Data%20Speci fication%20v2.pdf

346. Wolf, A., Dedman, D., Campbell, J., Booth, H., Lunn, D., Chapman, J., & Myles, P. (2019). Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International journal of epidemiology, 48(6), 1740–1740g. https://doi.org/10.1093/ije/dyz034

347. Jick, S. S., Hagberg, K. W., Persson, R., Vasilakis-Scaramozza, C., Williams, T., Crellin, E., & Myles, P. (2020). Quality and completeness of diagnoses recorded in the new CPRD Aurum Database: evaluation of pulmonary embolism. Pharmacoepidemiology and drug safety, 29(9), 1134–1140. https://doi.org/10.1002/pds.4996

348. Mahadevan, P., Harley, M., Fordyce, S., Hodgson, S., Ghosh, R., Myles, P., Booth, H., & Axson, E. (2022). Completeness and representativeness of small area socioeconomic data linked with the UK Clinical Practice Research Datalink (CPRD). Journal of epidemiology and community health, jech-2022-219200. Advance online publication. https://doi.org/10.1136/jech-2022-219200

349. Clinical Practice Research Datalink (2022, January 22). Hospital Episode Statistics (HES) Admitted Patient Care and CPRD primary care data Documentation. https://cprd.com/sites/default/files/2022-02/Documentation_HES_APC_set22.pdf

350. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D., & Hardelid, P. (2017). Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International journal of epidemiology, 46(4), 1093–1093i. https://doi.org/10.1093/ije/dyx015

351. Clinical Practice Research Datalink (2022, January 22). ONS death registration data and CPRD primary care data Documentation. https://cprd.com/sites/default/files/2022-02/Documentation_Death_set22_v2.6.pdf

352. Desai, R. J., & Franklin, J. M. (2019). Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ (Clinical research ed.), 367, l5657. https://doi.org/10.1136/bmj.l5657

353. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. E*pidemiology*. 2017;28(2):249-257. doi:10.1097/EDE.0000000000000595

354. White, I. R., & Royston, P. (2009). Imputing missing covariate values for the Cox model. Statistics in medicine, 28(15), 1982–1998. https://doi.org/10.1002/sim.3618

355. Rubin DB, Wiley I. (1987). *Multiple imputation for nonresponse in surveys*. John Wiley & Sons, Inc. http://dx.doi.org/10.1002/9780470316696

356. Eikelboom, J. W., & Weitz, J. I. (2023). Direct Oral Anticoagulants in the Very Elderly. Thrombosis and haemostasis, 123(4), 377–379. https://doi.org/10.1055/a-2021-8910

357. Fava, J. P., Starr, K. M., Ratz, D., & Clemente, J. L. (2018). Dosing challenges with direct oral anticoagulants in the elderly: a retrospective analysis. Therapeutic advances in drug safety, 9(8), 405–414. https://doi.org/10.1177/2042098618774498

358. Grymonprez, M., Petrovic, M., De Backer, T. L., Steurbaut, S., & Lahousse, L. (2023). Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study. *European heart journal. Quality of care & clinical outcomes*, qcad019. Advance online publication. https://doi.org/10.1093/ehjqcco/qcad019

359. Lip, G. Y. H., Keshishian, A. V., Kang, A. L., Dhamane, A. D., Luo, X., Li, X., Balachander, N., Rosenblatt, L., Mardekian, J., Pan, X., Di Fusco, M., Garcia Reeves, A. B., Yuce, H., & Deitelzweig, S. (2021). Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study. Journal of internal medicine, 289(1), 42–52. https://doi.org/10.1111/joim.13140