Effectiveness and safety of apixaban versus rivaroxaban in patients with nonvalvular atrial fibrillation and type 2 diabetes mellitus

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Abstract

Background: Patients with both diabetes mellitus and nonvalvular atrial fibrillation (NVAF) have a 70% increased risk of stroke compared with patients having NVAF alone. Thus, oral anticoagulation, preferably with direct oral anticoagulants, is recommended for stroke prevention in this high-risk population. Apixaban and rivaroxaban are the most commonly prescribed direct oral anticoagulants in patients with NVAF. However, there is limited evidence on the comparative effectiveness and safety of apixaban and rivaroxaban in patients with both NVAF and diabetes mellitus. This knowledge gap needs to be addressed to guide decision-making for patients and clinicians.

Objectives: The overall objective of this thesis was to evaluate the effectiveness and safety of apixaban compared with rivaroxaban in patients with NVAF and type 2 diabetes mellitus (T2DM). Specifically, we assessed separately the risk of ischemic stroke and major bleeding associated with apixaban compared with rivaroxaban. We also assessed the risk of major adverse limb events as a secondary outcome.

Methods: This study was conducted using the United Kingdom's Clinical Practice Research Datalink linked to the Hospital Episode Statistics repository, and the Office for National Statistics database. We assembled a cohort of all patients with NVAF and T2DM newly treated with apixaban or rivaroxaban between January 1, 2013 and March 31, 2020. Cohort entry was defined as the date of the first prescription following AF diagnosis and patients were censored at the date of treatment switching or discontinuation. We used propensity score with standardised mortality ratio weighting to control for confounding. Weighted Cox proportional hazards models with robust sandwich variance were used to estimate separately the hazard ratios (HRs) with 95% confidence intervals (CIs) of ischemic stroke, major bleeding, and major limb events associated with current use of apixaban compared with current use of rivaroxaban. In secondary analyses, we assessed whether the risk was modified by age, sex, microvascular and macrovascular complications of diabetes, nephropathy, CHA_2DS_2-VASc and HAS-BLED (for major bleeding) scores. Finally, we performed several sensitivity analyses to assess the robustness of our results.

Results: The cohort included 11,561 apixaban users and 8,265 rivaroxaban users. Apixaban was as effective as rivaroxaban in preventing ischemic stroke (incidence rates 23.4 vs. 18.4 per 1000 person-years, respectively; HR 0.99, 95% CI 0.79-1.23). Apixaban was associated with a 32% reduced risk of major bleeding (43.6 vs. 54.7 per 1000 person-years, respectively; HR 0.68, 95% CI 0.59-0.78), compared with rivaroxaban. Finally, the risk of major adverse limb events was similar between apixaban and rivaroxaban (9.3 vs. 9.5 per 1000 person-years, respectively; HR 0.75, 95% CI 0.54-1.04). Overall, the risk of ischemic stroke and major bleeding was not modified by age, sex, duration of diabetes, vascular complications of diabetes, nephropathy, CHA_2DS_2-VASc or HAS-BLED scores. The results were consistent across sensitivity analyses.

Conclusions: In patients with NVAF and T2DM, apixaban had similar effectiveness, and was associated with a lower risk of bleeding compared with rivaroxaban. The results of this study may help inform the choice of an oral anticoagulant in this high-risk population.

Résumé

Contexte: Les patients souffrant à la fois de diabète et de fibrillation auriculaire non valvulaire (FA) présentent un risque d'accident ischémique cérébrale (AIC) accru de 70 % par rapport aux patients atteints de FA. Ainsi, l'anticoagulation orale, de préférence avec des anticoagulants oraux directs, est recommandée en prévention des AIC dans cette population à haut risque. L'apixaban et le rivaroxaban sont les anticoagulants oraux directs les plus couramment prescrits chez les patients atteints de FA. Cependant, il existe peu de données sur l'efficacité et l'innocuité de l'apixaban comparativement au rivaroxaban chez les patients atteints de FA et de diabète. Cette lacune dans les connaissances doit être comblée afin de guider les cliniciens et leurs patients dans le choix d'un traitement anticoagulant.

Objectifs: L'objectif global de cette thèse était d'évaluer l'efficacité et l'innocuité de l'apixaban comparativement au rivaroxaban chez les patients atteints de FA et de diabète de type 2. Plus précisément, nous avons évalué séparément le risque d'AIC et de saignement majeur associés à l'apixaban par rapport au rivaroxaban. Nous avons également évalué le risque d'événements indésirables majeurs des membres (ischémie artérielle et amputation) en objectif secondaire.

Méthodes: Cette étude a été menée en utilisant le Clinical Practice Research Datalink du Royaume-Uni lié aux données hospitalières Hospital Episode Statistics, et aux données de mortalité de l'Office for National Statistics britannique. Nous avons constitué une cohorte incluant tous les patients atteints de FA et de diabète de type 2 nouvellement traités par apixaban ou rivaroxaban entre le 1er janvier 2013 et le 31 mars 2020. L'entrée dans la cohorte a été définie comme la date de la première prescription après le diagnostic de FA et les patients ont été censurés à la date de changement ou d'arrêt du traitement. Nous avons utilisé les scores de propension avec pondération de la cohorte par le ratio de mortalité standardisé (*standardized mortality ratio weights*) pour contrôler les facteurs de confusion. Des modèles des risques proportionnels de Cox ont été utilisés pour estimer séparément les rapports de taux d'incidence (*hazard ratio*, HR) avec intervalles de confiance (IC) à 95% d'AIC, de saignement majeur et d'événements majeurs des membres associés à l'utilisation de l'apixaban comparativement au rivaroxaban. En analyses secondaires, nous avons évalué si le risque était modifié par l'âge, le sexe, les complications microvasculaires et macrovasculaires du diabète, la néphropathie, les scores CHA_2DS_2-VASc et

HAS-BLED (pour les saignements majeurs). Enfin, nous avons effectué plusieurs analyses de sensibilité pour évaluer la robustesse de nos résultats.

Résultats: La cohorte incluait 11 561 utilisateurs d'apixaban et 8 265 utilisateurs de rivaroxaban. L'apixaban était aussi efficace que le rivaroxaban dans la prévention des AIC (taux d'incidence 23,4 vs 18,4 pour 1000 personnes-années respectivement; HR 0,99, IC 95% 0,79-1,23). L'apixaban était associé à une réduction de 32% du risque de saignement majeur (43,6 vs 54,7 pour 1000 personnes-années respectivement; HR 0,68, IC 95% 0,59-0,78), comparé au rivaroxaban. Enfin, le risque d'événements indésirables majeurs des membres était similaire entre l'apixaban et le rivaroxaban (9,3 vs 9,5 pour 1000 personnes-années respectivement; HR 0,75, IC 95% 0,54-1,04). Dans l'ensemble, le risque d'AIC et de saignement majeur n'était pas modifié par l'âge, le sexe, les complications vasculaires du diabète, la néphropathie, les scores CHA_2DS_2-VASc ou HAS-BLED. Les résultats étaient concordant dans toutes les analyses de sensibilité.

Conclusions: Chez les patients atteints de FA et de diabète de type 2, l'apixaban a une efficacité similaire et est associé à un risque de saignement majeur plus faible que le rivaroxaban. Les résultats de cette étude pourraient contribuer à éclairer le choix d'un anticoagulant oral dans cette population à haut risque.

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Abbreviations

AF	Atrial fibrillation
ARISTOTLE trial	Apixaban for Reduction in Stroke and Other Thromboembolic Events
BMI	Body mass index
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CPT-4	Current procedural terminology
Dm+d	Dictionary of Medicines and Devices
DOAC	Direct oral anticoagulant
DPP-4	Dipeptidyl peptidase-4
EC	Electrocardiogram
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin A1c
HES	Hospital Episode Statistics
HRT	Hormone replacement therapy
ICD	International classification of diseases
ICD-9 CM	International classification of diseases-9 clinical modification
ICHPCC-2	International classification of health problems in primary care
ICPC	International classification of primary care
INR	International normalized ratio
IPCW	Inverse probability of censoring weights
NHS	National health service
NVAF	Nonvalvular atrial fibrillation
OGTT	Oral glucose tolerance test
ONS	Office for National Statistics
OPCS	Office of Population, Censuses and Surveys' Classification of Surgical Operations and Procedures
PS	Propensity score

PT	Prothrombin time
T2DM	Type 2 diabetes mellitus
HR	Hazard ratio
RCT	Randomized controlled trial
ROCKET-AF trial	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial
SD	Standard deviation
SE	Systemic embolism
SNOMED-CT	Systematized Nomenclature of Medicine-Clinical Terms
SGLT2 inhibitors	Sodium-glucose co-transporter 2 inhibitors
UK	United Kingdom
US	United States
VKA	Vitamin K antagonist

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Contribution of authors

Krishna Roy Chowdhury drafted all the sections of this thesis and manuscript. Dr. Christel Renoux conceived the thesis topic. Krishna Roy Chowdhury, Drs. Laurent Azoulay, Christel Renoux and Oriana Yu contributed in designing the study. Krishna Roy Chowdhury, Jonathan Michaud, Hui Yin and Dr. Christel Renoux contributed to the statistical analyses. All authors critically revised the manuscript for important intellectual content. Dr. Christel Renoux acquired the data and supervised the study.

Chapter 1: Introduction

Atrial fibrillation (AF) is the most common and sustained cardiac arrhythmia with an estimated prevalence of approximately 46 million people worldwide (1). AF is associated with a five-fold increased risk of stroke (2). Moreover, patients with diabetes have a 49% higher risk of developing AF compared with those who do not have diabetes (3). In patients with both AF and diabetes, the risk of stroke is 70% higher compared with those with AF only (4). As a result, having both AF and diabetes pose a notable burden to patients and clinicians.

Anticoagulation therapy is the cornerstone of AF management to prevent stroke occurrence in patients with AF. Although the efficacy of vitamin K antagonists in reducing the risk of stroke is well-established in patients with AF, they are limited by frequent drug-drug interactions and narrow therapeutic index, which warrant close monitoring and dose adjustments (5, 6). In the last decade, direct oral anticoagulants (DOACs) have been approved for stroke prevention in nonvalvular AF (NVAF). These newer drugs are easier to use because of fixed doses, predictable dose response, no need for monitoring, and fewer interactions with other drugs. DOACs have been shown to be at least as effective and safe compared to vitamin K antagonists in pivotal randomized controlled trials, including for patients with diabetes (7-14). Thus, DOACs are now recommended as first-line oral anticoagulants for patients with NVAF, including those with diabetes (7-11). Additionally, cohort studies in patients with NVAF and diabetes found that all DOACs were associated with a similar or lower risk of stroke (15-18) and major bleeding (15, 16, 18, 19), compared with warfarin. Moreover, DOACs may also reduce the risk of major adverse lower limb events such as revascularization procedure or amputation in this population, compared with warfarin (17, 19).

Although randomized controlled trials and observational studies have well established the similar efficacy and safety of DOACs compared with vitamin K antagonists, there is limited evidence on the comparative effectiveness and safety of individual DOACs in this high-risk population of patients with NVAF and diabetes. No randomized controlled trial conducted head-to-head comparison of DOACs, and only two cohort studies assessed the efficacy and safety of individual DOACs in patients with NVAF and diabetes. The first cohort study reported that dabigatran, compared with rivaroxaban, was associated with a similar risk of stroke and major

bleeding (20). The other cohort study compared the effectiveness and safety of apixaban, rivaroxaban, and dabigatran and found that apixaban was associated with a similar risk of stroke or systemic embolism (SE) and a lower risk of major bleeding compared with rivaroxaban (21). Additionally, apixaban was associated with a lower risk of stroke/SE and major bleeding compared with dabigatran and dabigatran was associated with a similar risk of stroke/ SE and a lower risk of major bleeding compared with rivaroxaban (21).

To date, there is limited evidence on the comparative effectiveness and safety of individual DOACs to inform prescribing choice in this high-risk population, in particular apixaban and rivaroxaban, the two most commonly prescribed DOACs in many countries including the United Kingdom and the United States (24-29). Moreover, it remains unclear whether their comparative effectiveness varies with the duration and severity of diabetes and whether they are associated with a similar risk of major adverse limb events.

Thus, given this knowledge gap, the objective of this study was to evaluate the effectiveness and safety of apixaban compared with rivaroxaban, in a large population-based cohort of patients with NVAF and type 2 diabetes (T2DM).

Chapter 2: Literature review

The following chapter has six sections. The first section provides an overview of atrial fibrillation, including its epidemiology, pathophysiology, types, diagnosis and the risk of stroke and systemic embolism in patients with atrial fibrillation. The second section offers an overview of VKAs and DOACs, which are used for prevention of atrial fibrillation. The third section gives an overview of the association between AF and type 2 diabetes. The fourth section describes type 2 diabetes, including its epidemiology, pathophysiology, diagnosis and clinical management. The fifth section gives an understanding of the risk of stroke in patients with AF and type 2 diabetes. The last section describes the effectiveness and safety of DOACs in patients with atrial fibrillation and type 2 diabetes.

2.1 Atrial fibrillation

2.1.1 Epidemiology of AF

Atrial fibrillation (AF) is the most common cardiac arrhythmia (22). Worldwide, AF is prevalent in approximately 46 million people and almost 4 million people get newly diagnosed with AF each year. Furthermore, about half of these prevalent and incident cases are in men and half are in women (1). Although men are more prone to developing AF than women, the cumulative lifetime risk of AF is similar in men and women, at about 30% (23). The prevalence of AF increases with age. The risk of AF for people aged less than 49 years is estimated between 0.12%–0.16% and this risk rises to 3.7%–4.2% in those aged 60–70 years. Also, for those above 80 years, prevalence can be as high as 10%–17% (24). The prevalence of AF varies across different countries. In the United States, at least 3 to 6 million people have AF and it is predicted to reach from 6 to 16 million by 2050 (25, 26). Moreover, in Europe, approximately 9 million people over 55 years had prevalent AF in 2010, and cases are expected to reach 14 million by 2060 (27, 28). According to the Heart and Stroke Foundation, AF affects approximately 2 lacs Canadians (29). Additionally, the Stroke Association estimates that there are over 1 million people with AF in United Kingdom (30). By 2050, AF will be incident in approximately 72 million individuals in Asia (31).

The underlying risk factors for AF include modifiable risk factors and non modifiable risk factors. The nonmodifiable risk factors are genetics, age, sex, race and the modifiable risk factors are inactive lifestyle, diabetes, hypertension, smoking, and obesity (32).

2.1.2 Pathophysiology of AF

AF is characterized by dyssynchronous atrial contraction and irregularity of ventricular excitation caused by high frequency excitation of atrium (32). Normal cardiac rhythm is described as regular rhythm in the sinoatrial node, followed by atrial and then ventricular activation (33). However, nonsynchronized activity in the atrium prevents effective atrial contraction, leading to clot formation in the atrial appendage (33).

The onset of AF is initiated by triggers that induce the irregularity in heart rhythm. These triggers include sympathetic or parasympathetic stimulation, bradycardia, atrial premature beats or tachycardia, accessory atrioventricular pathways, and acute atrial stretch (34, 35). All of these contribute to irregular heartbeat and conduction disturbances, thus initiating AF (35). The rapid triggering generates reentrant waves in a vulnerable atrial substrate. As the AF substrate advances, the significance of the initiating trigger decreases and AF becomes more steady (32). In the formation and composition of AF substrate, risk factors like genetics, age, sex, lifestyle, diabetes and other comorbid conditions play a major role. These risk factors also induce structural and electrical remodeling of the atria. Atrial abnormalities which are structural, architectural and electrophysiological, promote the maintenance of AF by stabilizing reentry (32). As a result, AF is maintained in the patient and thus, leads to possible heart failure and ischemic stroke.

2.1.3 Types of AF and classification

There are two types of AF on the basis of etiology: valvular AF and nonvalvular AF. Valvular AF is defined as AF in the presence of any valvular heart disease (22, 36, 37). Non valvular AF (NVAF) is defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair (38).

AF can be categorized into four types on the basis of its duration. It includes paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF (38). Paroxysmal AF stops spontaneously or with intervention within 7 days of onset. Persistent AF continues for more than

7 days. Long-standing persistent AF continues for more than 12 months and strategies are taken for controlling rhythm. Permanent AF occurs when the patient and doctor decide to no longer try to restore sinus rhythm (38).

The most common symptoms of AF include fatigue, anxiety, palpitations, dyspnea, chest pain, dizziness, and less commonly, syncope or presyncope. However, approximately 15-30% of AF patients are asymptomatic (39-41). Some studies even suggest about 70% AF episodes to be silent (42).

2.1.4 Diagnosis of AF and evaluation

AF is a major cause of ischemic stroke and other heart related problems which can lead to long-term paralysis and disability, congestive heart failure and even death. For those reasons, it is important to diagnose AF (43). Different approaches to diagnose AF include electrocardiogram (ECG), Holter monitor, event monitor, stress test, and echocardiogram (38, 43, 44). Among these, the ECG machine is commonly used to confirm the diagnosis, record the electrical activity of the heart and is the preferred method by physicians to assess the condition of a patients heart (43). Up until now, the ECG has been the gold standard for diagnosing AF. The Holter monitor, event monitor, and stress test also produce ECG signals that are recorded over an extended period of time. However, in contrast to these approaches, the ECG use sound waves to build up cardiac images (43). It is also important for physicians to perform a physical examination of the patient in order to identify risk factors and comorbidities. Additionally, physicians should assess blood pressure, heart rate, presence of cardiac murmurs (such as aortic or mitral stenosis), and evidence of heart failure. Physicians should also inquire about the patients use of illicit drugs, alcohol, diet pills and catheterization in order to evaluate for ischemia or coronary artery disease (44).

