NOVEL ORAL ANTICOAGULANTS IN THE UK:
USE, EFFECTIVENESS, AND SAFETY IN A PRIMARY CARE SETTING

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Summary

Oral anticoagulants such as vitamin-K antagonists (VKA) are prescribed for the prevention and management of venous thromboembolism, and for the prevention of ischemic stroke in atrial fibrillation (AF). Although effective, VKA have a narrow therapeutic window, and may require cumbersome monitoring due to their potential for adverse bleeding. Hence, the introduction of novel oral anticoagulants (NOAC) in 2008 presented attractive treatment options for patients averse to VKA therapy. Using the UK's Clinical Practice Research Datalink, a database of electronic medical records, the aim of this thesis research was to determine how NOAC have been adopted in a primary care setting, and to evaluate the clinical effectiveness and safety of NOAC compared to VKA in non-valvular AF patients in routine clinical practice.

In our first objective, we used Poisson regression to describe the trends in first-time prescriptions of NOAC and VKA in the UK, between 2009 and 2015. Over the study period, we observed a significant increase in the rate of any oral anticoagulant initiation (RR 1.58; 95% CI 1.23-2.03). The rate of new users of VKA decreased over this same period (RR 0.69; 95% CI 0.52-0.93), while the rate of new users of NOAC increased by a substantial 17-fold between 2012 and 2015 only (RR 17.68; 95% CI 12.16-25.71). Using multivariate logistic regression, we also found that, compared to VKA, new users of NOAC were less likely to have a history of coronary artery disease, congestive heart failure, and peripheral vascular disease, while more likely to have a history of ischemic stroke.

In our second objective, we evaluated the effectiveness and safety of NOAC compared to VKA in a cohort of new users with non-valvular AF, between 2011, when

NOAC were approved for these patients, and 2016. Up to 6,818 new users of NOAC were matched 1:1 to new users of VKA on high-dimensional propensity scores, age, and sex. In Cox regression analyses, and using an as-treated definition of exposure, the rates of ischemic stroke and systemic embolism were similar (HR 0.94; 95% CI 0.62-1.42) between NOAC and VKA, as were the rates of major bleeding (HR 0.86; 95% CI 0.56-1.33), and myocardial infarction and all-cause mortality. While NOAC tended to be associated with a lower risk of intracranial bleeding (HR 0.51; 95% CI 0.18-1.44), these new medications also increased the risk of gastrointestinal bleeding (HR 1.78; 95% CI 1.27-2.48). Our results were generally unchanged in time-dependent analyses, and when stratified by concurrent chronic kidney disease.

In the UK, NOAC have been widely prescribed since their introduction in 2008, and these medications are comparable to VKA in the prevention of ischemic stroke in AF. NOAC also appear to have improved the rates of oral anticoagulation in patients with AF, and the introduction of these medications therefore represents an important step forward for stroke prevention in AF. The growing preference for NOAC may be partly explained by their established effectiveness and safety, as well as their relative ease of use. Future studies should evaluate the extent to which other factors may have played a role in the substantial and rapid uptake of these new medications, while continuing to monitor the trends in their prescription.

Résumé

Les anticoagulants oraux, tels que les antagonistes de la vitamine K (AVK), sont utilisés en prévention des thromboses veineuses et des accidents ischémiques cérébraux (AIC) chez les patients présentant une fibrillation auriculaire (FA). Bien qu'ayant fait la preuve de leur efficacité, les AVK ont une fenêtre thérapeutique étroite et nécessitent donc une surveillance régulière en raison du risque hémorragique qui leur est associé. Pour cette raison, les nouveaux anticoagulants oraux (NACO), introduits en 2008, représentent une option thérapeutique intéressante, notamment pour les patients peu enclins à prendre des AVK. En utilisant le « Clinical Practice Research Datalink » britannique, une base de données de dossiers médicaux électroniques, l'objectif de cette thèse était d'évaluer les tendances de prescription, l'efficacité, et la sécurité des NACO en pratique clinique quotidienne.

Dans le premier objectif, nous avons utilisé une régression de Poisson pour décrire les tendances de prescription des NACO et des AVK au Royaume-Uni, entre 2009 et 2015. Au cours la période d'étude, nous avons observé une augmentation significative des taux d'initiation des anticoagulants oraux (RR 1,58; IC 95% 1,23-2,03). Le taux de nouveaux utilisateurs d'AVK a diminué au cours de cette même période (RR 0,69; IC 95% 0,52-0,93), tandis que le taux de nouveaux utilisateurs de NACO a été multiplié par 17 fois entre 2012 et 2015 (RR 17,68; IC 95% 12,16-25,71). A l'aide d'une régression logistique multivariable, nous avons également trouvé que, comparativement aux AVK, les nouveaux utilisateurs de NACO avaient moins d'antécédents de coronaropathie, d' insuffisance cardiaque congestive,

et de maladie vasculaire périphérique, mais plus d'antécédents d'AIC au moment de leur première prescription.

Dans le deuxième objectif, nous avons évalué l'efficacité et la sécurité des NACO comparativement aux AVK dans une cohorte de patients atteints de FA et nouvellement traités par un anticoagulant oral entre 2011 et 2016. Jusqu'à 6818 nouveaux utilisateurs de NACO ont été appariés en nombre égal à de nouveaux utilisateurs d'AVK en fonction de l'âge, du sexe, et du score de propension de haute dimension. En utilisant une définition d'exposition « as-treated » dans les analyses de régression de Cox, nous avons trouvé que les NACO et les AVK réduisaient le risque d'AIC et d'embolisme systémique d'une manière comparable (HR 0,94; IC 95% 0,62-1,42), avec des taux similaires de saignement majeur (HR 0,86; IC 95% 0,56-1,33), d'infarctus du myocarde, et de mortalité toute causes confondues. Alors que les NACO étaient associés à une diminution du risque de saignement intracérébral (HR 0,51; IC 95% 0,18-1,44), ils augmentaient le risque de saignement gastro-intestinal de manière significative (HR 1,78; IC 95% 1,27-2,48). Des résultats similaires ont été obtenus en utilisant une définition d'exposition dépendante du temps. Enfin, nous avons confirmé ces résultats chez les patients présentant une insuffisance rénale chronique.

La préférence croissante pour les NACO observée au Royaume-Uni pourrait être liée à leur efficacité et à leur sécurité, ainsi qu'à leur facilité d'utilisation comparativement aux AVK. L'introduction de ces médicaments sur le marché semble s'être accompagnée d'une amélioration des taux d'anticoagulation orale chez les patients présentant une FA au Royaume-Uni, et l'introduction de ces médicaments représente donc une avancée importante pour la prévention des AIC dans cette pathologie. Les études futures devraient permettre de préciser le rôle potentiel d'autres facteurs dans l'adoption rapide des NACOs

en prévention des AIC dans la FA. Par ailleurs, il parait important de poursuivre la surveillance des tendances de prescription de ces molécules et leur impact sur la prise en charge des patients atteints de FA.

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All glory, praise, and thanks be to Him, who, according to His great power and love, continues to do immeasurably more than I could ever ask or imagine.

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Preface

The contents of this thesis are based two manuscripts, one which has been accepted for publication, and another which is in preparation for submission for publication. The contribution of all collaborating authors is as follows:

Simone Loo (Thesis Candidate)	Contributed to the study designs, prepared the protocols, conducted statistical analyses, interpreted the data, and prepared the manuscripts.
Janie Coulombe (Research Assistant)	Conducted supplementary statistical analyses and interpreted the data for the second study.
Sophie Dell'Aniello (Biostatistician)	Contributed to the study designs, reviewed the protocols, extracted the data, conducted statistical analyses, interpreted the data, reviewed the manuscripts, and provided statistical and analytical oversight.
Dr. Laetitia Huiart (Collaborator)	Reviewed the design and the manuscript of the first study
Dr. James Brophy (Collaborator)	Reviewed the design and the manuscript of the second study.
Dr. Samy Suissa (Thesis Co-Supervisor)	Reviewed the protocols and the manuscripts, and provided oversight and supervision.
Dr. Christel Renoux (Thesis Co-Supervisor)	Conceived and designed the studies, reviewed the protocols, interpreted the data, reviewed the manuscripts, and provided oversight, supervision, and funding.

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INTRODUCTORY REMARKS

Novel oral anticoagulants (NOAC) were first licensed and marketed in 2008 as alternatives to the long-standing vitamin-K antagonists (VKA) for the prevention of thromboembolic events. Given their recent introduction, the objectives of this thesis were:

1. To identify temporal trends in the prescription of NOAC, and to describe the baseline profile of patients who are initiated on these medications in the UK; and
2. To evaluate the effectiveness and safety of NOAC compared to VKA in patients with non-valvular atrial fibrillation in the UK.

In completing these objectives, this thesis will explore how NOAC have been adopted in routine clinical practice. The results of this thesis will also inform physicians and patients as to whether NOAC can be considered suitable alternatives to VKA for the treatment of atrial fibrillation, using data from a primary care setting.

CHAPTER 1: BACKGROUND

1.1 INDICATIONS FOR ORAL ANTICOAGULATION

1.1.1 Atrial Fibrillation and Stroke

In atrial fibrillation (AF), a persistently irregular heart beat reduces the heart's ability to effectively contract and to circulate blood. AF is the most common type of cardiac arrhythmia, and was estimated to be prevalent in over 45 million patients worldwide in 2010 [1]. Men are more often affected than women, as are the elderly, with a prevalence of almost 20% in those aged 85 or older [2]. Therefore, the incidence of AF is increasing with the aging population. In previous studies, it was estimated that the prevalence of AF would double over 20 years in USA, and over 30 years in Europe, with over 12 and 14 million affected patients by 2030, respectively [3, 4].

Compared to patients without the disease, AF patients experience a 50% and 90% increased likelihood of mortality, in men and women, respectively [5]. AF is further associated with a significant number of comorbid conditions which collectively increase the burden that it poses on patients. The prevalence of congestive heart failure and hypertension in AF are both reported to be over 50% [6, 7]. Among other conditions, coronary artery disease, diabetes, and peripheral vascular disease have also been independently associated with AF [8-10].

In addition to its numerous comorbidities, the major burden imposed by AF stems from its association with ischemic stroke. In AF, the ineffective circulation of blood causes it to pool in the atria of the heart [11]. This stagnation in blood flow facilitates the formation of clots, which risk traveling throughout the circulatory system and occluding

smaller vessels in the brain as well as in other parts of the body. Consequently, patients with AF are prone to systemic embolisms, and are approximately five times more likely to experience an ischemic stroke, compared to the general population [12].

The majority of ischemic strokes are nonfatal, and it has been estimated that around 22.9% of patients die within 30 days of an event [13]. The remaining survivors often experience chronic cognitive and/or motor impairments, which may significantly reduce their quality of life [14]. Importantly, ischemic strokes in AF are caused by emboli originating from the heart, and are thus cardioembolic in nature. Cardioembolic strokes are more severe compared to ischemic strokes of other mechanisms, presenting a higher risk of mortality, severe disability, and event recurrence [15]. Taken together, ischemic stroke thus poses a significant burden on AF patients.

1.1.2 Venous Thromboembolism

Venous thromboembolism (VTE) is the formation of blood clots in the vein, and encompasses both deep vein thrombosis and pulmonary embolism. These occur primarily as a result of prolonged periods of stasis which facilitate the formation of blood clots, such as in cases of bedrest or surgery. Thus, it is estimated that up to 60% of VTE cases occur in either a hospital or a nursing home setting [16]. The incidence of VTE has been reported at up to 117 cases per 100,000 persons per year, with a 1-year survival rate of less than 65% [17, 18]. Furthermore, approximately 20% of cases experience a recurrent event within less than four years [19]. Among survivors of deep vein thrombosis, complications are reported in up to 50% of patients and include, among others, swelling, pain, and induration of the skin in the affected limb [20]. VTE further has a significant economic impact, costing over $1.5 billion per year in the USA alone [21].

1.1.3 Thromboprophylaxis

The prevention of ischemic stroke in AF and the prevention and management of VTE is based on treatment with oral anticoagulants. These medications reduce the formation of blood clots by interrupting the coagulation cascade and thereby decreasing the risk of thromboembolic events. At present, the major classes of oral anticoagulants for AF patients are the long-standing vitamin-K antagonists, and the more recent novel oral anticoagulants.

1.2 VITAMIN-K ANTAGONISTS

Vitamin-K antagonists (VKA) reduce the formation of blood clots by inhibiting vitamin K, a necessary component for the activation and synthesis of several clotting factors [22]. Warfarin, the most commonly used VKA, was first identified to have such hemorrhagic properties in the early 1940s, and has been used extensively since the 1950s for the prevention of thromboembolic events [23]. In randomized controlled trials (RCTs), warfarin reduced the risk of ischemic stroke by 64% compared to placebo in AF patients over an average follow-up of 1.5 years [24]. A similar risk reduction was observed in trials on the prevention of recurrent VTE, comparing warfarin to placebo [25]. Observational studies have also suggested that warfarin reduces the risk of thromboembolic events, compared to no antithrombotic therapy [26].

While there is surmounting evidence on the benefits of VKA therapy in AF, the limitations of these medications are equally well described. VKA reduce the risk of thromboembolic events by interfering with the coagulation cascade, but also increase the risk of bleeding by this same process. Interestingly, it was for this reason that warfarin was initially used as a rat poison [23]. Thus, in addition to causing minor bleeds, patients who

are treated with VKA may experience more serious and potentially fatal events, such as major intracranial or gastrointestinal hemorrhages [27]. Optimal oral anticoagulant treatment in AF therefore requires a careful balance of the risk of both ischemic stroke and adverse bleeding.

