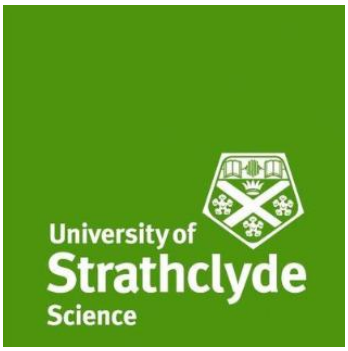

Oral Anticoagulant Prescribing in Scotland, 2010–2020: A Population-Based Multi-Study Analysis

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Glasgow, UK

February 2026

Declaration

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Acknowledgements

“In the name of Allah, the most Gracious, the most Merciful”

This research would not have been possible without the support of many individuals whom I wish to acknowledge with sincere gratitude. I am deeply grateful to my supervisors, Dr. Tanja Mueller and Dr. Amanj Kurdi, for their invaluable guidance and continued support throughout this work. I sincerely thank them for generously sharing their knowledge and expertise, and for guiding me patiently through every stage of this research. I will always be grateful for the time, effort, and the many valuable skills I gained under their supervision during this journey.

I would also like to thank all my colleagues and friends for making this journey enjoyable and for the many skills I gained through our meetings and learning sessions. I am grateful for our constructive discussions, and mutual support.

My deepest and most heartfelt thanks go to my family. I am profoundly grateful to my beloved mother, to whom I am forever indebted. Words cannot fully express my appreciation for everything she has done for me. Her endless care, sacrifices, and unwavering support, including taking care of my children, made it possible for me to complete this work. I will remain grateful to her for the rest of my life.

I am equally grateful to my wonderful father, my constant support and strength. Without his encouragement, guidance, and belief in me, I would not have been able to continue or complete this work. I owe this thesis to my mother and father, who always supported my decisions, stood by me during the most difficult times, and guided me with their advice in all aspects of my life.

I would also like to sincerely thank my sister Hiba and my brother Ahmad for taking care of my children during the time I was completing my studies, and for their constant and invaluable support throughout the most challenging moments.

My deepest thanks also go to my beloved children, Eleen and Omar, for their patience, love, and unwavering support. Their love and kindness gave me motivation every day. Finally, I extend my sincere gratitude to the rest of my family for their love, and encouragement.

Publications and Poster Presentation

- **Abunimeh H**, NoorSaeed S, Alkhlaifat R, Kurdi A, Mueller T. A scoping review of factors associated with the prescribing choice of direct oral anticoagulant drugs. Expert Review of Cardiovascular Therapy. 2025 Aug 3;23(8):427-45. https://doi.org/10.1080/14779072.2025.2536043
- **Abunimeh H**, Mueller T, Kurdi A, Noorsaeed SM, Alkhlaifat RG. A scoping review of factors associated with the prescribing of direct oral anticoagulant drugs (DOACs). Pharmacoepidemiology and Drug Safety. 2024 Nov 19;33(S2):516. Poster presented at International Conference on Pharmacoepidemiology (ICPE), Germany, 2024. https://doi.org/10.1002/pds.5891
- **Abunimeh H**, Kurdi A, Mueller T. Impact of the COVID-19 pandemic on the prescribing patterns of oral anticoagulant use in the Scottish primary care setting: population-based time series analysis with segmented regression. Presented at the European Drug Utilisation Research Group (EuroDURG) Conference, Uppsala, Sweden, 2025 (short oral communication/poster).
- **Abunimeh H,** Kurdi A, Mueller T. Prescribing trends of Direct Oral Anticoagulant Drugs (DOACs) across Scotland from 2011 to 2020: a population-based, retrospective study. Presented at the European Drug Utilisation Research Group (EuroDURG) Conference, Uppsala, Sweden, 2025 (short oral communication/poster).
- Alkhlaifat, R., Madanat, F., Abunimeh, H., Weir, N. M., & Mueller, T. (2025). The real-world use of medicines for the management of haematological malignancies in paediatric populations: a scoping review. Expert Review of Anticancer Therapy, 2025;1–12. https://doi.org/10.1080/14737140.2025.2610260

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Glossary

AF	Atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
BNF	British National Formulary
CAD	Coronary artery disease
CHF	Congestive heart failure
CHD	Coronary heart disease
CHI	Community Health Index
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DM	Diabetes mellitus
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESRD	End-stage renal disease
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
HF	Heart failure
HR	Hazard ratio
HTN	Hypertension
ICD-10	International Classification of Diseases, Tenth Revision
ICH	Intracranial haemorrhage
IHD	Ischemic heart disease
INR	International normalized ratio
IQR	Inter-quartile range
ITS	Interrupted time series
IVC	Inferior vena cava
KDIGO	Kidney Disease: Improving Global Outcomes
LMWH	Low molecular weight heparins
MHRA	Medicines and Healthcare products Regulatory Agency

MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	National Records for Scotland
NSAID	Non-steroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PIS	Prescribing Information System
RCTs	Randomized controlled trials
SCI	Scottish Care Information
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMD	Standardized mean difference
SMR	Scottish Morbidity Record
SSCA	Scottish Stroke Care Audit
SVT	Supraventricular tachycardia
TIA	Transient ischemic attack
TTR	Time in therapeutic range
UK	United Kingdom
VAF	Valvular atrial fibrillation
VKAs	Vitamin K antagonists
VTE	Venous thromboembolism

Abstract

Introduction: Direct oral anticoagulants (DOACs) have largely replaced vitamin K antagonists (VKAs) such as warfarin for the prevention and treatment of thromboembolic disorders. Despite guideline recommendations for DOACs as first-line therapy, uncertainty remains regarding optimal agent selection in routine practice, particularly among patients with complex comorbidities, renal impairment, or varying risk profiles. Real-world prescribing may also be influenced by non-clinical factors and external pressures such as the COVID-19 pandemic.

Methods: This thesis comprised complementary studies using linked, population-based healthcare data from Scotland. A scoping review (2010–2023) identified factors influencing anticoagulant prescribing choice. Retrospective cohort analyses examined trends in oral anticoagulant (OAC) prescribing between 2010 and 2020, stratified by age, sex, and geographic region. The impact of the COVID-19 pandemic on OAC initiation, prevalence, and switching from VKAs to DOACs was assessed using time-series and segmented regression analyses (2018–2021). Factors associated with switching were evaluated using Cox regression models, and clinical outcomes following switching were analysed using time-to-event and survival methods. Additional analyses explored the role of renal function in anticoagulant selection among incident OAC users.

Results: The scoping review identified anticoagulant choice as multifactorial, influenced by demographic factors such as age and sex, and clinical factors including renal impairment, prior stroke, heart failure, and thromboembolic risk. OAC initiation increased 72% between 2011 and 2019, followed by a modest decline in 2020. DOACs progressively replaced VKAs, accounting for over 90% of new OAC initiations by 2020. Early variation in prescribing by age group and geographic region diminished over time. Apixaban and edoxaban became most commonly prescribed. COVID-19 pandemic was associated with a temporary reduction in incident OAC prescribing and a marked increase in switching from warfarin to DOACs. Switching was associated with lower rates of intracranial haemorrhage, but higher rates of ischaemic stroke, myocardial infarction, and mortality compared with continued warfarin use. DOAC prescribing increased across all levels of renal function, with apixaban most commonly used among patients with impaired kidney function.

Conclusion: OAC prescribing in Scotland underwent substantial transformation between 2010 and 2020, driven by evolving evidence, guidelines, and external pressures. COVID-19 accelerated this transition, revealing how external factors can rapidly reshape prescribing practices.

Thesis structure overview

This thesis comprises multiple complementary studies investigating oral anticoagulant (OAC) prescribing in Scotland. Chapter 1 provides a general introduction, outlining the background to anticoagulation therapy. It describes the coagulation pathway and provides an overview of vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). The chapter also discusses atrial fibrillation (AF), including its epidemiology, diagnosis, classification, and management strategies, with emphasis on stroke prevention. Venous thromboembolism (VTE) and pulmonary embolism (PE) are also introduced, alongside their management. Current guideline recommendations from the European Society of Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE) for anticoagulant prescribing are summarised, with particular focus on risk assessment tools for stroke and bleeding. The chapter concludes with the rationale for the thesis and its aims and objectives.

Chapter 2 presents a scoping review (2010–2023) exploring factors influencing prescribing choices between DOACs and VKAs, as well as among individual DOACs. The findings were categorised into patient-related, clinical, sociodemographic, and prescriber-related factors.

Chapter 3 describes the data sources and the processes of data cleaning and preparation used for the subsequent population-based analyses (Chapters 4–8). These chapters report a series of analyses using linked healthcare data in Scotland. Prescribing trends for OACs between 2010 and 2020 were analysed, focusing on prevalence and incidence use. Incident prescribing was further stratified by age, sex, and geographic location (urban–rural and health board) to examine how these factors shaped prescribing patterns over time (Chapter 4). The impact of the COVID-19 pandemic on OAC prescribing was assessed between January 2018 and May 2021 using time-series and segmented regression analyses in terms of incident and prevalent OAC use and switching from VKA to DOAC (Chapter 5). Subsequently, factors associated with switching from VKAs to DOACs were examined in the same period, applying Cox regression models to compare pre- and post-COVID-19 periods (Chapter 6). Clinical outcomes following switching were assessed between January 2018 and May 2021, with effectiveness and safety evaluated using time-to-event and survival analyses (Chapter 7). In addition, renal function was examined as a factor affecting prescribing choice among incident OAC

users between 2011 and 2020, with analyses stratified by estimated glomerular filtration rate (eGFR) categories in a subset of patients with available laboratory data (Chapter 8).

Chapter 9 summarises and discusses the findings from the scoping review and the empirical studies included in this thesis and considers their implications for clinical decision-making and healthcare policy and provides future research recommendations.

Collectively, these studies provide real-world evidence on OAC utilisation, highlighting temporal shifts in prescribing practice, patient-level factors, and broader implications for practice and policy

1 Chapter 1: Background

Oral anticoagulants (OACs) are central to the prevention and treatment of thromboembolic disorders, particularly atrial fibrillation (AF) and venous thromboembolism (VTE), including pulmonary embolism (PE). This chapter provides an overview of thromboembolic disease, OAC therapy, and current guideline recommendations, and highlights the real-world complexities and evidence gaps that motivate the research presented in this thesis.

1.1 Thromboembolic events

Heart diseases include a wide range of conditions that affect the heart and circulatory system. Among these, cardiovascular disease (CVD) is one of the leading causes of death and disability in the United Kingdom (UK) (1). CVD is an umbrella term for disorders involving the heart and blood vessels, and it includes several major subtypes such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (2).

CHD develops when the supply of oxygen-rich blood to the heart muscle is reduced or blocked, typically due to atherosclerosis, the accumulation of fatty deposits within the arterial walls (2). This can manifest clinically as angina or myocardial infarction (MI), where a blockage in the coronary arteries disrupts blood flow to the heart (2). Similarly, cerebrovascular diseases such as stroke and transient ischemic attack (TIA) occur when blood supply to part of the brain is stopped or reduced, potentially leading to neurological damage or death in severe cases (2). Peripheral artery disease, another form of CVD, arises when narrowed arteries restrict blood flow to the limbs, most commonly the legs (2).

Another major group of cardiac conditions is arrhythmias, which result from abnormalities in the heart's electrical conduction system. Under normal circumstances, the heart's electrical impulses maintain a regular and coordinated cardiac rhythm; however, disturbances in these signals can cause the heart to beat too quickly (tachycardia), too slowly (bradycardia), or irregularly (1). Principal types of arrhythmias include AF, ventricular fibrillation, supraventricular tachycardia (SVT), heart block, sinus tachycardia, and bradycardia (3). The European Society of Cardiology (ESC) defines AF as a "supraventricular tachyarrhythmia with uncoordinated atrial electrical activation, resulting in ineffective atrial contraction."

Closely related to these cardiovascular disorders is VTE, a significant thromboembolic condition comprising deep vein thrombosis (DVT) and PE. DVT occurs when a blood clot forms within a deep vein, most commonly in the legs, causing pain, swelling, and redness. If a clot fragment dislodges and travels to the lungs, it may obstruct a pulmonary artery, resulting in PE. VTE represents a major global cause of morbidity and mortality and shares several risk factors with other cardiovascular and thromboembolic diseases, including prolonged immobility, recent surgery or trauma, malignancy, and inherited thrombophilia (4).

1.1.1. Atrial fibrillation

1.1.1.1. Epidemiology, diagnosis, and classification of Atrial fibrillation

AF is the most prevalent cardiac arrhythmia in the world, which affects more than 2% of adults and is anticipated to rise internationally (5,6). In Europe, AF affects approximately 1–2% of the general population, and is predicted to double by 2050 (7). In the UK, contemporary data (2024/2025) indicate that AF affects approximately 2.2% of the adult population (8), increasing markedly with age and exceeding 6% among individuals aged 65 years and older in Scotland (9). Due to aging populations, improved survival of patients with CHD and heart failure (HF), enhanced screening and diagnosis, and better treatment options, both prevalence and incidence are expected to increase considerably over the coming decades (10). However, prevalence rates are most likely underestimated (11), as AF may remain undetected for prolonged periods, and symptoms are usually non-specific.

AF patients can be symptomatic or asymptomatic. Symptomatic patients usually present with breathlessness, palpitations, syncope, chest discomfort, tachycardia, fatigue, weakness, dizziness, light-headedness, reduced exercise capacity, or mild dyspnoea (6). Asymptomatic AF is of particular concern, as it has been independently associated with an increased risk of stroke and mortality compared with symptomatic AF (18), and many cases of AF are diagnosed only after a patient has experienced a stroke (12).

Given the rising incidence of AF and the high prevalence of asymptomatic disease, screening using AF detection tools is crucial (12). Available screening approaches include pulse palpation, automated blood pressure monitors, single-lead ECG devices, smartphone applications, and smartwatches (5).

While all these screening tools demonstrate good sensitivity and specificity, the 12-lead ECG remains the gold standard for AF diagnosis. AF screening offers

numerous significant advantages, including reduction in disease morbidity, mortality, and hospitalisation rates, prevention and reversal of electrical and atrial remodelling, and facilitation of OAC therapy to reduce stroke risk in at-risk individuals. Screening can also identify cases of known but sub-optimally managed AF (11). Current ESC guidelines recommend opportunistic screening for AF using pulse palpation or ECG rhythm assessment in individuals aged 65 years and older (5).

Patients with AF experience a high comorbidity burden and impaired quality of life (QoL), which will increase demands on health systems (13,14). AF is associated with a twofold increased mortality (15) due to elevated risk of stroke and HF (16). Patients with AF are five times more likely to experience stroke (16), and without anticoagulation, the annual thromboembolic risk may exceed 20% (17). Moreover, AF-associated cardioembolic strokes are more likely to be fatal, recurrent, and cause severe disability compared to strokes from other causes (18).

This elevated thromboembolic risk arises from the underlying pathophysiology of AF and its impact on cardiac blood flow. In AF, the atria (the upper chambers of the heart) do not contract effectively, because the atrioventricular (AV) conduction system is overrun by multiple electrical stimuli, causing uncoordinated impulse transmission. The absence of effective atrial contractions predisposes to thrombus formation, as blood is not pumped efficiently from the atria and may pool within these chambers. This stagnant blood increases the likelihood that a clot will form there before moving to the ventricles (the lower chambers of the heart). Subsequently, the clot may be pumped to the lungs or travel to the brain, causing an embolic stroke (19).

According to guidelines, clinical diagnosis of AF requires a standard 12-lead electrocardiogram (ECG) recording or a single-lead ECG tracing of at least 30 seconds demonstrating heart rhythm with absence of distinct repeating P waves, irregular RR intervals, and irregular atrial activations (5). AF is classified according to episode duration and pattern into five categories: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent (**Table 1.1**) (5). Although patients with persistent AF can subsequently experience episodes of paroxysmal AF, the condition is generally considered progressive (5).

Table 1.1: Atrial fibrillation classification according to its duration and length (5)

AF pattern	Definition
First diagnosed	AF not previously diagnosed, irrespective of duration or the presence/severity of AF-related symptoms.
Paroxysmal (intermittent or self-terminating)	AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency.
Persistent	AF that is continuously sustained for more than 7 days, including episodes reverted by cardioversion (pharmacological or electrical) after ≥7 days.
Long-standing persistent	Continuous AF lasting >12 months' duration when a rhythm control strategy is adopted.
Permanent	AF where sinus rhythm cannot be restored and both patient and clinician agree to accept permanent AF, with no further attempts to restore or maintain sinus rhythm.