2.1.5 Risk of stroke and systemic embolism in patients with AF

AF is a common risk factor for ischemic stroke and is associated with a five-fold increased risk of stroke (2). Moreover, AF causes irregular rhythm of the heart due to disorganized electrical signals. As a result, the atria beats abnormally and blood is inefficiently pumped from the heart. Due to this inefficient pumping, blood gets accumulated in the atria and creates blood clots. These

blood clots then move from their point of origin, potentially causing an ischemic stroke or a systemic embolism. An ischemic stroke occurs when blood flow to the brain is interrupted by a clot in a blood vessel in the brain (45, 46). The presence of comorbidities including diabetes, hypertension, heart failure, prior stroke along with AF increase the risk of stroke (47). In order to predict probabilty of stroke, stratification schemes such as $CHADS_2$ and CHA_2DS_2-VASc scores have been developed. $CHADS_2$ allocates 1 point for patients aged ≥ 75 years, as well as 1 point for patients with congestive heart failure, hypertension and diabetes mellitus, and 2 points for a history of stroke. In addition to these risk factors, CHA_2DS_2-VASc assigns 1 point to female patients, as well as those with a history of vascular disease and stroke, and those aged 65–74 years, and 2 points for patients aged ≥ 75 years (48). Throughout the world, there are 13.7 million strokes occuring every year, of which 9.5 million are ischemic strokes. Among these, 52% of cases are in men and 48% are in women (1). AF causes about 1 in 7 of these ischemic strokes (49).

2.1.6 Mortality and morbidity from AF

AF is associated with a 50% increase in mortality for men and a 90% increase in mortality for women in comparison to non AF patients (50). Moreover, AF patients have a significantly lower quality of life than the general population, measured by different validated quality of life instruments. Also, patients with AF have been shown to have a 24% decrease in measures of physical health, a 23% decrease in social functioning, a 16% decrease in mental health and a 30% decrease in general health, compared to healthy individuals (51). Furthermore, patients with AF suffer from different comorbidities and complications, which include type 2 diabetes, heart diseases, chronic kidney disease, cancer and dementia (52). As a result of these impairments, AF inflicts a serious burden of cost on the healthcare system. A study done in the U.S.A reported that AF is associated with an 11% rise in cost of hospitalization (53). Thus, AF also has economic implications.

2.2 Treatment of AF

Treatment of AF depends on the duration of AF and the existence of comorbidities (44). Management of AF consists of reducing symptoms and reducing the risk of stroke.

2.2.1 Reducing symptoms of AF

Symptoms of AF can be reduced by rate control and rhythm control. Rate control is recommended as it gives better outcomes with respect to mortality compared to rhythm control (54). Moreover, since many AF patients are asymptomatic, rate control is the preferred initial approach. A randomized controlled trial showed that patients allocated to rhythm control have more hospitalizations from adverse cardiovascular events and more serious adverse effects from medications compared to that of rate control (55). The goal of rate control is to reduce the number of abnormal electric impulses to make the heart rate steady. Moreover, rate control slows ventricular response, reduces myocardial oxygen demand, improves coronary perfusion and mechanical function, thus restoring the cardiac function. The medications used for rate control are beta blockers (such as metoprolol), calcium channel blockers (such as adiltiazem) and cardiac glycosides (such as digoxin) (54). Among these medications, beta blockers and calcium channel blockers are the most frequently used (54).

On the other hand, rhythm control is used less often compared to rate control as its purpose is to restore a regular heart rhythm and can be achieved using medications or procedures. Rhythm control medications include amiodarone, sotalol, ibutilide, flecainide, dofetilide and propafenone (54). The two types of procedures available for rhythm control include electrical cardioversion and catheter ablation. Electrical cardioversion is a short-term solution that delivers a direct current shock to the heart. Catheter ablation is a nonoperative procedure that identifies and destroys abnormal foci caused by AF (44).

2.2.2 Reducing the risk of ischemic stroke and sytemic embolism

The other component in managing AF is to reduce the risk of stroke. Oral anticoagulation is recommended by American, European, Canadian guidelines (35, 37, 56) to reduce the risk of

stroke in patients with AF. Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) are the two types of anticoagulants used for reducing the risk of stroke.

2.2.2.1 Vitamin K antagonists

Vitamin K antagonists (VKAs) have been the main anticoagulation therapy for more than 50 years (5). One of the VKAs, warfarin, is the most widely used anticoagulant in the world. In the UK, at least 1% of the population and 8% of people over 80 years take it regularly (57). Warfarin inhibits vitamin K, an essential cofactor for activating and synthesizing vitamin K-dependent clotting factors and thus, reduces blood clot formation (6). In randomized controlled trials, VKAs reduced the rate of stroke by approximately 60% compared to placebo in AF patients (58). Moreover, observational studies showed that warfarin reduces the risk of stroke compared to no antithrombotic therapy in routine clinical practice (59-61).

Despite the benefits, a serious adverse effect of warfarin is bleeding. A major haemorrhage (e.g., intracranial haemorrhage) can occur at any site on the body. The risk of bleeding depends on many factors, including the intensity of anticoagulation and patient vulnerability (6). In consequence, patients taking warfarin, should be closely monitored to assess their prothrombin time (PT) and international normalized ratio (INR) by undergoing periodic blood testing (6). PT and INR are the laboratory parameters utilized to monitor warfarin therapy. PT is defined as the number of seconds it takes the blood to clot, and INR is the standardization of the PT measurement. As a result of the standardized measurement, patients' INR is strongly preferred over PT (5, 6). The INR of a patient not on anticoagulation therapy, is approximately 1. In comparision, an INR of 2 or 3 would indicate that the individuals blood takes two to three times longer to clot than someone who does not take any anticoagulants. Most patients on warfarin have an INR goal of 2 to 3 (6). Poor INR control is associated with increased risk of stroke (INR <2.0) and bleeding (INR >3.0) (62). Warfarin has numerous drug interactions that either raise the risk of adverse effects or decrease its anticoagulant effect. As a result, factors including dosage adjustments and close monitoring must be considered when prescribing warfarin with other medications (6).

2.2.2.2 Direct oral anticoagulants

Direct oral anticoagulants (DOACs) were introduced in late 2010 in many countries including the United States, Canada and the United Kingdom to overcome the limitations of VKA therapy (63-65). DOACs directly inhibit specific proteins in contrast to VKAs, which inhibit the synthesis of vitamin K-dependent clotting factors. The four DOACs currently approved for stroke prevention in patients with NVAF are, namely dabigatran, rivaroxaban, apixaban and edoxaban.

Dabigatran is a potent and direct inhibitor of thrombin, and is rapidly converted from dabigatran etexilate by serum esterase. Moreover, it has an absolute bioavailability of 6.5%. About 80% of a given dose is excreted by the kidneys, and its serum half-life is 12 to 17 hours (9, 66). Rivaroxaban is a direct factor Xa inhibitor providing more consistent and predictable anticoagulation than warfarin (8). It does not require a cofactor (such as anti-thrombin III) for activity and inhibits free coagulation factor Xa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, rivaroxaban decreases thrombin generation (67). Likewise, apixaban is a direct oral factor Xa inhibitor with rapid absorption, a 12-hour half-life, and has 25% renal excretion (11). Similar to rivaroxaban, apixaban also does not require anti-thrombin III for antithrombotic activity and indirectly inhibits platelet aggregation induced by thrombin, decreasing thrombin generation (68). Edoxaban is a predictable, oral direct factor Xa inhibitor, like rivaroxaban and apixaban, with a 62% oral bioavailability. Edoxaban also achieves maximum concentrations within 1 to 2 hours and has a 50% renal excretion (13, 69).

2.2.2.3 Effectiveness and safety of DOACs compared with VKAs

DOACs are approved worldwide for the prevention of stroke in patients with NVAF. DOACs have several advantages over VKAs. The most important advantage of DOACs in contrast to warfarin is that it does not require regular monitoring. The other advantages of DOACs over warfarin include fixed dosing and fewer drug–drug interactions (63). Moreover, both randomized controlled trials and observational studies showed that DOACs were at least as effective and safe as warfarin in patients with NVAF. Thus, American, Canadian and European guidelines

recommend DOACs over VKAs for prevention of stroke or systemic embolism in patients with NVAF (35, 38, 56). The main findings of randomized controlled trials and observational studies on the effectiveness and safety of DOACs compared with VKAs are discussed in the following subsections.

Randomized controlled trials

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran (110 mg) was associated with similar rates of stroke to warfarin (9). The rate of stroke for dabigatran (110 mg) was 1.5% per year compared to 1.69% per year with warfarin (relative risk with dabigatran 0.91, 95% confidence interval (CI) 0.74- 1.11). However, a dose of 150 mg dabigatran was associated with 1.11% rate of stroke per year compared to 1.69% per year with warfarin (relative risk 0.66, 95% CI 0.53- 0.82). In terms of safety, dabigatran (110 mg) was associated with a 2.71% rate of major bleeding per year compared to 3.36% per year with warfarin (relative risk 0.80, 95% CI 0.69- 0.93) and dabigatran (150 mg) was associated with 3.11% rate of major bleeding per year compared to 3.36% per year with warfarin (relative risk 0.93, 95% CI 0.81- 1.07) (9).

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) trial indicated that rivaroxaban was associated with a stroke rate of 1.7% per year, compared to warfarin, which was associated with a 2.2% stroke rate per year (hazard ratio (HR) 0.79, 95% CI 0.66- 0.96). In terms of safety, rates of major bleeding were similar in the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively) (HR 1.04, 95% CI 0.90- 1.20) (8). Thus, rivaroxaban was associated with reduced rates of stroke and similar risk of bleeding compared to warfarin.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the rate of stroke was 1.27% per year with apixaban, compared to 1.60% per year with warfarin (HR 0.79, 95% CI 0.66- 0.95). Moreover, the rate of major bleeding was 2.13% per year with apixaban compared to 3.09% per year with warfarin (HR 0.69, 95% CI, 0.60- 0.80) (11). Therefore, apixaban was associated with greater reduction of stroke and caused less bleeding than warfarin.

In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, a high-dose of edoxaban was associated with a stroke rate of 1.18% per year compared with 1.50% per year with warfarin (HR vs. warfarin 0.79, 97.5% CI 0.63- 0.99) and a low-dose edoxaban was associated with a stroke rate of 1.61% per year compared with 1.50% per year with warfarin (HR vs. warfarin 1.07, 97.5% CI 0.87- 1.31). Furthermore, the rate of major bleeding was 2.75% per year with a high-dose of edoxaban compared to 3.43% per year with warfarin (HR 0.80, 95% CI 0.71- 0.91) and low-dose of edoxaban was associated with a major bleeding rate of 1.61% compared with 3.43% with warfarin per year (HR 0.47, 95% CI 0.41- 0.55). Therefore, edoxaban was associated with lower rates of major bleeding for both doses, but similar rates of stroke for a low-dose and lower rates of stroke for a high dose compared with warfarin (13). These randomized controlled trials show that DOACs are at least as effective and safe compared with warfarin.

Observational studies

Observational studies have compared DOACs with warfarin and have conducted head-to-head comparisons of DOACs in patients with NVAF. Some cohort studies have shown DOACs to be as effective as warfarin, apixaban being the most effective among the DOACs. A cohort study by Hernandez et al. showed that compared with warfarin, apixaban reduced the composite risk of ischemic stroke, systemic embolism, and death by 14%, dabigatran had a reduction of 27% and rivaroxaban had a reduction of 18% (70). However, the effectiveness was similar across apixaban, dabigatran and rivaroxaban. In terms of safety, risk of bleeding was 21% lower with apixaban and 15% higher with rivaroxaban compared with warfarin. Moreover, the risk of bleeding was similar between dabigatran and warfarin (70). A cohort study by Yao et al. showed that compared to warfarin, apixaban was associated with a 33% lower risk of stroke or systemic embolism, whereas rivaroxaban and dabigatran were associated with a similar risk of stroke. Furthermore, apixaban was associated with a 55% lower risk of bleeding, dabigatran had a 21% lower risk and rivaroxaban had a similar risk compared with warfarin (71). Similarly, Chan et al. indicated that DOACs were associated with a lower risk of stroke and major bleeding compared to warfarin (72). In addition, cohort studies comparing apixaban and rivaroxaban showed that apixaban was associated with a lower risk of stroke and bleeding than rivaroxaban (73, 74). However, some cohort studies found

that dabigatran and rivaroxaban performed better than apixaban in reducing ischemic stroke (75, 76). A meta-analysis of observational studies reported that all DOACs were associated with similar rates of stroke when compared with each other (77). In terms of safety, apixaban was associated with lower major bleeding compared with rivaroxaban (HR 2.0, 95% CI 1.6–2.5) and dabigatran (HR 1.6, 95% CI 1.3–2.1) (77).

2.3 Association between AF and type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a chronic disease that occurs when the body cannot produce enough insulin, hence causing sugar to build up in the blood (78). Individuals with T2DM are at an increased risk for both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities) (79). In addition, AF and T2DM commonly coexist (80). Although the pathophysiologic relation between AF and T2DM is unknown, the link between these conditions is possibly by pathways including coronary artery disease, hypertension and abnormal sympathetic tone. Additionally, the causal link between AF and T2DM can also be possibly by direct effect of T2DM on atrial tissue (81). Patients with T2DM have a 49% higher risk of developing AF than those who do not have T2DM (3). Many studies have shown the association between AF and T2DM. For instance, one randomized controlled trial showed a 49% increased risk of AF in patients with T2DM compared to individuals without T2DM (81). Also, a case control study showed diabetes to be independently associated with AF with an odds ratio of 2.13 (82). Likewise, a meta-analysis on studies adjusting for multiple risk factors found a 24% increased risk of AF with diabetes than with no diabetes (83). Figure 1 represents a meta-analysis of all the studies on the risk of AF in patients with T2DM (3).

Moreover, diabetes is one of the factors in the risk stratification scheme CHA_2DS_2-VASc-score used to identify patients at high-risk of stroke (80). AF is associated with an increased risk of stroke (2), which is elevated further with coexistence of T2DM and AF. Indeed, the risk of stroke is 70% higher in patients with T2DM and AF than those with only AF (4).

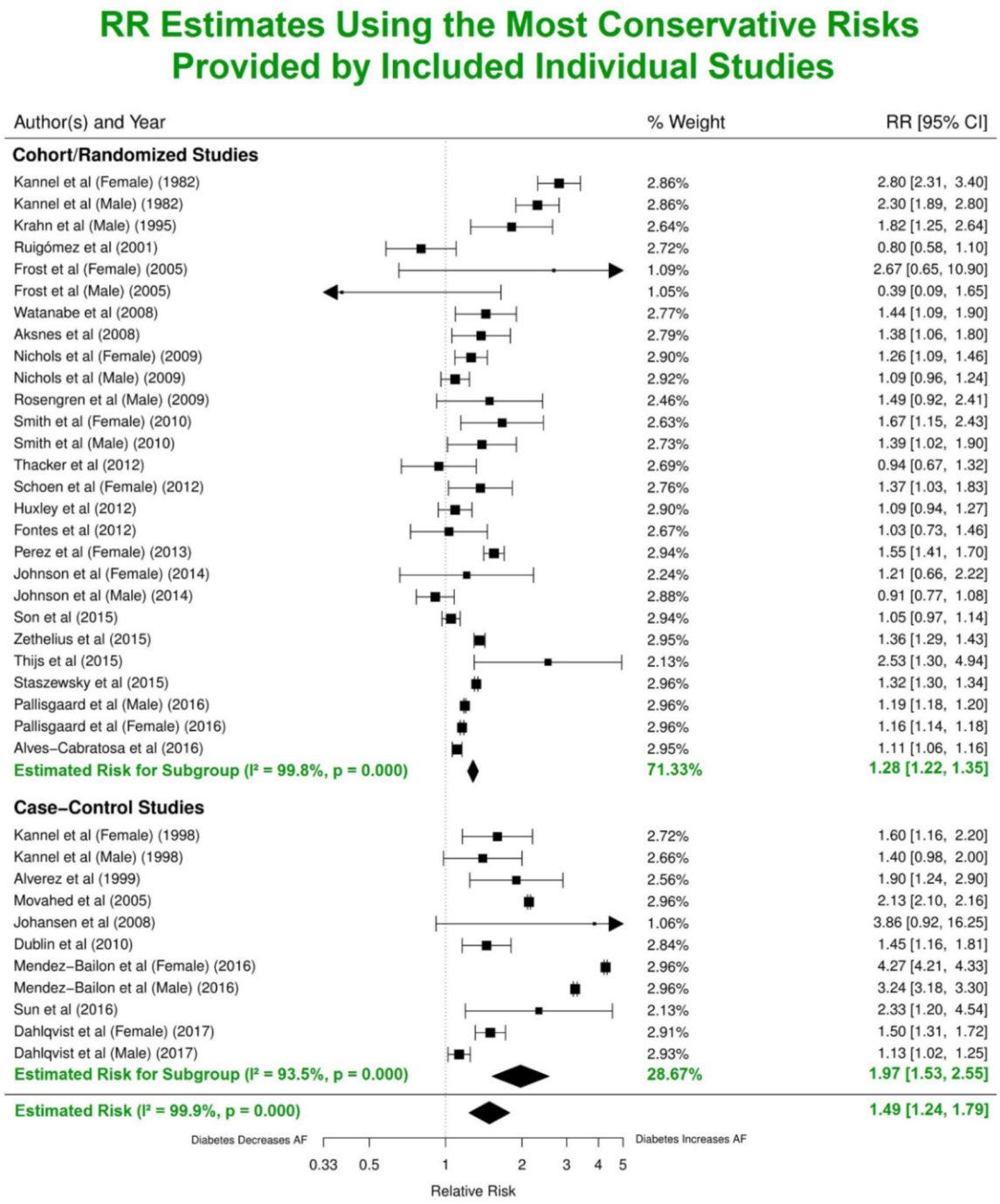

Figure 1: Forest plot showing estimated risk of AF in patients with T2DM taken from a meta-analysis of the relative risk of AF in patients with diabetes mellitus*

*(Reprinted with the permission from the Journal Frontiers in Physiology) (3)

2.4 Type 2 diabetes mellitus

2.4.1 Epidemiology of type 2 diabetes

The prevalence of diabetes has been increasing worldwide (84). It is estimated that globally, 463 million people have diabetes and it is projected to hit 578 million by 2030 and 700 million by 2045. Among these 463 million cases, there are about 17.2 million more men than women living with diabetes (85). Moreover, about 20.8 million new cases of diabetes are diagnosed each year, with 52% of the cases being men (1). According to Diabetes Canada, in 2021, there are approximately 11.5 million people living with type 1 diabetes, type 2 diagnosed and undiagnosed diabetes, and prediabetes in Canada, and this total is expected to reach 13.7 million by 2031. Among the 11.5 million, about 3.9 million include type 1 diabetes and type 2 diagnosed diabetes, and this total is projected to hit 5 million by 2031 (86). According to Diabetes UK, there are approximately 4.7 million people with diabetes, but only 3.8 million are diagnosed (90% of 3.8 million people have T2DM). The remaining 1 million people are estimated to have undiagnosed T2DM (87). Furthermore, it is projected that by 2030, the UK will have 5.5 million people with diabetes (87). Approximately 90% of all diabetes are T2DM, 5% are type 1 and 5% are other subtypes (including gestational diabetes and rarer inherited and syndromic forms such as monogenic diabetes of the youth) (84). There is an increasing prevalence of diabetes by age, the lowest prevalence of 1.4% is seen in people aged 20-24 years, increasing to 20% in people aged 75-79 years and projected to increase to 20.4% in 2030 and 20.5% in 2045 respectively in the latter age group (85).