Accurately weighing the risks of stroke and of bleeding with VKA is challenging for several reasons. Firstly, VKA interact with numerous medications and foods which can either decrease or increase its biological activity [28]. Secondly, VKA have a narrow therapeutic window, and treatment must therefore be closely monitored. Management of VKA therapy involves regular blood tests to determine the degree of anticoagulation, followed by any necessary dose adjustments [29]. For patients who are unable to maintain the required therapeutic range, the need for such routine monitoring can be impractical, especially in the elderly and the frail [30]. In some cases, these challenges may ultimately cause patients to discontinue VKA treatment [31]. Accordingly, many studies had reported a suboptimal use of oral anticoagulant therapy in AF, with less than 70% of high-risk patients receiving treatment [32]. Therefore, the recent introduction of novel oral anticoagulants marked a pivotal change in the prospects for oral anticoagulation in AF patients.

1.3 NOVEL ORAL ANTICOAGULANTS

In most countries throughout Europe and North America, novel oral anticoagulants (NOAC) were officially licensed and marketed in 2008, beginning with dabigatran etexilate, the oral pro-drug form of dabigatran. NOAC also reduce the risk of thromboembolic events by interfering with the coagulation cascade, however, unlike VKA, NOAC act by directly

acting on specific clotting factors [33]. For example, dabigatran directly inhibits Factor IIa, which is responsible for synthesizing the insoluble fibrin component of blood clots. Similarly, rivaroxaban, apixaban, and edoxaban directly inhibit Factor Xa, another key factor in the coagulation cascade. For this reason, these newer medications are also known as direct oral anticoagulants.

NOAC have been evaluated in several landmark RCTs that paved the way for their licensing and marketing. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the risk of ischemic stroke was reduced by 24% in AF patients who were treated with high-dose dabigatran, compared to those treated with warfarin [34]. In their respective trials, rivaroxaban, apixaban, and high-dose edoxaban were non-inferior to warfarin in the prevention of ischemic stroke [35-37]. Similarly, all NOAC were non-inferior to warfarin in the treatment of acute VTE [38-41]. With respect to safety, NOAC were associated with a reduced risk of hemorrhagic stroke and intracranial bleeding. Compared to warfarin, apixaban and edoxaban also decreased the risk of major bleeding, while dabigatran and rivaroxaban were associated with a higher risk of gastrointestinal bleeding. Based on the overall positive results of these RCTs, NOAC were licensed in the UK in 2008, initially for the prevention of VTE in hip and knee surgery patients only. These medications were subsequently approved for stroke prevention in AF, as well as for the treatment and secondary prevention of VTE in adult patients.

RCTs are often considered the gold standard of clinical research, as randomizing interventions reduces the potential for confounding bias between treated and untreated patients [42]. However, RCT study populations are typically highly selected, and often fail to be representative of the population in routine clinical practice [43]. For example, in

some of the AF trials, some participants were excluded if they had severe renal impairments or if they had a recent and severe stroke, among other exclusion criteria [44]. However, these AF patients are often the most vulnerable, presenting greater risks of stroke and bleeding events [45], and therefore, the results of the various NOAC RCTs may not apply to these specific patient subgroups. Further to this limitation, patients enrolled in RCTs typically receive a very high level of care and monitoring, which is not experienced by primary care patients [43]. Therefore, while RCTs have suggested that the efficacy and safety of NOAC are comparable to that of VKA, there exists a place for observational studies to complement these RCT results, using routine clinical practice data.

The effectiveness and safety of NOAC compared to VKA have been evaluated in several large-scale observational studies among AF patients. Overall, most of these have suggested that NOAC are as, if not more, effective than VKA in the prevention of ischemic stroke in AF [46-49]. However, the evidence concerning NOAC safety has been inconclusive. In 2015, Hernandez et al. found that compared to warfarin, dabigatran increased the risk of any and major bleeding events by 30% and 57%, respectively [50], in concordance with the high number of adverse bleeding reports in the USA [51]. Other studies found no such increased risk [52, 53], and in some cases, NOAC were observed to decrease the risk of any and major bleeding, by up to 39% and 47%, respectively [48, 54]. Similarly, whereas most studied have suggested that dabigatran and rivaroxaban increase the risk of gastrointestinal bleeding compared to warfarin [52, 53], others have shown either the opposite [55], or no such association [56, 57].

Observational studies are subject to analytical challenges which introduce the potential for biases in results. For example, information bias resulting from exposure

misclassification is a prominent limitation that may have contributed to the conflicting evidence with respect to NOAC safety. In some cases, such misclassification may have been caused by using intention-to-treat analyses, which consider patients "exposed" to their first treatment prescription and for the specified duration of follow-up, regardless of whether this was truly the case [58]. Alternatively, as-treated analyses may have also led to such misclassification, if the treatment exposure was not appropriately defined, and/or if the analyses did not take into account the potential for informative censoring, in which changes in a course of treatment may be associated with an outcome of interest [59]. Importantly, some studies do not contain sufficient information for readers to determine whether exposure misclassification may have occurred.

Thus, in light of some conflicting evidence, as well as the potential for methodological limitations in previous studies, there is room to further evaluate the effectiveness and safety of NOAC in AF patients in routine clinical practice.

1.4 STATEMENT OF OBJECTIVES

Overall, the aim of this thesis research was to describe the use, effectiveness, and safety of NOAC in the UK in a primary care setting. In Chapter 2, this thesis will explore the temporal trends in the prescription of NOAC, and in the baseline profile of patients newly prescribed these medications. This will provide an indication of how these medications have been adopted in the UK since their recent introduction. In Chapter 3, this thesis will evaluate the effectiveness and safety of NOAC compared to VKA in new users with AF, so as to determine whether the results of RCTs hold true in routine clinical practice.

CHAPTER 2: TRENDS IN THE PRESCRIPTION OF NOVEL ORAL ANTICOAGULANTS IN UK PRIMARY CARE

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2.1 ABSTRACT

Aims: Novel oral anticoagulants (NOAC) are alternatives to vitamin-K antagonists (VKA) for the prevention of thromboembolism. It is unclear how NOAC have been adopted in the UK since first introduced in 2008. This study was conducted to describe the trends in the prescription of NOAC, including dabigatran, rivaroxaban, and apixaban.

Methods: Using the UK's Clinical Practice Research Datalink, the rates of new users of NOAC and VKA from 2009 to 2015 were calculated with Poisson regression. Patient characteristics associated with NOAC initiation were identified using multivariate logistic regression.

Results: The overall rate of oral anticoagulant initiation increased by 58% over the study period (RR 1.58; 95% CI 1.23-2.03), even as the rate of new VKA users decreased by 31% (RR 0.69; 95% CI 0.52-0.93). Contrastingly, the rate of new NOAC users increased, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16-25.71). In 2015, NOAC accounted for 56.5% of oral anticoagulant prescriptions, with rivaroxaban prescribed most frequently, followed by apixaban and then dabigatran. Compared to VKA, new NOAC users were less likely to have congestive heart failure, coronary artery disease, and peripheral vascular disease, and more likely to have a history of ischemic stroke.

Conclusions: In the UK, the initiation of NOAC has increased substantially since 2009, and NOAC have now surpassed VKA as the anticoagulant of choice. Moreover, the characteristics of patients initiated on NOAC have changed over time, and this should be accounted for in future studies comparing NOAC and VKA.

2.2 INTRODUCTION

For the past six decades, vitamin K antagonists (VKA) have been the preventative treatment of choice for patients with atrial fibrillation (AF) and/or venous thromboembolism (VTE). Although clinically effective at reducing thromboembolic events [24, 25], VKA have been associated with significant bleeding risks [61]. The use of VKA further requires close monitoring on account of their narrow therapeutic window and variable anticoagulant effects [62].

Novel oral anticoagulants (NOAC) are attractive alternatives for patients in whom traditional oral anticoagulant (OAC) therapy may be contraindicated or impractical. Clinical trials have reported NOAC to be non-inferior, and in some cases, superior to VKA in reducing the risk of ischemic stroke and VTE [34, 39, 40]. In addition to having a potentially more favorable safety profile [35, 36, 38], NOAC have also been hailed as substantially more practical and easier to use [63]. Accordingly, the first NOAC, dabigatran, was placed on the market throughout the European Union and in the UK in 2008, followed by rivaroxaban in the same year, and by apixaban in 2011.

The UK's National Health Services (NHS) has issued guidelines on the prescription of NOAC [64]. Guidance documents on the use of these medications have also been published by the UK's National Institute for Health and Care Excellence (NICE), which recommends NOAC as possible alternatives to VKA in specific subgroups of patients with AF or VTE [65-67]. These include AF patients aged 75 or older, and those with heart failure and a history of stroke or systemic embolism, among others. However, little is known about how these medications have been prescribed in everyday practice in the UK since their licensing and

approval, and it remains unclear to what extent official recommendations and guidelines have been adopted by general practice clinicians.

The objective of this study was to address these uncertainties, and to provide insight as to how the recent introduction of NOAC has affected the way OAC are being received by primary care patients in the UK. To this end, this study examined the temporal trends in the rates of OAC initiation, and in the patient characteristics associated with a first prescription for NOAC as compared to VKA.

2.3 METHODS

2.3.1 Data Source

This study was conducted using the UK's Clinical Practice Research Datalink (CPRD). The data within the CPRD is documented by trained general practitioners (GP), and includes information related to patient demographics, medical diagnoses and procedures, referrals, and drug prescriptions. As of 2013, with over 11 million registered patients from over 670 medical practices, the CPRD comprises approximately 7% of the total UK population, of which it is broadly considered to be representative with respects to age, sex, and ethnicity [68]. As one of the world's largest databases of electronic medical records, the CPRD has been used extensively for observational research, including pharmacoepidemiologic studies of drug safety and utilization [69, 70]. The completeness and quality of CPRD data have been validated previously [71-73].

2.3.2 Study Population

A cohort was defined comprising CPRD patients aged 18 or older and registered with a GP for at least one day between 1 January 2009 and 31 December 2015. The study

period began in 2009 so as to analyze only complete years of prescription data since NOAC were introduced in the UK in March 2008. The cohort was limited to OAC-naïve patients with no record of an OAC prescription in the 12 months prior to the start of follow-up. Follow-up began at the latest of the study start date (1 January 2009), the patient's 18th birthday, one year after the patient's registration date with the general practice, or one year after the date the practice started to contribute up-to-standard data to the CPRD. Follow-up ended at the earliest of the study end date (31 December 2015), or the patient's death or transfer out of the practice.

2.3.3 Oral Anticoagulants

All OAC available in the UK over the course of the study period were identified. VKA included warfarin, phenindione, and acenocoumarol, and NOAC included dabigatran, rivaroxaban and apixaban. The NOAC edoxaban was licensed throughout the European Union in June 2015. Considering the study timeframe, edoxaban was not analyzed in the context of this study, and first-time edoxaban users were censored at the time of first prescription.

2.3.4 Study Covariates

The following patient characteristics were identified at the time of first OAC prescription: age and sex; the comorbidities obesity, smoking, hyperlipidemia, hypertension, diabetes, coronary artery disease (including myocardial infarction and ischemic heart disease), congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, cancer, liver disease, and a history of bleeding and ischemic stroke/transient ischemic attack (TIA); concomitant use of antiplatelets, antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAID), and

lipid lowering drugs; and number of physician visits as a measure of healthcare utilization. All patient characteristics were identified based on CPRD records from the 12 months prior to first OAC prescription. The absence of relevant codes or data will be assumed to imply an absence of the specific comorbidity. However, some missing data are expected for BMI and smoking, and in these cases, patients will be classified as "unknown", and regression models will be fitted with these covariates as factor variables. Considering our extensive list of covariates, we do not expect this missing data to substantially affect the model results.

In patients with AF, a $CHADS_2$ score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA) and a CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/TIA, vascular disease, age 65–74, sex) were calculated as measures of the risk of stroke [74, 75]. Finally, a modified HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke/TIA, bleeding, labile international normalized ratio (INR), age >65, antiplatelet/NSAID use or alcohol abuse) was estimated as a measure of the risk of major bleeding [76]. Labile INR was omitted from the HAS-BLED score in this study, considering that new OAC users are unlikely to have an extensive history of INR results, and that INR monitoring is irrelevant in NOAC treatment.

2.3.5 Statistical Analyses

Using a Poisson model, the rates of OAC initiation were calculated for VKA and NOAC separately and for each year of study as the number of new OAC users divided by the person-time of follow-up from all cohort members, up to their first OAC prescription. These rates were also estimated for each individual NOAC, and were further stratified by age, sex, and OAC indication in secondary analyses. The OAC indication was identified as either AF

or VTE using an algorithm developed after a blinded review of the records of a random sample of patients. Briefly, READ codes related to AF and VTE were identified in the six and one months prior to OAC initiation, respectively. Rate ratios (RR) were estimated to compare the annual rate of OAC initiation to the year 2009, as well as to the preceding year. Temporal changes in the distribution of new prescriptions between NOAC and VKA were evaluated using a chi-squared test for trend. Multivariate logistic regression models were fitted with the aforementioned covariates to identify predictors of NOAC initiation, and stratified by individual NOAC and calendar time period (2009-2012, 2013-2014, and 2015). Predictors of NOAC initiation were also estimated separately for patients with AF and patients with VTE for the year 2015. $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were excluded from these models, as each score component was included individually. Confidence intervals were calculated for all estimates using a 5% significance level. All statistical procedures were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC).

This study protocol (No. 16_167R) was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital (Montreal, Canada), and was made available to journal reviewers.

2.4 RESULTS

After applying all selection criteria, 5,417,063 patients were included in the study cohort, contributing a total of 21,962,610 person-years of follow-up. Within this cohort, 89,626 patients were newly prescribed an OAC during the study period, among whom 18 (<0.1%) were further excluded for having received two first prescriptions on the same day. Of the remaining and final 89,608 new users, 74,767 (83.4%) were initiated on VKA and

14,841 (16.6%) on NOAC. AF and VTE were identified as the primary OAC indication in 53,843 (60.1%) and 27,155 (30.3%) new users, respectively. The indication remained unknown for 8,610 (9.6%) patients.