The progression of AF to persistent/permanent is associated with adverse cardiovascular events, hospitalizations, and death (20). The progression is influenced by several factors, including previous stroke and left atrial size (21). Atrial remodelling serves as an indicator of AF progression from paroxysmal to non-paroxysmal forms, or from subclinical to symptomatic presentations (21,22). This worsening of atrial cardiomyopathy has an important role in AF mechanism and thrombogenicity (21). Moreover, older age is associated with permanent AF (21).

1.1.1.2. Risk factors for Atrial fibrillation

Risk factors for AF have been investigated and identified from large randomized controlled trials (RCTs) and observational studies (23). The most important risk factor for AF is increasing age. Other established risk factors include comorbidities such as diabetes mellitus (DM), hypertension (HTN), HF, coronary artery disease (CAD), chronic kidney disease (CKD), obesity, and obstructive sleep apnoea (5). Additional modifiable risk factors include smoking, alcohol consumption, abnormal lipid profiles, physical inactivity, and intense physical activity. Early intervention and control of modifiable risk factors are essential to reduce AF symptoms and improve patient outcomes (24).

1.1.2. Venous thromboembolism (VTE)

1.1.2.1. Epidemiology, diagnosis, and classification

VTE encompasses DVT and PE (25). It represents a major cause of cardiovascular morbidity and mortality worldwide and constitutes the third most common acute cardiovascular syndrome after MI and stroke (26).

DVT refers to thrombus formation within the deep venous system, most commonly affecting the lower extremities, particularly the femoral and popliteal veins. Less frequently, DVT involves upper extremity or splanchnic veins. PE occurs when thrombotic material, usually originating from lower limb DVT, embolizes to the pulmonary arterial circulation, causing partial or complete obstruction of pulmonary blood flow.

DVT and PE are now recognized as manifestations of a single disease spectrum, rather than separate entities. More than 50% of patients with confirmed proximal lower extremity DVT develop PE (27,28). A substantial proportion of patients with DVT have asymptomatic PE, and conversely, many patients presenting with PE have occult DVT on imaging.

Understanding VTE as a unified condition has important implications for diagnosis, treatment, and secondary prevention (27). The annual incidence of VTE in the general population is approximately 1–2 per 1,000 person years in Europe and the USA, with lower rates in other regions (4,29). True prevalence is difficult to determine due to underdiagnosis, but VTE remains a major cause of vascular disease worldwide.

Age is a major determinant of VTE risk, with incidence rising exponentially with advancing age (29), increasing from <5 cases per 100,000 persons <15 years old to approximately 500 cases per 100,000 persons at age 80 years (30). This increase reflects the accumulation of comorbidities, reduced mobility, age-related changes in haemostasis, and higher prevalence of triggers including hospitalization and cancer (29).

VTE is characterized by significant recurrence risk. After a first episode, cumulative recurrence risk is approximately 10% at 1 year and 25–30% at 5 years, with higher rates in patients with unprovoked VTE or persistent risk factors (31).

Mortality remains substantial, particularly with PE. Untreated DVT carries approximately 3% 30-day mortality, which increases 10-fold (to ~30%) if PE

develops (32). Sudden death may be the first manifestation in some cases, highlighting the importance of early recognition and treatment. However, among patients surviving the initial 30-day critical period following PE, 10-year mortality is not increased compared to patients with DVT when anticoagulant therapy is initiated and maintained (33).

The pathogenesis of VTE is classically explained by **Virchow's triad**, which describes three major interacting factors that predispose to thrombosis (34):

1. **Venous stasis** – Reduced blood flow from immobilization, HF, or prolonged travel promotes clot formation by allowing accumulation of activated coagulation factors.
2. **Endothelial injury** – Venous endothelium damage from surgery, trauma, or central venous catheterization exposes procoagulant surfaces.
3. **Hypercoagulability** – An imbalance favouring procoagulant over anticoagulant mechanisms, which may be inherited (e.g. factor V Leiden, prothrombin gene mutation, deficiencies of protein C/S or antithrombin) or acquired (e.g., malignancy, pregnancy, inflammation) thrombophilia.

VTE typically results from a combination of these factors rather than any single factor alone (32).

The clinical manifestations of DVT and PE can be variable, ranging from subtle symptoms to life-threatening events. DVT typically presents with unilateral limb swelling, pain, warmth, and erythema, although many cases are asymptomatic or have subtle findings. PE commonly manifests as acute dyspnoea, pleuritic chest pain, tachypnoea, tachycardia, and hypoxemia. In massive PE, patients can develop haemodynamic instability with hypotension, severe tachycardia, syncope, or obstructive shock and death (35). Importantly, silent or incidental PE is increasingly detected with widespread use of advanced imaging and carries a prognosis similar to symptomatic PE, warranting the same therapeutic approach (36).

Diagnosis of VTE relies on systematic assessment combining clinical probability, laboratory testing, and imaging. Clinical scoring systems such as the Wells score quantify pre-test probability and significantly improve diagnostic accuracy. The Wells DVT score assigns points for factors such as active cancer, recent immobilization, localized tenderness, and leg swelling, and subtracts points if an alternative

diagnosis is at least as likely as DVT. Similarly, the Wells PE score considers clinical signs of DVT, heart rate, immobilization or surgery, haemoptysis, history of VTE, cancer, and whether an alternative diagnosis is less likely than PE. Modern guidelines (e.g., NICE 2020) endorse using the two-level Wells score for both suspected DVT and PE to guide next steps (37).

D-dimer testing measures fibrin degradation products, which are elevated when there is active clot formation and breakdown. It is highly sensitive but nonspecific and is most useful for excluding VTE in patients with low or intermediate clinical probability (37). Definitive diagnosis requires imaging: venous duplex ultrasonography is the gold standard for DVT, while computed tomography pulmonary angiography is the modality of choice for PE (37).

1.1.2.2. Risk factors for venous thromboembolism

Risk factors for VTE are categorized as provoked or unprovoked, reflecting their implications for recurrence risk and anticoagulation duration (4).

- Provoked venous thromboembolism

Provoked VTE occurs in the presence of a transient or reversible risk factor typically within the preceding 3 months (4). Major provoked risk factors include surgery (particularly orthopaedic and major abdominal procedures), trauma, immobilization (from hospitalization or prolonged travel), pregnancy and the postpartum period, and oestrogen exposure (oral contraceptives or hormone replacement therapy).

- Unprovoked venous thromboembolism (including persistent or chronic risk factors)

Unprovoked VTE refers to events occurring in the absence of an identifiable transient risk factor. These cases are associated with a higher risk of recurrence and often prompt consideration of extended anticoagulation. This category also includes VTE events associated with persistent or chronic risk factors, which similarly carry an elevated risk of recurrence. Examples include active cancer (a well-established prothrombotic state), inherited thrombophilias (such as factor V Leiden or prothrombin gene mutation), and chronic inflammatory diseases (including inflammatory bowel disease).

Given the central role of thrombus formation in both AF related stroke and venous thromboembolism, anticoagulation represents the cornerstone of prevention and management for these conditions.

1.2 Anticoagulation

Over the past few decades, anticoagulant options have progressively increased, offering more agents for thromboembolic disease management and prevention. The term antithrombotic agent includes both antiplatelet agents (e.g., aspirin, clopidogrel) as well as anticoagulants and fibrinolytics (38).

Anticoagulants comprise a variety of agents that inhibit one or more steps in the coagulation pathway to prevent fibrin formation and clot development. In contrast, antiplatelet agents work on platelets; they prevent platelets from clumping together to form a thrombus or a clot. Antiplatelet monotherapy is ineffective for stroke prevention in AF (39), and dual antiplatelet therapy is associated with a bleeding risk similar to OAC therapy (40). Since the mechanism for developing embolic stroke in AF patients involves clot formation in the heart, and evidence demonstrates a hypercoagulable state in these patients, anticoagulants are more effective for preventing embolic stroke. Antiplatelet drugs are used when there is high risk of platelet activation because of plaque formation and atherosclerosis or in ischaemic stroke or other diseases. While platelet activation occurs in AF patients, studies have concluded that anticoagulants are more effective with at least similar bleeding risk (40). Hence, antiplatelet therapy is not recommended for stroke prevention in AF patients.

1.2.1. Coagulation pathway

The coagulation proteins (clotting factors) are essential elements of the clotting system that lead to a series of reactions resulting in the conversion of soluble fibrinogen to insoluble fibrin mesh, which forms a clot to stop bleeding following tissue damage (38) (**Figure 1.1**).

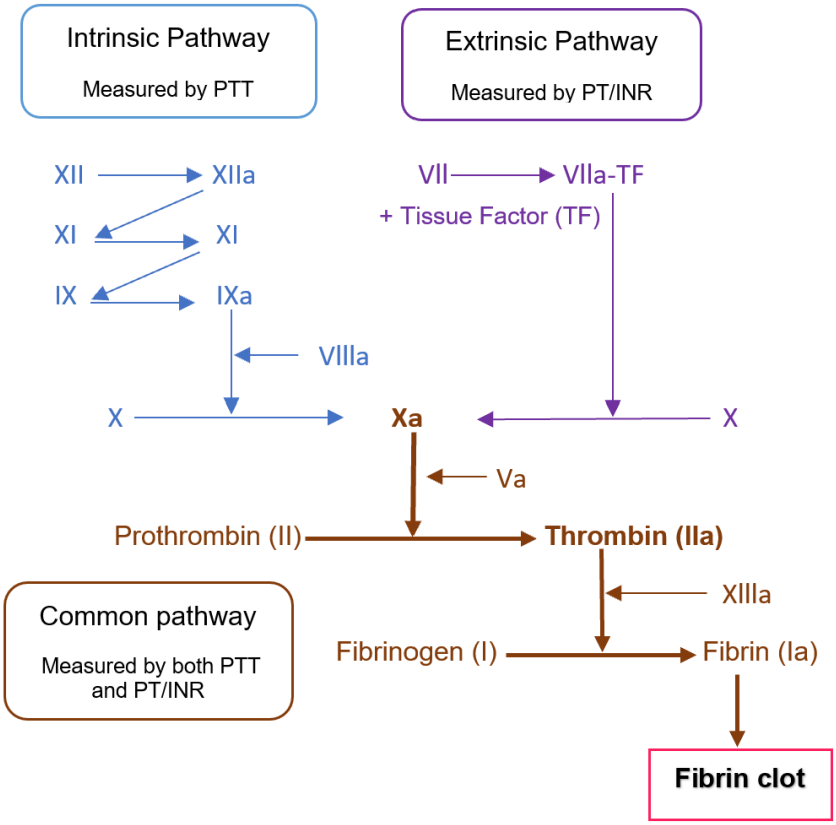

Figure 1.1: Simplified schematic of the coagulation cascade showing intrinsic, extrinsic, and common pathways leading to fibrin clot formation, adapted from (41).

Note: Thrombin represents the activated form of Factor II (Factor IIa), while its inactive precursor is Prothrombin (Factor II). Abbreviations: PTT = Partial Thromboplastin Time; PT/INR = Prothrombin Time/International Normalised Ratio.

Most clotting factors circulate in an inactive form as precursors of proteolytic enzymes known as zymogens (42). Coagulation factors are designated by Roman numerals, with the letter "a" added to indicate activation. Most blood coagulation factors are produced in the liver (42).

The coagulation cascade has been classified into intrinsic and extrinsic pathways, both of which lead to the activation of factor X (42) (**Figure 1.1**). The extrinsic pathway leads to activation of factor X to factor Xa, while the intrinsic pathway represents a parallel pathway for thrombin activation by factor XII, leading to the conversion of factor IX to factor IXa, which subsequently activates factor X to factor Xa. Both pathways are equally important in converting factor X to factor Xa.

In the common pathway, activated factor X (Xa) combines with factor V, tissue phospholipids, platelet phospholipids, and calcium to form the prothrombinase complex, which converts prothrombin to thrombin (42).

Thrombin (factor IIa) is the final enzyme of the clotting cascade that produces insoluble fibrin; it is formed by the cleavage of prothrombin by factor Xa (**Figure 1.1**). Thrombin plays a central role in coagulation: it cleaves fibrinogen to fibrin, activates factor XI to factor XIa (leading to further generation of factor IXa), activates other procoagulant factors including factors V, VIII, and XIII, and activates platelets (42).

1.2.2. Types of anticoagulants

Available anticoagulant agents include parenteral anticoagulants (unfractionated heparin, low molecular weight heparins, fondaparinux), VKAs, DOACs, and other drugs at different stages of development (43). Different agents exert their anticoagulant effect at different sites in the coagulation pathway (**Figure 1.2**).

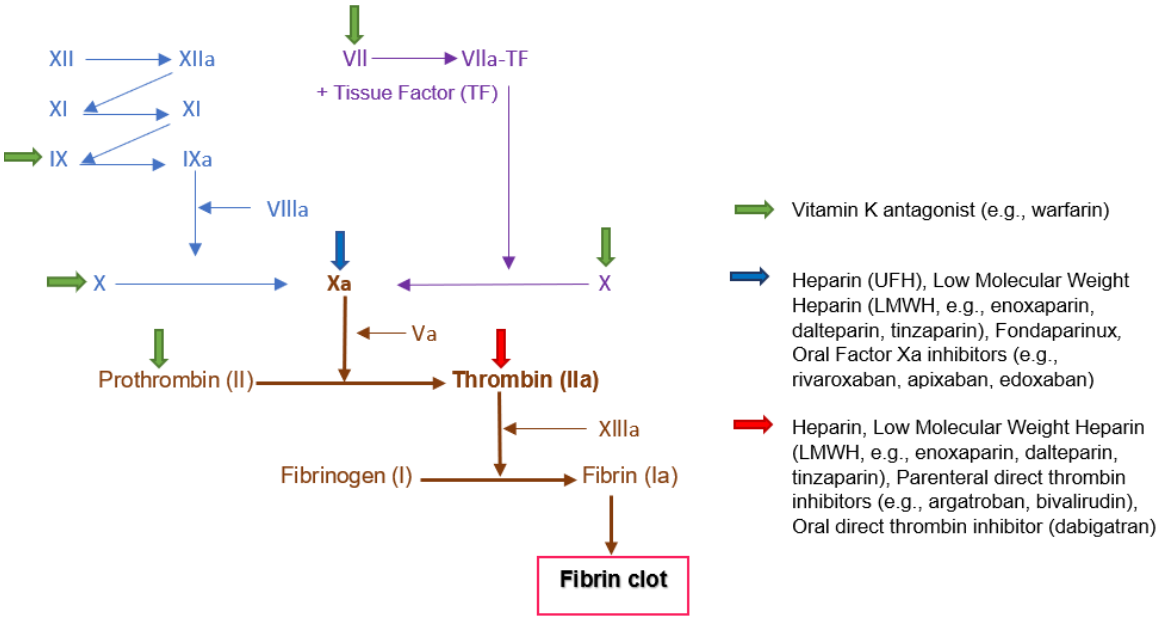

Figure 1.2: Site of action of the available anticoagulants in the coagulation pathway: Anticoagulant effects (44).

Note: Arrows indicate the primary targets of different classes of anticoagulants: vitamin K antagonists (green), heparins and factor Xa inhibitors (blue), and direct thrombin inhibitors (red). Heparin inhibits both factor Xa and thrombin (IIa), while low molecular weight heparin (LMWH) preferentially inhibits factor Xa and to a lesser extent thrombin. Vitamin K antagonists (e.g., warfarin) reduce synthesis of vitamin K–dependent factors (II, VII, IX, and X). Direct oral anticoagulants include factor Xa inhibitors (e.g., rivaroxaban, apixaban) and thrombin inhibitors (e.g., dabigatran).

1.2.2.1. Parenteral anticoagulants

Parenteral anticoagulants include unfractionated heparin and low molecular weight heparins (LMWH) such as enoxaparin, dalteparin, and tinzaparin. Both unfractionated and LMW heparins inhibit factor Xa and thrombin, thereby interrupting the blood coagulation cascade (45); however, LMW heparins have less effect on thrombin than unfractionated heparin. Fondaparinux is a synthetic factor Xa inhibitor that prevents thrombin formation and thrombus development (45). Parenteral direct thrombin inhibitors include bivalirudin, argatroban, and lepirudin (46).