Global health expenditure on diabetes is estimated to be 760 billion USD annually and projected to reach 825 billion USD by 2030 and 845 billion USD by 2045 (85). In 2019, the total diabetes related health expenditure in the UK was 14.1 billion USD, and 12.3 billion USD in Canada (85). In 2020, the Canadian health care system spent an estimated 3.95 billion CAD and this is projected to increase to 4.98 billion CAD by 2030 (86).

2.4.2 Pathophysiology of type 2 diabetes

T2DM is a metabolic disorder in which the body does not produce enough insulin or cannot respond to insulin, causing blood sugar (glucose) levels to be high. It occurs when insulin secretion from pancreatic beta-cells is not sufficient enough to compensate for insulin resistance (88). It is also a heterogeneous disease because of its multifactorial causes, including both genetic and environmental elements that affect beta-cell function and tissue insulin sensitivity (89).

The pathogenesis of T2DM is caused by two factors. The first is decreased insulin secretion by defective pancreatic beta-cells. In this case, reduced insulin secretion limits the body's capacity to maintain normal glucose levels. The second factor is increased insulin resistance, caused by the insulin-target tissues (muscle, liver, adipose tissue, pancreas) failing to respond to normal insulin levels over time (90). This insulin resistance contributes to increased glucose production in the liver and decreased glucose uptake in the insulin-target tissues. Even if both processes occur early in the progression of T2DM, beta-cell dysfunction is more severe than insulin resistance. Moreover, if both beta-cell dysfunction and insulin resistance coexist, hyperglycaemia is escalated, leading to the development of T2DM (90).

2.4.3 Diagnosis of type 2 diabetes

The required tests to diagnose T2DM are widely available; however, approximately 25% of newly diagnosed patients already have microvascular disease, suggesting that they had the disease for more than 5 years by the time of diagnosis (91). Therefore, early diagnosis of T2DM is important.

According to the 1997 American Diabetic Association guidelines and the 2006 World Health Organization National diabetic group, T2DM is diagnosed after an elevated glucose reading with symptoms of the disease (polyuria, polydipsia, polyphagia and weight loss), or by two elevated glucose readings on separate occasions without symptoms (91). The laboratory tests to diagnose T2DM may be performed through the fasting plasma glucose with levels above 126

mg/dL or 7.0 mmol/L, or the oral glucose tolerance test, with levels above 200 mg/dL or 11.1 mmol/L two hours after a 75g dose of glucose (92, 93). Similarly, Diabetes Canada also recommends a 75 g oral glucose tolerance test (OGTT) when the fasting plasma glucose is 6.1 to 6.9 mmol/L, in addition to the fasting plasma glucose tests (94). In addition to those tests, in 2009, the International Expert Committee appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation, suggested an additional diagnostic criteria of a glycated hemoglobin level, HbA1c above 6.5% to be indicative of T2DM. These committees also identified a high risk of developing T2DM for those who have HbA1c levels of 6.0% and less than 6.5% (91). According to the American Diabetic Association, Diabetes Canada, Diabetes UK and the World Health Organization, in the absence of symptoms of T2DM and if any of the tests (fasting plasma glucose test or oral glucose tolerance test or HbA1c) are in the diabetes range, a repeat confirmatory test (fasting plasma glucose test or oral glucose tolerance test or HbA1c) must be done on another day, preferably the same test in a timely manner in order to confirm T2DM (87, 92, 93, 95).

2.4.4 Clinical management of type 2 diabetes

There are two ways to manage T2DM, lifestyle and diet modification, and pharmacological treatment with antidiabetic drugs (96).

2.4.4.1 Lifestyle and diet modification

T2DM risk factors include a combination of genetic, metabolic and environmental factors that interact with one another and contribute to its prevalence (79). Among these, non-modifiable risk factors include ethnicity and family history/genetic predisposition. T2DM is inheritable however, the relative risk of developing T2DM in siblings of a type 2 diabetic patient, compared with families in which none of the siblings has the disease, is approximately 2–3. Furthermore, the relative risk of developing T2DM in other siblings, increases to 30 if two siblings have the disease (79). The modifiable and lifestyle risk factors are obesity, low physical activity/sedentary lifestyle, cigarette smoking, consumption of alcohol and an unhealthy diet. (79, 97). Moreover, a low-fiber

diet with a high glycemic index and specific dietary fatty acids have been associated with increased risk of T2DM (97).

Studies have shown that a reduced risk of developing T2DM is associated with a combination of body mass index of 25 kg/m^2, eating a high fibre diet, exercising regularly, not smoking and not consuming alcohol (96-98).

2.4.4.2 Antidiabetic drugs

In order to treat T2DM, three lines of treatment are recommended at different stages by American Diabetes Association and American College of Physicians (99-101). The first line treatment includes the biguanide drug class prescribed when diet and exercise alone cannot manage T2DM effectively. The biguanide drug class which includes phenformin, buformin and metformin were first introduced in Europe in 1959 and got approval by Canadian Diabetic Association advisory committee in Canada in 1972 (102). The use of metformin replaced phenformin and buformin, as they were removed from the market due to a connection with lactic acidosis (102, 103). Metformin was approved for use in 1995 in the United States after being used in Europe for 20 years (103). Since then, metformin has been the most used drug to reduce blood glucose levels (104). The second to third line treatments include sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, incretin-based therapies, dipeptidyl-peptidase 4 inhibitors and sodium-glucose co-transporter 2 inhibitors (96). These drugs are prescribed when the first line treatment cannot bring down the glucose level to an optimal range. Among these drugs, the first-generation sulfonylureas were approved in 1956 in Europe (103) and more potent second-generation sulfonylureas were approved for use in the United States in 1984 (103). Sulfonylureas have been shown to decrease HbA1c levels by 1-2% (103). Meglitinides, a non-sulfonylurea insulin secretagogues that reduces HbA1c levels by 1-1.5%, was approved in the United States in 1997 (103). Alpha-glucosidase inhibitors, an oral class of antidiabetic drugs, was first approved by the Food and Drug Administration (FDA) in 1995, decreasing HbA1c levels by 0.5% (103). The use of thiazolidinediones has been debatable as it has side effects such as liver damage, cardiovascular ischemia, edema and asssociations with bladder cancer (103). The incretin-based drugs, comprised of glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-

4) inhibitors were first approved in the United States and the United Kingdom in 2005 and 2007, respectively (103). These drugs have an incretin effect, where oral glucose stimulates more insulin release than intravenous glucose. Moreoever, GLP-1 analogues have shown to effectively reduce HbA1c levels by 1%, while DPP-4 inhibitors decrease levels by 0.8% (103). The newest class of antidiabetic drugs are sodium-glucose co-transporter 2 (SGLT2) inhibitors, first approved in Europe in 2012 and the United States in 2013, lowering HbA1c levels by 0.5-0.8% (105).

When the first two types of treatments are ineffective in bringing down glucose levels, the last line of treatment is insulin therapy, which is used in combination with the first and second to third line drugs (96). During insulin therapy, if some beta cell function still remain, patients are treated with basal insulin which controls blood glucose between meals (96). If patients have impaired beta cell function, they may require bolus insulin, taken before meals (96). The first short-acting insulin analogue, lispro, was approved by the FDA in 1996 as an alternative to traditional insulin therapies, followed by the approval of long-acting insulin analogues, glargine in 2000 (106).

2.5 Risk of stroke in patients with AF and type 2 diabetes

As discussed in section 2.1.5, patients with AF have a five-fold increased risk of stroke (2). When both AF and T2DM coexist, the risk of stroke is 70% higher than in patients with AF only (4). This increased risk of stroke can be attributed to the association of T2DM with a prothrombotic state, endothelial dysfunction, and platelet hyperactivity (107, 108). Different factors including increased circulating prothrombotic mediators, fibrinogen and tissue factor are found in patients with T2DM (109). Additionally, changes in glucose metabolism and insulin signaling, the presence of an inflammatory state, production of reactive oxygen species and advanced glycation end products contribute to endothelial dysfunction (107). Furthermore, hyperglycemia and insulin resistance are associated with hyperactive platelets that promote hypercoagulable state (107, 110). As a result of increased platelet activity and aggregability, increased circulating tissue factor levels, and alterations in circulating vitamin K–dependent coagulation factor levels, thrombus is likely to be formed (111). Thus, when thrombus formation increases, clot dissolution reduces. This happens due to an increase in circulating concentrations of plasminogen activator inhibitor 1 in metabolic syndrome, which prolongs clot lysis time. Metabolic syndrome is a combination of interconnected components including abdominal obesity, hypertension, dyslipidemia, insulin resistance, and glucose intolerance that directly increases the risk of coronary heart disease, other forms of cardiovascular atherosclerotic disease, and T2DM (112). Subsequently, the clot density increases, which leads to thrombus formation, including stroke (111, 113). A cohort study found that people who had atrial fibrillation on an ECG at the time of diabetes diagnosis, were over 8 times more likely to have a stroke during the first 8 years of diabetes compared to those in sinus rhythm (114). These findings suggest that atrial fibrillation is the most important risk factor for stroke in patients newly diagnosed with T2DM (114). Another study found that patients with both T2DM and AF, compared with diabetes alone, had a higher mortality rate with an adjusted HR of 2.65 (95% CI, 1.8-3.86), and an increased rate of myocardial infarction with an adjusted HR of 2.1 (95% CI, 1.33-3.31) (53). The subgroup analyses of ADVANCE (The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) trial found that patients with T2DM and AF compared to patients with only diabetes had a 61% greater risk for death and all-cause mortality (HR, 1.61; 95% CI, 1.31-1.96;) and a higher risk for cardiovascular death (HR, 1.77; 95% CI, 1.36-2.30) (115). The secondary analyses of the Anticoagulation and Risk Factors

in Atrial Fibrillation (ATRIA) study showed that diabetes lasting 3 years or longer was associated with an increased risk for ischemic stroke in patients with both AF and diabetes (116). This study suggests that stroke is likely to be thrombotic in patients with AF and diabetes because of increased thrombin generation, impaired fibrinolysis, and unstable clot structure associated with T2DM. (116).

The occurrence of stroke in patients with AF and T2DM can be prevented by oral anticoagulants, similar to the prevention of stroke in patients with AF only. The effectiveness and safety of direct oral anticoagulants in patients with both AF and T2DM is presented in the next section.

2.6 Effectiveness and safety of DOACs in patients with AF and diabetes mellitus

2.6.1 Randomized controlled trials

The effectiveness and safety of DOACs in the subgroup of patients with AF and diabetes have been evaluated in secondary analyses of randomized controlled trials. They are described below.

A secondary analysis of the ROCKET AF trial, comparing the efficacy and safety of rivaroxaban vs. warfarin, was conducted in patients with diabetes (type not specified) (7). There were 5695 diabetic patients, among these, 2878 patients were in the rivaroxaban group and 2817 patients were in the warfarin group. This study found that patients with diabetes faced 1.3 times higher risk of stroke and 1.2 times greater rates of major bleeding than those without diabetes. Furthermore, the rates of stroke (ischemic or hemorrhagic) or non–central nervous system embolism in patients with diabetes was 1.74 per 100 patient-years in the rivaroxaban group vs. 2.14 per 100 patient-years in the warfarin group (HR 0.82, 95% CI 0.63-1.08). In addition, the rate of ischemic stroke was 1.35 per 100 patient-years in the rivaroxaban group vs. 1.45 per 100 patient-years in the warfarin group (HR 0.94, 95% CI 0.69-1.30). In terms of safety, the rates of major bleeding were similar in the rivaroxaban and warfarin groups (incidence rates, 3.79 per 100 patient years vs. 3.90 per 100 patient years, respectively; HR 1.00, 95% CI 0.81-1.24) (7).

A subgroup analysis in patients with diabetes was also conducted in the RE-LY trial, to assess the efficacy and safety of dabigatran compared with warfarin (10). This study did not mention whether type 1 or type 2 diabetic patients were studied. The trial was comprised of 4221 diabetic patients, among these, 1410 patients were in the warfarin group, 1409 patients were in the 110 mg of dabigatran group and 1402 patients were in the 150 mg of dabigatran group. Results showed that in patients with diabetes, the rates of ischemic stroke (including stroke of uncertain origin) were 1.28% per year in the 150 mg of dabigatran group, compared with 1.65% per year in the warfarin group (HR 0.76, 95% CI 0.49-1.19). Additionally, the rates of ischemic stroke (including stroke of uncertain origin) were 1.62% per year in the 110 mg of dabigatran group (HR 0.97, 95% CI 0.64-1.40), compared with 1.65% per year in the warfarin group. In terms of safety, the rates of major bleeding were similar between the 150 mg of dabigatran group (4.66% per year) and the warfarin group (4.19% per year) (HR 1.12, 95% CI 0.87-1.44), and between the 110 mg

of dabigatran group (3.81% per year) and the warfarin group (4.19% per year) (HR 0.91, 95% CI 0.70-1.19) (10).

The effect of apixaban vs. warfarin in AF patients with and without diabetes was investigated in the ARISTOTLE trial (12). However, it was not mentioned whether type 1 or type 2 diabetic patients were studied. In this study, 4547 patients had diabetes, including 2284 patients randomized to apixaban and 2263 patients randomized to warfarin. The rates of stroke or systemic embolism were 1.40 per 100 patient-years in patients randomized to apixaban, compared with 1.86 per 100 patient-years in patients randomized to warfarin (HR 0.75, 95% CI 0.53–1.05). Moreover, the rates of major bleeding were similar in the apixaban (3.01 per 100 patient-years) and warfarin groups (3.13 per 100 patient-years) (HR 0.96, 95% CI 0.74- 1.25) (12).

The efficacy of edoxaban vs. warfarin in AF patients with diabetes (type not specified) was also assessed in a secondary analysis of the ENGAGE AF-TIMI trial (14). In this study there were 7624 diabetic patients, among these, 2559 diabetic patients received a high dose of edoxaban, 2544 diabetic patients received a low dose of edoxaban and 2521 diabetic patients received warfarin. The rates of stroke or systemic embolism in patients with diabetes were similar in high dose edoxaban regimen (60 mg) vs. warfarin (1.42% vs. 1.52% per year respectively; HR 0.93, 95% CI 0.71–1.23). In terms of safety, a high dose edoxaban regimen (60 mg) was associated with a 21% risk reduction in major bleeding compared to warfarin (3.20% vs. 4.07% per year; HR 0.79, 95% CI 0.65–0.96). The low dose edoxaban regimen (30 mg) was not associated with a lower rate of ischemic stroke compared with warfarin (1.90% vs. 1.52% per year; HR 1.20, 95% CI 0.97- 1.50, approximated from the figure in the article) (14).

2.6.2 Observational studies

The effectiveness and safety of DOACs vs. warfarin have been evaluated in patients with AF and diabetes in several observational studies. The majority of studies compared DOACs with warfarin and a few studies were head-to-head comparisons of individual DOACs.

2.6.2.1 Studies comparing DOACs with warfarin

A retrospective cohort study used the US Truven MarketScan to assess the effectiveness and safety of rivaroxaban compared with warfarin in patients with NVAF and T2DM (19). The cohort included 13,946 warfarin users and 10,700 rivaroxaban users with both AF and T2DM between January 2012 to December 2017. The authors used an as-treated exposure definition, where patients included were oral anticoagulant-naïve during the 12 months before the day of the first qualifying rivaroxaban or warfarin dispensing (index date). These patients were followed from January 2012 until endpoint occurrence, index oral anticoagulation discontinuation or switch (assuming a 30-day permissible gap), insurance plan disenrolment or end of claims data availability (December 2017). The study found that rates of major adverse cardiac events (ischemic stroke or myocardial infarction) were 1.26 per 100 person-years among rivaroxaban users and 2.07 per 100 person-years among warfarin users (HR 0.75, 95% CI 0.59-0.96), resulting in a 25% risk reduction in major adverse cardiac events (19). Additionally, the rates of major adverse limb events (major amputation or need for revascularization) were 0.2 per 100 person-years among rivaroxaban users and 0.75 per 100 person-years among warfarin users, with a 63% risk reduction of major adverse limb events in the rivaroxaban group (HR 0.37, 95% CI 0.21-0.65). Also, major bleeding (intracranial or gastrointestinal) rates were similar between rivaroxaban and warfarin (2.38 per 100 person years vs. 3.37 per 100 person years) (HR 0.95, 95% CI 0.79- 1.15) (19).