The crude rate of OAC initiators increased by approximately 58% from 2009 to 2015 (RR 1.58; 95% CI 1.23-2.03), as shown in Figure 2.1. During this time, there was a 31% decrease in the rate of new VKA users (RR 0.69; 95% CI 0.52-0.93). Contrastingly, the rate of new NOAC users increased substantially over the study period (Supp. Table 2.1), and particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI 12.16-25.71). Accordingly, NOAC accounted for 56.5% (95% CI 55.6-57.3) of all OAC prescriptions in 2015 ($p<0.0001$ for trend) (Supp. Figure 2.1). These NOAC prescriptions were primarily attributable to rivaroxaban (64.8%), followed by apixaban (29.3%) and dabigatran (5.9%). Whereas the rate of new dabigatran users was relatively low throughout the study period, the rates of rivaroxaban and apixaban initiation increased prominently, up to 200.1 (95% CI 181.8-220.3) and 90.7 (95% CI 81.9-100.4) new users per 100,000 persons per year in 2015, respectively (Figure 2.2).

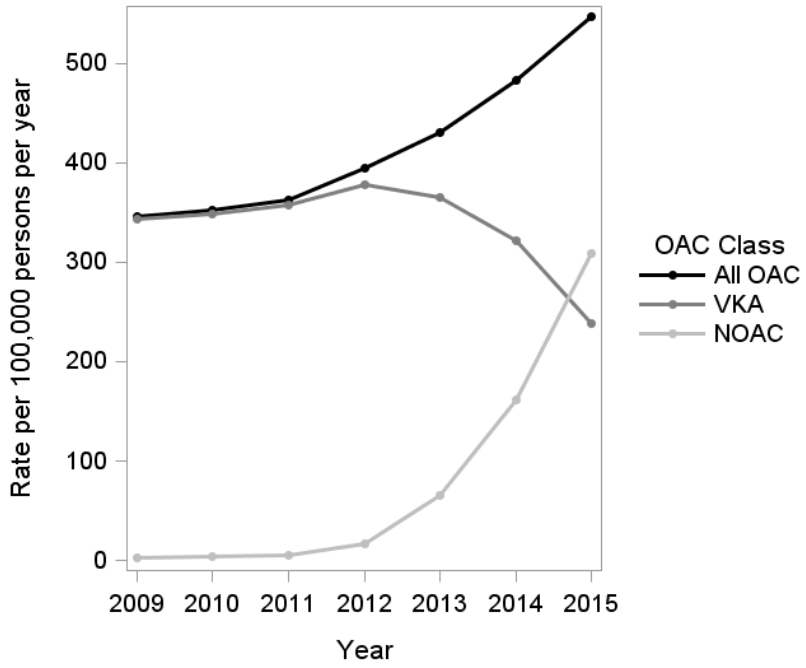


Figure 2.1 – Rates of new users of oral anticoagulants

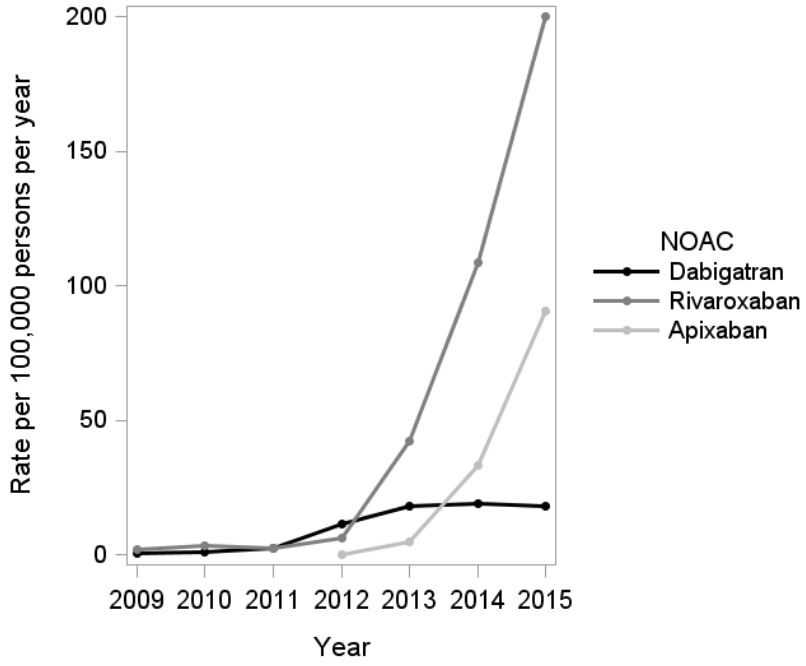


Figure 2.2 – Rates of new users of NOAC

For both VKA and NOAC, the rates of initiation increased with age and the most notable temporal changes occurred primarily among the elderly aged 75 and older (Figure 2.3). Although the rate of new OAC users with AF was considerably higher than the rate of those with VTE, the temporal initiation patterns suggest an increasing rate of NOAC initiation over time for both indications (Figure 2.4). For VTE patients, this increase was primarily attributable to first-time prescriptions of rivaroxaban (Supp. Figure 2.2). Contrastingly, there was an increased rate of initiation for all three NOAC in AF patients, which was more marked for both rivaroxaban and apixaban. There was no difference in the prescription trends between men and women, although men had slightly higher rates of OAC initiation overall (data not shown).

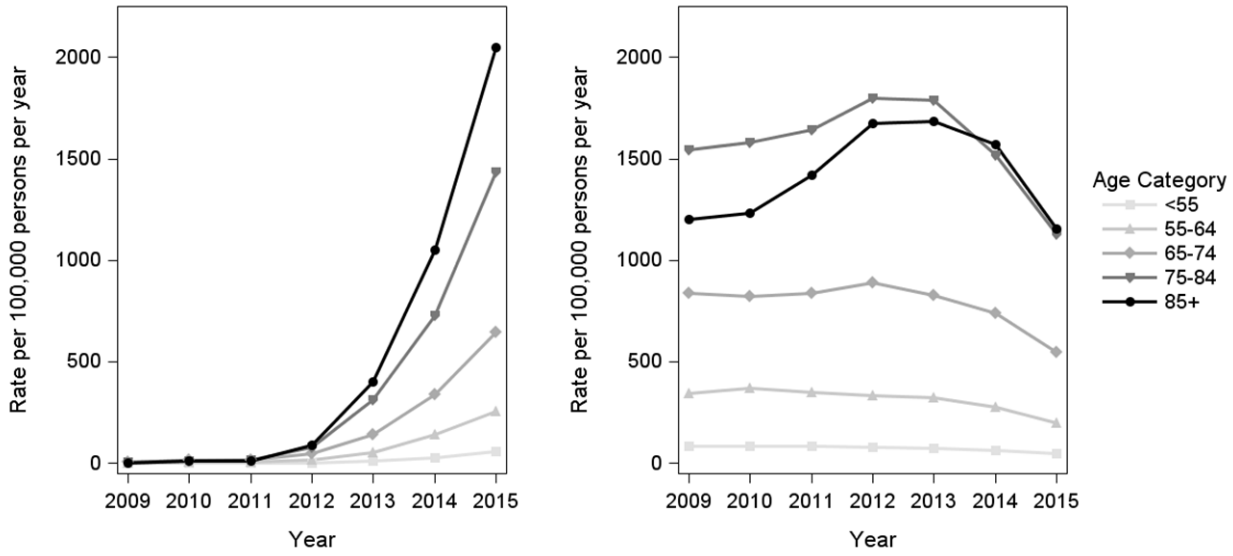


Figure 2.3 – Age-stratified rates of new users of NOAC (left) and VKA (right)

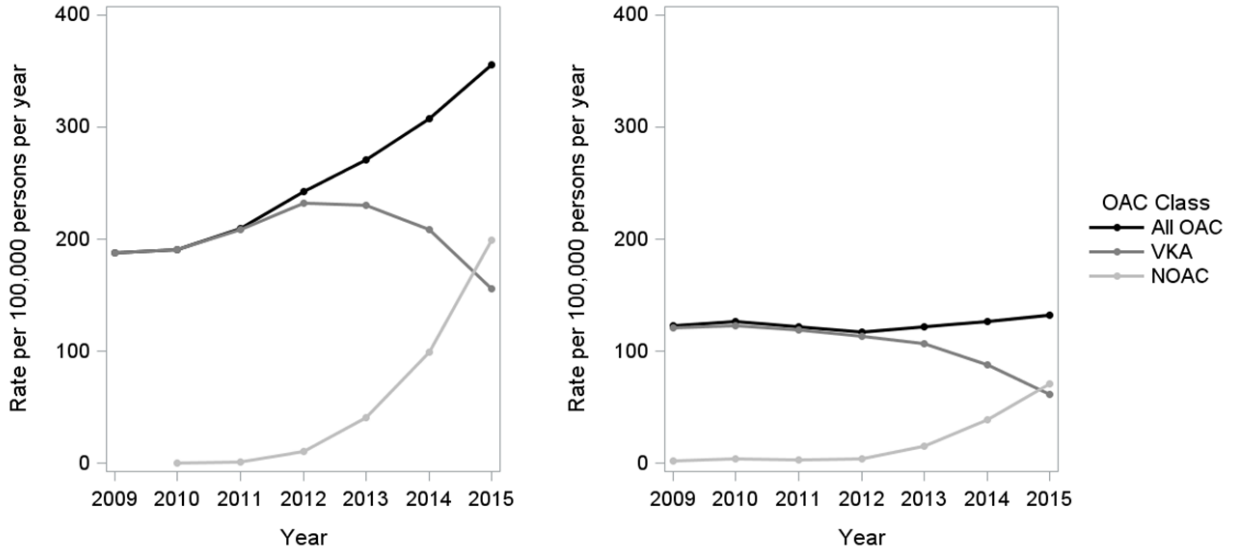


Figure 2.4 – Rates of new users of oral anticoagulants with an indication for AF (left) and VTE (right)

The baseline characteristics of first-time NOAC users changed over the course of the study period (Table 2.1) and furthermore differed between individual NOAC (Supp. Table 2.2). Based on the logistic regression analyses, patients initiated on NOAC in 2015 were more likely to have a history of stroke/TIA, and less likely to have cardiovascular conditions such as peripheral vascular disease, congestive heart failure, and coronary artery disease, as compared to patients initiating VKA (Table 2.2). Importantly, the baseline profile of new NOAC users changed substantially since the time NOAC were first introduced. For instance, patients with chronic kidney disease or cancer were less likely to be prescribed NOAC over VKA early after NOAC were introduced in the market, whereas these characteristics were not associated with choice of OAC class in 2015. The baseline profile of new NOAC users also differed between AF and VTE patients (Supp. Table 2.3). Notably, among patients with AF and compared to new users of VKA, new users of NOAC were less likely to have congestive heart failure and coronary artery disease, and more likely to have had a previous stroke/TIA. These characteristics were not associated with NOAC initiation in new users with VTE.

Table 2.1 – Temporal changes in the baseline characteristics of new users of NOAC

	2009-2012 (n=974)	2013-2014 (n=6,548)	2015 (n=7,319)
Age, mean (SD)	69.8 (12.5)	71.9 (14.1)	72.1 (13.9)
< 55	108 (11.1)	743 (11.3)	840 (11.5)
55-64	175 (18.0)	849 (13.0)	933 (12.7)
65-74	329 (33.8)	1,725 (26.3)	1,922 (26.3)
75-84	258 (26.5)	2,080 (31.8)	2,322 (31.7)
≥ 85	104 (10.7)	1,151 (17.6)	1,302 (17.8)
Sex, male	498 (51.1)	3,426 (52.3)	3,820 (52.2)
Physician Visits, mean (SD)	9.8 (8.8)	10.7 (8.9)	10.6 (9.2)
0	67 (6.9)	281 (4.3)	301 (4.1)
1-6	358 (36.8)	2,179 (33.3)	2,606 (35.6)
7-12	281 (28.9)	1,999 (30.5)	2,118 (28.9)
13-24	215 (22.1)	1,584 (24.2)	1,741 (23.8)
≥ 25	53 (5.4)	505 (7.7)	553 (7.5)
Indication			
Atrial fibrillation	391 (40.1)	4,050 (61.9)	4,727 (64.6)
Venous thromboembolism	421 (43.2)	1.578 (24.1)	1,668 (22.8)
Unknown	162 (16.6)	920 (14.1)	924 (12.6)
Comorbidities & Risk Factors			
Congestive heart failure	35 (3.6)	402 (6.1)	465 (6.4)
Coronary artery disease	87 (8.9)	608 (9.3)	741 (10.1)
Peripheral vascular disease	6 (0.6)	70 (1.1)	85 (1.2)
Hypertension	672 (69.0)	5,234 (79.9)	5,829 (79.6)
Ischemic stroke/TIA	92 (9.4)	733 (11.2)	700 (9.6)
Chronic kidney disease	48 (4.9)	363 (5.5)	477 (6.5)
Diabetes	139 (14.3)	1,111 (17.0)	1,283 (17.5)
Bleeding	57 (5.9)	353 (5.4)	354 (4.8)
Hyperlipidemia	436 (44.8)	3,352 (51.2)	3,767 (51.5)
Cancer	47 (4.8)	378 (5.8)	391 (5.3)
COPD	49 (5.0)	512 (7.8)	609 (8.3)
Liver disease	5 (0.5)	11 (0.2)	13 (0.2)
Obesity			
Obese	200 (20.5)	1,325 (20.2)	1,386 (18.9)
Not obese	269 (27.6)	2,077 (31.7)	2,205 (30.1)
Unknown	505 (51.8)	3,146 (48.0)	3,728 (50.9)
Smoking			
Never smoker	219 (22.5)	1,720 (26.3)	1,720 (23.5)
Former/current smoker	372 (38.2)	2,499 (38.2)	2,654 (36.3)
Unknown	383 (39.3)	2,329 (35.6)	2,945 (40.2)
Medication Use			
Antihypertensive drugs	671 (68.9)	5,207 (79.5)	5,805 (79.3)
Antiplatelets	447 (45.9)	3,367 (51.4)	3,421 (46.7)
Lipid lowering drugs	433 (44.5)	3,322 (50.7)	3,733 (51.0)

NSAIDs	352 (36.1)	1,199 (18.3)	1,206 (16.5)
$CHADS_2$*			
0	17 (4.3)	135 (3.3)	167 (3.5)
1	120 (30.7)	1,202 (29.7)	1,452 (30.7)
≥ 2	254 (65.0)	2,713 (67.0)	3,108 (65.7)
CHA_2DS_2-VASc*			
0	6 (1.5)	47 (1.2)	39 (0.8)
1	40 (10.2)	347 (8.6)	429 (9.1)
≥ 2	345 (88.2)	3,656 (90.3)	4,259 (90.1)
Modified HAS-BLED			
≤ 2	592 (60.8)	3,727 (56.9)	4,349 (59.4)
> 2	382 (39.2)	2,821 (43.1)	2,970 (40.6)

*$CHADS_2$ and CHA_2DS_2-VASc were calculated for AF patients only.
All values are expressed as *n* (%), unless otherwise specified. SD, standard deviation.