1.2.2.2. Oral anticoagulants

Vitamin K antagonist

The most commonly used VKA is warfarin, a coumarin derivative that acts by inhibiting vitamin K dependent clotting factors (II, VII, IX, X) by preventing their synthesis in the liver, in addition to the inhibition of anticoagulant proteins C and S (38,47).

VKAs were the most used anticoagulants for many decades. However, despite their well-known effectiveness, VKAs have a number of drawbacks (48). The use of VKAs is limited by the narrow therapeutic window to achieve therapeutic anticoagulation without excess risk of bleeding. VKAs also have a long half-life, and many drug-drug interactions (49). When used appropriately with time in therapeutic range (TTR) >70%, VKAs are effective and relatively safe. However, the quality of VKA management, quantified using TTR based on the percentage of international normalized ratios (INRs) in range, correlates with haemorrhagic and thromboembolic rates (50). Consequently, patients taking warfarin must undergo routine reviews, education or counselling, and frequent INR monitoring and dose adjustments. Moreover, due to concerns about falls and bleeding risks, warfarin usage has traditionally been limited in the elderly (51).

In AF patients with certain conditions such as with rheumatic mitral valve disease, moderate-to-severe mitral stenosis, or mechanical prosthetic heart valves, VKAs are still the only treatments with established safety (48); DOACs are not approved in these indications (5).

Direct oral anticoagulants (DOACs)

DOACs are anticoagulants with a novel mode of action, with each direct inhibitor only blocking one enzyme to prevent fibrin clot generation (**Figure 1.2**).

- **Direct factor Xa inhibitors** prevent factor Xa from converting prothrombin to thrombin by binding directly to factor Xa, rather than enhancing antithrombin activity indirectly as heparin does (46). Three oral agents available include rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Lixiana, Savaysa) (46).
- **Direct thrombin inhibitors** prevent thrombin from converting fibrinogen to fibrin by binding directly to thrombin, rather than enhancing antithrombin activity as indirect thrombin inhibitors do (46). The only oral direct thrombin inhibitor available is dabigatran etexilate (Pradaxa) (46).

With the development of DOACs, an alternative to traditional VKAs for the prevention and treatment of thrombosis became available (47). In four pivotal RCTs they were shown to be non-inferior or superior to VKA in the prophylaxis or treatment of thromboembolic events (52–55). Particularly regarding safety, they were associated with less major bleeding, including intracranial bleeding, thus providing superior benefit for stroke prevention in patients with AF (52–55). A meta-analysis of these randomized trials – RE-LY (dabigatran), ARISTOTLE (apixaban), ROCKET AF (rivaroxaban), and ENGAGE AF-TIMI 48 (edoxaban) – demonstrated that DOACs were associated with a 19% significant reduction in stroke/systemic embolism risk, a 51% reduction in haemorrhagic stroke, a 52% significant reduction in intracranial haemorrhage (ICH), and similar ischaemic stroke risk reduction compared with VKAs (56). Moreover, DOACs were associated with a significant 10% reduction in all-cause mortality (56). These findings reinforce the general conclusion that DOACs are preferable to adjusted-dose VKAs for most patients where appropriate; their proven safety and efficacy make them an attractive option for short- or long-term anticoagulation.

Advantages of DOACs

DOACs offer several advantages over warfarin. They are more convenient to use due to simple dosing, do not require frequent INR monitoring, and show predictable pharmacokinetic profiles (47). They exert their pharmacological effect in a concentration-dependent manner, providing predictable therapeutic effects (49).

Moreover, unlike warfarin which has a very long onset of action (days), DOACs have a rapid onset of action (approximately 3 hours), and they have shorter half-lives (5-17 hour) (**Table 1.2**) compared to warfarin (20-60 hour) allowing for the possibility of uncomplicated switching or bridging (49). Another important additional advantage is that they have less drug and food interactions compared to warfarin.

Table 1.2: Pharmacokinetic properties and clinically relevant drug interactions of direct oral anticoagulants, adapted from (57)

Anticoagulant	Bioavailability	Metabolism and clearance	Half-life	Pharmacokinetic drug interactions
Dabigatran	~3–7%	Renal clearance ~80%; P-gp substrate	12–17 h	P-gp inhibitors increase plasma concentrations; P-gp inducers reduce exposure
Apixaban	~50%	Renal clearance ~27%; metabolised mainly via CYP3A4; P-gp substrate	~12 h	Strong CYP3A4 and P-gp inhibitors increase exposure; CYP3A4 and/or P-gp inducers reduce exposure
Edoxaban	~62%	Renal clearance ~50%; minimal CYP metabolism; P-gp substrate	10–14 h	P-gp inhibitors increase plasma concentrations; P-gp inducers reduce exposure
Rivaroxaban	Dose-dependent (10 mg: 80–100%; 20 mg: ~66%, increased with food)	Renal clearance ~36%; metabolised primarily via CYP3A4; P-gp substrate	5–9 h	Strong CYP3A4 and P-gp inhibitors increase exposure; CYP3A4 and/or P-gp inducers reduce exposure

Abbreviations: P-gp, P-glycoprotein; CYP, cytochrome P450; AF, atrial fibrillation; CrCl, creatinine clearance.

Clinical considerations in DOAC selection

Clinicians often develop familiarity with one DOAC and preferentially prescribe that agent when anticoagulation is indicated. However, due to variations between these medications (**Figure 1.3**), alternative agents may be more appropriate for individual

patients. Effective DOAC use requires understanding each drug's unique characteristics, risks, and advantages.

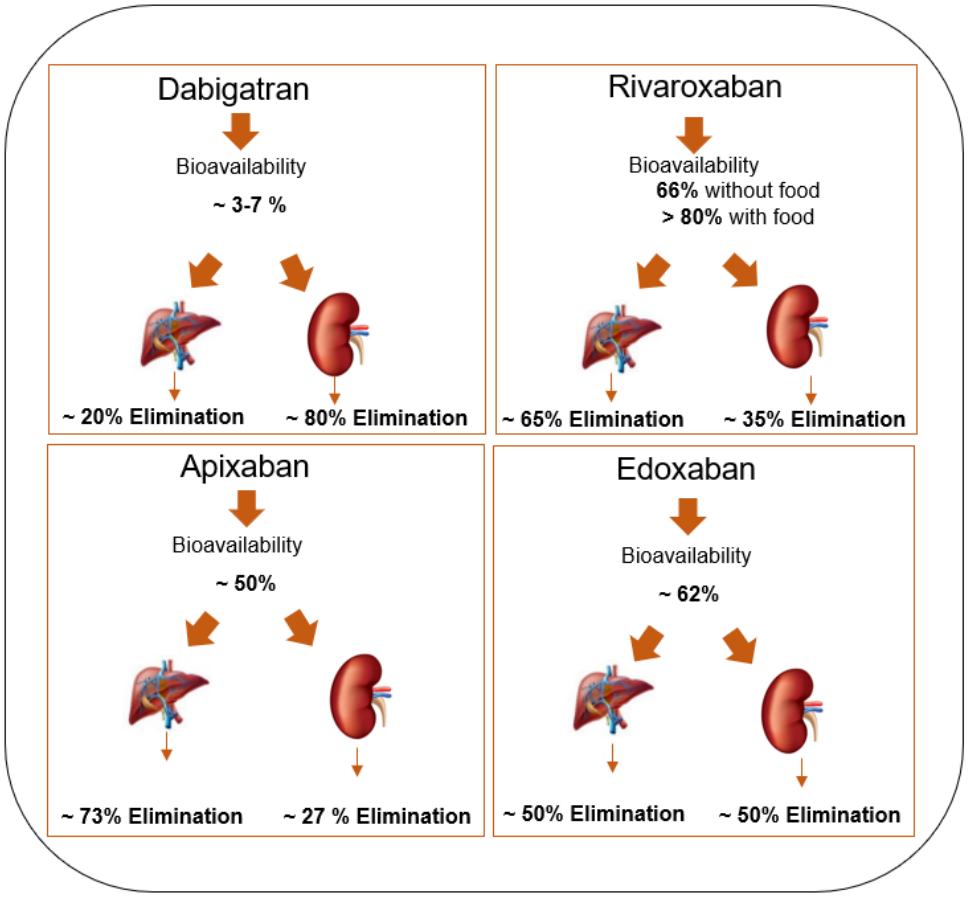

Figure 1.3: Pharmacokinetic characteristics of DOAC, adapted from (58)

1.3 Safety and effectiveness of DOACS in clinical practice

While real-world DOAC users may differ from clinical trial populations in terms of age and comorbidities, real-world evidence has confirmed the superior safety and effectiveness of DOACs compared to warfarin in patients with non-valvular atrial fibrillation (NVAF). A comprehensive systematic review and meta-analysis by Waranugraha et al. (2021) included 34 real-world studies involving 2,287,288 NVAF patients and demonstrated that DOACs are more effective than warfarin in reducing stroke risk (59). Moreover, DOACs effectively lowered the risk of all-cause mortality and significantly reduced both major bleeding risk and cerebral haemorrhage (59). These benefits extend to elderly patients aged ≥75 years, with systematic reviews and meta-analyses confirming consistent safety profiles in this high-risk population (60).

Gastrointestinal bleeding risk

One notable exception to the overall bleeding risk reduction is gastrointestinal bleeding (GIB). Waranugraha et al. found that DOAC administration failed to decrease GIB risk (59), which aligns with the meta-analysis of the four pivotal DOACs RCTs showing a 25% increase in GIB compared to warfarin (56). However, this increased GIB risk does not translate to an overall increase in major bleeding events.

Several studies have investigated this safety concern with varying conclusions. Miller et al. (2017) conducted a systematic review and meta-analysis of 43 RCTs comprising 166,289 patients and found no overall difference between DOACs and conventional anticoagulants in major GIB risk (61). However, their analysis suggested that dabigatran and rivaroxaban may be associated with increased odds of major GIB (61). A more recent systematic review and meta-analysis published in 2019 included 43 RCTs (183,752 patients) and 41 real-world studies (1,879,428 patients), confirming no significant difference in major GIB risk between DOACs and conventional treatment overall (62). Notably, rivaroxaban users specifically showed a 39% increase in risk for major GIB, while other DOACs did not demonstrate this association (62).

The cumulative evidence confirms that there is no notable difference in major GIB risk between DOACs and VKAs (63). Moreover, when GIB does occur in DOAC-treated patients, it appears to be less severe and requires less intensive management compared to warfarin-associated bleeding.

Comparative safety of direct oral anticoagulants

A meta-analysis of real-world studies by Deitelzweig et al. (2018) concluded that DOACs were associated with a lower or equivalent risk of major bleeding compared to warfarin, with apixaban demonstrating the lowest risk of major bleeding among all DOACs (64). Additionally, apixaban is associated with significantly lower hospitalization risk and all-cause healthcare costs and may represent the safest option for elderly patients (65).

Trends in adverse drug reaction reporting

After more than a decade of DOAC use, both prescribers and patients have become increasingly familiar with these agents and their associated adverse drug reactions

(ADRs). Afzal et al. (2021) identified a statistically significant reduction in the reporting of serious or fatal ADRs associated with OAC use in primary care in England between 2009 and 2019, likely reflecting the improved safety profiles of DOACs compared to warfarin (66). Specifically, the reporting of serious and fatal events associated with DOACs decreased by 6% per year (66). Among the DOACs, apixaban demonstrated the highest efficacy and safety profile (66).

1.4 Management of Atrial fibrillation

The ABC (AF Better Care) pathway is a structured and simplified approach to support clinicians in the comprehensive management of patients with AF. It has been endorsed in European guidelines, including those from the European Society of Cardiology (ESC), and is increasingly adopted in routine clinical practice across Europe and other healthcare settings (67). It serves as an easy-to-remember framework including key domains of AF care for both newly diagnosed and chronic patients. The three components of the ABC pathway are (68):

- **A** – Anticoagulation to prevent stroke.
- **B** – Better symptom management.
- **C** – Cardiovascular and comorbidity risk reduction.

Implementation of the ABC pathway has been shown to improve clinical outcomes, being associated with a lower risk of major adverse events and hospitalisation among patients with complex AF, multiple comorbidities, and polypharmacy (69).

Rate and rhythm control

The management of AF typically includes rate control and rhythm control strategies. Rate control aims to slow ventricular response, while rhythm control attempts to restore and maintain sinus rhythm. Both strategies are primarily used to reduce AF-related symptoms and enhance quality of life (6). Rhythm control may involve a combination of cardioversion, antiarrhythmic drugs (pharmacological) and/or catheter ablation. Rate control drugs, including standard beta-blockers or rate-limiting calcium-channel blockers (diltiazem or verapamil), should be prescribed as the first-line treatment strategy for AF (5).

In cases of uncertainty, the possible need for cardioversion should be discussed with the patient. If the patient is highly symptomatic or if new-onset AF is present

even in the absence of symptoms, an attempt to restore sinus rhythm to evaluate therapeutic response may be the first recommended step (5,6). Pharmacological and/or electrical rhythm control should be considered for people with AF whose symptoms persist after heart rate control has been achieved or for whom a rate-control strategy was unsuccessful (6). For patients undergoing cardioversion for AF that has persisted for longer than 48 hours, electrical cardioversion (rather than pharmacological) should be considered (6). Amiodarone should be considered starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm (6). If pharmacological cardioversion has been agreed on, flecainide or amiodarone should be offered (6).

It should be recognized that both rate and rhythm control approaches have the potential to fail at any stage. Therefore, as the disease progresses, many patients must be reconsidered for alternative therapeutic strategies (6).

Stroke prevention therapies

Long-term anticoagulation is required in most AF patients to prevent cardioembolic stroke and systemic embolism, in accordance with guideline recommendations outlined in **Section 1.5**.

1.5 Guidelines of prescribing anticoagulants in Atrial fibrillation

1.5.1. Stroke risk assessment

Since OACs significantly reduce stroke (by 64%) and all-cause mortality (by 26%) compared with control or placebo (70), every patient with AF should be evaluated for the need for antithrombotic therapy to prevent systemic embolization even for the first AF episode (5). Long-term oral anticoagulation should be given to most AF patients, as the benefit generally outweighs the associated increase in bleeding risk. The initial step in achieving optimal thromboembolic risk management in AF patients should involve conducting a structured, clinical, risk-score-based assessment of each patient's specific thromboembolic risk using the CHA_2DS_2-VASc score (5). The CHA_2DS_2-VASc score [CHF, HTN, Age ≥75 years, DM, Stroke, Vascular disease, Age 65-74 years, Sex category (female)] includes the most common stroke risk factors with a score range of 0 to 9. The estimated one-year stroke rates for patients with a CHA_2DS_2-VASc score of 0 is approximately 0%, and for patients with a score of 9 approximately 15.2% (71) (**Table 1.3**). Low-risk patients [CHA_2DS_2-VASc 0 (male patient), or 1 (female patient)] have low ischaemic stroke or mortality

rates (< 1%/year) and do not need any stroke prevention treatment (5,6). Women with AF consistently have a considerably higher stroke risk than men when there are >1 non-sex stroke risk factor present. This is what is meant when it is said that female sex is an age-dependent stroke risk modifier rather than a risk factor per se (72).

However, uncertainty remains regarding optimal management of AF patients at low thromboembolic risk. A large multi-national cohort study from Sweden, Denmark, Norway, and Scotland examined outcomes in low-risk AF patients treated with DOACs, VKAs, or no antithrombotic therapy. The study reported lower ischaemic stroke rates with DOACs compared with no treatment, without increased major bleeding, and lower ICH risk compared with VKAs (73). These findings suggest potential net clinical benefit of DOAC therapy even in selected low-risk patients, although randomized controlled trials are needed for confirmation (73).

All patients whose risk of embolization exceeds the risk of bleeding are candidates for long-term antithrombotic therapy. If the onset of AF is triggered by another acute medical diagnosis, e.g., hyperthyroidism, acute PE, myopericarditis, pneumonia, after cardiac surgery, or intake of certain drugs or supplements, then treatment of the underlying cause might lead to years without future AF episodes. Thus, if there is a transient cause of AF, an observational approach can be followed involving clinical follow-up of symptoms and ambulatory monitoring to screen for potential recurrence (74).