Another retrospective cohort study, using the same data as in Baker et al. (the study described above), compared the effectiveness and safety of rivaroxaban with warfarin in patients with NVAF and diabetes (97% of the population had T2DM) (15). The cohort included 5517 rivaroxaban users and 5517 warfarin users from 1 November 2011 to 31 December 2016. An as-treated exposure definition was used, and included oral anticoagulant-naïve individuals during the 12 months before the day of the first qualifying rivaroxaban or warfarin dispensing (index date). The individuals were followed from 1 November 2011 until the occurrence of an outcome of interest, oral anticoagulant switch or discontinuation (30-day permissible gap), insurance disenrolment or end of study follow-up, 31 December 2016. The rates of ischemic stroke were 0.69 per 100 person-years among rivaroxaban users and 1.93 per 100 person-years among warfarin users (HR 0.78, 95% CI 0.48-1.30). Also, the rates of major bleeding were similar for the two

groups, 2.71 per 100 person-years among rivaroxaban users and 3.01 per 100 person-years among warfarin users (HR 0.96, 95% CI 0.74- 1.37) (15).

The next retrospective cohort study compared the effectiveness and safety of DOACs vs. warfarin in patients with AF and T2DM, using the Clinical Practice Research Datalink (CPRD) (16). The cohort included 8,555 patients, of which 3,437 patients were in the DOACs group, and 5,118 patients were in the warfarin group. The study used an as-treated exposure definition, and included patients who had not been exposed to either a DOAC or warfarin within 1 year prior to their first prescription. Patients were followed from 1 August 2011, the index date, until either the end of follow-up period (20 June 2018), death, discontinuation of medication of interest, treatment switching (DOACs to warfarin and vice versa) or an outcome of interest, whichever date came first. The authors reported no difference in the risk of ischemic stroke (including unspecified stroke) between DOACs and warfarin (adjusted HR 1.23, 95% CI 0.86–1.76) (16). The incidence rates for major bleeding outcome for DOAC users were 2.73 per 100 person years and 2.98 per 100 person years for warfarin users (adjusted HR 0.83, 95% CI 0.68–1.03) (16).

The effectiveness and safety of DOACs vs. warfarin in patients with NVAF and diabetes (type not specified) was assessed in a cohort study using the Taiwan National Health Insurance Research Database (17). The cohort included 20,967 patients in the DOACs group and 5,812 patients in the warfarin group. This study used an intention to treat exposure definition, and patients newly treated with DOACs or warfarin, were followed from June 1, 2012, the index date until the first occurrence of any study outcome, or until the end date of the study period (December 31, 2017), whichever came first. Compared to warfarin, the use of DOACs was associated with a similar risk of ischemic stroke or systemic embolism (adjusted HR 0.89, 95% CI 0.79–1.02). Additionally, DOACs were associated with a 28% lower risk of major adverse limb events (lower limb revascularization or amputation) (adjusted HR 0.72, 95% CI 0.57–0.92) and with a 33% lower risk of all major bleeding (summation of hospitalized events of intracranial haemorrhage, major gastrointestinal bleeding, and other sites of critical bleeding) (adjusted HR 0.67, 95% CI 0.59–0.76) compared to warfarin (17).

The effectiveness and safety of edoxaban vs. vitamin K antagonists in patients with NVAF and diabetes (type not specified) was conducted in another cohort study using the Atrial Fibrillation Research Database (18). This study included 557 patients, of which 230 patients were

in the edoxaban group and 327 patients were in the vitamin K antagonist group. The authors used an as-treated exposure definition, and included patients from March 2013 to July 2018. This study excluded patients with a follow-up of ≤360 days from the first qualifying anticoagulant prescription. The study also excluded patients that had a vitamin K antagonist in therapeutic range <70% of the time. The incidence rates of thromboembolic events (composite of ischemic stroke, transient ischemic attack, systemic embolism) were 1.11 per 100 person-years in edoxaban vs. 1.9 per 100 person-years in the vitamin K antagonist group. There was a similar risk of thromboembolic events in the edoxaban group (HR 0.59, 95% CI 0.14- 2.52) compared to vitamin K antagonist group (18). Moreover, the incidence rates of major bleedings were 1.2 per 100 person-years in edoxaban vs. 2.7 per 100 person-years in the vitamin K antagonist group (HR 0.43, 95% CI 0.10- 1.40) (18).

2.6.2.2 Studies comparing individual DOACs

The first retrospective cohort study evaluated the effectiveness of dabigatran, rivaroxaban and warfarin in patients with NVAF and T2DM (20). The cohort included participants from the pay-for-performance diabetes program implemented by Taiwan's national health insurance administration. The study included 2541 patients of which 322 patients were given dabigatran, 320 patients were given rivaroxaban and 1899 patients were given warfarin. This study used an intention to treat exposure definition, and patients on NOACs or warfarin only at the AF episodes, were followed up from the initiation date of the first oral anticoagulant treatment (the index date) until either the occurrence of death or the end of the study period, December 31, 2015. The median follow-up duration was 1.7 years. The incidence rates of ischemic stroke were 13.7% in the rivaroxaban group compared to 7.1% in the warfarin group (HR 0.91, 95% CI 0.57- 1.46), 13% in the dabigatran group compared to 10% in the warfarin group (HR 0.90, 95% CI 0.61- 1.35) and 13.2% in the dabigatran group compared to 13.7% in the rivaroxaban group (HR 1.33, 95% CI 0.84- 2.1). In terms of safety, incidence rates of a composite safety end point (combination of intracranial haemorrhage, gastrointestinal bleeding and haematuria) were similar between dabigatran (8.9%) and warfarin groups (9.5%) (HR 0.67, 95% CI 0.43- 1.02), rates were 16.4% in the rivaroxaban group compared to 9.4% in the warfarin group (HR 1.20, 95% CI 0.77- 1.88) and rates were 9.4% in the dabigatran group compared to 15.7% in the rivaroxaban group (HR 0.66, 95% CI 0.41- 1.07). (20).

The following study evaluated the effectiveness and safety of apixaban, dabigatran and rivaroxaban, and warfarin in patients with NVAF and diabetes (type 1 and type 2 diabetes) (21). The cohort included 167,815 patients of which 37,558 patients were treated with apixaban, 51,200 patients treated with rivaroxaban, 13,128 treated with dabigatran and 65,929 treated with warfarin. All of these patients were newly treated with these NOACs or warfarin (index date) between 2013 and 2015. The study was conducted using fee-for-service Medicare data from the US Centers for Medicare & Medicaid Services and by 4 other US commercial claims databases including, the Truven MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database, the IMS PharMetrics Plus database, the Optum Clinformatics Data Mart, and the Humana Research database. The authors used an as-treated exposure definition where patients were followed from 1-day postindex date until either 30 days after the treatment discontinuation date, medication switch date, death, end of continuous medical or pharmacy plan enrollment, or end of study (September 30, 2015), whichever occurred earliest (21). The authors found that compared with warfarin, there was a 26% lower risk of ischemic stroke in the apixaban group (HR 0.74, 95% CI 0.65-0.85) and a 14% lower risk of ischemic stroke in the rivaroxaban group (HR 0.86, 95% CI 0.77-0.97). Also, there was no difference in ischemic stroke rate found between dabigatran and warfarin (HR 1.00, 95% CI 0.81-1.25). In terms of safety, there was a 40% lower risk of major bleeding in the apixaban group (HR 0.60, 95% CI 0.56-0.65) and a 22% lower risk of major bleeding in the dabigatran group (HR 0.78, 95% CI 0.69-0.88), each compared with warfarin. Furthermore, in the head-to-head comparison of individual DOACs, apixaban was associated with a 23% lower risk of ischemic stroke compared with dabigatran (HR 0.77, 95% CI 0.61-0.96) and a similar risk of ischemic stroke compared with rivaroxaban (HR 0.89, 95% CI 0.78-1.02). Similarly, apixaban was associated with a 27% lower risk of major bleeding compared with dabigatran (HR 0.73, 95% CI 0.63-0.84) and a 41% lower risk of major bleeding compared with rivaroxaban (HR 0.59, 95% CI 0.54-0.65). Also, Dabigatran was associated with a similar risk of ischemic stroke (HR 1.24, 95% CI 0.98-1.58) and a 24% lower risk of major bleeding (HR 0.76, 95% CI 0.66-0.86) compared with rivaroxaban (21).

Since vitamin K antagonists have several limitations such as increased risk of bleeding, the need for constant monitoring of international normalized ratio, frequent blood testing and interaction with other drugs (5, 6, 62), physicians are prescribing DOACs more frequently to treat patients with NVAF and diabetes. However, the main concern for physicians is determining which

DOAC they should prescribe, since most of the studies examined the effectiveness of all the DOACs together or compared DOACs with warfarin. Also, most of the studies have been done only in patients with NVAF only, rather than in patients with NVAF and diabetes. Among the DOACs, apixaban and rivaroxaban are the most prescribed by physicians in the UK and around the world (117-120). Yet, only one study has compared the effectiveness and safety of apixaban vs. rivaroxaban in patients with both NVAF and diabetes (21). To fill the knowledge gap, this thesis will assess the effectiveness and safety of apixaban compared with rivaroxaban in patients with AF and T2DM. The following chapters describe the objectives, methodology, and results of this thesis.

Chapter 3: Objectives and hypotheses

3.1 Objective

The overall objective of this thesis is to assess the effectiveness and safety of apixaban compared with rivaroxaban in patients with NVAF and T2DM.

3.1.1 Primary objectives

This thesis has two primary objectives:

1. To determine whether apixaban is associated with a decreased risk of ischemic stroke, compared with the use of rivaroxaban in NVAF patients with T2DM.
2. To determine whether apixaban is associated with a decreased risk of major bleeding, compared with the use of rivaroxaban in NVAF patients with T2DM.

3.1.2 Secondary objective

The secondary objective of this thesis is to determine whether apixaban is associated with a decreased risk of major adverse limb events, a composite of major limb amputation, surgical revascularization or endovascular revascularization when compared with the use of rivaroxaban in NVAF patients with T2DM.

3.2 Hypothesis

3.2.1 Primary hypotheses

This thesis has two primary hypotheses:

1. Apixaban is associated with a similar risk of ischemic stroke, compared with rivaroxaban in NVAF patients with T2DM.

2. Apixaban is associated with a similar risk of major bleeding, compared with rivaroxaban in NVAF patients with T2DM.

3.2.2. Secondary hypothesis

The secondary hypothesis of this thesis is that apixaban is associated with a similar risk of major adverse limb events, a composite of major limb amputation, surgical revascularization or endovascular revascularization when compared with rivaroxaban in NVAF patients with T2DM.

Chapter 4: Supplemental methods

This section will explain the methodology used in this thesis in greater details, providing details not covered in the manuscript in chapter 5. This section will give additional information on the data source, the description of linked data, confounding and missing data.

4.1 Data source

The UK's Clinical Practice Research Datalink (CPRD), one of the largest primary care databases worldwide, has been used in this study (121). It was established in 1987 as the Value Added Medical Products dataset, expanding to the General Practice Research Database, before becoming the CPRD in 2012 (121). This primary care database covers over 55 million patients enrolled in over 2000 practices in the UK (121-124), including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviour and referrals to secondary care, collected on a monthly basis (121). All the patients registered are included in the database unless they request to opt out on their own. Patients included in the CPRD have been shown to be representative of the general UK population in terms of age, sex and ethnicity (121-124). The CPRD can be linked to secondary care datasets, including hospitalization data from Hospital Episode Statistics and mortality data from the Office for National Statistics (121-126).

CPRD includes two databases, CPRD GOLD and CPRD Aurum databases. CPRD has been contributing to CPRD GOLD database for more than 30 years. CPRD Aurum has been launched in 2017, capturing diagnoses, symptoms, prescriptions, referrals and tests for over 19 million patients that represents around 13% of the population of England (123).

The data in the CPRD are recorded using a combination of Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT) (UK edition), the Read Version and local EMIS Web® codes. The Drug Dictionary has information on drug and device prescriptions recorded in EMIS Web® and coded using the Dictionary of Medicines and Devices (dm+d), existing within the SNOMED CT (127). SNOMED CT is the most comprehensive, precise and structured clinical vocabulary, used in an electronic health record (128). SNOMED CT helps in exchanging information between systems easier, safer and more accurate, giving clinical IT systems a single shared language. It contains every clinical term, from procedures and symptoms through to clinical measurements, diagnoses and medications, needed for the whole National Health Service (NHS).

Thus, the use of SNOMED CT helps ensure that the data is recorded consistently and accurately, as a consistent vocabulary to record patient clinical information across the NHS (128). The Read codes, a hierarchical clinical classification system having over 96,000 codes, is a computerised medical language designed to be comprehensive, hierarchical, coded, cross referenced, and dynamic (129, 130). The Read codes are five character alphanumeric codes having a lower or upper case letter or a number at each level of the code. Each level of the code has 58 available characters and a maximum of over 650 million available codes in total in the five levels of the code (129, 130). The classifications included and cross-referenced in the Read code system are the International Classification of Diseases, injuries, and causes of death (ICD 9), the international classification of diseases clinical modification (ICD 9-CM), the Office of Population, Censuses and Surveys' Classification of Surgical Operations and Procedures (OPCS), the physicians' current procedural terminology (CPT-4), the British National Formulary and the OPCS classification of occupations (129). Subsets of ICD 9 include the international classification of health problems in primary care (ICHPCC-2), the international classification of primary care (ICPC) and the Royal College of General Practitioners (1986) classification that are also cross referenced (129).
The medical diagnoses recorded in CPRD have been shown to be of high validity and quality (131-133), making it a favorable data source for epidemiological research, with 2000 research reports and over 1000 studies published in peer-reviewed journals (121). These publications cover a vast range of health outcomes including pharmacoepidemiology, comparative effectiveness research and other related health services research (121). Thus, the CPRD has been used widely for observational studies such as pharmacoepidemiologic studies of drug safety and utilization (134, 135).

4.2 Use of linked data

This study was conducted by linking the CPRD, the HES inpatient database, and the ONS (Office for National Statistics) mortality database. The HES repository contains all inpatient and day case admission information, including primary and secondary diagnoses, and procedures (125). HES is available for England primary care practices that have consented to linkage, which represent approximately 80% of the CPRD (136). The ONS database includes information on patients' date and causes of death (126). The linkage with HES database was necessary to

accurately ascertain the outcomes, defined as hospitalization with ischemic stroke/ transient ischemic attack/ systemic embolism, or major bleeding. The HES database was also used as an extra data source for the measurement of covariates before cohort entry. The linkage with ONS mortality database was necessary to identify all the deaths related to the outcomes of interest.

4.3 Confounding and missing data

We used propensity score (PS)-based standardised mortality ratio weighting to address confounding. In standardised mortality ratio weighting method, weights are set to 1 for the treated patients and reference patients are weighted by the odds of treatment probability (propensity score/(1−propensity score)). This method is at risk of extreme weights because of the direct use of propensity score for calculating the weights (137). The propensity score included numerous covariates ranging from demographic and lifestyle factors to comorbidities, medications and healthcare utilization. Moreover, use of an active comparator reduced confounding. Comparison was made between patients with the same condition (NVAF) starting different DOACs (apixaban vs. rivaroxaban). For variables with missing values, the primary analyses were repeated using multiple imputation (i.e., HbA1c, BMI, smoking). An ordinal logistic regression model was used to impute variables with missing information with explanatory variables and cumulative hazard and one of the exposure groups (at cohort entry), along with all confounders mentioned previously (138).

Chapter 5: Effectiveness and safety of apixaban versus rivaroxaban in patients with nonvalvular atrial fibrillation and type 2 diabetes mellitus

This chapter presents a manuscript on the effectiveness and safety of apixaban compared with rivaroxaban in patients with NVAF and T2DM. First, the introduction provides background information on NVAF and T2DM, and the study rationale. Second, the methods section describes the data source, cohort formation, covariates and the statistical models used. Then, the results are presented, including descriptive characteristics of the cohort and the results of the primary and secondary analyses. Finally, the discussion provides an interpretation of the findings, comparisons with previous literature, and strengths and limitations of the study. This manuscript will be submitted to a scientific journal soon for publication.

Effectiveness and safety of apixaban versus rivaroxaban in patients with nonvalvular atrial fibrillation and type 2 diabetes mellitus

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5.1 Abstract

Background: Limited evidence exists on the effectiveness and safety of apixaban compared with rivaroxaban, the most commonly prescribed direct oral anticoagulants, in patients with non-valvular atrial fibrillation (NVAF) and diabetes mellitus.

Objectives: To evaluate the effectiveness and safety of apixaban vs. rivaroxaban among patients with NVAF and type 2 diabetes (T2DM).

Methods: Using the United Kingdom's Clinical Practice Research Datalink linked to the Hospital Episode Statistics repository, and the Office for National Statistics database, we identified a cohort of patients with NVAF and T2DM newly treated with apixaban or rivaroxaban between 2013 and 2020. Propensity scores with standardised mortality ratio weighting were used to control for confounding. We used weighted Cox proportional hazards models to estimate separately the hazard ratios (HRs) with 95% confidence intervals (CIs) of ischemic stroke, major bleeding, and major adverse limb events associated with use of apixaban compared with rivaroxaban. We also evaluated whether the risk was modified by age, sex, duration of diabetes, microvascular and macrovascular complications of diabetes, nephropathy, CHA_2DS_2-VASc and HAS-BLED scores, and by dose (standard vs. low dose).