Table 2.2 – Odds ratios (95% CI) for the association between patient characteristics and the initiation of NOAC from 2009 to 2015

	2009-2012 (n=49,662)	2013-2014 (n=26,987)	2015 (n=12,959)
Age (vs. under 45)			
45-54	2.07 (1.38-3.11)	0.88 (0.75-1.04)	0.98 (0.80-1.20)
55-64	2.94 (2.02-4.26)	1.03 (0.89-1.20)	1.09 (0.90-1.32)
65-74	3.56 (2.48-5.13)	1.00 (0.87-1.15)	0.97 (0.81-1.17)
75-84	2.61 (1.79-3.79)	1.02 (0.89-1.18)	1.03 (0.86-1.23)
≥ 85	3.21 (2.14-4.81)	1.44 (1.24-1.68)	1.42 (1.17-1.73)
Male (vs. female)	0.88 (0.77-1.01)	0.98 (0.93-1.04)	0.95 (0.88-1.02)
Physician Visits	1.01 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Comorbidities & Risk Factors			
Congestive heart failure	0.55 (0.39-0.77)	0.83 (0.74-0.93)	0.84 (0.73-0.97)
Coronary artery disease	0.90 (0.71-1.14)	0.75 (0.68-0.83)	0.80 (0.71-0.91)
Peripheral vascular disease	0.38 (0.17-0.86)	0.64 (0.49-0.83)	0.72 (0.53-0.97)
Hypertension	0.67 (0.57-0.79)	1.02 (0.94-1.11)	0.99 (0.90-1.10)
Ischemic Stroke/TIA	1.16 (0.93-1.46)	1.51 (1.37-1.66)	1.61 (1.40-1.86)
Chronic kidney disease	0.75 (0.56-1.01)	0.85 (0.75-0.96)	0.96 (0.83-1.10)
Diabetes	1.03 (0.84-1.26)	0.97 (0.89-1.05)	0.97 (0.88-1.07)
Bleeding	1.13 (0.86-1.48)	1.03 (0.91-1.17)	0.98 (0.83-1.16)
Hyperlipidemia	0.98 (0.84-1.15)	1.04 (0.97-1.11)	1.12 (1.03-1.22)
Cancer	0.63 (0.46-0.85)	1.07 (0.95-1.21)	0.97 (0.83-1.14)
COPD	0.70 (0.52-0.94)	0.96 (0.86-1.07)	1.01 (0.89-1.16)
Liver disease	2.45 (0.99-6.06)	0.66 (0.35-1.27)	0.69 (0.33-1.45)
Obesity	1.00 (0.83-1.21)	0.99 (0.91-1.07)	0.91 (0.82-1.01)
Smoking	1.15 (0.97-1.36)	0.97 (0.90-1.05)	0.95 (0.87-1.05)
Medication Use*			
Antiplatelets	0.90 (0.77-1.05)	1.02 (0.95-1.08)	1.08 (0.99-1.17)
NSAIDs	2.11 (1.85-2.42)	1.12 (1.04-1.21)	1.11 (1.00-1.22)

*Concomitant use of antihypertensive and lipid lowering drugs were included in all models under the hypertension and hyperlipidemia covariates, respectively.

2.5 DISCUSSION

In this large population-based study, the rates of OAC initiation in the UK increased steadily from 2009 to 2015. NOAC were increasingly prescribed throughout the study period and accounted for over 50% of all new OAC prescriptions in 2015, while a substantial decrease in the rate of new VKA users was noted. Among NOAC, rivaroxaban was prescribed most frequently, followed by apixaban and dabigatran. Furthermore, the profile of patients who were prescribed NOAC changed significantly over time, as have the characteristics associated with initiating NOAC over VKA.

Increasing rates of OAC prescription have been described in several previous reports from Europe and Canada, in line with our results [77-79]. The observed increase in our study may be explained by the introduction and adoption of NOAC. Indeed, previous studies had repeatedly shown that VKA were underutilized in AF, especially among vulnerable patients, such as those with a high risk of bleeding [80, 81]. NOAC being potentially safer than VKA, as shown in some clinical trials, these at-risk AF patients would have been newly able to receive treatment when NOAC were introduced, and likely contributed significantly to the increasing number of new OAC users. Accordingly, the rate of OAC initiation increased almost solely in AF patients, who also constituted the majority of the new users in this study. This rate was also highest and most prominent in men and the elderly, which is further in keeping with the incidence of AF being higher in men and increasing with age [2]. Therefore, the introduction of NOAC may have overcome some of the barriers to using OAC therapy in AF. Future studies should reevaluate the extent to which AF remains undertreated and explore any possible underlying reasons.

As expected, new prescriptions of NOAC increased over the study period. Interestingly, there was a delay in the adoption of NOAC, with new user rates remaining negligible until after 2012. This may be explained, in part, by the fact that the indications for NOAC were initially limited to the primary prevention of VTE in post-operative hip and knee patients. It was not until 2011 that the indications were officially expanded to include non-valvular AF, and not until 2012 that recommendations from the UK's NICE were published in light of this amendment. This may be a reason for the prominent increase in NOAC prescriptions from 2012 onwards. Similar trends have been observed in Canada and France, where the proportion of OAC prescriptions attributable to NOAC also remained relatively low until NOAC were approved for stroke prevention in AF patients [77, 79]. In the USA and Denmark, NOAC increased to account for approximately 50% of all new OAC prescriptions within two years post-approval for AF [82, 83]. Although comparable, this is slightly faster than the time taken for NOAC to surpass VKA in our study. These differences in timing may be attributable to a number of factors that influence prescribing practices and that can vary substantially between countries, such as official prescription guidelines, medication costs and reimbursement rates, or even pharmaceutical marketing strategies [84].

Overall, the rate of dabigatran initiation was the lowest among the three NOAC. Previous research has suggested similar patterns in which over time, dabigatran prescriptions plateau and are eventually overtaken by rivaroxaban [77, 79, 82, 85], or in some cases, by both rivaroxaban and apixaban [86]. In guidance documents issued by the UK's NHS, rivaroxaban and apixaban are cited as suitable for most patients with non-valvular AF, whereas in some situations, dabigatran is not preferred or even

contraindicated [87, 88]. Rivaroxaban is furthermore identified as the NOAC of choice for the treatment and prevention of VTE in several UK counties [89, 90]. These recommendations offer possible explanations as to the observed differences between the rates of initiation of individual NOAC, and indeed, our results suggest that these guidelines have been well adopted by UK GPs. Dabigatran also differs from both rivaroxaban and apixaban in terms of its mechanism of action and other pharmacological characteristics. Notably, dabigatran has a longer half-life and is also primarily renally cleared [91]. A longer half-life heightens the risk of overdose, which may be further exacerbated in those with any form of renal impairment, and dabigatran may therefore also be infrequently prescribed for precautionary reasons. Conversely, a dramatic increase in new apixaban users was observed. Data on the temporal trends of apixaban initiation remains sparse, considering its more recent introduction as compared to dabigatran and rivaroxaban. Nevertheless, in Denmark, apixaban was found to be the most frequently prescribed among new users of NOAC in 2015 [86]. Future studies in the UK and in other countries will further inform the evolution of the initiation of individual NOAC over time.

Our results suggest that the patient profile associated with NOAC initiation has changed over time. NOAC may have been initially prescribed with greater caution due to preliminary uncertainties with regard to their effectiveness and safety in primary care. Indeed, over time, patients initiated on NOAC and those initiated on VKA were more similar in profile. Some patient characteristics were nonetheless significantly associated with a first-time NOAC prescription. For instance, in partial keeping with NICE guidelines, NOAC were preferentially initiated in elderly patients from 2009-2012, and in those with a history of stroke/TIA in 2015. Interestingly, the NICE also recommends NOAC in AF

patients with congestive heart failure, however, these patients were less likely to initiate NOAC in our study. Older age has been both positively and negatively associated with first-time NOAC use in previous studies in other countries, and conflicting conclusions have also been drawn with respects to the effect of patient sex, and history of bleeding and stroke/TIA [82, 83, 92-94]. As already mentioned, the decision to initiate a patient on either NOAC or VKA may be affected by how recently NOAC were marketed and introduced, and this time effect may also offer some explanation as to the differences in profile that can be observed across studies. The differences between first-time users of NOAC and VKA and the changes in these differences over time should be taken into consideration in any analyses comparing these distinct patients groups.

This study was conducted using the CPRD, which provided a large and representative study population and thereby allowed for an accurate depiction of the use of OAC in the UK. Furthermore, the seven-year study timeframe surpasses that of many previous studies, thus permitting a more thorough analysis of the longitudinal trends in OAC prescription, including more recent NOAC such as apixaban. A limitation of this study is that the CPRD contains only records of medications prescribed by primary care physicians. Nevertheless, GPs in the UK typically follow-up on medications prescribed in secondary or tertiary care, and the trends described herein may still be considered accurate and informative with respects to the global patterns of OAC use. Additionally, in primary care databases such as the CPRD, diagnoses are not systematically recorded in tandem with issued prescriptions. It was therefore not possible to analyze all new OAC users when stratifying by indication. Finally, no differentiation was made between the different doses of OAC in the context of this study. Because it is often recommended that

NOAC doses be adjusted under specific clinical conditions, further stratifying patients by prescribed dose could provide a more detailed depiction of their baseline profile.

In conclusion, the overall rate of OAC initiation increased in the UK from 2009 to 2015, primarily among AF patients, and with NOAC prescriptions now having surpassed VKA. The profile of patients initiating these medications has further changed over time. These trends likely reflect the interplay of several factors influencing prescribing practices, such as changes in the perceived utility and safety of NOAC, and/or official guidelines, among others. Further studies will explore the impact of these individual factors on OAC prescription trends, and will also establish the safety and effectiveness of NOAC in UK primary care. This will ultimately provide clinicians with more guidance in determining which NOAC is more suitable to prescribe to individual patients.

2.6 SUPPLEMENTARY INFORMATION

Supp. Table 2.1 – Temporal trends in the rate of new users of NOAC

Year	Crude Rate[1]	Adjusted Rate[1,2] (95% CI)	Crude Rate Ratio[3]	Adjusted Rate Ratio[2,3] (95% CI)
2009	2.1	3.4 (2.5-4.7)	-	-
2010	4.4	7.2 (5.7-8.9)	2.08	2.09 (1.42-3.08)
2011	4.9	7.8 (6.3-9.7)	1.10	1.09 (0.80-1.49)
2012	17.5	27.9 (24.9-31.3)	3.59	3.58 (2.80-4.56)
2013	65.1	103.8 (97.6-110.4)	3.73	3.72 (3.27-4.23)
2014	160.9	254.3 (243.8-265.2)	2.47	2.45 (2.28-2.64)
2015	308.9	489.4 (473.2-506.1)	1.92	1.92 (1.83-2.03)

[1] Rates expressed per 100,000 persons per year.
[2] Adjusted for sex and age category.
[3] Rate ratios calculated with each preceding year as reference.