The risk of stroke should be reassessed at each clinical review since risk factors are dynamic and the older AF population has several, often changing, comorbidities. Recent research has demonstrated that patients with altered risk profiles are more likely to experience strokes. Therefore, the first reassessment of stroke risk in patients with AF originally at low risk should be performed four to six months following the index examination (5). At the 2-year follow-up period, about 30% of patients will have acquired at least one stroke risk factor (75). Current risk stratification scores for thromboembolic events incorporate conventional risk factors but do not adequately account for emerging risk factors such as sleep apnoea, borderline HTN, renal disease, and obesity (5).

Table 1.3: CHA2DS2-VASc score, adapted from (5).

Score	Risk factor	Points	Comment
C	**Congestive heart failure**	1	Clinical heart failure, or evidence of moderate to severe left ventricular (LV) dysfunction
H	**Hypertension**	1	History of hypertension (regardless of current blood pressure or treatment status)
A	**Age ≥75 years**	2	Age is one of the most important stroke risk factors, with risk increasing markedly above 65 years. • 1 point is given for age 65–74 years • 2 points for age ≥75 years
D	**Diabetes mellitus**	1	• Treatment with oral hypoglycaemic drugs and/or insulin, or fasting blood glucose >125 mg/dL (7 mmol/L) • Both type 1 and type 2 diabetes confer similar thromboembolic risk in AF, although the risk may be slightly higher in older patients • The longer the duration of diabetes, the greater the thromboembolic risk
S	**Stroke / TIA / thromboembolism**	2	Previous stroke, transient ischaemic attack (TIA), or systemic thromboembolism AF patients with intracerebral haemorrhage (ICH) are also at high risk of subsequent ischaemic stroke
V	**Vascular disease**	1	Angiographically significant coronary artery disease (CAD), previous myocardial infarction, or peripheral arterial disease (PAD)
A	**Age 65–74 years**	1	1 point is given for age 65–74 years (as per age stratification above)
Sc	**Sex category (female)**	1	Female sex is a stroke risk modifier rather than an independent risk factor
Maximum score		**9**	

1.5.2. Bleeding risk assessment

Bleeding risk should be evaluated prior to initiating anticoagulant therapy. Various bleeding risk scores were created using modifiable and non-modifiable bleeding risk factors. According to ESC and NICE guidelines, the HAS-BLED score [Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage] (**Table 1.4**) should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score≥3) for early and more frequent clinical review and follow-up (5).

Table 1.4: Risk factors in the HAS-BLED score, adapted from (5).

Risk factor	Definition	Points
H – Uncontrolled hypertension	Systolic blood pressure (SBP) >160 mmHg	1
A – Abnormal renal and/or hepatic function	**Renal:** dialysis, transplant, or serum creatinine >200 µmol/L **Hepatic:** cirrhosis, bilirubin >2× upper limit of normal, or AST/ALT/ALP >3× upper limit of normal	1 (for each)
S – Previous ischaemic or haemorrhagic stroke	History of stroke	1
B – Bleeding history or predisposition	Previous major haemorrhage, anaemia, or severe thrombocytopenia	1
L – Labile INR	Time in therapeutic range (TTR) <60% in patients receiving VKA	1
E – Elderly	Age >65 years or extreme frailty	1
D – Drugs or excessive alcohol intake	Concomitant use of antiplatelet or NSAID; and/or excessive alcohol consumption per week	1 (for each)
Maximum score		**9**

Abbreviations: ALP=alkaline phosphatase; ALT= alanine aminotransferase; AST= aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.

A systematic review including 38 studies of bleeding risk prediction found that the HAS-BLED score provided the best evidence for predicting bleeding risk (moderate strength of evidence) (76). This is consistent with earlier systematic reviews and meta-analyses examining different approaches for bleeding risk prediction. Patients

with a low risk of bleeding were more accurately identified by HAS-BLED (HAS-BLED 0–2) compared to other bleeding risk scores (HEMORR$_2$HAGES and ATRIA) (77).

Importantly, OACs should not be withheld in patients with a high bleeding risk score since oral anticoagulation has an even greater overall therapeutic benefit in these patients (5). However, there are absolute contraindications to OACs including active serious bleeding (where the source should be identified and treated), associated comorbidities (e.g., severe thrombocytopenia <50 platelets μL), severe anaemia under investigation, or a recent high-risk bleeding event such as ICH (5).

The formal assessment of bleeding risk guides management of patients taking OACs by focusing attention on modifiable bleeding risk factors (**Table 1.5**) that should be managed and reassessed at every patient contact, and by identifying high-risk patients with non-modifiable bleeding risk factors who should be reviewed earlier (for example, in 4 weeks rather than 4–6 months) and more frequently (5). Identification of high bleeding risk patients is also needed when determining the antithrombotic strategy in specific AF patient groups, such as those undergoing percutaneous coronary intervention (PCI) (5).

Table 1.5: Risk factors for bleeding with OAC and antiplatelet therapy (5)

Risk factor type	**Examples**
Non-modifiable	Age >65 years
	Previous major bleeding
	Severe renal impairment (dialysis or transplant)
	Severe hepatic dysfunction (cirrhosis)
	Malignancy
	Genetic factors (e.g., CYP2C9 polymorphisms)
	Previous stroke
	Small-vessel disease
	Diabetes mellitus
	Cognitive impairment/dementia

Potentially modifiable	Extreme frailty ± excessive risk of falls
	Anaemia
	Reduced platelet count or function
	Renal impairment (moderate; CrCl-reduced)
Modifiable	Hypertension / elevated SBP
	Concomitant antiplatelet or NSAID use
	Excessive alcohol intake
	Non-adherence to OAC
	Hazardous hobbies or occupations
	Bridging therapy with heparin
	INR control (target 2.0–3.0; TTR >70%)
	Appropriate OAC choice and dosing

Abbreviations: OAC, oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; SBP, systolic blood pressure; CrCl, creatinine clearance; INR, international normalized ratio; TTR, time in therapeutic range.

1.5.3. Guideline recommendations (ESC and NICE)

During the study period (2010–2020), anticoagulation practice evolved substantially following the introduction of DOACs and successive updates to international and national clinical guidelines. In the UK, clinical practice was primarily informed by recommendations from the ESC and the NICE (5,6). Earlier ESC guidelines favoured VKA, whereas later updates recommended DOACs as first-line therapy for most patients with NVAF. NICE guidance applicable during the study period was primarily based on CG180 (2014). Subsequent surveillance updates during the study period did not result in substantive changes to anticoagulation recommendations and remained broadly concordant with contemporaneous ESC guidance. Key ESC guideline milestones relevant to this study are summarised in **Table 1.6**. These changes are considered when interpreting anticoagulation prescribing patterns observed in this study.

Table 1.6: Key ESC guideline milestones relevant to this study

Year	Guideline	Why it matters
2010	ESC AF Guidelines	Warfarin-dominant era
2012	Focused update	Early DOAC integration
2016	ESC AF Guidelines	DOACs become first-line
2020	ESC AF Guidelines	End-of-period benchmark

According to ESC and NICE guidance applicable during the study period, patients who require antithrombotic therapy include those in whom cardioversion to sinus rhythm is planned (irrespective of the method of cardioversion or baseline stroke risk), and patients who meet criteria for long-term anticoagulation based on stroke risk assessment. In contrast, patients with a single, clearly reversible episode of AF represent a heterogeneous group, for whom anticoagulation decisions should be individualised based on estimated future stroke risk.

Guideline-directed anticoagulation decision-making follows a stepwise approach. The first step is the identification of patients at truly low risk of stroke, in whom antithrombotic therapy is not recommended. For patients with one or more non-sex stroke risk factors, oral anticoagulation is recommended for stroke prevention. The choice of anticoagulant constitutes the subsequent step, with DOACs increasingly favoured during the study period.

ESC guideline updates published in 2016 and 2020 recommend DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) in preference to VKAs for most patients with NVAF, except in those with mechanical heart valves or moderate-to-severe mitral stenosis. When VKAs are used, a target INR of 2.0–3.0 is recommended, with an emphasis on maintaining a time in therapeutic range of at least 70%. For patients with poor VKA control, guidelines recommend either optimisation of INR management (through education, counselling, and more frequent monitoring) or switching to a DOAC, provided there are no contraindications.

Earlier UK guidance, including SIGN recommendations published in 2014, suggested that antiplatelet therapy could be considered when oral anticoagulation was declined (9). However, subsequent ESC and NICE guideline updates no longer supported antiplatelet therapy alone for stroke prevention in AF, reflecting evidence of its inferior efficacy and comparable bleeding risk to anticoagulation.

Importantly, both ESC and NICE guidelines applicable during the study period emphasise that the clinical pattern of AF (paroxysmal, persistent, or permanent) does not influence the indication for anticoagulation. Stroke risk assessment using the CHA_2DS_2-VASc score is central to decision-making, while bleeding risk scores such as HAS-BLED are recommended to identify and address modifiable bleeding risk factors rather than to exclude patients from anticoagulation. The ESC-recommended approach to anticoagulation decision-making in AF is illustrated in **Figure 1.4**.

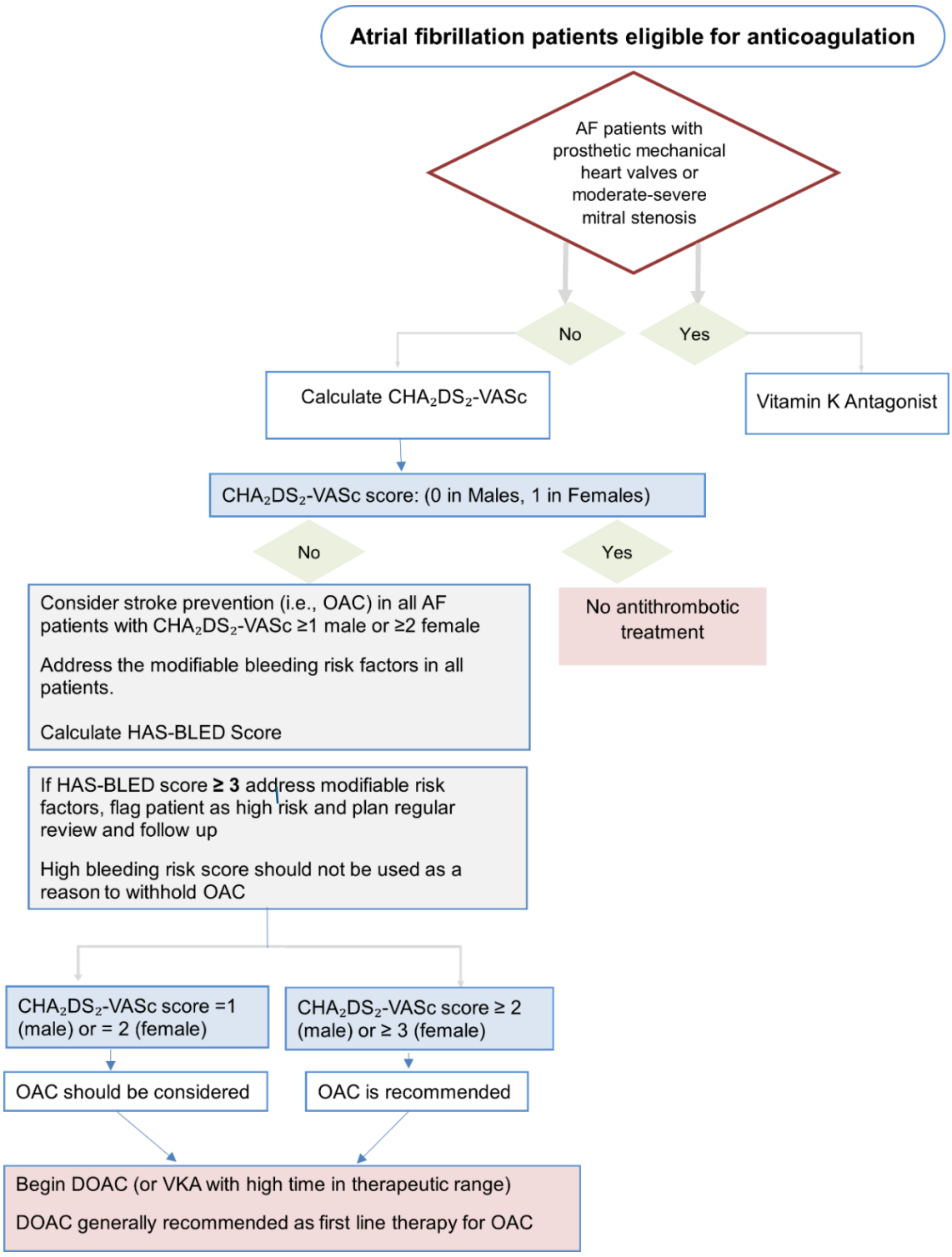

Figure 1.4: Guideline-directed approach to anticoagulation in atrial fibrillation according to ESC recommendations (2020), based on CHA_2DS_2-VASc and HAS-BLED scores, adapted from (5)

DOAC dosing

For patients with AF initiating a DOAC, therapeutic anticoagulation is achieved within hours, eliminating the need for heparin bridging therapy (78). DOAC selection and dosing should be individualized based on patient characteristics, potential drug–drug interactions and approved prescribing criteria for each agent (**Table 1.7**). Dose adjustments are recommended for specific subgroups based on age, body weight, renal function, and concomitant P-glycoprotein inhibitor use. The required dose adjustments vary significantly between the four DOACs, making dose selection more complex. Appropriate assessment of thromboembolic and bleeding risk using validated tools is recommended prior to prescribing.

In routine practice, adherence to label-recommended dosing is critical to replicate the efficacy and safety outcomes observed in RCTs (79). A 2019 meta-analysis demonstrated that appropriately dose-reduced DOACs in eligible patients had an improved benefit-harm profile compared with warfarin, consistent with the profile seen in patients receiving full-dose DOACs (80).

Table 1.7: Dose selection criteria for DOACs in atrial fibrillation (78)

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg twice daily (b.i.d.)	20 mg once daily (o.d.)	5 mg twice daily (b.i.d.)	60 mg once daily (o.d.)
Reduced dose	110 mg twice daily	15 mg once daily	2.5 mg twice daily	30 mg once daily
Dose-reduction criteria	• Age 75–79 years: 110–150 mg b.i.d. • Age ≥80 years • Concomitant use of verapamil or certain antivirals • Increased bleeding risk	• CrCl 15–49 mL/min	If ≥2 of: • Age ≥80 years • Body weight ≤60 kg • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of: • CrCl 15–50 mL/min • Body weight ≤60 kg
Renal impairment cautions / avoid use	eGFR <30 mL/min/1.73 m² (↑ bleeding risk)	eGFR <15 mL/min/1.73 m² (↑ bleeding risk)	eGFR <15 mL/min/1.73 m² or dialysis (↑ bleeding risk)	eGFR <15 mL/min/1.73 m² (↑ bleeding risk); CrCl >95 mL/min (↓ efficacy)
Use in liver disease	Contraindicated in hepatic impairment or liver disease affecting survival	Contraindicated in hepatic disease with coagulopathy	Contraindicated in hepatic disease with coagulopathy or clinically relevant bleeding risk	Not recommended in severe hepatic impairment

Abbreviations: b.i.d., twice daily; o.d., once daily; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation.

1.6 Management of venous thromboembolism

The cornerstone of VTE management is anticoagulation, initiated promptly once diagnosis is suspected or confirmed to prevent thrombus extension and reduce embolization risk (35). Initial therapy typically involves parenteral anticoagulants (low molecular weight heparin or fondaparinux) or DOACs, with DOACs recommended over VKAs when oral anticoagulation is initiated (81).

Anticoagulation duration depends on VTE classification and individual patient factors. The minimum treatment duration for first VTE is three months in virtually all cases (35). After this primary treatment period, decisions to stop or continue anticoagulation are based on recurrence risk and bleeding risk (35).

For **provoked VTE** associated with major transient risk factors (such as postoperative DVT), guidelines recommend stopping anticoagulation after three months since the triggering risk has resolved (35). For **unprovoked VTE** or VTE associated with persistent risk factors (such as active cancer or thrombophilia), recurrence risk remains elevated and extended anticoagulation beyond three months is usually recommended, with the intention to continue indefinitely unless bleeding risk is prohibitive (35).