Results: The cohort included 11,561 apixaban and 8,265 rivaroxaban users. Apixaban was associated with a similar risk of stroke (incidence rates 23.4 vs. 18.4 per 1000 person-years, respectively; HR 0.99, 95% CI 0.79-1.23), and a 32% reduced risk of major bleeding (43.6 vs. 54.7 per 1000 person-years, respectively; HR 0.68, 95% CI 0.59-0.78), compared with rivaroxaban. The risk of major adverse limb events was similar between apixaban and rivaroxaban (9.3 vs. 9.5 per 1000 person-years, respectively; HR 0.75, 95% CI 0.54-1.04). Overall, the risk of ischemic stroke and major bleeding was consistent in stratified analyses.

Conclusions: Among patients with NVAF and T2DM, apixaban was associated with a similar risk of stroke, and a lower risk of major bleeding compared with rivaroxaban.

5.2 Introduction

Atrial fibrillation (AF), the most common type of cardiac arrhythmia, is associated with a five-fold increased risk of stroke (1). Patients with diabetes have a 49% higher risk of developing AF compared with those who do not have diabetes (2). Furthermore, in patients with both AF and diabetes, the risk of stroke is 70% higher compared to those with AF only (3), and diabetes is included in stroke risk stratification schemes such as the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65-74 years, sex) (4). Therefore, oral anticoagulation is central to the management of patients with AF and diabetes. Direct oral anticoagulants (DOACs) have been recently approved to prevent stroke occurrence in patients with nonvalvular AF (NVAF) and have been shown to be at least as effective and safe compared to vitamin K antagonists in pivotal randomized controlled trials, including for patients with diabetes (5-12). As such, DOACS are now recommended as first-line oral anticoagulant for patients with NVAF (13-17). Similarly, cohort studies in patients with NVAF and diabetes found that all DOACs were associated with a similar or lower risk of stroke (18-21) and major bleeding (18, 19, 21, 22) compared with warfarin. Moreover, DOACs may also reduce the risk of major adverse lower limb events such as revascularization procedure or amputation in this population, compared with warfarin (20, 22).

Whereas the similar efficacy of DOACs compared with vitamin K antagonists is well established in patients with NVAF and diabetes, there is limited evidence on the comparative effectiveness and safety of individual DOACs to inform prescribing choice in this high-risk population. In particular, only one study compared apixaban and rivaroxaban, the two most commonly used DOACs (23-26), reporting that apixaban was associated with a similar risk of stroke or systemic embolism and a lower risk of major bleeding compared with rivaroxaban (27).

Moreover, it remains unclear whether their comparative effectiveness varies with the duration and severity of diabetes and whether they are associated with a similar risk of major adverse limb events. Thus, the objective of this study was to evaluate the effectiveness and safety of apixaban compared with rivaroxaban, in a large population-based cohort of patients with NVAF and type 2 diabetes (T2DM).

5.3 Methods

5.3.1 Data source

This study was conducted using the United Kingdom's Clinical Practice Research Datalink (CPRD), one of the world's largest primary care databases (28, 29). We linked the CPRD GOLD and Aurum databases to the Hospital Episode Statistics (HES) repository and the Office for National Statistics database (ONS). The CPRD contains the electronic medical records of more than 55 million patients enrolled in over 2000 practices in the UK and has been shown to be largely representative of the general UK population (28-30). Information collected includes demographic data, lifestyle factors, medical diagnoses, laboratory test results, prescriptions, and referrals to specialists and hospitals. Prescriptions dispensed by the general practitioners are automatically recorded in the computerized file. Quality control of data is performed regularly, and numerous studies have shown the validity and high quality of the recorded data (31, 32). The HES repository contains all inpatient and day case admission information, including primary and secondary diagnoses, and procedures (33). HES is available for England primary care practices that have consented to linkage, which represent approximately 80% of the CPRD (34). The ONS database includes information on patients' date and causes of death (35).

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol no. 21_000330) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

5.3.2 Study population

We assembled a cohort of patients with NVAF and T2DM newly treated with apixaban or rivaroxaban. First, we identified all patients ≥18 years of age with a first prescription for an antidiabetic drug between January 01, 1987 and March 31, 2020 and a new diagnosis of AF at the time or after the first antidiabetic prescription. We excluded patients with less than one year of medical history in the CPRD before the first AF diagnosis, and those with a prior AF diagnosis to only include patients with incident AF. We also excluded patients prescribed an oral anticoagulant in the year prior to the AF diagnosis. Finally, we excluded patients with no recorded diagnosis of T2DM before AF diagnosis.

Within this base cohort, we identified all patients with a new prescription for apixaban or rivaroxaban between 1 January 2013, since apixaban was the latest of the two direct oral anticoagulants approved at the end of 2012 for the treatment of AF in the UK, and March 31, 2020. Cohort entry was defined as the date of the first apixaban or rivaroxaban prescription following AF diagnosis. We excluded patients with prior use or rivaroxaban or apixaban at any time before cohort entry as well as patients initiating two oral anticoagulants at cohort entry. To only include patients with NVAF, we excluded patients with a history of valvular surgery or rheumatic valvular disease, and those with hyperthyroidism at any time before cohort entry. We also excluded patients who had a diagnosis of venous thromboembolism or underwent joint surgery of the hip or knee in the 30 days prior to and including cohort entry date. All patients were followed until the first occurrence of the outcome of interest (depending on the outcome being studied), oral anticoagulant discontinuation or switch, death from any cause, end of registration with the general practice, or end of the study period (March 31, 2020).

5.3.3 Exposure definition

Patients were considered exposed to apixaban or rivaroxaban from the date of the first prescription and censored at the date of treatment discontinuation, switch to another DOAC, or to VKAs. Patients were considered continuously exposed if the duration of one prescription overlapped with the date of the subsequent prescription, with a 30-day grace period in the event of non-overlapping prescriptions.

5.3.4 Outcome definition

The primary effectiveness outcome of interest was a composite of hospitalization with incident ischemic stroke (or stroke non otherwise specified), transient ischemic attack or systemic embolism. The safety outcome of interest was major bleeding defined as any bleeding requiring hospitalisation or resulting in death. The outcomes were defined using relevant ICD 10 codes in HES (primary position, non-elective hospitalizations) or in ONS (primary cause of death). The secondary outcome was major adverse limb events, a composite of major limb amputation, surgical or endovascular revascularization defined using corresponding procedure codes in HES.

5.3.5 Covariates

The potential confounders included demographic characteristics (age, sex, and calendar year of cohort entry) and lifestyle risk factors (alcohol abuse (measured in the year before cohort entry), body mass index and smoking, both measured in the five years before cohort entry). Microvascular complications of diabetes (neuropathy, retinopathy, nephropathy), duration of diabetes (defined by the date of the first of either a HbA1c $\geq$ 6.5%, a diagnosis of T2DM, or prescription for an antidiabetic drug), and HbA1c level last measured before cohort entry were

included as proxies for diabetes severity. We also included the following comorbidities, measured at any time before cohort entry: hypertension, hyperlipidemia, congestive heart failure, myocardial infarction, coronary artery disease, prior ischemic stroke/transient ischemic attack, systemic embolism, peripheral arterial disease, prior bleeding events, anaemia, depression, cancer (other than non-melanoma skin cancer), chronic obstructive pulmonary disease, liver disease, and time from NVAF diagnosis to apixaban/rivaroxaban initiation. We also considered the following medications measured in the year before cohort entry: antidiabetic medications (metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter-2, insulin, others), antihypertensive drugs (beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers), antiplatelet agents, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, antidepressants, antipsychotics, proton pump inhibitors, H2 blockers, and hormone replacement therapy. Finally, we included the total number of distinct drugs classes other than oral anticoagulants prescribed in the year before cohort entry, as well as the number of hospitalizations in the year before cohort entry as surrogate markers for overall health. Age, duration of diabetes and duration of NVAF were modelled using cubic splines. Missing data for HbA1c, body mass index and smoking were considered in a separate category.

5.3.6 Statistical analysis

To achieve balance in baseline characteristics between new users of apixaban and rivaroxaban, we used propensity score (PS) with standardised mortality ratio weighting (36). PS (the probability of receiving apixaban, conditional on observed baseline covariates described above) were estimated using multivariable logistic regression. We generated separate PS models

for patients with and without a history of anticoagulant use, and type of oral anticoagulant was included in the PS estimation for patients with previous use before cohort entry. Following PS estimation, we excluded patients in the non-overlapping regions of the PS distributions. Next, we used standardised mortality ratio weighting to reweight the cohort. Specifically, weights were set to 1 for patients treated with apixaban and patients treated with rivaroxaban (reference group) were weighted by the odds of treatment probability (PS/ (1−PS)).

Descriptive statistics were used to summarize the baseline characteristics of each exposure group before and after weighting. We used standardized differences to assess the covariate balance between treatment groups, with values lower than 10% suggesting good balance. Crude incidence rates of ischemic stroke, major bleeding and major limb events with 95% confidence intervals (CIs) were estimated in each exposure group based on a Poisson distribution. We plotted the weighted cumulative incidence curve of each outcome of interest for each exposure group. In the primary analyses, we fitted weighted Cox proportional hazards models with robust sandwich variance to estimate separately the hazard ratio (HR) with 95% CIs of ischemic stroke and major bleeding associated with use of apixaban compared with use of rivaroxaban. We also assessed the risk of major limb events as a secondary outcome.

Secondary analyses

First, we assessed whether the risk for each outcome varies with duration of use, stratified into 3 prespecified categories (<3, 3-6, and >6 months). Second, to assess effect measure modification, we performed stratified analyses by age (<75 yrs, ≥75 yrs), sex, duration of diabetes (<10 yrs, ≥ 10 yrs), microvascular complications, nephropathy, and macrovascular complications (history of ischemic stroke, coronary artery disease, peripheral arterial disease), and CHA_2DS_2-VASc score (for the risk of stroke and major limb events) and by dose (standard vs. low dose)

(37). In addition, we stratified patients according to a modified HAS-BLED score (hypertension, abnormal renal and/or liver function, ischemic stroke/TIA, bleeding, age >65 years, antiplatelet/non-steroidal anti-inflammatory drug use or alcohol abuse, given that international normalized ratio values were not available) (38) at cohort entry (<2 and ≥3) to assess a potential effect measure modification on the risk of major bleeding.

Sensitivity analyses

We performed four sensitivity analyses to assess the robustness of the findings. First, to assess the potential for exposure misclassification, we repeated the primary analyses using a 15 days and 60 days grace period between successive prescriptions. Second, to explore the impact of potential informative censoring due to treatment termination or switching, we repeated the primary analyses with exposure defined at cohort entry (analogous to an intention to treat analysis) and follow up limited to six months. Third, we used inverse probability of censoring weights to further account for potential informative censoring, and competing risk of death. Lastly, we used multiple imputations to account for missing data for BMI and smoking (39). All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina).

5.4 Results

After applying the inclusion and exclusion criteria, the cohort included 11,570 apixaban users and 8,274 rivaroxaban users (**Figure 2**). Nine patients in each group were excluded after propensity score distribution trimming, leaving final cohort of 11,561 apixaban users and 8,265 rivaroxaban users.

Table 1 presents the baseline characteristics by exposure group. Before propensity score weighting, apixaban users were older, and were more likely to have a history of stroke and hospitalization compared with rivaroxaban users. After weighting, all characteristics were well balanced across exposure groups. The median duration of follow-up varied from 285 to 293 days for apixaban users and from 300 to 313 days for rivaroxaban users.

Table 2 presents the results of the primary analyses. Apixaban was as effective as rivaroxaban in the prevention of ischemic stroke (incidence rates 23.4 vs. 18.4 per 1000 person-years, respectively; HR 0.99, 95% CI 0.79-1.23). Apixaban was associated with a decreased risk of major bleeding (43.6 vs. 54.7 per 1000 person-years, respectively; HR 0.68, 95% CI 0.59-0.78) compared to rivaroxaban. Finally, there was no difference between the two drugs on the risk of major limb events (9.3 vs. 9.5 per 1000 person-years, respectively; HR 0.75, 95% CI 0.54-1.04). Weighted cumulative incidence curves for the three outcomes are presented in **eFigures 1-3.**

Secondary analyses

In stratified analyses, the risk of ischemic stroke was not modified by age, sex, vascular complication of diabetes, duration of diabetes, nephropathy or CHA_2DS_2-VASc score (**eTable 1**). Similarly, there was no effect measure modification on the risk of major bleeding (**eTable 2**). For the risk of major limb events, apixaban was associated with a decreased risk of major limb events

in patients without nephropathy (HR 0.56, 95% CI 0.37- 0.86), but not in patients with nephropathy (HR 1.10, 95% CI 0.66- 1.82) (**eTable 3**). The risk of stroke and major bleeding was similar in patients with and without prior use of other anticoagulants, with a borderline significant decreased risk of major limb events associated with apixaban in patients with no prior use of anticoagulants (HR 0.69, 95% CI 0.48-1.00) (**eTables 4-6**). Results did not vary between standard and low doses of apixaban and rivaroxaban for the risk of stroke and major bleeding (**eTables 7-8**). However, apixaban was associated with a reduced risk of major limb events compared with rivaroxaban for standard doses (HR 0.68, 95% CI 0.47- 0.99), but no difference was observed with low doses (HR 0.91, 95% CI 0.43- 1.93) (**eTable 9**).

Sensitivity analyses

The results of the sensitivity analyses are presented in **Figure 3** and **eTables 10-12**. Overall, results were consistent with those of the primary analysis for each outcome.

5.5 Discussion

In this large population-based cohort study, we found that apixaban was as effective as rivaroxaban in reducing the risk of ischemic stroke in patients with NVAF and T2DM. Moreover, apixaban was associated with a reduced risk of major bleeding compared to rivaroxaban, while rates of major adverse limb events were similar between drugs. The risk of the three outcomes did not differ in the various stratified analyses and our findings remained consistent across sensitivity analyses.

T2DM is a common comorbidity in patients with NVAF and is associated with a higher risk of ischemic stroke (15, 40); Moreover, some studies suggested that patients with type 2 diabetes may have a worse prognosis after stroke compared with nondiabetic patients (41, 42), therefore, oral anticoagulation is a cornerstone of stroke prevention in this high-risk population. Since the approval of DOACs, there has been an increasing uptake of these drugs as first-line oral anticoagulants in patients with NVAF, including in those with type 2 diabetes (43). The most recent studies showed that DOACs have now surpassed warfarin, with apixaban and rivaroxaban being the most commonly prescribed oral anticoagulants in many countries (23-26). While subgroup analyses of randomized controlled trials and several observational studies showed that these two drugs were as effective and safe as warfarin in patients with type 2 diabetes, only one study compared the effectiveness and safety of apixaban and rivaroxaban in this population (27). Using US claims databases, the cohort included 37,558 patients prescribed apixaban and 51,200 prescribed rivaroxaban (27). Compared with rivaroxaban, apixaban was associated with a similar risk of ischemic stroke (HR, 0.89; 95% CI, 0.78-1.02) and a 41% lower risk of major bleeding (HR, 0.59; 95% CI, 0.54-0.65), in line with our results (27). We further extended these findings by showing that the lower risk of bleeding with apixaban was not modified by several relevant

characteristics such as age, sex, duration of diabetes, vascular complications of diabetes, nephropathy, and HAS-BLED score. Notably, we restricted our study population to patients with T2DM because type 1 diabetes is characterized by a different pathophysiology which may in turn influence the risk of thrombotic and bleeding events.

We also assessed whether apixaban decreases the risk of major limb events, a clinically relevant outcome in patients with T2DM, compared with rivaroxaban. Indeed, the prevalence of lower extremity arterial disease, including major adverse limb events, is two- to four-fold higher in diabetic patients compared with patients without diabetes, and is associated with worse outcomes in this population, in particular the risk of lower limb amputation (44). Moreover, in the recent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, patients with a major adverse limb event had a 3-fold increased risk of death and a 200-fold increase in the risk of subsequent total vascular amputation in the following year (45). Prevention of major limb events is therefore important and usually involve antiplatelet therapy but oral anticoagulants may have a place in the pharmacologic armamentarium. Indeed, the COMPASS trial suggested a benefit for combined aspirin and low-dose rivaroxaban for individuals with peripheral artery disease, including those with diabetes, compared with aspirin alone (45). We showed that, although the risk of major adverse limb events did not differ overall between apixaban and rivaroxaban, the risk may be lower with apixaban compared with rivaroxaban at standard doses. However, our study was not specifically designed to assess the potential benefit of DOACs in patients with diabetes on the prevention of major adverse limb events. Future large-scale observational studies may help to further clarify the role and respective effectiveness of DOACs in the prevention of major limb events in patients with NVAF and T2DM.

This study has several strengths. First, using CPRD as our data source provided a large and well-defined study population of 19,826 patients with NVAF and T2DM treated in the real-world setting. Second, linkage to the HES and ONS databases to define the outcomes likely minimized outcome misclassification. Third, the use of an active comparator reduced confounding at the design stage. Fourth, all models were adjusted for many potential confounders including lifestyle risk factors, that are not available in claims databases. We were also able to account for the duration of diabetes and HbA1c level, which are risk factors for thromboembolism in patients with diabetes (46, 47). Finally, the results remained consistent across sensitivity analyses, suggesting that our findings are robust.

Several potential limitations also need to be considered. First, misclassification of exposure is possible since the CPRD database only contains information on prescriptions issued by general practitioners and do not have those prescribed by specialists. However, general practitioners in the UK are extensively involved in the management and treatment of patients with AF, so that most prescriptions are likely issued by general practitioners (17). We also expect this misclassification to be non-differential between the exposure groups. Second, there is the possibility of outcome misclassification, which was minimized by using HES data to define the outcomes. Moreover, outcome misclassification is likely to be non-differential between the two exposure groups. Third, given the observational nature of our study, residual confounding needs to be considered. This potential bias was mitigated with the use of standardised mortality ratio weighting, which resulted in well-balanced covariates, including risk factors for thromboembolism in diabetes and diabetes severity, between exposure groups.

Overall, the results of this population-based cohort study suggest that apixaban is associated with similar risks of ischemic stroke and major adverse limb events, and a lower risk of

major bleeding compared with rivaroxaban in patients with NVAF and T2DM. These findings might inform prescribing choices in this population in everyday clinical practice.