Supp. Table 2.2 – Baseline characteristics of new users of NOAC

	Dabigatran (n=430)	Rivaroxaban (n=4,741)	Apixaban (n=2,148)
Age, mean (SD)	73.2 (11.6)	70.5 (14.7)	75.2 (11.8)
< 55	27 (6.3)	691 (14.6)	122 (5.7)
55-64	56 (13.0)	633 (13.4)	244 (11.4)
65-74	144 (33.5)	1,253 (26.4)	525 (24.4)
75-84	130 (30.2)	1,414 (29.8)	778 (36.2)
≥ 85	73 (17.0)	750 (15.8)	479 (22.3)
Sex, male	247 (57.4)	2,429 (51.2)	1,144 (53.3)
Physician visits, mean (SD)	10.2 (8.5)	10.6 (9.5)	10.7 (8.6)
0	5 (1.2)	210 (4.4)	86 (4.0)
1-6	176 (40.9)	1,710 (36.1)	720 (33.5)
7-12	132 (30.7)	1,355 (28.6)	631 (29.4)
13-24	84 (19.5)	1,102 (23.2)	555 (25.8)
≥ 25	33 (7.7)	364 (7.7)	156 (7.3)
Indication			
Atrial fibrillation	354 (82.3)	2,580 (54.4)	1,793 (83.5)
Venous thromboembolism	28 (6.5)	1,511 (31.9)	129 (6.0)
Unknown	48 (11.2)	650 (13.7)	226 (10.5)
Comorbidities & Risk Factors			
Congestive heart failure	27 (6.3)	248 (5.2)	190 (8.8)
Coronary artery disease	47 (10.9)	418 (8.8)	276 (12.8)
Peripheral vascular disease	< 5*	53 (1.1)	29 (1.4)
Hypertension	378 (87.9)	3,549 (74.9)	1,902 (88.5)
Ischemic stroke/TIA	36 (8.4)	321 (6.8)	343 (16.0)
Chronic kidney disease	24 (5.6)	295 (6.2)	158 (7.4)
Diabetes	71 (16.5)	817 (17.2)	395 (18.4)
Bleeding	14 (3.3)	228 (4.8)	112 (5.2)
Hyperlipidemia	244 (56.7)	2,221 (46.8)	1,302 (60.6)
Cancer	21 (4.9)	274 (5.8)	96 (4.5)
COPD	33 (7.7)	400 (8.4)	176 (8.2)
Liver disease	< 5*	7 (0.1)	< 5*
Obesity			
Obese	89 (20.7)	895 (18.9)	402 (18.7)
Not obese	115 (26.7)	1,390 (29.3)	700 (32.6)
Unknown	226 (52.6)	2,456 (51.8)	1,046 (48.7)
Smoking			
Never smoker	98 (22.8)	1,075 (22.7)	547 (25.5)
Former/current smoker	150 (34.9)	1,731 (36.5)	773 (36.0)
Unknown	182 (42.3)	1,935 (40.8)	828 (38.5)
Medication Use			
Antihypertensive drugs	378 (87.9)	3,530 (74.5)	1,897 (88.3)
Antiplatelets	229 (53.3)	1,970 (41.6)	1,222 (56.9)
Lipid lowering drugs	240 (55.8)	2,203 (46.5)	1,290 (60.1)

NSAIDs	86 (20.0)	810 (17.1)	310 (14.4)
$CHADS_2$**			
0	13 (3.7)	106 (4.1)	48 (2.7)
1	131 (37.0)	818 (31.7)	503 (28.1)
≥ 2	210 (59.3)	1,656 (64.2)	1,242 (69.3)
CHA_2DS_2-VASc**			
0	< 5*	26 (1.0)	9 (0.5)
1	39 (11.0)	238 (9.2)	152 (8.5)
≥ 2	311 (87.9)	2,316 (89.8)	1,632 (91.0)
Modified HAS-BLED			
≤ 2	237 (55.1)	3,063 (64.6)	1,049 (48.8)
> 2	193 (44.9)	1,678 (35.4)	1,099 (51.2)

*Cells with less than five events were suppressed owing to privacy restrictions, in accordance with CPRD policy

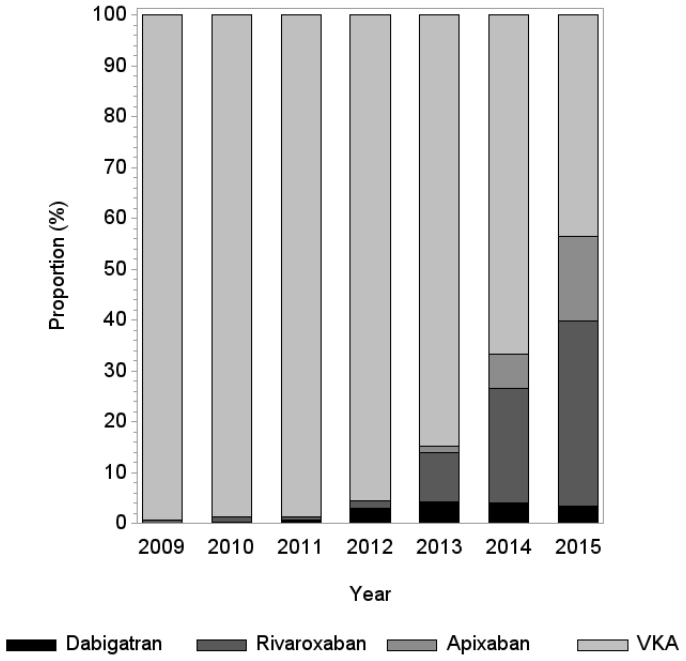
**$CHADS_2$ and CHA_2DS_2-VASc were calculated for patients with atrial fibrillation only.

All values are expressed as *n* (%), unless otherwise specified

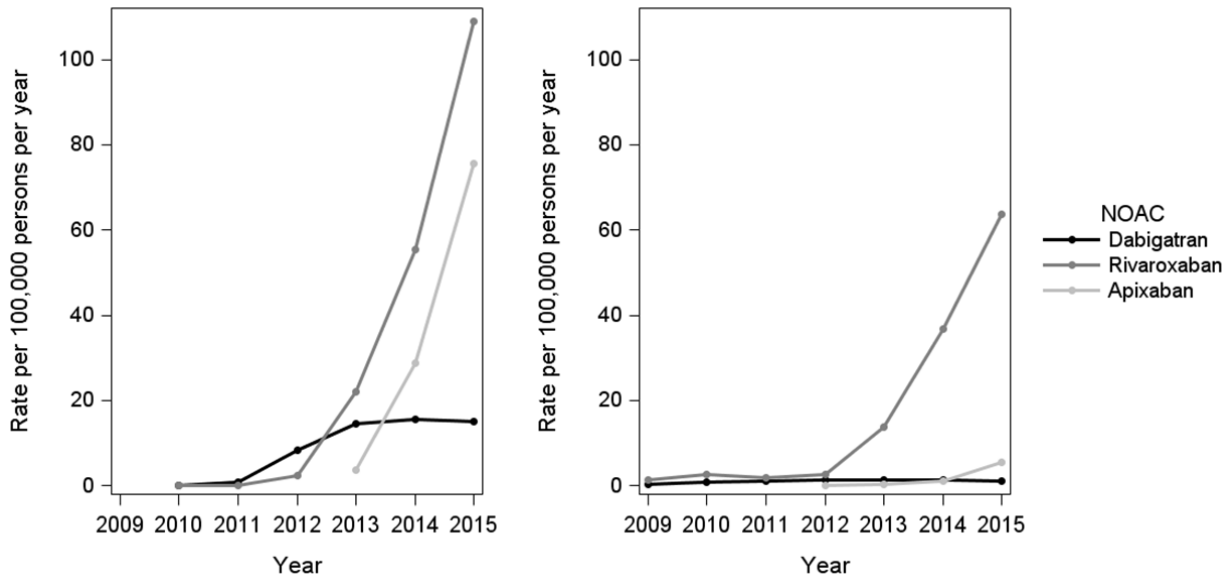
Supp. Table 2.3 – Odds ratios (95% CI) for the association between patient characteristics and the initiation of NOAC, stratified by OAC indication

	2015 AF patients n=8,424	2015 VTE patients n=3,122	2015 Unknown n=1,413
Age (vs. under 45)			
45-54	1.29 (0.83-1.99)	0.92 (0.70-1.21)	0.87 (0.50-1.50)
55-64	1.40 (0.94-2.11)	1.12 (0.86-1.47)	0.88 (0.53-1.46)
65-74	1.26 (0.85-1.87)	0.95 (0.73-1.22)	1.09 (0.66-1.80)
75-84	1.34 (0.91-2.00)	0.97 (0.74-1.27)	1.06 (0.65-1.75)
≥ 85	1.88 (1.25-2.81)	1.12 (0.81-1.55)	1.72 (1.00-2.95)
Male (vs. female)	1.00 (0.91-1.09)	0.97 (0.84-1.12)	0.77 (0.61-0.97)
Physician visits	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.98-1.01)
Comorbidities & Risk Factors			
Congestive heart failure	0.85 (0.74-0.99)	0.98 (0.56-1.70)	0.94 (0.46-1.93)
Coronary artery disease	0.80 (0.70 -0.91)	1.04 (0.73-1.47)	0.76 (0.48-1.21)
Peripheral vascular disease	0.71 (0.50-1.01)	0.98 (0.48-2.00)	0.67 (0.18-2.43)
Hypertension	1.11 (0.96-1.30)	0.96 (0.80-1.14)	0.77 (0.58-1.04)
Ischemic stroke/TIA	1.85 (1.58-2.16)	0.67 (0.41-1.10)	1.07 (0.62-1.83)
Chronic kidney disease	0.95 (0.80-1.13)	1.05 (0.75-1.47)	0.89 (0.55-1.45)
Diabetes	1.01 (0.89-1.14)	0.79 (0.63-0.99)	0.99 (0.72-1.36)
Bleeding	0.95 (0.77-1.17)	0.93 (0.69-1.26)	1.64 (0.89-3.00)
Hyperlipidemia	1.08 (0.98-1.20)	1.25 (1.03-1.52)	1.11 (0.84-1.47)
Cancer	0.96 (0.77-1.19)	1.01 (0.77-1.34)	0.80 (0.52-1.23)
COPD	1.09 (0.93-1.28)	0.89 (0.67-1.18)	0.73 (0.48-1.11)
Liver disease	1.15 (0.40-3.34)	0.47 (0.12-1.92)	0.29 (0.05-1.66)
Obesity	0.89 (0.79-1.02)	0.92 (0.74-1.14)	1.05 (0.74-1.51)
Smoking	0.91 (0.81-1.02)	1.03 (0.84-1.27)	1.19 (0.85-1.67)
Medication Use*			
Antiplatelets	1.07 (0.97-1.18)	1.05 (0.86-1.30)	1.12 (0.86-1.47)
NSAIDs	1.08 (0.95-1.23)	1.09 (0.91-1.30)	1.30 (0.95-1.79)

*Concomitant use of antihypertensive and lipid lowering drugs were included in all models under the hypertension and hyperlipidemia covariates, respectively



Supp. Figure 2.1 – Distribution of new users of oral anticoagulants



Supp. Figure 2.2 – Rates of new users of NOAC with an indication for AF (left) and VTE (right)

CHAPTER 3: COMPARATIVE EFFECTIVENESS AND SAFETY OF NOVEL ORAL ANTICOAGULANTS

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The following chapter will explore two factors that may have played a role in the substantial uptake of novel oral anticoagulants (NOAC) in the UK, namely, the medications' clinical effectiveness and safety.

Patients with atrial fibrillation constitute the majority of oral anticoagulant users, and the prescription trends presented in Chapter 2 appear to have been driven by these patients. Atrial fibrillation is also a chronic disease that requires long term oral anticoagulant treatment, in contrast to venous thromboembolism which is acute and therefore treated for shorter durations. In light of these points, the analyses of this chapter will focus on a population of patients with atrial fibrillation only.

The contents of this chapter are based on a manuscript currently in preparation for submission to a scientific journal.

3.1 ABSTRACT

Aims: Novel oral anticoagulants (NOAC) are recent alternatives to vitamin-K antagonists (VKA) for the prevention of ischemic stroke in non-valvular atrial fibrillation (NVAF). The objective of this study was to evaluate the effectiveness and safety of NOAC compared to VKA in a cohort of NVAF patients in a primary care setting, as well as in vulnerable subgroups, including patientss with chronic kidney disease (CKD).

Methods: Using the UK's Clinical Practice Research Datalink, we created a cohort of NVAF patients newly treated with a NOAC or VKA between 2011 and 2016. New users were matched 1:1 on age, sex, and high-dimensional propensity score, and Cox regression was used to compare the rate of events within matched groups.

Results: Within a cohort of 34,094 patients with a first OAC prescription during the study period, we identified up to 6,818 matched pairs of new NOAC and VKA users. In as-treated analyses, NOAC were comparable to VKA in the prevention of ischemic stroke and systemic embolism (HR 0.94; 95% CI 0.62-1.42), and with respect to major bleeding (HR 0.86; 95% CI 0.56-1.33). NOAC tended to decrease the risk of intracranial bleeding (HR 0.51; 95% CI 0.18-1.44), but significantly increased the risk of gastrointestinal bleeding (HR 1.78; 95% CI 1.27-2.48). Similar results were obtained in time-dependent analyses, and the effectiveness and safety of NOAC remained unchanged in patients with CKD.

Conclusions: Our results suggest that in the UK primary care, NOAC are overall effective and safe alternatives to VKA, among NVAF patients altogether, as well as in vulnerable patient subgroups.

3.2 INTRODUCTION

Patients with atrial fibrillation (AF) experience an estimated five-fold increased risk of ischemic stroke [12]. Consequently, these patients require treatment with oral anticoagulants (OAC) such as vitamin-K antagonists (VKA), which have been shown to reduce the risk of stroke by approximately 60% compared to placebo in randomized controlled trials (RCTs) [95]. Although effective, VKA therapy may be challenging due to bleeding concerns, as well as the need for close and impractical routine monitoring [61, 62].

In the UK, NOAC were licensed for stroke prevention in non-valvular AF in August 2011. Based on the results of RCTs, these medications have generally been accepted as effective and safe alternatives to VKA [96], and these conclusions have been echoed in several observational studies evaluating NOAC in routine clinical practice [48, 53, 97, 98]. In contrast, the effectiveness and safety of NOAC has been less extensively explored in subgroups of more vulnerable AF patients. In particular, those with chronic kidney disease (CKD) experience an increased risk of ischemic stroke and adverse bleeding events [45]. However, few observational studies have compared NOAC and VKA treatment in CKD patients, and there is room to explore the clinical utility of these medications in such at-risk subgroups.

The objective of this study was to assess the effectiveness and safety of NOAC compared to VKA using an observational study design, in AF patients from a UK primary care setting. Notably, this study will also explore the clinical utility of NOAC in subgroups of vulnerable populations, including those with CKD.

3.3 METHODS

3.3.1 Data Source

The UK's Clinical Practice Research Datalink (CPRD) is one of the largest databases of primary care electronic medical records, and details patient demographic characteristics and lifestyle habits, in addition to their clinical history. The information is documented by general practitioners (GP) from over 670 medical practices, which collectively represent over 7% of the total UK population [68]. Importantly, GP-issued drug prescriptions are automatically transcribed into patients' computerized file, and the database thus contains comprehensive patient prescription data. The CPRD has therefore been used extensively for pharmacoepidemiologic studies of drug effectiveness and safety [69, 70], and the validity and representativeness of its data have previously been evaluated [68, 71-73].