Special considerations include Indefinite anticoagulation with VKA is recommended for patients with antiphospholipid syndrome (35), as DOACs are associated with higher rates of recurrent thrombosis in this population (82). Additionally, in patients with recurrent VTE, long-term or indefinite anticoagulation is generally advised. Advanced therapies such as systemic thrombolysis are reserved for selected patients with high-risk PE and haemodynamic instability, where the benefits outweigh bleeding risk (35).

Systemic thrombolysis involving the intravenous administration of fibrinolytic agents (e.g. alteplase) to rapidly dissolve thrombus, is reserved for selected patients with high-risk PE and haemodynamic instability, where the benefits outweigh the bleeding risk is reserved for selected patients with high-risk PE and haemodynamic instability, where the benefits outweigh bleeding risk (35). Inferior vena cava (IVC) filters have a limited role and are generally indicated only when anticoagulation is

contraindicated or ineffective. Routine use is discouraged due to lack of mortality benefit and potential complications (35).

1.7 Thesis rationale

There is a clear consensus in clinical practice on the DOACs' efficacy and safety, and they have replaced warfarin in most countries as the first line treatment for most patients requiring oral anticoagulation. However, recommendations on the selection of one DOAC over another are lacking any agreement which results in creating a debate about optimal drug choice for individual patients. Consequently, the choice of anticoagulant drugs is highly variable over time and across countries, influenced by several clinical and non-clinical factors including age, sex, weight, renal function, and others. There is a need to explore the factors associated with prescribing choices among the four available DOAC agents compared to each other and compared to warfarin, to inform clinical decision-making and support clinicians in selecting the most appropriate DOAC for individual patients.

The profile of patients initiated on DOACs has changed over time, likely reflecting the interaction of several factors influencing prescribing practices, such as evolving perceptions of efficacy and safety and changes in guideline recommendations. However, population-level evidence describing the evolution of OAC prescribing in Scotland remains limited, particularly beyond 2016 and following the full introduction of all licensed DOACs, including edoxaban. This PhD project examines the evolution of individual DOAC initiation over time and investigates the changes in prescribing trends using data from Scotland. Conducting research on prescribing patterns is essential for assessing the rational use of medications, understanding drug utilization trends, and evaluating physicians' adherence to regional and national clinical guidelines.

Previous studies have examined DOAC prescribing in Scotland using real-world data (83). However, these studies did not include edoxaban because it was not approved in the UK until 2015. Moreover, they did not cover the period of the COVID-19 pandemic, during which changes in healthcare delivery may have influenced anticoagulant prescribing practices. Therefore, this research investigates the impact of the COVID-19 pandemic on anticoagulant prescribing in Scotland by comparing patterns of DOAC and warfarin use before and after March 2020.

In addition, understanding switching from warfarin to DOACs is particularly important, as a substantial number of patients were switched during the pandemic. While the effectiveness and safety of switching from warfarin to DOACs have been examined previously, there is limited evidence evaluating switching patterns and outcomes in the context of the accelerated and widespread switching observed during the COVID-19 period and the more recent post-2018 era. This surge in switching may have involved a broader patient population with different clinical and demographic characteristics than those included in earlier studies. Accordingly, this research examines factors associated with switching from VKAs to DOACs and evaluates subsequent safety and effectiveness outcomes, including thromboembolic events, major bleeding, and mortality, using contemporary real-world data.

Moreover, robust evidence supports the safety and efficacy of DOACs compared to warfarin in patients with mild to moderate renal failure. However, evidence in patients with advanced renal impairment remains limited, as most pivotal trials excluded those with severe renal impairment, resulting in limited evidence to guide anticoagulation decisions in this population. Despite this, DOACs are prescribed across a range of CKD stages in routine clinical practice, highlighting the need to examine real-world prescribing patterns in patients with renal impairment. Accordingly, this PhD project includes an analysis of DOAC prescribing patterns in incident OAC users with renal impairment, restricted to patients with sufficient renal function data. This analysis focuses on how different stages of renal impairment influence anticoagulant selection.

Based on available evidence, studies on the changes in prescribing trends of DOACs in Scotland are scarce, especially after the introduction of edoxaban in 2015. Furthermore, no prior study has comprehensively evaluated DOAC prescribing choices in patients with renal impairment or assessed the impact of the COVID-19 pandemic on anticoagulant prescribing in Scotland. Conducting these studies therefore provides new insights into real-world anticoagulation practice in Scotland, with the potential to inform optimisation of DOAC prescribing, guide switching decisions, and improve clinical outcomes for the local population.

1.7.1. Aims and objectives

The aims of this thesis were to comprehensively understand and investigate the change in prescribing patterns of OAC over time and explore factors influencing the prescribing choice of OAC in clinical practice. It also aimed to assess how these

patterns evolved in response to emerging evidence, clinical guidelines, and the COVID-19 pandemic. Furthermore, the thesis sought to evaluate the real-world effectiveness and safety outcomes associated with switching from VKAs to DOACs in a national cohort. Overall, this work provides a comprehensive evidence base to inform future clinical decision-making and optimise anticoagulant use in Scotland. The objectives of this thesis were to:

1. Conduct a scoping review to identify and summarise key factors reported in the literature that are associated with the choice of OACs prescribed for all indications, to identify the gaps in the literature and understand which factors were more frequently studied. (Chapter 2)
2. To describe national prescribing patterns of OACs in Scotland between 2011 and 2020, including the total number of prescriptions, prevalent use, and incident use among new users, using linked administrative healthcare datasets. (Chapter 4)
3. To investigate changes in the incidence and prevalence of OAC use and the rate of switching from VKAs to DOACs before and during the COVID-19 pandemic, using national prescribing data from January 2018 to April 2021. (Chapter 5)
4. To identify factors associated with switching from VKAs to DOACs among adults in Scotland between January 2018 to April 2021, and to determine whether these associations changed between the pre-COVID and COVID-19 periods. (Chapter 6)
5. To evaluate the real-world effectiveness and safety outcomes of patients who switched from VKAs to DOACs compared with those who remained on VKA therapy, between January 2018 and May 2021, including individuals switched before and during the pandemic, and assessing the comparative effectiveness and safety of different DOAC types after adjusting for baseline demographic and clinical characteristics. (Chapter 7)
6. To investigate the influence of renal function on OAC prescribing among incident users in Scotland between 2011 and 2020, using routinely collected laboratory and prescription data, by examining how different stages of renal impairment affect the choice between VKAs and DOACs. (Chapter 8)

2 Chapter 2: Factors associated with the prescribing of direct oral anticoagulants (DOACs): a scoping review

2.1 Introduction

For decades, traditional VKAs such as warfarin were the only options when oral anticoagulation was indicated. However, in the past decade, with the introduction of DOACs – apixaban, dabigatran, edoxaban, and rivaroxaban – there are now additional options. Following their approval, DOACs have become the preferred choice for anticoagulation in clinical practice because of their documented non-inferior efficacy and safety (84–88). They are now widely used for preventing stroke and systemic embolism in AF, for preventing and/or treating thrombotic events commonly associated with conditions such as DVT and PE, and as thromboprophylaxis in patients undergoing hip or knee arthroscopy (89,90).

Many studies reported a significant rise in DOAC prescriptions and a corresponding decrease in VKA use over the past decade (91–95), with up to 80% of new OAC users for AF, DVT, and PE being initiated on DOACs (96). Current guidelines from the ESC and the American Heart Association/American College of Cardiology (AHA/ACC) recommend DOACs as the first-choice treatment over warfarin for DVT, PE, and AF, but do not specify which DOAC should be preferred. The four available DOACs have differences in bioavailability, renal clearance, drug interactions, dosing regimen, antidote availability, and safety (97); all of these factors contribute to the decision-making when selecting among DOACs.

There have been shifts in OAC prescribing patterns over the last decade (VKA vs DOACs) (96), along with variations in DOAC adoption and prescribing practices across nations. Nevertheless, no previous studies provided an overview of important factors associated with OAC choice for the major indications, and how these drive anticoagulant selection in clinical practice. Therefore, the primary aim of this scoping review was to provide a comprehensive overview of the key factors that impact anticoagulant choice between VKAs and DOACs, as well as among various DOACs, in real-world clinical practice.

2.2 Methods

Reporting of this Scoping Review (SCR) was done in line with the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR). The protocol was registered on the PURE research portal (98).

The search strategy was guided using the Population, Concept, and Context framework: patients prescribed OACs for any indication (population), factors affecting prescribing and choice of OAC (concept), and observational studies analyzing factors that influence prescribing of anticoagulants in any healthcare setting (context). Medline, Embase, Scopus, and Web of Science were searched for studies published from January 2010 until the search date (18.03.2023). An additional supplementary search included screening of reference lists. An expert academic librarian and a second experienced researcher reviewed the search strategy independently.

2.2.1. Eligibility criteria

Only quantitative observational studies analysing factors affecting the choice of DOACs (including dabigatran, rivaroxaban, edoxaban, and apixaban) compared to VKA (e.g., warfarin) or the choice among individual DOACs in any setting (primary care or hospital, long-term care facilities, and nursing homes) were included. Studies involving critically ill patients were excluded, as they are more likely to receive parenteral anticoagulation rather than OACs, which was not within the scope of this review. Studies exclusively on warfarin or other VKAs were excluded, as this review focused on factors influencing the choice of DOACs. Although in some countries the first DOAC was approved as early as 2008, the literature search started in 2010 to capture the relevant literature following the approval and subsequent utilization and adoption of DOACs, covering their widespread use, particularly in patients with AF, across different regions and healthcare systems. **Table 2.1** summarizes the applied inclusion and exclusion criteria.

Table 2.1: Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion criteria
Population & setting	Adult patients (≥18 years) prescribed DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) for any indication, in any healthcare setting	Studies focusing exclusively on warfarin or other VKAs; studies involving patients <18 years; studies conducted exclusively in critical care/ICU settings
Year of Publication	Published between January 2010 and March 2023	Published before January 2010
Study Design	Quantitative observational studies: cohort, case-control, cross-sectional, or registry studies	Editorials, opinion pieces, case reports/series, narrative reviews, letters, conference abstracts, systematic reviews/meta-analyses, RCTs, qualitative studies
Language	English (original or translated)	Non-English publications
Outcomes	Studies examining factors affecting the choice of oral anticoagulant between DOAC and VKA and among different DOACs	Studies without a focus on prescribing factors (e.g. treatment outcomes, lab studies, or healthcare utilization without prescribing choice detail) Studies without the relevant prescribing choice outcome (e.g. factors related to inappropriate prescribing or dose selection, under prescribing, switching, and discontinuation)

2.2.2. Study selection, and quality assessment

Using the Covidence software (99), the selection of studies was conducted in two stages. During the initial stage, screening of the titles and abstracts of all imported results was carried out; subsequently, a full-text screening was undertaken.

Data extraction was done using Excel spreadsheets. The extraction table was created following the Joanna Briggs Institute (JBI) methodology guidance for data extraction, adapted as appropriate, and piloted on 10% of included studies (100).

The included studies were evaluated for the risk of bias using the JBI checklists for cohort studies or cross-sectional studies (101). The JBI appraisal checklist comprises 11 items for cohort studies and 8 items for cross-sectional studies, each

with response options: "Yes," "No," "Unclear," and "Not applicable". No universal threshold has been established for categorizing the results obtained from JBI tools; hence, the score was categorized as reported in previous systematic reviews (102), applying the following thresholds for cross-sectional studies: Studies with 7–8 "Yes" were classified as having a low risk of bias, those with 5–6 "Yes" as moderate risk, and those with fewer than 5 "Yes" as high risk. For the cohort study checklist, items 8, 9, and 10 (evaluating follow-up) were considered not applicable. Removing these three items allowed following the same scoring categorisation scheme as for the cross-sectional studies. At each step of screening, extraction, and quality assessment, a total of 10% of the included studies were validated by another independent reviewer. An agreement >80% was considered acceptable (103).

2.2.3. Data synthesis

Firstly, tables were created to summarise the factors examined, the number of studies investigating each factor, and the direction of association. For each factor, the number of studies reporting statistically significant associations was recorded based on p-values and confidence intervals.

Secondly, a narrative synthesis was conducted using grouping and clustering techniques. Factors were categorised into four groups: demographic, clinical, socioeconomic, and prescriber-related factors. These categories were informed by existing literature and refined through piloting on 10% of included studies. The direction of association (positive, negative, or no association) and the consistency of findings across studies were described narratively. Positive and negative associations refer to statistically significant findings, while non-significant results were classified as showing no association.

2.3 Results

Of the 4659 identified studies, 661 possibly eligible articles were reviewed for full-text screening. Ultimately, 60 articles met the criteria, as detailed in the PRISMA flowchart (**Figure 2.1**) and were extracted and synthesised. During the validation of title/abstract and full-text screening, the agreement percentages between reviewers were 85.5% and 89.3% respectively.

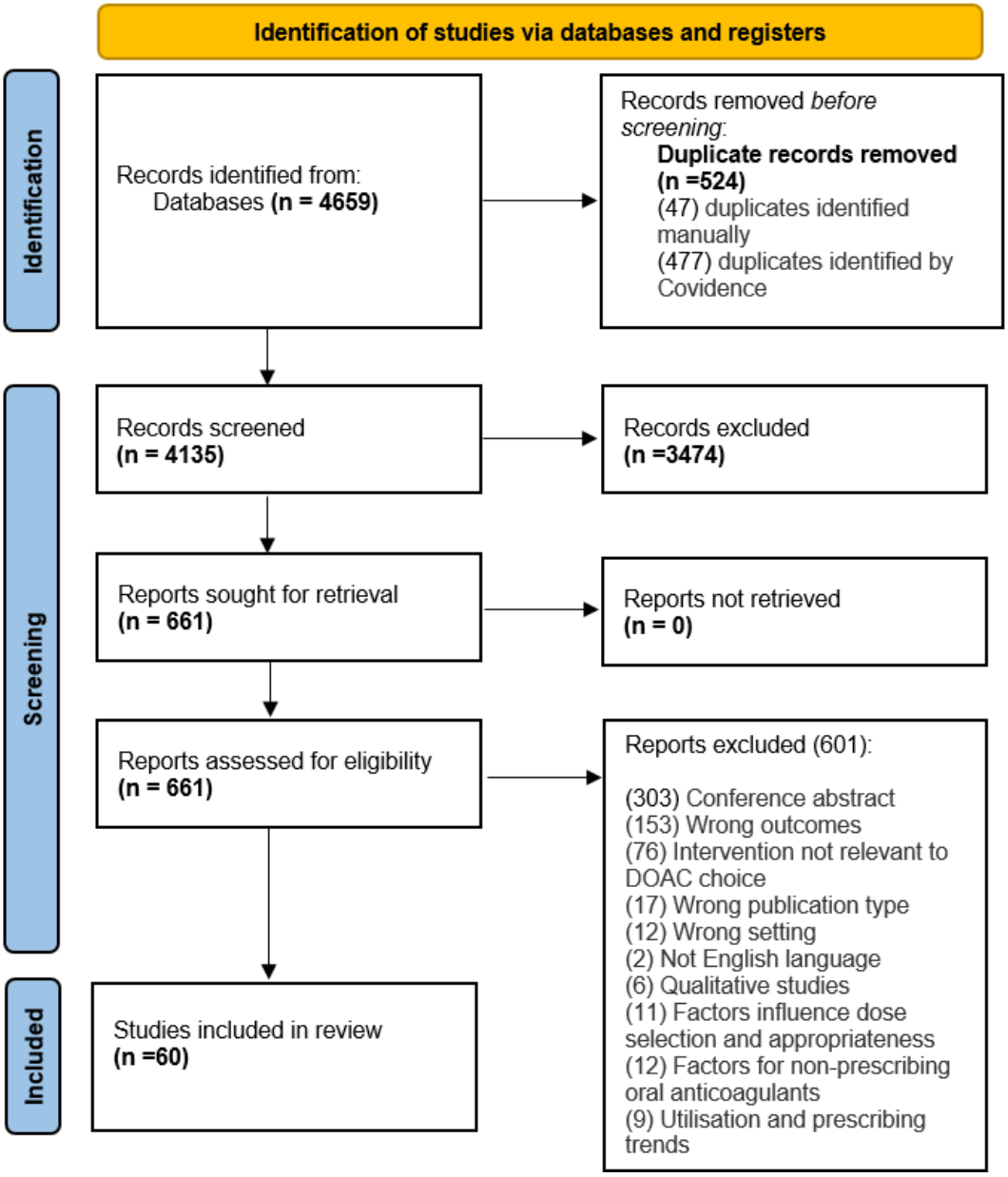

Figure 2.1: PRISMA flow chart of screening process to identify relevant studies. Adapted from the PRISMA 2020 flow diagram template (104).