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5.7 Figures and tables

FIGURE LEGENDS

Figure 2. Flow chart describing cohort definition of new users of apixaban and rivaroxaban

Figure 3. Forest plot summarizing the results of the primary and sensitivity analyses for the association between apixaban and the risk of stroke, major bleeding, and major limb events

Figure 2. Flow chart describing cohort definition of new users of apixaban and rivaroxaban

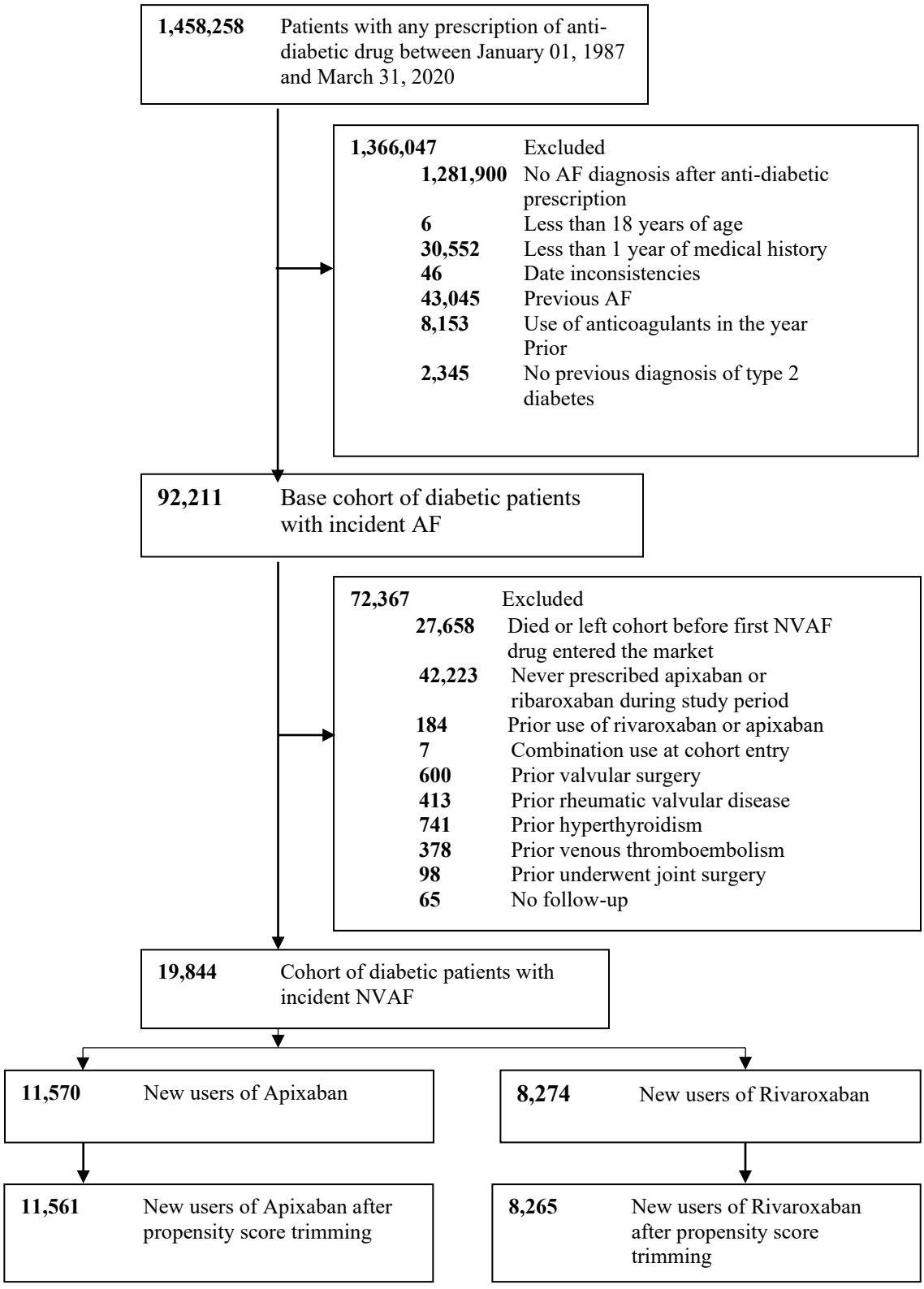

Figure 3. Forest plot summarizing the results of the primary and sensitivity analyses for the association between apixaban and the risk of stroke, major bleeding, and major limb events

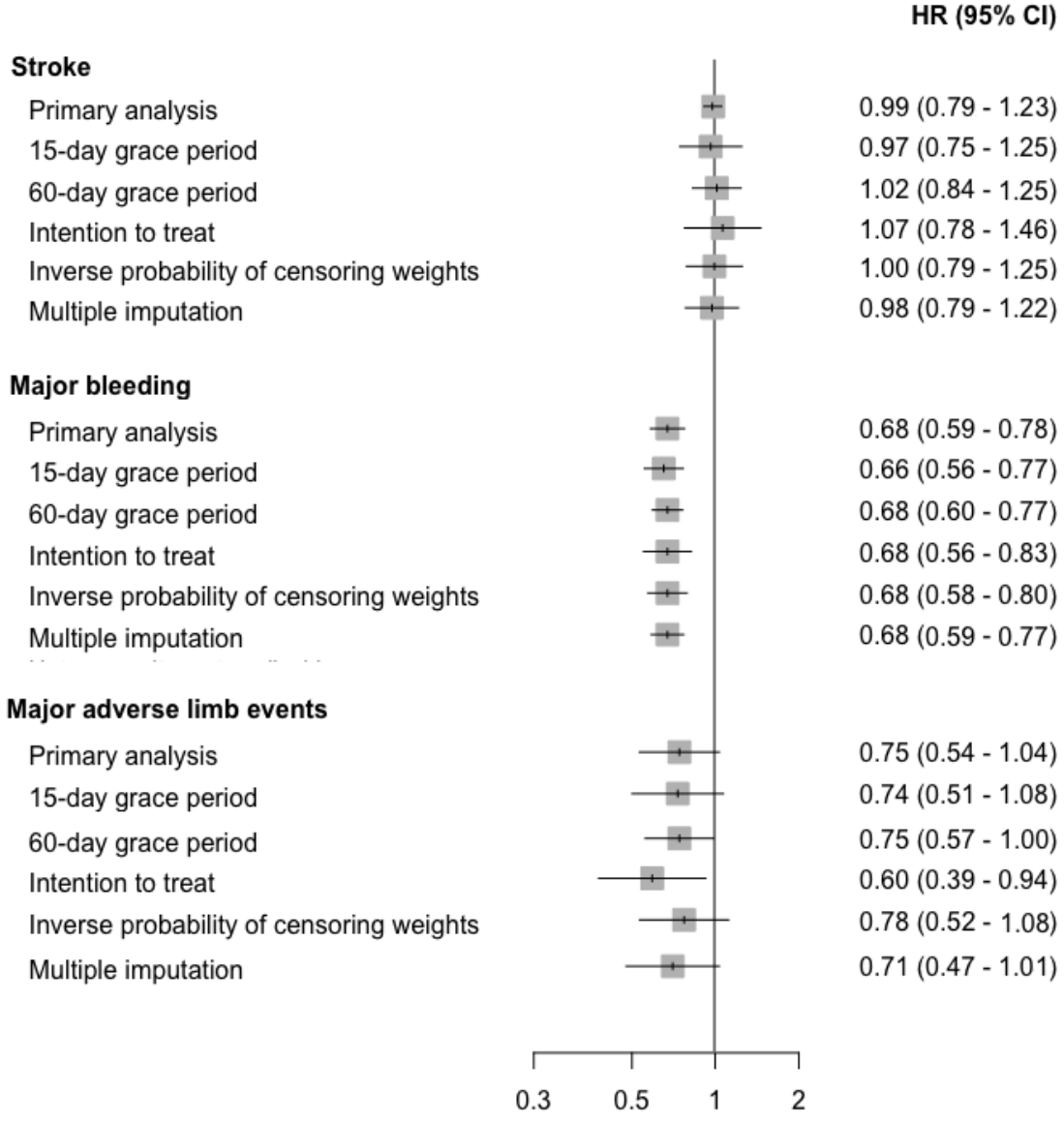

Table 1. Baseline Characteristics of New Users of Apixaban and Rivaroxaban Before and After Propensity Score Weighting*

Characteristic	Before Weighting			After Weighting		
	Apixaban (n=11,561)	Rivaroxaban (n=8,265)	Std. Diff.	Apixaban (n=11,561)	Rivaroxaban (11,695)	Std. Diff.
Age, years, mean (SD)	76.2 (9.7)	75.0 (9.7)	0.12	76.2 (9.7)	76.1 (11.6)	0.01
Male	7010 (60.6)	5263 (63.7)	0.06	7010 (60.6)	7157 (61.2)	0.01
Year of cohort entry						
2013	57 (0.5)	400 (4.8)	0.27	57 (0.5)	129 (1.1)	0.06
2014	364 (3.2)	826 (10.0)	0.28	364 (3.2)	384 (3.3)	0.01
2015	975 (8.4)	1483 (17.9)	0.28	975 (8.4)	1011 (8.6)	0.02
2016	1722 (14.9)	1684 (20.4)	0.14	1722 (14.9)	1649 (14.1)	0.03
2017	2306 (20.0)	1395 (16.9)	0.08	2306 (20.0)	1993 (17.0)	0.07
2018	2650 (22.9)	1236 (15.0)	0.20	2650 (22.9)	2523 (21.6)	0.03
2019	2770 (24.0)	998 (12.1)	0.31	2770 (24.0)	2922 (25.0)	0.02
2020	717 (6.2)	243 (2.9)	0.16	717 (6.2)	1083 (9.3)	0.12
Smoking Status						
Non-smoker	3253 (28.1)	2260 (27.3)	0.02	3253 (28.1)	3254 (27.8)	0.01
Smoker	8163 (70.6)	5895 (71.3)	0.02	8163 (70.6)	8306 (71.0)	0.01
Unknown	145 (1.3)	110 (1.3)	0.01	145 (1.3)	135 (1.2)	0.01
Body Mass Index, kg/m^2						
<18.5	64 (0.6)	31 (0.4)	0.03	64 (0.6)	63 (0.5)	0.00
18.5-24.9	1599 (13.8)	1066 (12.9)	0.03	1599 (13.8)	1634 (14.0)	0.00
25-30	3442 (29.8)	2427 (29.4)	0.01	3442 (29.8)	3446 (29.5)	0.01
>30	6063 (52.4)	4401 (53.3)	0.02	6063 (52.4)	6171 (52.8)	0.01
Unknown	393 (3.4)	340 (4.1)	0.04	393 (3.4)	380 (3.3)	0.01
Hemoglobin A1c						
≤7%	5601 (48.4)	3902 (47.2)	0.02	5601 (48.4)	5723 (48.9)	0.01
7.1%-8%	3152 (27.3)	2291 (27.7)	0.01	3152 (27.3)	3079 (26.3)	0.02
>8%	2798 (24.2)	2067 (25.0)	0.02	2798 (24.2)	2886 (24.7)	0.01
Unknown	10 (0.1)	5 (0.1)	0.01	10 (0.1)	7 (0.1)	0.01
Duration of diabetes, years, mean (SD)	15.4 (12.6)	14.2 (10.7)	0.10	15.4 (12.6)	15.3 (14.6)	0.00
Time to OAC initiation, years, mean (SD)	1.7 (3.2)	1.8 (3.1)	0.04	1.7 (3.2)	1.7 (3.8)	0.01

Comorbidities						
Alcohol abuse	402 (3.5)	387 (4.7)	0.06	402 (3.5)	410 (3.5)	0.00
Neuropathy	3934 (34.0)	2582 (31.2)	0.06	3934 (34.0)	4027 (34.4)	0.01
Retinopathy	6031 (52.2)	4209 (50.9)	0.02	6031 (52.2)	6059 (51.8)	0.01
Nephropathy	4563 (39.5)	3046 (36.9)	0.05	4563 (39.5)	4518 (38.6)	0.02
Congestive heart failure	2820 (24.4)	1849 (22.4)	0.05	2820 (24.4)	2864 (24.5)	0.00
Myocardial infarction	1944 (16.8)	1410 (17.1)	0.01	1944 (16.8)	2055 (17.6)	0.02
Coronary artery disease	2765 (23.9)	1997 (24.2)	0.01	2765 (23.9)	2859 (24.4)	0.01
Stroke/Transient ischemic attack	2920 (25.3)	1647 (19.9)	0.13	2920 (25.3)	2952 (25.2)	0.00
Systemic embolism	66 (0.6)	52 (0.6)	0.01	66 (0.6)	73 (0.6)	0.01
Peripheral arterial disease	1185 (10.3)	788 (9.5)	0.02	1185 (10.3)	1185 (10.1)	0.00
Anaemia	3233 (28.0)	1967 (23.8)	0.10	3233 (28.0)	3241 (27.7)	0.01
Bleeding	4553 (39.4)	3032 (36.7)	0.06	4553 (39.4)	4623 (39.5)	0.00
Depression	3249 (28.1)	2288 (27.7)	0.01	3249 (28.1)	3297 (28.2)	0.00
Cancer	2227 (19.3)	1533 (18.6)	0.02	2227 (19.3)	2231 (19.1)	0.00
Chronic obstructive pulmonary disease	1791 (15.5)	1276 (15.4)	0.00	1791 (15.5)	1758 (15.0)	0.01
Liver disease	816 (7.1)	528 (6.4)	0.03	816 (7.1)	854 (7.3)	0.01
Medications						
Metformin	8694 (75.2)	6419 (77.7)	0.06	8694 (75.2)	8837 (75.6)	0.01
Sulfonylureas	3788 (32.8)	2839 (34.4)	0.03	3788 (32.8)	3824 (32.7)	0.00
Thiazolidinediones	451 (3.9)	374 (4.5)	0.03	451 (3.9)	449 (3.9)	0.00
GLP1-RAs	474 (4.1)	357 (4.3)	0.01	474 (4.1)	494 (4.2)	0.01
Dipeptidyl peptidase 4 inhibitors	2600 (22.5)	1615 (19.5)	0.07	2600 (22.5)	2673 (22.9)	0.01
Sodium-glucose cotransporter-2	538 (4.7)	303 (3.7)	0.05	538 (4.7)	592 (5.1)	0.02
Insulin	2918 (25.2)	1988 (24.1)	0.03	2918 (25.2)	2915 (24.9)	0.01
Other classes of antidiabetics	60 (0.5)	34 (0.4)	0.02	60 (0.5)	65 (0.6)	0.01
Beta-blockers	8039 (69.5)	5638 (68.2)	0.03	8039 (69.5)	8163 (69.8)	0.01
Thiazides	2354 (20.4)	1728 (20.9)	0.01	2354 (20.4)	2350 (20.1)	0.01
Angiotensin-converting enzyme inhibitors	6204 (53.7)	4503 (54.5)	0.02	6204 (53.7)	6263 (53.6)	0.00
Angiotensin II receptor blockers	2931 (25.3)	2159 (26.1)	0.02	2931 (25.3)	2917 (24.9)	0.01
Calcium channel blockers	5530 (47.8)	3977 (48.1)	0.01	5530 (47.8)	5549 (47.4)	0.01
Antidepressants	2986 (25.8)	2048 (24.8)	0.02	2986 (25.8)	3052 (26.1)	0.01

Antipsychotics	702 (6.1)	481 (5.8)	0.01	702 (6.1)	707 (6.0)	0.00
Lipid-lowering drugs	9851 (85.2)	6945 (84.0)	0.03	9851 (85.2)	9945 (85.0)	0.00
Nonsteroidal anti-inflammatory drugs	958 (8.3)	820 (9.9)	0.06	958 (8.3)	964 (8.2)	0.00
Proton pump inhibitors	6239 (54.0)	4215 (51.0)	0.06	6239 (54.0)	6281 (53.7)	0.00
Antiplatelets	5968 (51.6)	4444 (53.8)	0.04	5968 (51.6)	6091 (52.1)	0.01
Oral anticoagulants	2606 (22.5)	2142 (25.9)	0.08	2606 (22.5)	2653 (22.7)	0.00
DOACs	264 (2.3)	181 (2.2)	0.01	264 (2.3)	306 (2.6)	0.02
VKAs	2420 (20.9)	2020 (24.4)	0.08	2420 (20.9)	2442 (20.9)	0.00
H2 blockers	868 (7.5)	527 (6.4)	0.04	868 (7.5)	858 (7.3)	0.01
HRT**	110 (2.4)	75 (2.5)	0.01	110 (2.4)	104 (2.3)	0.01
Number of hospitalizations						
0	4159 (35.9)	3765 (45.5)	0.20	4159 (35.9)	4286 (36.6)	0.01
1-3	6728 (58.2)	4108 (49.7)	0.17	6728 (58.2)	6772 (57.9)	0.01
4-7	631 (5.5)	360 (4.4)	0.05	631 (5.5)	596 (5.1)	0.02
>8	43 (0.4)	32 (0.4)	0.00	43 (0.4)	42 (0.4)	0.00

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

**Percentage in women.

Abbreviations: Std. Diff., standardized difference; SD, standard deviation; GLP-1-RA, glucagon-like peptide 1 receptor agonist; DOACs, direct oral anticoagulants; VKA, vitamin K antagonists; HRT, hormone replacement therapy.