3.3.2 Study Population

We identified all CPRD patients aged 18 or older with a first ever diagnosis for AF. At the time of diagnosis, those with less than 12 months of valid and up to standard records were excluded, as were patients with valvular AF, hyperthyroidism, and/or a history of OAC use. Within this population, we selected all new users of NOAC or VKA who received their first prescription between 1 August 2011, when NOAC were first approved for the treatment of non-valvular AF, and 30 September 2016. The date of first prescription was considered the date of cohort entry, and follow-up ended at the earliest of 30 September 2016, occurrence of the outcome of interest, or the date of the patient's death or transfer out of the practice.

3.3.3 Exposure Definition

We identified all OAC available in the UK between 2011 and 2016. The NOAC of interest included dabigatran, rivaroxaban, apixaban, and edoxaban, and the VKA included warfarin, acenocoumarin, and phenindione. Continuous exposure was defined starting from the date of first prescription, for the intended duration of the prescription, plus the duration of any overlapping and successive prescriptions of the same OAC class. The duration of each prescription was extended by a grace period of seven days to account for residual anticoagulation effects and delays between prescription refills. In primary as-treated analyses, patients were censored after treatment switching (NOAC to VKA, or vice versa) or treatment discontinuation. In secondary analyses, exposure was defined as a time-dependent variable, and each day of follow-up was classified as exposed to either NOAC or VKA, both, or neither.

3.3.4 Outcome Definition

The primary effectiveness outcome was a composite of ischemic stroke and systemic embolism (SE). Safety outcomes of interest included major bleeding, intracranial bleeding, gastrointestinal (GI) bleeding, myocardial infarction (MI), and all-cause mortality. Major bleeding was defined as any bleeding requiring hospitalization or resulting in death. All outcomes were identified over the course of follow-up through the identification of corresponding READ codes in patients' electronic files. A previous study had shown that CPRD records of stroke and MI were concordant with patients' paper files in 89% and 94% of cases, respectively [99]. The CPRD has also been used successfully in our previous research, to evaluate outcomes of interest similar to those in this present study [100, 101].

3.3.5 Statistical Analyses

New users of NOAC were matched 1:1 to new users of VKA on age, sex, and high-dimensional propensity score (hd-PS) using caliper matching [102]. Briefly, using all data from within the year prior to cohort entry, hd-PS were calculated for each patient as the probability of being exposed to NOAC, based on the 500 covariates that were most likely to bias the exposure-outcome association. Thus, for each patient, a separate hd-PS was calculated for each outcome of interest. Age, sex, and time between AF diagnosis and first prescription were forced into all hd-PS models. Patients were not matched on the date of prescription, considering the uneven distribution of NOAC and VKA users over the relatively short study period. After matching, Poisson regression was used to calculate the rates of event occurrence, and Cox regression was used to compute the hazard ratio of events, comparing exposure to NOAC versus VKA. In primary analyses, OAC exposure was defined using an as-treated approach, and in secondary analyses, using a time-dependent approach, as described above. In addition to hd-PS matching, all Cox models were adjusted for antiplatelet use, hypertension, diabetes, and CKD as time-dependent covariates. These analyses were also conducted in subgroups of patients defined by patient age (< 75 and ≥ 75), sex, CKD status, as well as CHA_2DS_2-VASc [75] and HAS-BLED [76] scores at cohort entry. CKD was defined using an algorithm based on patient GFR and serum creatinine values, as well as READ codes related to CKD, renal transplantation and/or dialysis, recorded in the year prior to cohort entry. Serum creatinine results were used to estimate GFR using the CKD-EPI creatinine equation [103].

Several sensitivity analyses were conducted to verify the robustness of our results. Firstly, in as-treated analyses, the exposure window was extended by an additional 30 days

after treatment switching or discontinuation, in order to account for potential informative censoring. The grace period between prescriptions was also increased to 15 and to 30 days so as to evaluate the impact of potential exposure misclassification. We also evaluated the effectiveness and safety of NOAC using an intention-to-treat analysis. Finally, primary analyses were repeated in the full cohort, trimmed to exclude patients with an hd-PS below and above the 5th and 95th percentile of scores, respectively, and with models adjusted for covariates measured at cohort entry, rather than using hd-PS matching.

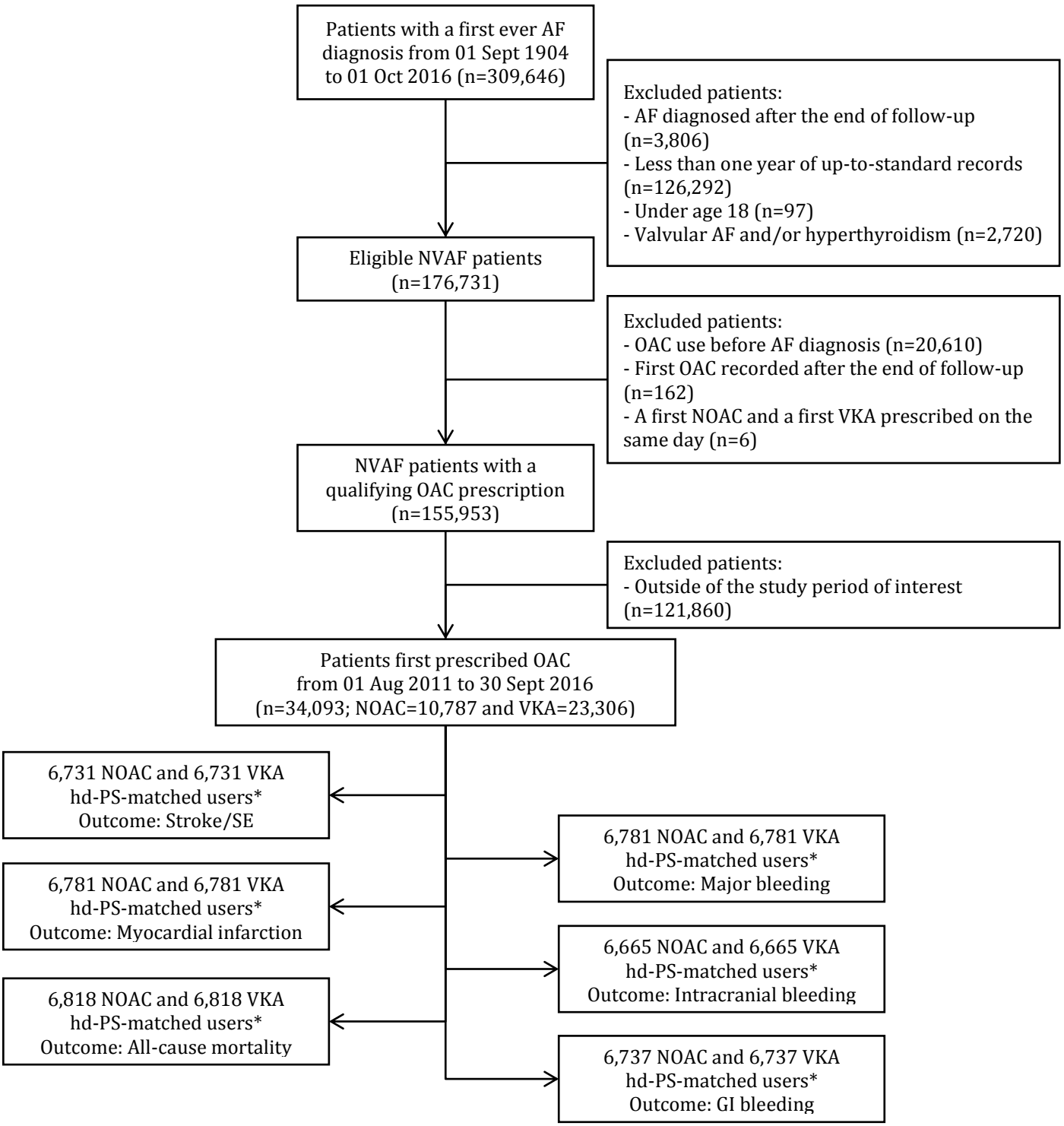
All statistical procedures were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

This study protocol (No. 16_271R) was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital (Montreal, Canada), and was made available to journal reviewers.

3.4 RESULTS

We identified 309,646 patients who were ever diagnosed with AF, among whom 155,953 with a first OAC prescription were eligible for study (Figure 3.1). A total of 34,093 patients received their prescription between 1 August 2011 and 30 September 2016, including 23,306 (68.36%) new users of VKA and 10,787 (31.64%) new users of NOAC. Rivaroxaban comprised the majority of first ever NOAC prescriptions (52.11%), followed by apixaban (34.06%), dabigatran (13.61%), and edoxaban (0.22%). Up to 6,818 new users of NOAC were matched 1:1 to new users of VKA on age, sex, and hd-PS, and overall, covariates were well balanced within all matched groups (Table 3.1).

Figure 3.1 – Cohort definition flowchart



*hd-PS are outcome specific, and in this study, were based on the 500 covariates that were most likely to bias the exposure-outcome association. Therefore, a separate hd-PS was calculated for each patient and for each outcome of interest, resulting in a total of six different matched groups.

Table 3.1 – Baseline characteristics of new users of NOAC and VKA before and after matching on hd-PS to evaluate the risk of ischemic stroke/SE

	All cohort patients		Matched patients	
	NOAC (n=10,787)	**VKA (n=23,306)**	**NOAC (n=6,731)**	**VKA (n=6,731)**
Age, mean years (SD)	75.44 (11.02)	74.72 (10.25)	74.91 (10.29)	74.91 (10.29)
18-55	485 (4.5)	987 (4.2)	284 (4.2)	284 (4.2)
55-64	1,169 (10.8)	2,412 (10.3)	706 (10.5)	706 (10.5)
65-74	2,960 (27.4)	6,893 (29.6)	2,041 (30.3)	2,041 (30.3)
75-84	3,814 (35.4)	9,237 (39.6)	2,471 (36.7)	2,471 (36.7)
≥ 85	2,359 (21.9)	3,777 (16.2)	1,229 (18.3)	1,229 (18.3)
Sex				
Men	5,862 (54.3)	12,797 (54.9)	3,720 (55.3)	3,720 (55.3)
Women	4,925 (45.7)	10,509 (45.1)	3,011 (44.7)	3,011 (44.7)
Comorbidities & Risk Factors				
Congestive heart failure	865 (8.0)	2,280 (9.8)	544 (8.1)	547 (8.1)
Coronary artery disease	1,141 (10.6)	2,958 (12.7)	739 (11.0)	721 (10.7)
Peripheral vascular disease	92 (0.9)	290 (1.2)	60 (0.9)	57 (0.8)
Hypertension	7,657 (71.0)	17,331 (74.4)	4,815 (71.5)	4,706 (69.9)
Ischemic Stroke/TIA/SE	1,254 (11.6)	2,258 (9.7)	782 (11.6)	739 (11.0)
Venous thromboembolism	184 (1.7)	738 (3.2)	131 (1.9)	152 (2.3)
Chronic kidney disease	4,274 (39.6)	9,432 (40.5)	2,684 (39.9)	2,508 (37.3)
Diabetes	1,996 (18.5)	4,425 (19.0)	1,228 (18.2)	1,191 (17.7)
Bleeding	516 (4.8)	1,099 (4.7)	328 (4.9)	288 (4.3)
Hyperlipidemia	6,100 (56.5)	13,199 (56.6)	3,829 (56.9)	3,586 (53.3)
Cancer	519 (4.8)	1,004 (4.3)	322 (4.8)	287 (4.3)
COPD	921 (8.5)	2,040 (8.8)	512 (7.6)	545 (8.1)
Liver disease	28 (0.3)	45 (0.2)	19 (0.3)	15 (0.2)
Alcohol abuse	186 (1.7)	291 (1.2)	115 (1.7)	80 (1.2)
Obesity				
Obese	2,950 (27.3)	7,002 (30.0)	1,899 (28.2)	1,828 (27.2)
Not obese	5,079 (47.1)	10,824 (46.4)	3,137 (46.6)	3,138 (46.6)
Unknown	2,758 (25.6)	5,480 (23.5)	1,695 (25.2)	1,765 (26.2)
Smoking				
Never	3,893 (36.1)	8,257 (35.4)	2,467 (36.7)	2,360 (35.1)
Ever	5,348 (49.6)	12,369 (53.1)	3,355 (49.8)	3,430 (51.0)
Unknown	1,546 (14.3)	2,680 (11.5)	909 (13.5)	941 (14.0)
Medications				
Amiodarone	348 (3.2)	787 (3.4)	218 (3.2)	215 (3.2)
Antidiabetic drugs	1,454 (13.5)	3,223 (13.8)	895 (13.3)	874 (13.0)
Cardioprotective drugs	9,836 (91.2)	21,330 (91.5)	6,147 (91.3)	6,049 (89.9)
ACE inhibitors	4,078 (37.8)	9,706 (41.6)	2,616 (38.9)	2,554 (37.9)
ARBs	1,919 (17.8)	4,199 (18.0)	1,205 (17.9)	1,129 (16.8)
Beta-blockers	7,238 (67.1)	15,481 (66.4)	4,539 (67.4)	4,488 (66.7)
Calcium-channel blockers	4,061 (37.6)	9,307 (39.9)	2,571 (38.2)	2,537 (37.7)
Loop diuretics	2,916 (27.0)	6,868 (29.5)	1,751 (26.0)	1,782 (26.5)
Thiazide diuretics	2,089 (19.4)	5,437 (23.3)	1,353 (20.1)	1,319 (19.6)
Antiplatelets	5,961 (55.3)	14,574 (62.5)	3,832 (56.9)	3,873 (57.5)

Antipsychotic drugs	626 (5.8)	1,278 (5.5)	390 (5.8)	378 (5.6)
H2 receptor antagonists	495 (4.6)	1,062 (4.6)	284 (4.2)	290 (4.3)
HRT*	266 (5.4)	522 (5.0)	160 (5.3)	154 (5.1)
Lipid lowering drugs	6,057 (56.2)	13,089 (56.2)	3,805 (56.5)	3,560 (52.9)
NSAIDs	1,546 (14.3)	3,722 (16.0)	988 (14.7)	1,004 (14.9)
Proton pump inhibitors	4,940 (45.8)	10,307 (44.2)	2,960 (44.0)	2,924 (43.4)
$CHADS_2$				
0	1,244 (11.5)	2,549 (10.9)	802 (11.9)	882 (13.1)
1	3,269 (30.3)	6,816 (29.3)	2,033 (30.2)	2,011 (29.9)
≥ 2	6,274 (58.2)	13,941 (59.8)	3,896 (57.9)	3,838 (57.0)
$CHADS_2VASc$				
0	367 (3.4)	728 (3.1)	215 (3.2)	249 (3.7)
1	1,034 (9.6)	2,120 (9.1)	638 (9.5)	669 (9.9)
≥ 2	9,386 (87.0)	20,458 (87.8)	5,878 (87.3)	5,813 (86.4)
HAS-BLED				
≤ 2	5,789 (53.7)	11,570 (49.6)	1,470 (21.8)	1,545 (23.0)
> 2	4,998 (46.3)	11,736 (50.4)	5,261 (78.2)	5,186 (77.0)

*HRT was identified in women only.