Study characteristics

Table 2.2 shows the characteristics of the included studies. Although the search period for this scoping review began in 2010, all studies were published between 2014 and 2023; slightly over half (n=31/60, 51.6%) of the studies were published before 2015.

The majority (n=45, 75%) were cohort studies, while the remaining (n=15, 25%) were cross-sectional studies. One-third of the studies (n=18, 30%) were conducted

in the United States and six studies (n=6, 10%) originated from Canada, with the remainder from a wide range of other countries (**Table 2.2**).

The most frequently examined OACs were VKA/warfarin (n=58, 96.6%), dabigatran (n=46, 76.6%), rivaroxaban (n=45, 75%), and apixaban (n=39, 65%); edoxaban was the least studied agent (n=13, 21.6%).

The primary indication for prescribing oral anticoagulation was AF or atrial flutter, accounting for 86.6% (n=52) of studies. Some studies focused on specific AF cohorts such as those with type II DM (105) or liver disease (106), or undergoing PCI (107). Three studies examined OAC use in AF patients with prior ischaemic stroke (108–110). Other indications included VTE or AF (111,112), acute PE (91), VTE or PE (113), or VTE only (95). One study reported potential indications such as VTE, AF, CAD, and cancer (114); whereas one study investigated the relation between prescriber specialty and OAC choice without specifying an indication (115). In total, 93% (n=56/60) included DOAC treatment for AF and 11.6% (n=7/60) for venous or pulmonary embolism.

A total of 26 studies (43.3%) specifically included OAC-naïve patients who were newly prescribed an OAC. In 29 studies (48.3%), both new and prevalent OAC users were included. Four studies (6.7%) did not clearly specify whether patients were OAC-naïve or already on OAC (113,116–118). One study focused on the choice of OAC based on prescriber specialty rather than including patients (115).

Nearly all studies (n=58, 96%) examined factors influencing the choice between DOACs and VKAs (or specifically warfarin), while nine studies (15%) evaluated factors for the choice among DOACs (96,113,119–125). Some studies reported the influence of only one or two factors on OAC choice, but most studies examined five or more factors **(Appendix S.2.1).** Some studies reported results for all factors included in the logistic regression models (including both significant and non-significant associations), whereas others reported only statistically significant associations.

Table 2.2: Characteristics of the included studies examining factors associated with OAC prescribing choice (n = 60)

Author, Year, Country	Study Design/ Study Period	Sample Size (n)	Age/Sex	Indication of OAC	DOAC(s) Studied	Comparison Group	OAC-naïve	% on OAC	Analysis
Chopard R et al 2019, France	Prospective cohort study (Sep 2012 - April 2017)	1,082	Mean age 66.2 /F:53.2%	Acute pulmonary embolism	Rivaroxaban, apixaban	Non-DOAC	Yes	100%	Hierarchical modified Poisson regression model
Ha HS et al 2020, Korea(92)	Prospective cohort study (June 2016 - May 2019)	10,529	Mean age all 66.9; Warfarin 67.9 DOACs 69.6	AF patients	Dabigatran, rivaroxaban, apixaban, edoxaban	Warfarin	No	70%	Multivariable logistic regression
Grymonprez M. et al 2022, Belgium(93)	Cohort study (Jan 2013 - Dec 2019)	448,661	Mean age DOAC 76.2 VKA 70.9/F: DOAC 47.6% VKA 46.7%	NVAF patients ≥45 years	Dabigatran, rivaroxaban, apixaban, edoxaban	VKA (warfarin, acenocoumarol, phenprocoumo)	No	100%	Multivariable logistic regression
Halvorsen S et al 2022, Norway(94)	Cohort study (Jan 2010 - Dec 2018)	92,936	All ≥18; Mean age 71.31 /F: 44.1%	AF	Dabigatran, rivaroxaban, apixaban, edoxaban	Warfarin	No	69.0%	Multivariable logistic regression

Nathan A.S et al 2019, USA(95)	Retrospective cohort analysis (Jan 2010 - Dec 2016)	14,140	Mean age 58.7	Incident diagnosis of VTE	Dabigatran, rivaroxaban, edoxaban, apixaban	VKA	Yes	100%	Multivariable logistic regression
Zhu J 2018, USA(96)	Cohort Study (Oct 2010– Mar 2017)	112,187	Adults >18. Mean Age (All): 71.6 Warfarin: F 43.5%, Dabigatran: F 37.2 Rivaroxaban : F 40.1%, Apixaban: F 46.8%	NVAF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	100%	Multivariable logistic regression
Alwafi H. et al, 2020, UK(105)	Retrospective cohort (2001–2016)	23,124	>18 years; mean age OAC 73.4 No OAC 77.5 /F:38.6%	T2DM + AF	Dabigatran, apixaban, rivaroxaban, edoxaban	Warfarin	Yes	52.4%	Multivariable logistic regression
Douros A. et al 2021, UK(106)	Cohort study (2011 – 2020)	3,167	Mean age 70.7/ F:40%	NVAF patients with liver disease	Apixaban, dabigatran, edoxaban, rivaroxaban	VKA	Yes	100%	Logistic regression

Boivin-Proulx L.-A et al 2022, Canada(107)	Retrospective cohort (2010–2017)	3,740	Mean age 75.3 years/ F: 34.3%	AF diagnosis, after AF diagnosis: the date of PCI is the date of cohort entry	DOACs	Warfarin	No	100%	Multivariable logistic regression analysis
Luger S et al 2014, Germany(108)	Cohort study (Oct 2011 - Sep 2012)	758	Mean age 80/ F: 58%	Diagnoses of ischemic stroke or TIA and AF	Dabigatran, rivaroxaban	VKA	No	49.3%	Multivariate analysis
Patel P.A et al 2015, USA(109)	Cohort study (Oct 2010 – Sep 2012)	61,655	Median age 79/F: 53.1	AF and Ischemic stroke or TIA	Dabigatran, rivaroxaban	Warfarin	No	100%	Multivariable logistic regression
Sur N B et al 2019, USA (110)	Cohort Study (Jan 2010– Dec 2016)	24,040	Mean age: 79; F: 53.8%	Patients with ischemic stroke and AF	Dabigatran, rivaroxaban, Apixaban	Warfarin	No	52%	Multilevel logistic regression
Jobski K et al 2018, Germany(111)	Cohort study (Jan 2010 - Dec 2014)	16, 804	Median age 85 /F:75%	AF or VTE	Rivaroxaban, apixaban, dabigatran	VKA (Phenprocoumon, warfarin)	Yes	13.2%	logistic regression models
Efird L.E et al 2016, USA(112)	Retrospective cross-sectional	All 5,632	Mean age all 70 years, 69 . warfarin	61% AF only, 16% VTE only,	Dabigatran, rivaroxaban	Warfarin	No	100%	bivariate and multivariate

	study (April 2012 - April 2013)	AF only 3,424 VTE only 881	71.9 DOAC/F:44 % Warfarin 54.6 DOAC 60.8	4% both AF & VTE, 19% other indications for anticoagulation					
Lorenzo A et al 2022, Spain(113)	Cohort study (March 2013 – Sep 2021)	41,678 (VTE), 56% initially had with PE	Mean age 65/F 50%	Acute VTE or PE	Dabigatran, rivaroxaban, edoxaban, apixaban	VKA or LMWH	Not clear	100%	Multivariable analysis
Chen Q et al 2021, USA(114)	Point prevalence cross-sectional study (Oct 2016)	506,482	Age group 65–74 20.6%, 75–84 31.1%, 85–89 21.2%, 90–94 17.7% ≥95 9.4 / F: 71.5%	Potential Indications for Anticoagulation AF or flutter Stroke CAD Acute MI VTE Cancer Inpatient surgery in the past 6 months	Dabigatran, rivaroxaban, apixaban, edoxaban	Warfarin	No	11.8 %	Poisson regression model

Wheelock K M 2021, USA(115)	Retrospective Cohort (2013–2018)	325,666	Not applicable	NA	Dabigatran, rivaroxaban, apixaban	Warfarin	NA	NA	Multilevel repeated measures
AbuDagga et al., 2014, USA(126)	Retrospective cohort (Oct 2009–Apr 2012)	20,320	Mean: 67; F: 29.1% (dabigatran), 39.2% (warfarin)	AF	Dabigatran	Warfarin	12%	100%	Multivariable logistic regression
Bang O.Y et al, 2022, Korea(127)	Retrospective cohort (Jan 2007–Nov 2016	129,465 (before DOACs) 196,243 (After DOACs)	>18 years; mean age 70.6 before DOACs, 71.9 after DOACs / F: 43.8% before DOACs, 44.0% after DOACs	AF had a CHA2DS2-VASc score ≥2	Apixaban, dabigatran, rivaroxaban	Warfarin	No	100%	Multivariable logistic regression
Beier L et al, 2022, 38 countries (international)(128)	Cross-sectional (Jan 2014–Dec 2016)	21,241	>18 years; mean age 70.5/F: 44.9%	AF had ≥1 CHA2DS2-VASc score	Dabigatran, apixaban, rivaroxaban, edoxaban	VKA	Yes	82.2%	log-binomial multivariable regression
Bezabhe W.M et al 2021, Australia(119)	Retrospective cohort (2009–2019)	63,212	> 18 years, mean age all 72.4 OAC 73.4, NO	Newly diagnosed AF patients	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	64.6%	Binary and multinomial logistic regression

			OAC 70.6 / F: all 46.3%, OAC 34.4% No OAC 65.6						
Bielecka B et al 2021, Poland(129)	Cross-sectional, single-center (2014–2018)	4,027	Mean age 71.7, DOAC 72.2 VKA 71.3 /F all 42.6 DOAC 43.6% VKA 41.2%	AF	Apixaban, dabigatran, rivaroxaban	VKA	Not clear	91.4%	Multivariate logistic regression analysis
Brais C et al 2017, Canada(130)	Cross-sectional study (Oct 2011 – Oct 2014)	439	Mean age 79.6 warfarin, 73.9 DOAC / F: 54.2% warfarin, 50%	AF	Apixaban, dabigatran, rivaroxaban	Warfarin	Yes	100%	Multiple logistic regression analysis
Brown J et al 2016, USA(131)	Cohort study (2005 – 2013)	105,610 (before DOAC), 11,992 (From 2013)	Mean age all 78.2 received OAC 77.3 /F: 49.6% received OAC 54.9%	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	In 2013, OAC use was 54.0% (6,474/11,992).	univariate logistic regression models

Campitelli M.A et al 2021, Canada(132)	Retrospective cohort study (April 2011 - March 2018)	36,466	>65 years; 66–75 8.4% 76–85 38.1%, >86 53.5%/F: 61.5%	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	No	50.8%	log-binomial regression models
Cheng W. H et al 2021, Taiwan(133)	Cohort study (2009 – 2015)	33,539	≥85 years; mean age of the last year 2015 89.02/F:53.3 % in 2015	AF newly diagnosed ≥85 years old	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	34.3%	Multivariate logistic regression model
Desai N.R. et al 2014, USA(134)	Retrospective cohort study (Oct 2010 - June 2013)	6,893	Mean age 61.3 / F:27.2%	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	100 %	Multivariable logistic models
Douros A et al 2017, Canada(135)	Population-based cohort study (2011 – 2014)	138, 616	Mean age DOACs 75.07 VKAs 76.78/F: 50.39% DOACs 51.47% VKA	AF	Dabigatran, rivaroxaban, apixaban	VKA	Yes	52%	logistic regression models
Ehrlinder H et al 2020, Sweden(136)	Cross-sectional analysis (2010 – 2017)	2,943	All patients >75 years, Mean age 82/F:58.4%	AF & atrial flutter	Dabigatran, rivaroxaban. apixaban, edoxaban	Warfarin	No	74.3%	logistic regression analysis

Fohtung R.B et al 2017, USA(137)	Retrospective cohort study (Oct 2010 – Sep 2015)	6,568	All >75 years / F: 50%	AF older than ≥75	Apixaban, dabigatran, rivaroxaban	Warfarin	No	51.8%	Multivariable logistic regression
García-Sempere A. et al 2017, Spain(138)	Retrospective cohort study (Nov 2011 – Feb 2014)	21,879	Mean age 75/ F: 48%	AF	dabigatran, rivaroxaban, apixaban	VKA (warfarin, acenocoumarol)	Yes	17.97%	Multilevel regression analyses
Gorczyca I et al 2020, Poland(139)	Retrospective single-center cohort study (2014 – 2017)	1,236	Mean age 82 VKA 81.3 DOAC 82.2/F:56%	AF aged ≥75	Dabigatran, rivaroxaban, apixaban	Warfarin	Not clear	90.1%	Multivariate model logistic regression analysis
Gorczyca I. et al 2020, Poland(120)	Prospective cohort study (Jan- Dec 2019)	2,971	All > 18; Mean age 72/F: 43%	AF	Apixaban, dabigatran, rivaroxaban	DOACs (Apixaban, dabigatran, rivaroxaban)	No	100%	Multivariable logistic regression
Guerriero F 2018, Italy(140)	Cohort study (2014)	967	All ≥75; Mean age 81.5/ F: 61.4%	AF older than ≥75	Apixaban, dabigatran, rivaroxaban	Warfarin	Yes	100%	Multivariable logistic regression analysis
Gurusamy V.K. et al 2019, Sweden(141)	Cross-sectional study (Dec 2011 – Dec 2014)	68,056	All ≥18; Mean age DOAC 74.4 Warfarin. 73.7/F:45%	NVAF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	100%	Multivariable logistic regression

Ha AC et al 2016, Canada(116)	Cross-sectional retrospective analysis (Dec 2012 - July 2013)	936	All ≥18; Median age 75.7 Warfarin 77.8 DOACs 75.7/ F:44.7%	NVAF	DOACs	Warfarin	Not clear	83%	Multivariable logistic regression
Huiart L et al 2018, France(142)	Retrospective cross-sectional study (Jan 2011 - Dec 2015)	814,446	All ≥18; Mean age 74.9/ F: 49.8.2%	NVAF	Dabigatran, rivaroxaban, apixaban	VKA (warfarin, acenocoumarol, fluindione)	Yes	100%	Multivariate analysis using logistic regression
Ilomäki J et al 2019, Australia(143)	Cross-sectional analysis (July 2013 - June 2017)	356,000 (general population), 7,476 + 8,870 (AD)	patients with Alzheimer Age 65–74 5.3% to 8.1% Age 75–84 n 9.4 % to 12.1% Age ≥85 or older 7.5 % to 12.3% The proportion of people aged ≥85 was ~40% in people with AD and	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	7.5% to 12.3% of people with AD were on OAC and 6.7% to 19% of the general	Multivariable logistic regression

			~12% in the general population sample/F: warfarin 61.1% DOAC 51.1 % General population warfarin 46.9% DOAC 49.1%						
Kjerpeseth L J et al 2018, Norway(121)	Retrospective cohort study (Jan 2010 - Dec 2015)	62,865	All >18; Mean age 73.2 in 2010, 73.9 years in 2015/F: 43%	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	Yes	100%	Multiple logistic regression analyses in 2015
Komen J et al 2017, Sweden(122)	Retrospective cohort study (March 2015 - Febr 2016)	6,765	Mean age 74.3 /F:45.3	AF	Dabigatran, rivaroxaban, apixaban) or DOACs Vs DOACs	Warfarin	Yes	100%	Multivariate models
Koziel M et al 2021, USA(117)	Prospective cohort study (2011 – 2016)	27,432		AF	Dabigatran, rivaroxaban, apixaban	VKA	Not clear	80-85%	log-binomial regression