Table 2. Crude and adjusted hazard ratios for the association between the use of apixaban and the risk of stroke, major bleeding and major limb events

Exposure	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI)†
Stroke					
Rivaroxaban	209	11356.82	18.4 (16.1-21.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	319	13658.37	23.4 (20.9-26.1)	1.23	0.99 (0.79-1.23)
Duration of use, months					
<3	95	2549.68	37.3 (30.5-45.6)	1.37	1.02 (0.66-1.56)
3-6	52	2087.97	24.9 (19.0-32.7)	1.18	1.04 (0.61-1.77)
>6	172	9020.71	19.1 (16.4-22.1)	1.19	0.96 (0.72-1.28)
Major Bleeding					
Rivaroxaban	607	11097.83	54.7 (50.5-59.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	590	13538.84	43.6 (40.2-47.2)	0.77	0.68 (0.59-0.78)
Duration of use, months					
<3	181	2540.18	71.3 (61.6-82.4)	0.79	0.71 (0.55-0.91)
3-6	90	2077.71	43.3 (35.2-53.3)	0.67	0.57 (0.41-0.81)
>6	319	8920.96	35.8 (32.0-39.9)	0.79	0.70 (0.58-0.84)
Major limb events					
Rivaroxaban	108	11389.41	9.5 (7.9-11.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	128	13765.61	9.3 (7.8-11.1)	0.95	0.75 (0.54-1.04)

Duration of use, months					
<3	33	2556.01	12.9 (9.2-18.2)	0.92	0.70 (0.38-1.29)
3-6	25	2096.15	11.9 (8.1-17.7)	0.84	0.48 (0.23-1.01)
>6	70	9113.45	7.7 (6.1-9.7)	1.00	0.95 (0.62-1.46)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio;

Effectiveness and safety of apixaban versus rivaroxaban in patients with nonvalvular atrial fibrillation and type 2 diabetes mellitus

Supplementary material

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eTable 1. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of stroke in stratified analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
<75 years					
Rivaroxaban	52	5497.09	9.5 (7.2-12.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	94	5852.46	16.1 (13.1-19.7)	1.66	1.33 (0.89-2.00)
≥75 years					
Rivaroxaban	157	5859.73	26.8 (22.9-31.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	225	7805.9	28.8 (25.3-32.9)	1.05	0.88 (0.67-1.13)
Female					
Rivaroxaban	80	4147.12	19.3 (15.5-24.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	154	5304.37	29.0 (24.8-34.0)	1.48	1.16 (0.80-1.67)
Male					
Rivaroxaban	129	7209.70	17.9 (15.1-21.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	165	8354.00	19.8 (17.0-23.0)	1.06	0.87 (0.66-1.15)
No microvascular complications					
Rivaroxaban	41	3063.09	13.4 (9.9-18.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	59	3228.84	18.3 (14.2-23.6)	1.33	1.13 (0.69-1.85)
Microvascular complications					
Rivaroxaban	168	8293.73	20.3 (17.4-23.6)	1.00 [Reference]	1.00 [Reference]
Apixaban	260	10429.53	24.9 (22.1-28.2)	1.20 (0.98-1.45)	0.95 (0.74-1.22)

No macrovascular complications					
Rivaroxaban	66	6849.49	9.6 (7.6-12.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	89	7387.62	12.1 (9.8-14.8)	1.23 (0.89-1.70)	0.94 (0.64-1.37)
Macrovascular complications					
Rivaroxaban	143	4507.33	31.7 (26.9-37.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	230	6270.74	36.7 (32.2-41.7)	1.13 (0.92-1.40)	0.99 (0.76-1.30)
No nephropathy					
Rivaroxaban	117	7468.97	15.7 (13.1-18.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	173	8500.71	20.4 (17.5-23.6)	1.26 (1.00-1.60)	1.05 (0.79-1.40)
Nephropathy					
Rivaroxaban	92	3887.85	23.7 (19.3-29.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	146	5157.66	28.3 (24.1-33.3)	1.17 (0.89-1.52)	0.91 (0.65-1.28)
Diabetes duration <10 years					
Rivaroxaban	46	4335.9	10.6 (7.9-14.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	84	4558.1	18.4 (14.9-22.8)	1.69 (1.18-2.42)	1.54 (1.00-2.35)
Diabetes duration ≥10 years					
Rivaroxaban	163	7020.92	23.2 (19.9-27.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	235	9100.26	25.8 (22.7-29.4)	1.09 (0.89-1.33)	0.85 (0.66-1.10)
CHA_2DS_2-VASc ≤3					
Rivaroxaban	11	2929.51	3.8 (2.1-6.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	19	2805.79	6.8 (4.3-10.6)	1.65 (0.79-3.46)	1.02 (0.41-2.53)

CHA_2DS_2-VASc >3					
Rivaroxaban	198	8427.3	23.5 (20.4-27.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	300	10852.57	27.6 (24.7-31.0)	1.15 (0.96-1.38)	0.97 (0.78-1.22)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio 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.

eTable 2. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major bleeding in stratified analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
<75 years					
Rivaroxaban	190	5398.89	35.2 (30.5-40.6)	1.00 [Reference]	1.00 [Reference]
Apixaban	160	5802.48	27.6 (23.6-32.2)	0.75	0.65 (0.50-0.83)
≥75 years					
Rivaroxaban	417	5698.94	73.2 (66.5-80.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	430	7736.36	55.6 (50.6-61.1)	0.74	0.68 (0.58-0.80)
Female					
Rivaroxaban	212	4055.19	52.3 (45.7-59.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	222	5274.4	42.1 (36.9-48.0)	0.78	0.70 (0.55-0.88)
Male					
Rivaroxaban	395	7042.64	56.1 (50.8-61.9)	1.00 [Reference]	1.00 [Reference]
Apixaban	368	8264.44	44.5 (40.2-49.3)	0.77	0.66 (0.56-0.78)
No microvascular complications					
Rivaroxaban	118	3009.36	39.2 (32.7-47.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	98	3213.27	30.5 (25.0-37.2)	0.73	0.73 (0.54-0.99)
Microvascular complications					
Rivaroxaban	489	8088.47	60.5 (55.3-66.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	492	10325.57	47.7 (43.6-52.1)	0.77	0.66 (0.57-0.77)

No macrovascular complications					
Rivaroxaban	277	6676.97	41.5 (36.9-46.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	269	7297.18	36.9 (32.7-41.5)	0.85	0.75 (0.62-0.92)
Macrovascular complications					
Rivaroxaban	330	4420.86	74.7 (67.0-83.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	321	6241.66	51.4 (46.1-57.4)	0.68	0.61 (0.51-0.74)
No nephropathy					
Rivaroxaban	335	7334.86	45.7 (41.0-50.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	311	8435.93	36.9 (33.0-41.2)	0.78	0.69 (0.57-0.83)
Nephropathy					
Rivaroxaban	272	3762.97	72.3 (64.2-81.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	279	5102.91	54.7 (48.6-61.5)	0.74	0.65 (0.53-0.81)
Diabetes duration <10 years					
Rivaroxaban	174	4241.95	41.0 (35.4-47.6)	1.00 [Reference]	1.00 [Reference]
Apixaban	146	4524.28	32.3 (27.4-38.0)	0.76 (0.61-0.95)	0.73 (0.57-0.95)
Diabetes duration ≥10 years					
Rivaroxaban	433	6855.89	63.2 (57.5-69.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	444	9014.56	49.3 (44.9-54.1)	0.75 (0.66-0.86)	0.65 (0.56-0.77)
HAS-BLED ≤2					
Rivaroxaban	61	2388.3	25.5 (19.9-32.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	47	2536.45	18.5 (13.9-24.7)	0.71	0.61 (0.39-0.94)

HAS-BLED >2					
Rivaroxaban	546	8709.53	62.7 (57.7-68.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	543	11002.38	49.4 (45.4-53.7)	0.76	0.68 (0.59-0.79)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio; HAS-BLED (modified), hypertension, abnormal renal/liver function, stroke, bleeding, elderly (>65 years), alcohol or drugs predisposing to bleeding.

eTable 3. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major limb event in stratified analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
<75 years					
Rivaroxaban	57	5485.28	10.4 (8.0-13.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	53	5874.59	9.0 (6.9-11.8)	0.82	0.65 (0.41-1.01)
≥75 years					
Rivaroxaban	51	5904.13	8.6 (6.6-11.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	75	7891.02	9.5 (7.6-11.9)	1.08	0.87 (0.55-1.38)
Female					
Rivaroxaban	28	4163.39	6.7 (4.6-9.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	33	5373.09	6.1 (4.4-8.6)	0.89	0.82 (0.41-1.64)
Male					
Rivaroxaban	80	7226.02	11.1 (8.9-13.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	95	8392.52	11.3 (9.3-13.8)	0.99	0.73 (0.51-1.05)
No microvascular complications					
Rivaroxaban	16	3073.57	5.2 (3.2-8.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	15	3256.18	4.6 (2.8-7.6)	0.84	0.68 (0.29-1.60)
Microvascular complications					
Rivaroxaban					
Apixaban	92	8315.84	11.1 (9.0-13.6)	1.00 [Reference]	1.00 [Reference]
	113	10509.43	10.8 (8.9-12.9)	0.94	0.75 (0.53-1.07)

No macrovascular complications					
Rivaroxaban	36	6846.55	5.3 (3.8-7.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	35	7411.57	4.7 (3.4-6.6)	0.89	0.56 (0.30-1.03)
Macrovascular complications					
Rivaroxaban	72	4542.86	15.9 (12.6-20.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	93	6354.04	14.6 (11.9-17.9)	0.90	0.83 (0.57-1.21)
No nephropathy					
Rivaroxaban	69	7476.93	9.2 (7.3-11.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	59	8569.6	6.9 (5.3-8.9)	0.72	0.56 (0.37-0.86)
Nephropathy					
Rivaroxaban	39	3912.48	10.0 (7.3-13.6)	1.00 [Reference]	1.00 [Reference]
Apixaban	69	5196.01	13.3 (10.5-16.8)	1.30	1.10 (0.66-1.82)
Diabetes duration <10 years					
Rivaroxaban	20	4341.69	4.6 (3.0-7.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	22	4596.59	4.8 (3.2-7.3)	0.99 (0.54-1.83)	0.94 (0.45-1.93)
Diabetes duration ≥10 years					
Rivaroxaban	88	7047.71	12.5 (10.1-15.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	106	9169.02	11.6 (9.6-14.0)	0.91 (0.68-1.20)	0.71 (0.50-1.02)
CHA_2DS_2-VASc ≤3					
Rivaroxaban	18	2919.5	6.2 (3.9-9.8)	1.00 [Reference]	1.00 [Reference]
Apixaban	14	2807.93	5.0 (3.0-8.4)	0.78	0.50 (0.22-1.12)

CHA_2DS_2-VASc >3					
Rivaroxaban	90	8469.9	10.6 (8.6-13.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	114	10957.68	10.4 (8.7-12.5)	0.96	0.81 (0.57-1.15)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio 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.

eTable 4. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of stroke in patients with and without prior use of oral anticoagulants

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
No prior use of anticoagulants					
Rivaroxaban	143	8554.54	16.7 (14.2-19.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	213	10604.28	20.1 (17.6-23.0)	1.15	0.96 (0.75-1.22)
Prior use of anticoagulants					
Rivaroxaban	66	2802.28	23.6 (18.5-30.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	106	3054.09	34.7 (28.7-42.0)	1.42	1.25 (0.88-1.78)

* Per 1,000 person-years.
† Adjusted using standardized mortality ratio weighting.
Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 5. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major bleeding in patients with and without prior use of oral anticoagulants

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
No prior use of anticoagulants					
Rivaroxaban	430	8358.83	51.4 (46.8-56.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	442	10496.6	42.1 (38.4-46.2)	0.78	0.68 (0.60-0.79)
Prior use of anticoagulants					
Rivaroxaban	177	2739.00	64.6 (55.8-74.9)	1.00 [Reference]	1.00 [Reference]
Apixaban	148	3042.24	48.7 (41.4-57.2)	0.74	0.67 (0.53-0.86)

* Per 1,000 person-years.
† Adjusted using standardized mortality ratio weighting.
Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 6. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major limb event in patients with and without prior use of oral anticoagulants

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
No prior use of anticoagulants					
Rivaroxaban	75	8575.06	8.7 (7.0-11.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	77	10675.59	7.2 (5.8-9.0)	0.78	0.69 (0.48-1.00)
Prior use of anticoagulants					
Rivaroxaban	33	2814.34	11.7 (8.3-16.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	51	3090.02	16.5 (12.5-21.7)	1.37	1.26 (0.71-2.25)

* Per 1,000 person-years.
† Adjusted using standardized mortality ratio weighting.
Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 7. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of stroke in patients stratified by dose

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
Standard dose					
Rivaroxaban	146	9013.68	16.2 (13.8-19.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	197	9692.18	20.3 (17.7-23.4)	1.21	1.05 (0.80-1.39)
Low dose					
Rivaroxaban	63	2294.66	27.5 (21.5-35.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	122	3952.5	30.9 (25.9-36.9)	1.13	0.90 (0.62-1.32)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 8. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major bleeding stratified by dose

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
Standard dose					
Rivaroxaban	428	8816.58	48.5 (44.2-53.4)	1.00 [Reference]	1.00 [Reference]
Apixaban	375	9608.2	39.0 (35.3-43.2)	0.77	0.71 (0.60-0.84)
Low dose					
Rivaroxaban	176	2233.89	78.8 (68.0-91.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	213	3917.04	54.4 (47.5-62.2)	0.68	0.63 (0.49-0.80)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 9. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major limb event stratified by dose

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
Standard dose					
Rivaroxaban	81	9034.58	9.0 (7.2-11.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	83	9765.62	8.5 (6.9-10.5)	0.90	0.68 (0.47-0.99)
Low dose					
Rivaroxaban	25	2308.99	10.8 (7.3-16.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	45	3986.3	11.3 (8.4-15.1)	1.08	0.91 (0.43-1.93)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

Abbreviations: CI, confidence interval; HR, hazard ratio.

eTable 10. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of stroke in sensitivity analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
15-day grace period					
Rivaroxaban	147	7947.71	18.5 (15.7-21.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	223	9715.56	23.0 (20.1-26.2)	1.21	0.97 (0.75-1.25)
60-day grace period					
Rivaroxaban	269	14383.43	18.7 (16.6-21.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	394	16403.11	24.0 (21.8-26.5)	1.24	1.02 (0.84-1.25)
Intention-to-treat					
Rivaroxaban	98	3825.76	25.6 (21.0-31.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	168	5145.3	32.7 (28.1-38.0)	1.29	1.07 (0.78-1.46)
IPCW					
Rivaroxaban	209	142014	1.5 (1.3-1.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	319	171672	1.9 (1.7-2.1)	1.22	1.00 (0.79-1.25)
Multiple imputation					
Rivaroxaban	209	11356.82	18.4 (16.1-21.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	319	13658.37	23.4 (20.9-26.1)	1.23	0.98 (0.79-1.22)

* Per 1,000 person-years.
† Adjusted using standardized mortality ratio weighting.
Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights.

eTable 11. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major bleeding in sensitivity analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
15-day grace period					
Rivaroxaban	446	7801.09	57.2 (52.1-62.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	434	9647.85	45.0 (40.9-49.4)	0.76	0.66 (0.56-0.77)
60-day grace period					
Rivaroxaban	742	13974.96	53.1 (49.4-57.1)	1.00 [Reference]	1.00 [Reference]
Apixaban	698	16268.45	42.9 (39.8-46.2)	0.78	0.68 (0.60-0.77)
Intention-to-treat					
Rivaroxaban	287	3777.87	76.0 (67.7-85.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	307	5110.5	60.1 (53.7-67.2)	0.79	0.68 (0.56-0.83)
IPCW					
Rivaroxaban	607	138876	4.4 (4.0-4.7)	1.00 [Reference]	1.00 [Reference]
Apixaban	590	170235	3.5 (3.2-3.8)	0.77	0.68 (0.58-0.80)
Multiple imputation					
Rivaroxaban	607	11097.83	54.7 (50.5-59.2)	1.00 [Reference]	1.00 [Reference]
Apixaban	590	13538.84	43.6 (40.2-47.2)	0.77	0.68 (0.59-0.77)

* Per 1,000 person-years.

† Adjusted using standardized mortality ratio weighting.