All values are expressed as *n* (%), unless otherwise specified. SD, standard deviation; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drugs.

The rate of ischemic stroke/SE was 1.4 (95% CI 1.3-1.5) and 1.9 (95% CI 1.7-2.1) events per 100 persons per year among matched new users of NOAC and of VKA, respectively. New users of NOAC also experienced an overall rate of 1.3 (95% CI 1.2-1.4) major bleeding events per 100 persons per year, compared to 1.7 (95% CI 1.5-1.8) in new users of VKA. In as-treated analyses, NOAC were as effective as VKA in the prevention of ischemic stroke/SE (HR 0.94; 95% CI 0.62-1.42), without increasing the risk of major bleeding (HR 0.86; 95% CI 0.56-1.33) (Table 3.2). NOAC significantly increased the risk of GI bleeding, and tended to decrease the risk of intracranial bleeding, though with large confidence intervals around the point estimate. The risk of mortality was slightly higher with NOAC compared to VKA, and there was no difference between OAC with respect to the risk of MI. Similar tendencies were observed in time-dependent analyses, with moderate changes in effect estimates (Table 3.3).

In sensitivity analyses extending the exposure window by 30 days after continuous exposure, we observed no differences in mortality between NOAC and VKA, however, NOAC remained associated with a higher risk of GI bleeding (HR 1.47; 95% CI 1.09-2.00) and a lower, although non-significant, risk of intracranial bleeding (HR 0.65; 95% CI 0.24, 1.74) (Supp. Table 3.1). The as-treated results were virtually unchanged when increasing the grace period between prescriptions to 15 and to 30 days (data not shown). NOAC also remained comparable to VKA with respects to ischemic stroke/SE and major bleeding in intention-to-treat analyses, and when using a standard covariate adjustment technique to address confounding (data not shown).

Table 3.2 – As-treated analyses of the comparative effectiveness and safety of NOAC

Outcome	Drug Exposure	Events	Person-time in years	Crude HR (95% CI)	Adjusted* HR (95% CI)
Ischemic Stroke/SE	VKA	44	2,341.07	1.00 (ref.)	1.00 (ref.)
	NOAC	47	3,379.05	0.92 (0.61-1.39)	0.94 (0.62-1.42)
Major Bleeding	VKA	40	2,389.38	1.00 (ref.)	1.00 (ref.)
	NOAC	44	3,391.36	0.83 (0.54-1.29)	0.86 (0.56-1.33)
Intracranial Bleeding	VKA	10	2,337.03	1.00 (ref.)	1.00 (ref.)
	NOAC	6	3,359.16	0.49 (0.18-1.36)	0.51 (0.18-1.44)
GI Bleeding	VKA	51	2,346.59	1.00 (ref.)	1.00 (ref.)
	NOAC	116	3,351.07	1.74 (1.25-2.43)	1.78 (1.27-2.48)
Myocardial Infarction	VKA	25	2,388.46	1.00 (ref.)	1.00 (ref.)
	NOAC	28	3,399.32	0.89 (0.52-1.53)	0.94 (0.54-1.63)
Death	VKA	88	2,411.62	1.00 (ref.)	1.00 (ref.)
	NOAC	144	3,433.39	1.22 (0.94-1.60)	1.20 (0.92-1.58)

*Adjusted for hypertension, diabetes, antiplatelet use, and chronic kidney disease, as time-dependent covariates.

Table 3.3 – Time-dependent analyses of the comparative effectiveness and safety of NOAC

Outcome	Drug Exposure*	Events	Person-time in years	Crude HR (95% CI)	Adjusted** HR (95% CI)
Ischemic Stroke/SE	VKA	91	7,652.58	1.00 (ref.)	1.00 (ref.)
	NOAC	90	8,387.21	0.93 (0.70, 1.25)	0.93 (0.70, 1.25)
	Neither	71	5,025.71	1.58 (1.14, 2.19)	1.54 (1.11, 2.14)
Major Bleeding	VKA	101	7,884.40	1.00 (ref.)	1.00 (ref.)
	NOAC	115	8,502.21	1.04 (0.80, 1.36)	1.06 (0.81, 1.38)
	Neither	63	5,004.50	1.04 (0.75, 1.43)	0.99 (0.72, 1.37)
Intracranial Bleeding	VKA	21	7,584.61	1.00 (ref.)	1.00 (ref.)
	NOAC	19	8,382.86	0.82 (0.44, 1.53)	0.84 (0.45, 1.57)
	Neither	18	5,103.91	1.56 (0.81, 3.02)	1.43 (0.73, 2.79)
GI Bleeding	VKA	161	7,592.96	1.00 (ref.)	1.00 (ref.)
	NOAC	228	8,301.75	1.29 (1.05, 1.57)	1.30 (1.06, 1.59)
	Neither	95	4,889.23	1.05 (0.81, 1.36)	1.01 (0.78, 1.31)
Myocardial Infarction	VKA	52	7,803.54	1.00 (ref.)	1.00 (ref.)
	NOAC	48	8,498.77	0.84 (0.57, 1.24)	0.87 (0.59, 1.30)
	Neither	28	5,141.91	1.05 (0.66, 1.69)	0.95 (0.59, 1.53)
Death	VKA	245	7,812.37	1.00 (ref.)	1.00 (ref.)
	NOAC	348	8,574.31	1.28 (1.09, 1.51)	1.25 (1.06, 1.47)
	Neither	651	5,244.68	4.33 (3.72, 5.03)	4.46 (3.83, 5.19)

*Regression models also included simultaneous exposure to both VKA and NOAC.
**Adjusted for hypertension, diabetes, antiplatelet use, and chronic kidney disease, as time-dependent covariates.

The results of the main analyses were unchanged in analyses stratified by age and sex (data not shown). NOAC non-significantly decreased both the risk of ischemic stroke/SE in high stroke risk patients (CHA_2DS_2-VASc ≥ 2) (HR 0.83; 95% CI 0.53-1.24), and the risk of major bleeding in high risk bleeding patients (HAS-BLED > 2) (HR 0.77; 95% CI 0.42-1.40).

In up to 2,664 matched pairs of new NOAC and VKA users with CKD, the rate of ischemic stroke/SE was 1.2 (95% CI 1.1-1.4) and 1.9 (95% CI 1.6-2.1) events per 100 persons per year, respectively. In Cox regression analyses, NOAC tended to reduce the risk of ischemic stroke/SE compared to VKA (HR 0.79; 95% CI 0.40-1.58) (Table 3.4). Similarly, NOAC users experienced a rate of 1.7 (95% CI 1.5-2.0) major bleeding events per 100 persons per year, compared to 2.1 (95% CI 1.8-2.4) in those treated with VKA (HR 0.88; 95% CI 0.47-1.62). Results for other outcomes were consistent with the main analyses except for the risk of GI bleeding, which was not increased with NOAC treatment (HR 0.99; 95% CI 0.63-1.55) in this patient subgroup. These results were consistent in time-dependent analyses (Table 3.5), and in sensitivity analyses with 30 days added to the end of continuous exposure (Supp. Table 3.2).

Table 3.4 – As-treated analyses of the comparative effectiveness and safety of NOAC in a subgroup of patients with CKD

Outcome	Drug Exposure	Events	Person-time in years	Crude HR (95% CI)	Adjusted* HR (95% CI)
Ischemic Stroke/SE	VKA	17	913.13	1.00 (ref.)	1.00 (ref.)
	NOAC	16	1,303.89	0.76 (0.38-1.51)	0.79 (0.40-1.58)
Major Bleeding	VKA	19	899.66	1.00 (ref.)	1.00 (ref.)
	NOAC	23	1,321.58	0.89 (0.48-1.64)	0.88 (0.47-1.62)
Intracranial Bleeding	VKA	<5**	904.46	1.00 (ref.)	1.00 (ref.)
	NOAC	<5**	1,325.62	0.76 (0.11-5.47)	0.73 (0.10-5.28)
GI Bleeding	VKA	34	896.15	1.00 (ref.)	1.00 (ref.)
	NOAC	43	1,302.43	0.96 (0.61-1.51)	0.99 (0.63-1.55)
Myocardial Infarction	VKA	12	929.92	1.00 (ref.)	1.00 (ref.)
	NOAC	14	1,323.15	0.90 (0.41-1.95)	0.98 (0.45-2.14)
Death	VKA	44	939.43	1.00 (ref.)	1.00 (ref.)
	NOAC	79	1,343.47	1.36 (0.94-1.98)	1.34 (0.92-1.94)

*Adjusted for hypertension, diabetes, and antiplatelet use, as time-dependent covariates.
**Cells with less than five events were suppressed owing to privacy restrictions, in accordance with CPRD policy.

Table 3.5 – Time-dependent analyses of the comparative effectiveness and safety of NOAC in a subgroup of patients with CKD

Outcome	Drug Exposure*	Events	Person-time in years	Crude HR (95% CI)	Adjusted** HR (95% CI)
Ischemic Stroke/SE	VKA	33	3,005.67	1.00 (ref.)	1.00 (ref.)
	NOAC	38	3,285.07	1.06 (0.66, 1.69)	1.07 (0.67, 1.71)
	Neither	35	1,791.84	2.15 (1.31, 3.52)	2.03 (1.23, 3.35)
Major Bleeding	VKA	47	2,940.65	1.00 (ref.)	1.00 (ref.)
	NOAC	58	3,294.41	1.09 (0.74, 1.61)	1.10 (0.75, 1.62)
	Neither	33	1,724.79	1.29 (0.82, 2.03)	1.28 (0.81, 2.02)
Intracranial Bleeding	VKA	10	2,992.39	1.00 (ref.)	1.00 (ref.)
	NOAC	7	3,333.11	0.63 (0.24, 1.65)	0.62 (0.24, 1.64)
	Neither	9	1,788.24	1.46 (0.59, 3.63)	1.53 (0.61, 3.83)
GI Bleeding	VKA	80	2,928.80	1.00 (ref.)	1.00 (ref.)
	NOAC	98	3,266.84	1.10 (0.82, 1.49)	1.11 (0.83, 1.49)
	Neither	45	1,777.39	1.05 (0.72, 1.52)	1.00 (0.69, 1.45)
Myocardial Infarction	VKA	25	3,029.20	1.00 (ref.)	1.00 (ref.)
	NOAC	23	3,328.41	0.82 (0.47, 1.45)	0.86 (0.49, 1.52)
	Neither	13	1,749.45	1.09 (0.55, 2.18)	1.03 (0.51, 2.05)
Death	VKA	131	3,100.51	1.00 (ref.)	1.00 (ref.)
	NOAC	180	3,387.33	1.26 (1.00, 1.57)	1.24 (0.99, 1.55)
	Neither	315	1,834.89	4.39 (3.56, 5.41)	4.48 (3.63, 5.53)

*Regression models also included simultaneous exposure to both VKA and NOAC.
**Adjusted for antiplatelet use, hypertension, and diabetes as time-dependent covariates.

3.5 DISCUSSION

In this study, we found that NOAC were as effective as VKA in reducing the risk of ischemic stroke/SE in primary care patients with NVAF. While the rates of adverse major bleeding were also similar overall, compared to VKA, NOAC were associated with a non-significantly lower risk of intracranial bleeding, as well as a higher risk of GI bleeding. We observed no difference between OAC in the risk of MI and all-cause mortality. Overall, the effectiveness and safety of NOAC remained comparable to VKA in patients with CKD, as well as in subgroups defined by patient age, sex, and HAS-BLED and CHA_2DS_2-VASc scores.

Our results are in line with RCTs, in which the rates of ischemic stroke, major bleeding, and MI associated with NOAC were overall comparable to warfarin [96]. Several observational studies also showed that individual NOAC were similar, if not better than warfarin in the prevention of thromboembolic events in patients with AF [48, 53, 97, 98]. Moreover, rates of major bleeding were comparable to warfarin for dabigatran and rivaroxaban in other studies of routine clinical practice [52, 53, 104]. In clinical trials, all NOAC reduced the risk of intracranial bleeding compared to warfarin [34-37], as shown in our results and other observational studies [52, 98]. Conversely, the association between NOAC and GI bleeding varied between individual NOAC in RCTs [34-37]. The increased risk that we observed is consistent with the results of the ROCKET AF trial on rivaroxaban [35], which constituted the majority of NOAC prescriptions in our cohort. Several observational studies have also shown an increased risk of GI bleeds associated with dabigatran and rivaroxaban [47, 48, 97]. Indeed, it has been suggested that the low bioavailability of dabigatran and the high dosing of rivaroxaban may increase GI bleeding due to a higher concentration of active metabolites in the intestinal tract, in which VKA are not active [105].

In contrast, apixaban has consistently been associated with a lower risk of most forms of bleeding in the few studies available to date [36, 98]. Therefore, the heightened risk of GI bleeds that we observed might have been primarily attributable to rivaroxaban and dabigatran.