Lauffenburger JC et al 2015, USA(123)	Retrospective cohort study (2009 – 2012)	70,498	Mean age 70/F:40%	AF.	Dabigatran, rivaroxaban or DOACs Vs DOACs rivaroxaban vs dabigatran	Warfarin	Yes	100%	Multivariable modified Poisson regression
Lee KK et al 2023, Scotland(144)	Cohort study (2010 – 2019)	172,989	Mean age 75.3/F: 48%	Incident admissions to the hospital with AF	DOACS	VKA	No	51.3%	Multivariable logistic regression
Lodzinski P et al 2020, Poland(145)	Prospective cohort study (2013 – 2016)	701	Median age VKA 67 DOAC 68/F: VKA 43% DOAC 44%	AF	Dabigatran or rivaroxaban	VKA	No	100%	Multivariable logistic regression analyses
Martinez K A 2022, USA(146)	Retrospective cohort study (2015 – 2018)	5,253	86% were over 65 years/ F:48%	NVAF	DOACs	Warfarin	No	47%	Mixed effects logistic regression
Marzec L.N et al 2017, USA(147)	Cohort study (April 2008 - Sep 2014)	655,000	Mean age 74.3/ F:45.8%	NVAF and CHA2DS2-VASc score of >1	Dabigatran, rivaroxaban, apixaban	Warfarin	No	55 %	Multivariable hierarchical logistic regression

McDermott A et al 2022, USA(148)	Retrospective cohort study (Jan 2014 - Dec 2020)	161,089	Mean age 73.0/ F:2.2%	Incident AF	Apixaban, dabigatran, rivaroxaban, edoxaban	Warfarin	Yes	65.5%	Mixed-effects logistic regression
McIntyre WF et al 2018, USA and Canada(149)	Cross-sectional study (Nov 2011 - Feb 2014)	3,320	All ≥18; Mean age All 71 VKA 72 DOAC 71/ F:43.4%	Patients with a CHA2DS2-VASc score ≥1 and newly diagnosed NVAF	Dabigatran, abixaban, rivaroxaban, edoxaban	Warfarin	Yes	79.3%	Multivariable logistic regression
Mostaza J.M. et al 2021, Spain(150)	Cross-sectional study (March - Oct 2015)	961	All ≥18; Median age 81/ F: 50.5%	NVAF	Apixaban, rivaroxaban, dabigatran	VKAs (acenocumarol or warfarin)	No	88.7%	binary logistic regression analyses
Olesen J.B et al 2014, Denmark(151)	Cohort study (Aug 2011 - Oct 2013)	18,611	Mean age All 72.0/ F:45.3%	AF	Dabigatran, rivaroxaban, apixaban	VKA (warfarin)	Yes	100%	Multivariate logistics regression
Pandya E.Y. et al 2017, Australia(152)	Retrospective Cohort Study (Jan - Dec 2014)	199	Mean age 73.8/ F:45.7%	Inpatients diagnosed with AF	Dabigatran, rivaroxaban, apixaban	Warfarin	No	51.8% (103)	Multivariate logistic regression
Park S. et al 2021, Korea(124)	Cross-sectional analysis (Jan 2018 - June 2018)	6,061	Age>=75 56.6%. dabigatran 11.6%	AF or atrial flutter	Dabigatran, rivaroxaban, apixaban, edoxaban	DOACs	No .	100%	Multinomial logistic regression

			rivaroxaban 32.2% Apixaban 29.3% Edoxaban 27.0%/F:49						
Gregory Y.H. Lip 2015, Europe(125)	Cross-sectional (pilot survey) (Feb 2012 - March 2013)	902	34% ≤ 65 years, 39.5% 65–74 years, 26.5% ≥75 years /F:42%	AF	Dabigatran, rivaroxaban	VKA	No	74.8%	Univariate analysis
Potpara TS et al 2017, BALKAN (Albania Bosnia and Herzegovina Bulgaria Croatia Montenegro Romania and Serbia)(153)	Cross-Sectional Study (Dec 2014–Feb 2015)	2,712	Mean age 68.95; DOAC 68.47 VKA 69.05/F: 44.6%	AF	Dabigatran, rivaroxaban, apixaban	VKA	No	73.6%	Multivariable logistic regression
Rodríguez-Bernal C.L. et al 2017, Spain(154)	Retrospective cohort study (Nov 2011 - Feb 2014)	21,881	Mean age 74.5/F: 48%	Naïve patients with NVAF	Dabigatran, rivaroxaban, Apixaban	VKA (warfarin, acenocoumarol)	Yes	100%	logistic multivariate regression
Sanghai S R et al 2021, USA(118)	Cohort study (Feb 2010 - Sep 2015)	308,664	Mean age 77.7/F: 2.1%	NVAF and CHA2DS2-VASC ≥2	Dabigatran, rivaroxaban, apixaban	VKA	Not clear	39.4%	logistic regression models

Baaik S.H et al 2016, USA(155)	Cohort study (Oct 2010 - Oct 2012)	17193	≤65: Dabigatran 5.26%, Rivaroxaban 5.22%, Warfarin 11.04% 65–74: Dabigatran 40.83%, Rivaroxaban 36.19%, Warfarin 33.88% ≥75: Dabigatran 53.91%, Rivaroxaban 58.58%, Warfarin 55.08% Gender Distribution (Women): Dabigatran 55.51%, Rivaroxaban 61.75%,	Newly diagnosed AF patients	Dabigatran, rivaroxaban	Warfarin	Yes	100%	Multinomial logistic regression

			Warfarin 58.19						
Shurrab M et al 2019, Canada(156)	Retrospective Cohort (May 2015)	433	Median age: 87; F: 64.4% (CHESS <2), 74.1% (CHESS ≥2)	AF patients ≥65 years	Dabigatran, rivaroxaban, Apixaban	Warfarin	No	100%	Multivariable logistic regression
Urbaniak A M et al 2017, Norway(157)	Retrospective Cohort (2012–2015)	156,124	Mean age: 69.8–75.9; F: Variable across groups	AF	Dabigatran, rivaroxaban, apixaban	Warfarin	No	100%	logistic regression model
Yong C M 2017, USA(158)	Retrospective Cohort (Jan 2011–Dec 2014)	363,309	Mean: 75 years; F: 49%	AF and CHA2DS2-VASc ≥2	Dabigatran, rivaroxaban, apixaban	Warfarin	No	52%	Hierarchical multivariable logistic regression

OAC, oral anticoagulant; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism; T2DM, type 2 diabetes mellitus; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; DVT, deep vein thrombosis; PE, pulmonary embolism; CAD, coronary artery disease; MI, myocardial infarction; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or TIA, vascular disease, age 65–74 years, female sex; AD, Alzheimer's disease; NA, not available

2.3.1. Quality assessment

The total quality score of included studies ranged from 4 to 8; most studies were of high quality (n= 36, 60%) and were rated as having a low risk of bias. One study was at high risk of bias with a total score of 4, while the remaining studies (n=23, 38%) were rated as moderate risk of bias. Further details on the quality assessment are provided in **Appendix S.2.2**.

2.3.2. Factors influencing prescribing

The most frequently studied factors influencing prescribing were demographic factors, primarily age (n=46, 76.6%) and gender (n=42, 70%); as well as clinical factors, mainly kidney function (n=35, 58.3%), HF (n=29, 48.3%), previous stroke/TIA (n=26, 43.3%), thromboembolic risk (n=26, 43.3%), bleeding history (n=24, 40%), antiplatelet or non-steroidal anti-inflammatory drug (NSAID) use (n=24, 40%), bleeding risk (n=22, 36.6%), and other comorbidities such as HTN (n= 22, 36.6%), DM (n=24, 40%) and liver disease (n=13, 21.6%).

The most frequently studied socioeconomic factors were income (n=7,11.6%) and type of health insurance (n=7, 11.6%), and the most frequently studied prescriber-related factor was the prescriber specialty (n=14, 23.3%). The direction of association between the key factors examined and OAC selection – both in comparisons between DOACs and warfarin and among different DOACs – is summarized in **Appendix S.2.3.**

Demographic and prescriber-related factors

Age

Among the 60 eligible studies, 76% (n=46) examined the relationship between patient age and OAC selection. Of these, 95.6% (n=44) specifically investigated age as a factor influencing the choice between DOACs and warfarin, while 15.9% (n=7) focused on individual DOACs.

Overall, 43% of studies (n=19/44) (94,96,108,109,112,114,116,126,132,135,135,140–144,146,147,154,157) found a statistically negative association between increasing age and initiation of DOACs compared to VKA, particularly for patients aged 80 years and above (108,109); additionally, 9% (n=4/44) (113,130,137,157) reported younger age as a statistically positive factor for prescribing DOACs. The negative impact of increasing age on

DOAC prescribing was statistically significant across various age ranges: >65 (126,154), ≥75 (75-84 and ≥85) (141,142), ≥80 (135,146,157), ≥86 (132,143), ≥90 (146), 85-89, 85-94, >95 (the oldest had the lowest prevalence of using DOACs) (114).

In contrast, 18% (n=8/44) of studies (93,105,121,129,131,139,151,155) found increasing age was a significantly positive factor for initiating DOACs over warfarin. However, none of these studies included patients > 80 years. Among DOAC users, 85.7% (n=6/7) of studies (106,113,119,120,122,124) found a statistically positive association between increasing age and apixaban prescribing compared to other DOACs, especially in patients >85 years. However, there was no significant association in the choice of apixaban for individuals aged 65-74 compared to those below 65 years. Conversely, increasing age was a statistically negative factor for using dabigatran in three studies (96,120,122). Results for rivaroxaban varied; one study found no association between increasing age and the choice of rivaroxaban (122), while another study found a higher likelihood of using rivaroxaban in individuals under 65 years (113) and two studies found increasing age as a statistically negative factor for using rivaroxaban (113,120). Neither age> 79 year nor below 65 years was a significant factor for the choice of edoxaban (113). Furthermore, 34% (n=14/44) (95,106,107,111,119,121,122,127,133,134,136,138,153,156) of studies found no significant association between age and OAC choice.

Sex

Just over half of the studies (n=20/39, 51%) found no significant association between sex and DOAC initiation over VKA (105–109,111–113,119,130–133,135,136,138,140,141,149,156). Nevertheless, 35.8% of studies (n=14/39) (92,94,96,110,114,121,127,137,143,150,151,157) reported that female patients were more likely to receive DOACs, with this association becoming more significant over time (96). Conversely, 15% of studies (n=6/39) showed a contrasting pattern where female patients were less likely to be initiated on DOACs compared to men (93). The association between gender and specific DOAC prescribing patterns was mixed, with male gender positively associated with rivaroxaban and negatively with apixaban (113), while female gender showed a statistically positive association with apixaban (96,124) and rivaroxaban (155), and a statistically negative association with dabigatran (120).

Race/ ethnicity

The association of ethnicity with the prescribing choice of OACs was examined in eight studies. Half of the studies (50%, n=4/8) found that black patients were significantly less likely to be prescribed a DOAC compared to white patients (95,110,146) and other racial groups (155). This negative association persisted over time. Two studies reported that white patients had a statistically significant positive association with DOAC use compared to other ethnicities (109,137), while Hispanic patients (110), Asian/Pacific Islanders and Hispanics (114) were more likely than whites to be prescribed a DOAC, with no association observed between blacks and whites. One study found no association between ethnicity and the choice between warfarin and DOACs or among DOACs (96). All the studies investigating ethnicity and OAC prescribing were conducted in the United States.

Body weight

Ten studies evaluated the association of weight (BMI) with OAC choice. All examined the effect of weight on the choice between DOACs and warfarin, while two studies also examined the effect of weight on the choice among DOACs. The majority of studies (80%, n=8/10) (92,105,106,117,130,136,137,147) found no significant association between BMI class (<25, 25-29, ≥30 kg/m2) and the choice between DOACs and warfarin; in all eight studies, the indication for OAC use was AF.

However, 20% (n=2/10) of studies showed a significant association. One study conducted in US nursing homes (114) found that lower BMI (<18.5 kg/m²) was positively associated with DOAC prescribing, whereas higher BMI (25–40 and >40 kg/m²) was associated with lower DOAC use. The second study found that body weight <50 kg or >120 kg was a statistically negative factor for DOAC use compared with weights of 50–120 kg in patients with acute DVT or PE (113). Among DOACs, body weight >120 kg was a statistically negative factor for edoxaban use, while no significant association was found for rivaroxaban or apixaban with weight <50 kg (113). Additionally, apixaban initiators were less likely to be overweight (BMI >30) compared to users of other DOACs (106).

Region or Area of living

The geographic location where OACs were prescribed played a significant role in numerous studies (12 in total). The association varied by region, showing distinct

prescribing preferences between European countries and between Europe and the United States (113,117,125). Variations were also noted within individual countries, such as different prescribing patterns in the northern, central, and southern regions of the USA and Sweden (96,109,126,131,134,134,141). Differences were also observed among Australian states (119). Additionally, prescribing patterns varied between urban and rural settings, with urban patients generally more likely to receive DOACs compared to rural patients (131,141). However, two studies indicated that rurality did not significantly influence the initiation of warfarin over DOACs or the choice among DOACs (109,119).

Prescriber-related factors

Prescriber specialty as a factor was investigated in 13 studies, with 92% of studies (n=12/13) (93,96,111,115,126,128,130,132,138,142,153,154) showing that specialists, such as cardiologists and neurologists, were statistically significantly more likely to initiate DOACs relative to VKAs compared to general practitioners, primary care physicians, and family doctors (96,111,115,126,127,130,132,142). This association was strongest between 2012 and 2014 but declined over time (132). Three studies reported no significant association of prescriber specialty with the choice between DOACs and VKA (128,130,149).

Clinical factors

Thromboembolic risk

The impact of CHA2DS2-VASc scores on OAC choice was assessed in 26 studies. Nearly half (46%, n=12/26) found that these scores did not statistically significantly influence the choice between DOACs and warfarin (93,105,106,114,119,121,122,129,131,133,146,156). However, 30% (n=8/26) found that increased thromboembolic risk, indicated by higher CHA2DS2-VASc scores ≥ 2 (96,117,123,134,135,138), ≥ 4 (141), and ≥5 (136), reduced the odds of DOAC use, particularly in the early years of DOAC availability (2010-2014); however, most of these studies (62.5%, 5/8) were conducted within the first three years after DOAC approval (117,123,134,135,141). In contrast,19% (n=5/26) reported that higher thromboembolic risk significantly favoured DOAC initiation (94,112,127,128,144). Studies reporting a statistically significant positive association with higher thromboembolic risk were mostly conducted in later periods: 2010- 2019 (144), 2010- 2018 (94), 2014- 2016 (128), and 2007- 2016 (127), except one study 2012-

2013 (112). Among DOACs, 50% of studies (n=3/6) (96,106,122) found that patients with higher baseline thromboembolic risk (CHA2DS2-VASc score ≥ 3) were more likely to be initiated on apixaban compared to dabigatran or rivaroxaban. Conversely, 50% (n=3/6) of studies found no association between CHA2DS2-VASc score for the choice among DOACs (107,119,123).

Prior stroke or TIA

Among the 25 studies that specifically examined the choice between DOACs and warfarin, 36% (n=9/25) reported that a history of stroke or TIA a statistically significantly favoured DOAC use (106,111,121,126,137,138,150,151,154), while 40% (n=10/25) indicated a preference for warfarin (95,109,127,132,134,135,142,145,147,155). The remaining 24% (n=6/25) found no significant association (94,105,107,130,149,156).

In comparisons among DOACs, apixaban was preferred over rivaroxaban for patients with a history of stroke or TIA (106,124). One study found that patients with a history of prior stroke were more likely to use dabigatran and less likely to use edoxaban compared to rivaroxaban (124).

Bleeding risk

More than half of studies that assessed the association of bleeding risk scores with OAC prescribing (52%, n=11/21) found that these did not significantly influence OAC choice (93,105–107,114,119,124,128,129,131,146). Higher bleeding risk scores were associated with lower odds of DOAC use in 43% (n=9/21) of the studies (94,117,122,123,126,134,136–138), while one study from Korea indicated that higher HAS-BLED scores favoured DOACs (127). Among DOACs, higher bleeding risk was linked to a preference for apixaban over dabigatran and rivaroxaban (96,122).