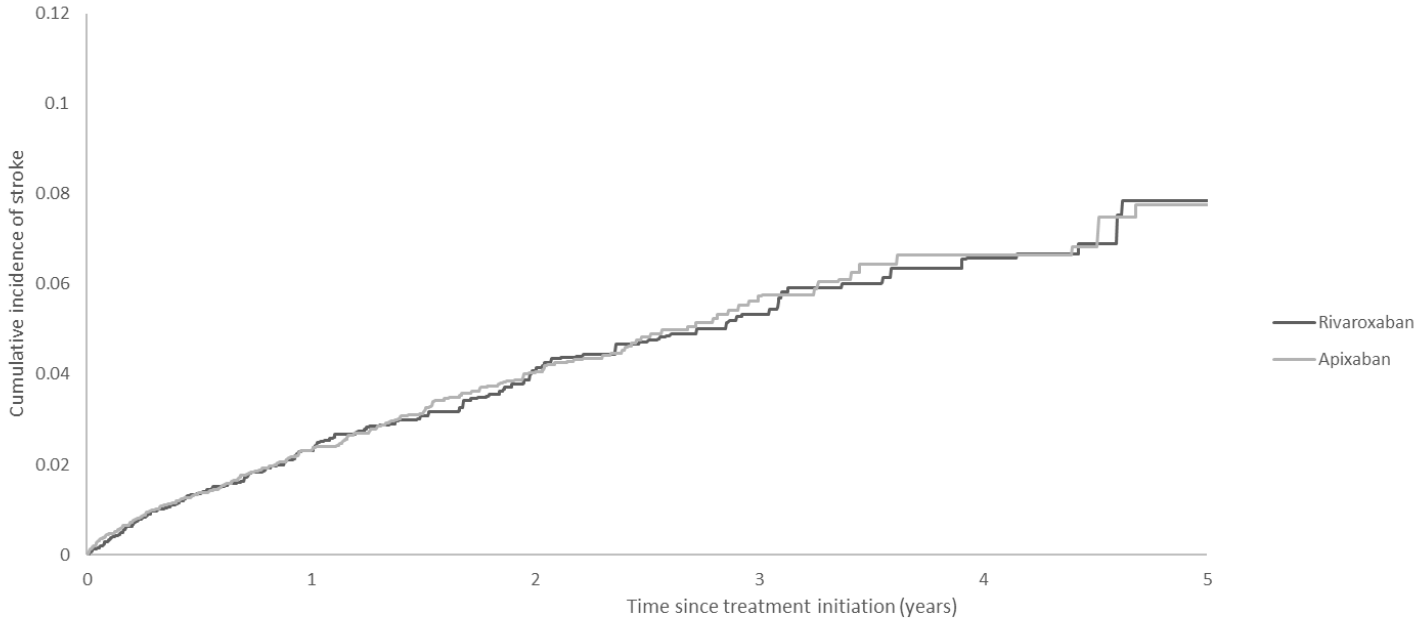
Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights.

eTable 12. Crude and adjusted hazard ratios for the association between use of apixaban and the risk of major limb event in sensitivity analyses

Exposure	Events	Person-years	Incidence rate* (95% CI)	Crude HR	Adjusted HR† (95% CI)
15-day grace period					
Rivaroxaban	76	7959.99	9.5 (7.6-12.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	89	9770.96	9.1 (7.4-11.2)	0.93	0.74 (0.51-1.08)
60-day grace period					
Rivaroxaban	151	14365.92	10.5 (9.0-12.3)	1.00 [Reference]	1.00 [Reference]
Apixaban	150	16585.04	9.0 (7.7-10.6)	0.84	0.75 (0.57-1.00)
Intention-to-treat					
Rivaroxaban	63	3832.27	16.4 (12.8-21.0)	1.00 [Reference]	1.00 [Reference]
Apixaban	64	5165.94	12.4 (9.7-15.8)	0.77	0.60 (0.39-0.94)
IPCW					
Rivaroxaban	108	142411	0.8 (0.6-0.9)	1.00 [Reference]	1.00 [Reference]
Apixaban	128	172981	0.7 (0.6-0.9)	0.95	0.78 (0.52-1.08)
Multiple imputation					
Rivaroxaban	108	11389.41	9.5 (7.9-11.5)	1.00 [Reference]	1.00 [Reference]
Apixaban	128	13765.61	9.3 (7.8-11.1)	0.95	0.71 (0.47-1.01)

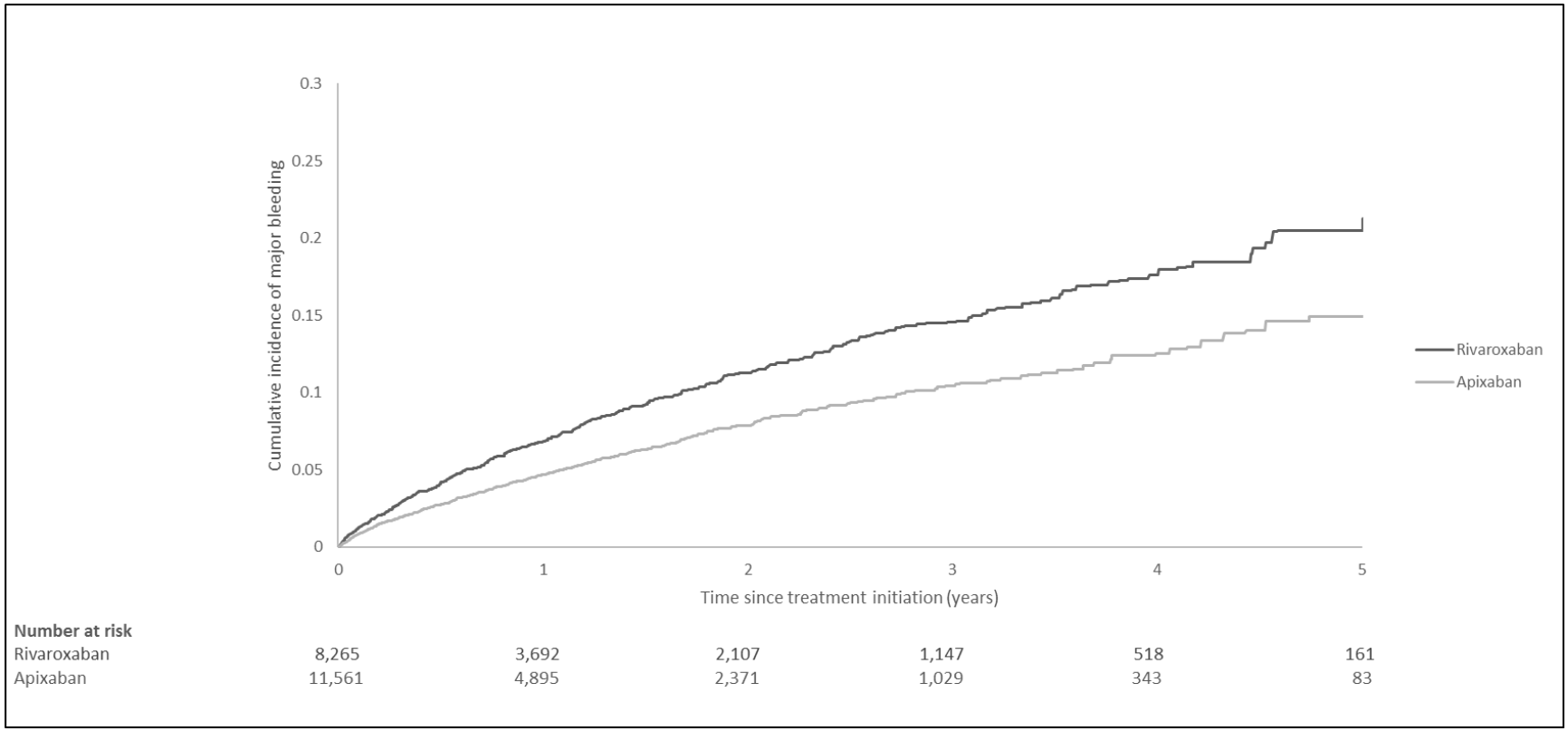
* Per 1,000 person-years.
† Adjusted using standardized mortality ratio weighting.
Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights.

eFigure 1. Weighted cumulative incidence curves of stroke for new users of apixaban and rivaroxaban



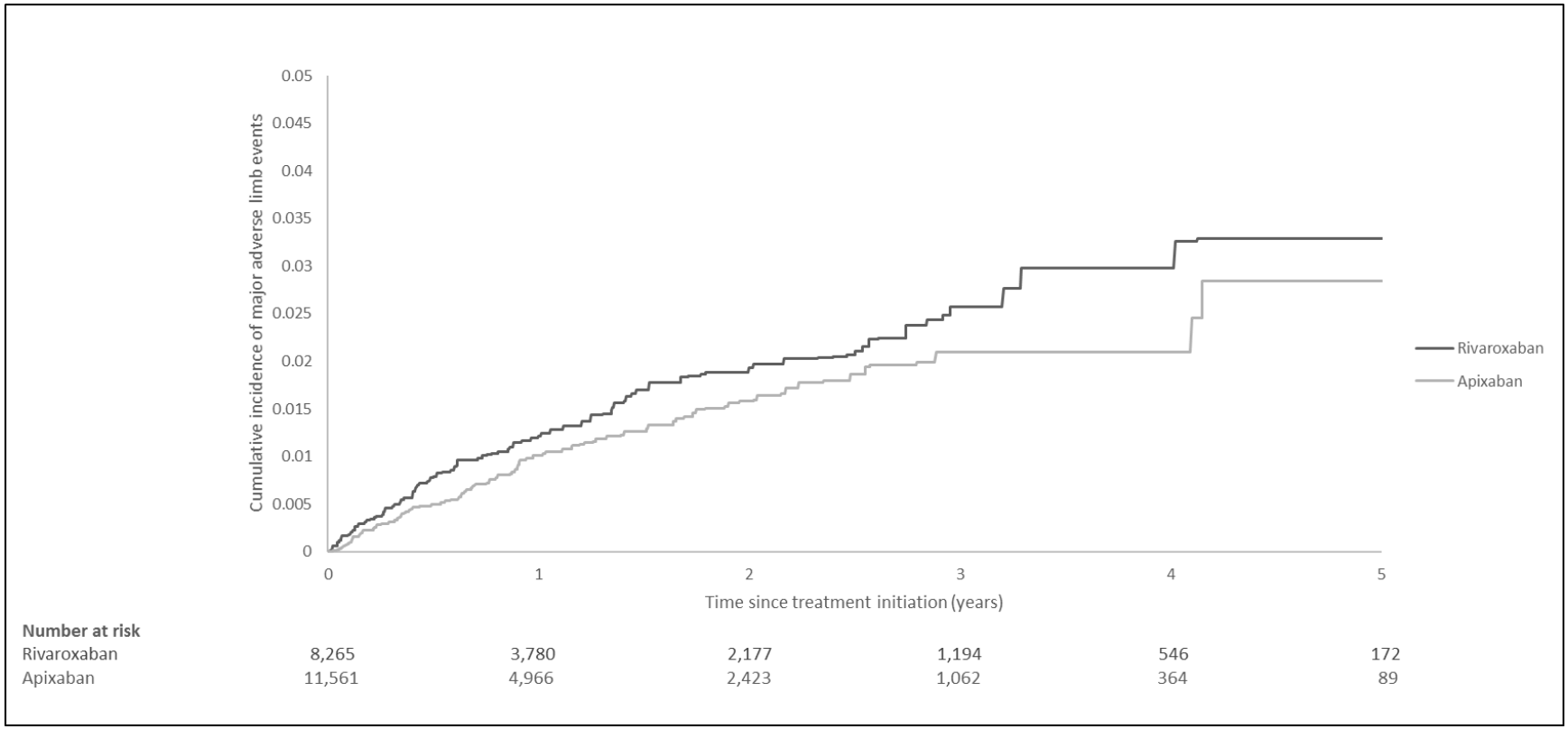
Number at risk						
Rivaroxaban	8,265	3,774	2,161	1,184	545	172
Apixaban	11,561	4,948	2,397	1,042	351	86

eFigure 2. Weighted cumulative incidence curves of major bleeding for new users of apixaban and rivaroxaban



Number at risk						
Rivaroxaban	8,265	3,692	2,107	1,147	518	161
Apixaban	11,561	4,895	2,371	1,029	343	83

eFigure 3. Weighted cumulative incidence curves of major adverse limb events for new users of apixaban and rivaroxaban



Number at risk						
Rivaroxaban	8,265	3,780	2,177	1,194	546	172
Apixaban	11,561	4,966	2,423	1,062	364	89

Chapter 6: Discussion

6.1 Summary of objectives and results

This thesis investigated the effectiveness and safety of apixaban compared with rivaroxaban in patients with NVAF and T2DM. As described in Chapter 2, there has been no randomized controlled trial and only one cohort study comparing the effectiveness and safety of apixaban versus rivaroxaban in this vulnerable population. To address this knowledge gap, the primary objective of this thesis was to determine whether apixaban was associated with a decreased risk of ischemic stroke and major bleeding, compared with rivaroxaban in NVAF patients with T2DM. Additionally, the secondary objective of this thesis aimed to determine whether apixaban was associated with a decreased risk of major adverse limb events, a composite of major limb amputation, surgical revascularization or endovascular revascularization, when compared with rivaroxaban.

To our knowledge, this study is the second one to investigate the effectiveness and safety of apixaban versus rivaroxaban in the above population. We conducted population-based cohort study using data from the United Kingdom's CPRD. We found that apixaban had similar effectiveness as rivaroxaban in preventing ischemic stroke (HR 0.99, 95% CI 0.79-1.23). Apixaban was associated with a decreased risk of major bleeding (HR 0.68, 95% CI 0.59-0.78), compared with rivaroxaban. Additionally, similar risk of major limb events (HR 0.75, 95% CI 0.54-1.04) were observed between apixaban and rivaroxaban.

6.2 Strengths and limitations

This section will give details about the advantages and disadvantages of using the CPRD database in addition to the strengths and limitations of this study described in the manuscript in Chapter 5. This thesis used the Clinical Practice Research Datalink (CPRD) that consists of patient prescription data, automatically transcribed into the electronic database. This database has been shown to be broadly representative of the population in terms of age, sex and ethnicity (121-124). Moreover, the CPRD has information on lifestyle factors such as smoking and alcohol consumption patterns, not found in other health care databases such as administrative databases.

Thus, availability of these potential confounders in this database helps us in adjusting them in our analyses. Additionally, the validity and quality of CPRD data have been well established (131-133). As a result of these advantages, the CPRD has been used widely for observational studies such as pharmacoepidemiologic studies of drug safety and utilization (134, 135).

Although use of CPRD data has significant advantages, some limitations are noteworthy. In this thesis, exposure to apixaban and rivaroxaban was determined based on available prescription data. As a result, it is unknown whether these prescriptions were filled at the pharmacy, and whether patients were compliant to their treatment. Finally, there were missing data on variables HbA1c, BMI and smoking. In order to avoid the risk of selection bias, a separate category was created to classify this missing information and multiple imputations was done in a sensitivity analysis.

6.3 Implications of findings

To prevent ischemic stroke in patients with NVAF and diabetes, the introduction of DOACs have been a great advantage. Before the introduction of DOACs, there were vitamin K antagonists which had some important limitations. Patients taking warfarin, should be closely monitored to assess the patient's prothrombin time (PT) and international normalized ratio (INR) by periodic blood testing (6). However, DOACs do not need this monitoring and have similar effectiveness and better safety profile compared with vitamin K antagonists, including for patients with diabetes (7-14). As a result, DOACS are now recommended as first-line oral anticoagulant for patients with NVAF (35, 37, 56, 139, 140). The most recent studies showed that DOACs have now surpassed warfarin, with apixaban and rivaroxaban being the most commonly prescribed oral anticoagulants in many countries (117-120). While stratified analyses of randomized controlled trials and several observational studies showed that these two drugs were as effective and safe as warfarin in patients with T2DM, only one study compared the effectiveness and safety of apixaban and rivaroxaban in this population (21), reporting that apixaban was associated with a similar risk of stroke or systemic embolism (SE) and a lower risk of major bleeding compared with rivaroxaban.

In addition to our primary analyses, we further showed in our stratified analyses that the lower risk of bleeding with apixaban was not modified by several relevant characteristics such as age, sex, duration of diabetes, vascular complications of diabetes, nephropathy, and HAS-BLED score. We also assessed whether apixaban decreases the risk of major limb events, a clinically relevant outcome in patients with T2DM, compared with rivaroxaban. We showed that, although the risk of major adverse limb events did not differ overall between apixaban and rivaroxaban, the risk may be lower with apixaban compared with rivaroxaban at standard doses. Future large-scale observational studies may help to further add to this dearth of knowledge on the effectiveness of DOACs in the prevention of major limb events in patients with NVAF and T2DM.

Nevertheless, there is a scarcity of evidence on the effectiveness and safety of apixaban vs. rivaroxaban in this population. Our study adds to this knowledge gap, by studying outcomes like ischemic stroke, major adverse limb events and major bleeding in a large cohort of patients providing updated evidence to help clinicians and patients make an informed choice when choosing an anticoagulant.

6.4 Future directions

While the findings of this thesis indicate that apixaban was as effective as rivaroxaban in reducing ischemic stroke and apixaban has better safety profile compared with rivaroxaban, a secondary analysis suggests that apixaban was associated with a reduced risk of major limb events compared with rivaroxaban for standard doses, with no difference being observed with low doses.

Although these results may be indicative of preferring apixaban over rivaroxaban to prevent ischemic stroke in patients with NVAF and T2DM, there has been only two studies on apixaban vs. rivaroxaban in this high-risk population, including our study. Thus, further well conducted observational studies on this topic must be carried out to confirm our findings in other populations and settings.

The future directions include conducting an RCT on the effectiveness and safety of apixaban vs. rivaroxaban in patients with NVAF and T2DM. Although it can be useful, this type of study may be logistically difficult to implement and more costly. Also, RCTs have some limitations such as small sample size and highly selected patient populations. As a result,

population-based observational studies remain important to assess the effectiveness and safety of apixaban vs. rivaroxaban in patients with NVAF and T2DM in a real-world setting. Moreover, no study to date has considered major adverse limb events as an outcome in this high-risk population. So, future studies should include this outcome in their analyses. Also, studies should be carried out on the effectiveness and safety of other DOACs in the future, such as dabigatran and edoxaban, that we did not assess in this study. Future studies should also consider conducting stratified analyses by duration and severity of diabetes as these variables can modify the association between the drugs and the outcomes of ischemic stroke, major adverse limb events and major bleeding.

Overall, this study provides clinicians and patients with important information to inform prescribing for the management of patients with NVAF and T2DM.

Chapter 7: Conclusion

Overall, this thesis examined the effectiveness and safety of apixaban compared with rivaroxaban in patients with both NVAF and T2DM. Using a large cohort of patients treated with apixaban or rivaroxaban, our results showed that apixaban was associated with a similar risk of ischemic stroke and a reduced risk of major bleeding compared with rivaroxaban, at both low and standard doses of the drugs. The risk of major adverse limb events did not differ overall between apixaban and rivaroxaban; however, the risk may be lower with apixaban compared with rivaroxaban at standard doses. In the secondary analyses, the risk of the three outcomes did not differ and our results remained consistent across sensitivity analyses. Our findings may provide some reassurance of the effectiveness and safety of apixaban compared with rivaroxaban, used in everyday practice and may facilitate clinical decision making for physicians and regulatory agencies. Nevertheless, while this thesis provides an important addition to the limited body of literature on the effectiveness and safety of DOACs, further large observational studies are required to investigate these drugs effectiveness and safety in patients with NVAF and T2DM. Ultimately, the choice between these drugs will depend on individual patient characteristics and preference of the physicians and patients.

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