Contrary to most studies, some have noted no increased risk of GI bleeding associated with rivaroxaban and/or dabigatran, as compared to warfarin [49, 56, 57]. These conflicting conclusions may be partially explained by different definitions of bleeding events, which can vary substantially when considering their degree of severity. The International Society on Thrombosis and Haemostasis has developed a standard definition for major bleeds [106], however, this was intended for clinical studies, and some healthcare databases, including the CPRD, may not have adequate patient data to identify the stipulated criteria. Thus, in observational studies such as this, the classification of events as major bleeds may be influenced by investigator-based definitions. The inconsistent results may also be partly explained by limitations in study design, such as the inclusion of prevalent users, the use of intention-to-treat analyses only, and/or the potential for immortal time bias. Finally, different study populations resulting from different exclusion criteria may have also contributed to these conflicting findings.

There is limited evidence regarding NOAC effectiveness and safety in NVAF patients with CKD. In accordance with our results, subgroup analyses of RCTs have suggested that NOAC are as effective as VKA in reducing the risk of stroke, and further do not increase the risk of bleeds within this population [34-36]. These conclusions are generally consistent with studies of routine clinical practice, however, most of these evaluated the comparative effectiveness and safety of dabigatran only [97, 107, 108]. One nested case-control study of

elderly patients with CKD found that neither dabigatran nor rivaroxaban increased the risk of major hemorrhage compared to warfarin [109]. Similarly, a recent cohort study found no difference in the rate of major bleeds in patients with impaired renal function, but also a significant decrease in the risk of ischemic stroke associated with rivaroxaban compared to warfarin [110]. Our results contribute evidence towards the effectiveness and safety of rivaroxaban and apixaban in NVAF patients with CKD, which have been less extensively in this population, compared to dabigatran. However, given the limited evidence, future large-scale observational studies would help to further assess the safety of the various NOAC within this patient subgroup, as well as in patients with different stages of CKD.

Use of the CPRD as a data source provided several advantages for our study. Firstly, we were able to evaluate the comparative effectiveness and safety of NOAC in a well-defined and representative cohort of NVAF patients in the UK. Secondly, we classified treatment exposure using comprehensive CPRD prescription data, which is automatically transcribed into patients' electronic records by the clinician, at the time of prescribing. Although we were not able to assess patients' compliance to their prescribed treatment, we obtained consistent results when evaluating the potential for exposure misclassification using different exposure definitions, as well as in various sensitivity analyses. Several limitations also have to be considered in our study. Firstly, observational studies are susceptible to residual confounding, however, in matching on hd-PS, we were able to minimize imbalances in the distribution of covariates between exposure groups. Also, hd-PS were calculated using the entirety of available CPRD data, and may have therefore incorporated proxies for unmeasured confounders. Secondly, owing to the small number of observed outcome events, we obtained wide confidence intervals around many of our point

estimates. Although these may preclude definitive conclusions, the consistency of our results and their concordance with previous studies still allow for an informative interpretation of our analyses. Finally, our cohort size did not allow for an analysis of individual NOAC.

To conclude, our results suggest that NOAC are overall effective and safe alternatives to VKA for the prevention of ischemic stroke/SE in NVAF. Importantly, the effectiveness of these two medications remained comparable in NVAF patients with CKD, without increasing the risk of adverse events. However, the effectiveness and safety of these medications may vary from one NOAC to the next, and therefore, large-scale observational studies should be conducted to evaluate each NOAC compared to VKA, separately. This would further inform clinicians as to the most appropriate treatment options for their individual patients.

3.6 SUPPLEMENTARY INFORMATION

Supp. Table 3.1 – As-treated sensitivity analyses of the comparative effectiveness and safety of NOAC, accounting for informative censoring

Outcome	Drug Exposure	Events	Person-time in years	Crude HR (95% CI)	Adjusted* HR (95% CI)
Ischemic Stroke/SE	VKA	48	2,815.13	1.00 (ref.)	1.00 (ref.)
	NOAC	50	3,773.79	0.94 (0.63-1.40)	0.95 (0.64-1.42)
Major Bleeding	VKA	43	2,869.60	1.00 (ref.)	1.00 (ref.)
	NOAC	47	3,790.54	0.89 (0.58-1.34)	0.92 (0.61-1.40)
Intracranial Bleeding	VKA	10	2,808.32	1.00 (ref.)	1.00 (ref.)
	NOAC	7	3,753.26	0.60 (0.23-1.59)	0.65 (0.24-1.74)
GI Bleeding	VKA	67	2,819.65	1.00 (ref.)	1.00 (ref.)
	NOAC	117	3,741.32	1.44 (1.07-1.95)	1.47 (1.09-2.00)
Myocardial Infarction	VKA	30	2,867.63	1.00 (ref.)	1.00 (ref.)
	NOAC	32	3,796.18	0.91 (0.55-1.51)	0.95 (0.57-1.57)
Death	VKA	152	2,894.39	1.00 (ref.)	1.00 (ref.)
	NOAC	195	3,835.57	1.03 (0.83-1.28)	1.01 (0.82-1.25)

*Adjusted for hypertension, diabetes, antiplatelet use, and chronic kidney disease, as time-dependent covariates.

Supp. Table 3.2 – As-treated sensitivity analysis of the comparative effectiveness and safety of NOAC in a subgroup of patients with CKD, accounting for informative censoring

Outcome	Drug Exposure	Events	Person-time in years	Crude HR (95% CI)	Adjusted* HR (95% CI)
Ischemic Stroke/SE	VKA	18	1,095.30	1.00 (ref.)	1.00 (ref.)
	NOAC	18	1,455.21	0.87 (0.45-1.69)	0.90 (0.47-1.75)
Major Bleeding	VKA	22	1,082.23	1.00 (ref.)	1.00 (ref.)
	NOAC	24	1,472.19	0.88 (0.49-1.57)	0.87 (0.48-1.56)
Intracranial Bleeding	VKA	<5**	1,088.42	1.00 (ref.)	1.00 (ref.)
	NOAC	<5**	1,477.20	0.88 (0.12-6.33)	0.84 (0.12-6.07)
GI Bleeding	VKA	44	1,079.08	1.00 (ref.)	1.00 (ref.)
	NOAC	45	1,454.48	0.86 (0.56-1.30)	0.88 (0.58-1.34)
Myocardial Infarction	VKA	15	1,112.88	1.00 (ref.)	1.00 (ref.)
	NOAC	15	1,474.08	0.84 (0.41-1.72)	0.92 (0.44-1.90)
Death	VKA	70	1,127.60	1.00 (ref.)	1.00 (ref.)
	NOAC	98	1,498.09	1.17 (0.89-1.59)	1.14 (0.83-1.55)

*Adjusted for antiplatelet use, hypertension, and diabetes as time-dependent covariates.
**Cells with less than five events were suppressed owing to privacy restrictions, in accordance with CPRD policy.

CHAPTER 4: INTERPRETATION

4.1 SUMMARY OF OBJECTIVES AND RESULTS

As presented in Chapter 1, the results of randomized controlled trials paved the way for the approval and licensing of novel oral anticoagulants (NOAC) in 2008. However, clinical trials may not accurately represent the patients or the level of care that would be seen in routine clinical practice, and it is important for trial results to be complemented by observational analyses. Therefore, the objective of this thesis was to explore the use, effectiveness, and safety of NOAC in a primary care setting, using data from the UK's Clinical Practice Research Datalink.

In Chapter 2, we described a substantial and rapid increase in the uptake of oral anticoagulants between 2009 and 2015, which was driven by an increasing number of first-time NOAC prescriptions among patients with atrial fibrillation (AF). The rate of new users of NOAC surpassed VKA in 2014, with rivaroxaban prescribed most frequently. Overall, compared to VKA, new users of NOAC tended to be slightly older and healthier, with a lower likelihood of chronic cardiovascular conditions. This was especially the case in the early years after NOAC were introduced. To our knowledge, these patterns in the prescription of NOAC had not previously been studied in the UK. Also noteworthy is our description of the temporal changes in the baseline characteristics of new users of NOAC, which are not commonly presented in similar trends studies.

In Chapter 3, we determined that within a cohort of new oral anticoagulant users with non-valvular AF, NOAC were comparable to VKA in the prevention of ischemic stroke and systemic embolism, without being associated with an overall increased risk of serious

adverse events. New users of NOAC were found to have a lower risk of intracranial bleeding, and a higher risk of gastrointestinal bleeding. Importantly, these results were unchanged across several subgroups of vulnerable patients, including those with chronic kidney disease. Overall, the results of our analyses were also concordant with the conclusions drawn from previous clinical trials.

4.2 STRENGTHS AND LIMITATIONS

As detailed in Chapters 2 and 3, the analyses presented in this thesis were conducted using the Clinical Practice Research Datalink (CPRD). As clinician-issued prescriptions are automatically transcribed into the electronic database, the CPRD contains comprehensive patient prescription data and was therefore an ideal data source for this thesis in pharmacoepidemiology. The CPRD also contains information on lifestyle habits such as smoking and alcohol consumption patterns, which are generally not found in other health care databases such as administrative databases. Such lifestyles habits may be risk factors for ischemic stroke and/or bleeding events [111, 112], and using the CPRD, it was possible to account for these as potential confounders within our analyses. Finally, the validity and quality of CPRD data have been well established [71, 73, 113].

In spite of its strengths, use of the CPRD as a data source also presents certain limitations. Most notably for this thesis, exposure to NOAC and VKA was determined based on available prescription data. It was not possible to determine whether these prescriptions were filled at the pharmacy, and there was furthermore no way to verify whether patients were compliant to their treatment. We were also unable to account for prescriptions issued in secondary care. Consequently, the presented results may have been

affected by a misclassification in exposure. However, we do not expect this misclassification to differ substantially between NOAC and VKA users. Furthermore, in the sensitivity analyses presented in Chapter 3, we defined exposure to NOAC and to VKA using several methods and still attained consistent results, suggesting any misclassification in exposure to be slight.

The analyses of this thesis are based on primary care data from a UK population. Nevertheless, all of the oral anticoagulants that were evaluated in these studies are widely available, and the indications for these medications do not vary substantially from country to country. Furthermore, we do not expect the biological mechanism of action of NOAC and of VKA to differ significantly between primarily Caucasian populations. Therefore, the conclusions drawn from the results of these analyses remain generalizable to AF patients in Canada, and elsewhere in Europe and North America.

4.3 IMPLICATIONS AND FUTURE DIRECTIONS

The introduction of NOAC represents a significant step forward for stroke prevention in AF. Perhaps owing to the limited number of treatment options, AF was previously reported to be undertreated [32], but with the availability of NOAC, patients would have had access to new medications which were claimed to be altogether effective and safe. Indeed, based on our results, the uptake of NOAC increased dramatically shortly after their licensing for AF, and NOAC further appear to have driven the increasing rates of oral anticoagulation overall.

In accordance with trial data, we found that overall, NOAC were as effective as VKA in reducing the risk of ischemic stroke and systemic embolism. NOAC were also associated

with a decreased risk of intracranial bleeding, however, owing to the small number of events, it is difficult to ascribe the observed trends to this advantage alone. Furthermore, the presented prescription patterns are unlikely entirely attributable to the safety of NOAC, when considering that these medications simultaneously increase the risk of gastrointestinal bleeding. Thus, our results suggest that the growing preference for NOAC is not fully explained by their effectiveness and safety, and we suspect that there are likely other aspects of these medications that may have influenced their prescription trends.

Physician prescribing practices often reflect the interplay of multiple factors in addition to a medication's effectiveness and safety [84]. One of the key and novel aspects of NOAC is that treated patients do not require routine monitoring of levels of anticoagulation, as in the case of VKA [114]. Although the available evidence is limited, compared to VKA, these new medications have been reported to interact with fewer medications and foods [115]. NOAC therefore present notable practical benefits over VKA. On one hand, the ease of use of NOAC would have been significantly advantageous for AF patients who were long unable to maintain appropriate levels of anticoagulation while on VKA. On the other hand, new users of oral anticoagulants may have been preferentially prescribed NOAC as more practical alternatives to VKA, without having to compromise on effectiveness and safety. Indeed, the results of Chapter 2 suggested that NOAC were preferentially prescribed to older patients who may have been averse to the cumbersome management of VKA-therapy. Thus, we suspect that the rapid uptake of NOAC that we observed in our study may not have been driven by any clinical superiority, but rather by their practical benefits.

Importantly, irrespective of the underlying reasons for their rapid uptake, it is evident that NOAC are drastically changing the clinical outlook of patients with AF. A

formal and updated assessment of the rates of AF treatment should be conducted to quantitatively establish the impact of the introduction of NOAC. Further studies evaluating patients' adherence to NOAC compared to VKA would also be informative, as these would help to determine whether the practical aspects of NOAC have contributed to improving treatment adherence. An analysis of the rates and reasons for NOAC treatment discontinuation would also highlight some of the limitations of these new medications. Finally, assessments of individual NOAC in routine clinical practice would inform clinicians as to the most appropriate and specific option for oral anticoagulation in each of their individual patients. Taken together with the results of this thesis, these analyses will provide clinicians and patients with a comprehensive and in-depth evaluation of the use of NOAC in a primary care setting.

CONCLUDING REMARKS

This thesis explored the temporal patterns in the prescription of novel oral anticoagulants (NOAC) in the UK, and also examined the suitability of these medications against vitamin-K antagonists (VKA) in the treatment of atrial fibrillation (AF). Based on the results of our analyses, we determined that:

1. NOAC have been rapidly adopted in the UK primary care since their recent introduction; and
2. The effectiveness and safety of NOAC is comparable to that of VKA in AF patients.

It is our hope that the presented results will be informative for both clinicians and patients who may be weighing the available options for oral anticoagulation. While further studies are warranted, we suspect that the introduction of NOAC has and will continue to improve the rate of oral anticoagulation in AF, and this is encouraging for the prospects of achieving optimal AF treatment. Ultimately, we expect that such changes will have a positive impact on the management and prognosis of AF patients, and will thereby contribute to reducing the global burden of AF and stroke.

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