History of bleeding

Out of 24 studies investigating the impact of bleeding history on the choice between DOAC and warfarin, 25% (n=6/24) found that a history of bleeding (105,151) or haemorrhagic stroke (132,138,141,154) increased the likelihood of initiating DOACs. Conversely, another 25% (n=6/24) of studies identified prior bleeding as a statistically significant negative factor for DOAC use (93,113,127,134,142,144). A shift in trends can be observed over time; while studies from the early post-approval

years (2011–2013) reported a statistically significant positive associations, more recent studies identified bleeding history as a negative factor for DOAC initiation (113,142) (144) (93,127). Additionally, one study found that the absence of intracranial bleeding was associated with a higher likelihood of receiving DOACs (137).

However, nearly half of the studies (47.8%, n=11/23) (92,94,106,107,111,130,132,133,135,137,149), reported no significant association between various bleeding types and OAC choice. Among DOACs, apixaban was preferred for patients with a bleeding history compared to rivaroxaban and dabigatran, with no association observed with edoxaban (113,120).

Kidney-related problems

CKD, lower glomerular filtration rate (eGFR), and higher serum creatinine levels were associated with a reduced likelihood of DOAC use, favouring warfarin, in 72.2% of studies (n=24/33) (91–93,107,109,111,113,119,122,127,128,132–136,138,141–143,151,152,154,155). This statistically significant negative association persisted across different periods, particularly from 2012-2015 and in the subsequent period from 2016-2021 (132,142). The negative association was mostly in lower GFR (30 to 50 ml/min and <30 ml/min), with no significant association between choosing DOACs over warfarin in patients with a higher GFR (50 to < 80 ml/min vs GFR ≥80 ml/min) (119,128). In contrast, in 21% of studies (n=7/33) (92,108,120,129,130,137), higher eGFR levels, creatinine clearance CrCl≥30 ml/min, CrCl ≥50 ml/min, or lower serum creatinine levels were identified as a statistically significant factors for DOAC use. Two studies found that abnormal renal function was not identified as a factor associated with the choice of DOACs compared to VKAs (106,150). However, one of these studies included patients with both NVAF and liver disease (106). Among DOACs, five studies (113,119,120,122,124) found that apixaban was consistently preferred for patients with renal impairment (GFR <60 ml/min).

Anti-platelet/NSAID medications

The effect of prior antiplatelet or NSAID use on OAC choice was investigated in 24 studies. About 30.4% (n=7/23) found that antiplatelet use – specifically clopidogrel (93,126,130), clopidogrel and ticagrelor (157), aspirin (135), or all antiplatelet (107,140) – was statistically significantly associated with an increased likelihood of

initiating DOACs. Similarly, 21.7% (n=5/23) found that NSAID use was statistically positively associated with DOAC initiation (114,127,132,142,155). One study suggested a change in the trend over time; a significant association was observed during the early years (2012–2014), which disappeared in later years (2016–2018) (132).

In contrast, 47.8% (n=11/23) found that antiplatelet use negatively influenced DOAC prescribing (105,107,109,129,135,139,142,143,149,153). However, one study reported that antiplatelet use reduced the likelihood of DOAC initiation in 2014 and 2015, but not in 2011 and 2012 (142).

A fifth (21.7%, n=5/23) (93,114,120,134,151) and 13% (n=3/23) of the studies reported no significant association between antiplatelet use and NSAID use on OAC choice, respectively (106,134,151). One study found no relationship between antiplatelet use and the choice among individual DOACs (124).

Pre-index heart failure (HF)

Heart failure's influence on OAC choice was examined in 29 studies. A majority (60%, n=17/28) revealed a negative association between HF and DOAC use, favouring warfarin (112,119,121,126,127,132,134,135,138,141–143,147,149,151,153,155). One study showed that this negative association got stronger over time in all years from 2011 to 2015 (142). Another study indicated a decrease in the strength of this negative association over time, with a weaker effect observed in the period from 2016 to 2018 compared to 2012-2014 (132). Additionally, 76% (13 out of 17 studies) that found negative association were conducted before 2016. Only 7% (n=2/28) found HF significantly favoured DOAC use (93,137), while 32% (n=9/28) reported no significant influence of HF on OAC choice (105,109,111,129,130,139,150,154,156); 66.6% (n=6/9) of these studies were conducted in 2015 or later. No association between HF and the choice among different DOACs was found (124).

For additional clinical factors, see **Appendix S.2.3**.

Socioeconomic factors

Socioeconomic factors were related to the medical institution/ clinical care setting or the patients. Several indicators such as income level, out-of-pocket expenses, insurance coverage/self-pay, type of insurance, employment status and occupation,

level of education, the poverty rate in the country, and the deprivation level were used to assess these factors. The influence of insurance type on OAC choice was examined in seven studies. However, the diverse range of health insurance systems across different countries led to associations that were specific to each country.

Overall, while the type of insurance showed a notable impact on OAC choice, other socioeconomic factors were less frequently studied.

For other socio-demographic factors, see **Appendix S.2.3**.

2.4 Discussion

This review identified several key factors influencing OAC choice, highlighting the complexity and multifaceted nature of OAC prescribing decisions in clinical practice.

2.4.1. Key factors affecting the choice between VKAs and DOACs

Of the demographic factors, age significantly influenced the choice between DOACs and VKAs. In most studies, increasing age (especially over 75, 80, and 90 years) was associated negatively with DOAC selection, particularly evident in AF patients. A negative association between age and DOAC use could potentially arise from safety concerns reported in a systematic review, as DOACs were associated with an increased risk of GI bleeding in patients aged ≥ 75 (159). However, DOACs had better efficacy in reducing stroke and systemic embolism, along with a decreased risk of intracranial bleeding, fatal bleeding, and haemorrhagic stroke compared to VKAs (159).

Furthermore, the greatest clinical benefit from increased use of OACs after the introduction of DOACs in real-world practice was observed among elderly patients at the highest risk of both stroke and bleeding (160). Despite the increase in OAC use since the introduction of DOACs, older patients remain less likely to receive anticoagulant therapy overall (161,162), and DOACs specifically. However, advanced age alone should not be the only factor in deciding for or against anticoagulation; instead, a comprehensive geriatric assessment and consideration of the net clinical benefit of anticoagulation is now recommended (163).

DOACs have been shown to reduce gender disparities in AF treatment (144). However, the results revealed a significant variation regarding gender as a determinant for DOAC vs. VKA initiation. While most studies (51%) did not find gender as a significant factor, a substantial proportion (35.8%) reported a positive

association between female gender and DOAC prescription, possibly due to the higher stroke risk in women with AF when multiple non-sex stroke risk factors are present (164,165). Geographic location significantly influences OAC prescribing patterns, with differences between European countries, and between Europe and the U.S., suggesting that regional factors including differences in healthcare systems, reimbursement policies, and prescribing guidelines play a role (166). Additionally, the intra-country differences, such as the differences in rural versus urban settings, may be influenced by factors such as regional healthcare practices, access to healthcare, and local treatment preferences. Strategies to ensure equitable access to optimal anticoagulation therapy for all patients regardless of gender, ethnicity, or geographic location should be applied, along with further research into the factors driving these variations.

In patients with AF, the efficacy and safety of DOACs are comparable to warfarin in obese patients and may be better in underweight, normal-weight, and overweight patients (167). This aligns with current treatment recommendations showing no association between weight and the selection of OACs in AF patients. However, for patients with DVT or PE, weights below 50 kg or above 120 kg had a significant negative impact on DOAC selection. This is consistent with guidelines that advise against DOAC use in patients weighing over 120 kg or with a BMI over 40 kg/m² due to limited data and concerns about suboptimal dosing in this group (168). Despite these concerns, real-world data shows that the use of DOACs at recommended doses in obese VTE patients result in similar rates of recurrence or major bleeding compared to those of normal weight (169). A meta-analysis of RCTs supports that DOACs are a safe and effective option for managing acute VTE, even in patients with extreme body weights (170). These findings suggest that weight should not influence the decision to prescribe DOACs in VTE patients.

Of the clinical factors, approximately 73% of studies (24/33) found that renal impairment was associated with a reduced likelihood of prescribing DOACs, favouring warfarin. In contrast, preserved kidney function was a strong factor for choosing DOACs. These findings could be due to the pharmacokinetics of DOACs and their varying degrees of renal excretion, which is highest for dabigatran. Initially, limited data on DOACs' safety and efficacy in patients with renal impairment made healthcare providers cautious, preferring warfarin. However, evidence has evolved (171), showing that DOACs are safe and effective in mild to moderate renal

impairment, with current guidelines recommending their use in creatinine clearance ≥30 mL/min (5,6). Patients with severe kidney disease (eGFR <30 mL/min/1.73m²) or on dialysis were excluded from the major RCTs. European guidelines (ESC and NICE [National Institute for Health and Care Excellence]) recommend cautious use of DOACs at reduced doses in these patients, with dabigatran contraindicated (5,6). However, in Europe, DOACs are not approved for CrCl ≤15 ml/min or in dialysis patients. The U.S. (AHA/ACC) guideline, however, recommends warfarin or apixaban for AF patients with ESRD or on dialysis (172). Recent reviews support DOACs in advanced CKD with CrCl <30 mL/min (173) and in ESRD/dialysis patients with AF(174), showing at least similar risks of stroke, thromboembolism, and major bleeding compared to warfarin, indicating a shift towards their preference. Similarly, findings present a mixed picture regarding the relationship between liver disease and DOAC vs warfarin use. Nearly 6/13 (46%) found liver disease was negatively associated with DOAC initiation, likely due to initial DOAC trials excluding patients with significant liver enzyme elevations. Thus, there is limited data on their use in liver disease settings. Moreover, some DOACs are partially metabolized in the liver which could be affected by liver dysfunction (175). However, an equivalent proportion of studies found no association between liver disease and OAC choice, indicating practice variations. This may reflect early evidence suggesting that DOACs are safe in patients with mild to moderate liver disease (176). Overall, the mixed findings highlight the need for further research and updated clinical guidelines to clarify the optimal anticoagulation strategy for patients with renal impairment and for those with liver disease, including evaluation of effectiveness outcomes and differences between individual DOACs in these populations.

More than half the studies found no association between bleeding risk or history of bleeding and the selection of DOACs vs. warfarin. Initially, within the first three years after DOAC approval, a history of bleeding was positively associated with DOAC prescribing; this could be due to findings from pivotal RCTs showing DOACs had less major bleeding, including ICH, compared to VKAs (85–88). Later, trends showed a shift where a history of bleeding became a negative factor for DOAC use, likely influenced by a 2013 meta-analysis raising concerns about increased GIB risk with DOACs (177). However, subsequent reviews found no significant difference in major GIB risk between DOACs and VKAs (61).

Results show that patients with higher CHA2DS2-VASc scores (≥ 2) were more likely to be initiated on DOACs, in agreement with guidelines recommendations (5,6). However, about 8/26 (30%) found that increased thromboembolic risk was associated with lower odds of DOAC initiation primarily in studies conducted between 2010-2014. During this period, warfarin was likely preferred for higher-risk patients due to concerns about the new DOACs' efficacy and safety (178). Studies showing positive associations between higher CHA2DS2-VASc scores and DOAC use were generally conducted later. Over time, real-world evidence has demonstrated DOACs' effectiveness and safety, increasing provider comfort and experience in prescribing them for higher-risk patients.

Clinical factors such as comorbidities are rarely directly included in therapeutic decisions. However, results showed that DOACs were significantly less likely to be prescribed compared to warfarin in patients with comorbidities such as HF, MI, or vascular disease; for instance, 17/28 (60%) of studies reported a significant negative association between having HF and the use of DOACs, with warfarin preference. A systematic review found clinicians perceived old age, associated comorbidities, and increased bleeding potential as barriers to optimizing anticoagulation with DOACs (178). This likely contributed to the preference for warfarin in patients with significant comorbidities. However, as evidence of better outcomes of DOACs in HF patients evolved and experience with these medications grew (179,180), the preference may have shifted, indicated by a study showing that the negative HF association weakened over time (132).

Similarly, studies revealed mixed results on the association between previous stroke/TIA history, CAD history, and OAC choice, likely due to factors such as patient characteristics, antiplatelet/anticoagulant use from previous events, and evolving evidence on DOAC use in these patients. Nearly half of the studies (11/23; 47.8%) found that concomitant antiplatelet use, common in patients with previous strokes or previous CAD, was negative factor for DOAC prescribing compared to warfarin. CAD was also a negative factor for initiating DOACs compared to warfarin. These findings suggest that healthcare providers were less likely to choose a DOAC in patients who were already on antiplatelet therapy due to concerns over bleeding risks with combined antithrombotic therapy. However, approximately one-third of studies (7/23; 30.4%) reported that concomitant antiplatelet use was associated with higher odds of DOAC prescribing, and nearly half (9/19; 47%) found no association

between CAD and the choice of anticoagulant. These results could be explained by recent research suggesting that DOAC-antiplatelet combinations may have similar GI bleeding risks, but lower ICH and other major bleeding risks compared to VKA-antiplatelet use (181).

Studies primarily examined demographic and clinical factors influencing OAC choice, with less focus on socioeconomic factors. However, socioeconomic status, such as income, plays a significant role. Patients with higher socioeconomic status had better access to newer, more expensive DOACs, leading to increased utilization. Out-of-pocket expenses and insurance coverage (private, military, and public) also contributed to these disparities. Moreover, specialists like cardiologists and neurologists initially prescribed DOACs more frequently than general practitioners, but this trend weakened as DOACs gained wider acceptance. These findings emphasize the importance of clinician expertise and experience in selecting anticoagulation therapy and suggest that education on appropriate OAC use for all providers may promote more consistent anticoagulation management.

2.4.2. Key factors affecting the choice among DOACs

Various factors significantly influenced the choice of individual DOACs, possibly due to differences in their pharmacological characteristics and safety profiles. Apixaban is the preferred choice across various demographic and clinical factors, particularly in advanced age, renal impairment, high risk of bleeding or history of previous bleeding, and higher thromboembolic risk patients.

The preference for apixaban in older patients may be partly attributed to its favourable safety profile (96,182,183) and lower hospitalization risk and healthcare costs (184). Moreover, it has shown the highest efficacy and safety compared to other DOACs (66). In renal impairment, apixaban is recommended for patients with stage 4 or 5 CKD or those on dialysis due to its safety, efficacy, and lower dependence on kidney function for clearance compared to other DOACs (185). A systematic review found apixaban and edoxaban more effective in preventing stroke/thromboembolism in AF patients with advanced CKD, with apixaban having the lowest major bleeding risk (173).

The higher prescribing of apixaban in patients with high bleeding risk or previous bleeding history could be due to its lower major bleeding risk compared to other DOACs (84). Additionally, research indicates dabigatran and rivaroxaban are associated with higher major GIB (61). A recent study found that rivaroxaban had

higher rates of GIB compared to apixaban and dabigatran, which was attributed to its once-daily dose and higher peak levels (186). Thus, although all DOACs showed a reduction in the risk of ICH, variations in major and other bleeding outcomes exist among these agents. However, only a small percentage of studies examined factors influencing DOAC choice. More studies are needed to further investigate the factors affecting the selection among different DOACs. Furthermore, direct head-to-head comparisons between different DOACs are limited, and most evidence comes from observational studies, making it difficult to draw definitive conclusions regarding superiority.

Future trends in DOAC prescribing may also be influenced by patent expiration and the subsequent introduction of generic formulations. As costs might decrease, DOACs may become accessible to broader patient populations, particularly in health systems with limited reimbursement or high out-of-pocket expenses. This could further shift prescribing patterns, potentially eliminating the traditional cost advantage of VKA and accelerate DOAC adoption. Moreover, the choice among DOACs may increasingly reflect cost considerations over clinical factors, with prescribers favouring the earliest available generics. Early generic entry may also prompt health systems to revise prescribing policies and coverage decisions.

2.4.3. Strength and limitations

This review provides comprehensive data on each factor's association with OAC selection and includes all indications for OAC use.

Despite its broad scope, this review has limitations. First, a limited number of studies examined the factors influencing the choice among individual DOACs, limiting robust conclusions. Additionally, factors such as socioeconomic status and prescriber-related influences were much less frequently studied, highlighting the need for further research. At the review level, restriction to English-language publications may have limited the inclusion of additional evidence.

2.5 Conclusion

Several key factors were identified as being associated with the choice of OAC. The association of certain factors with treatment choice is changing over time; between DOACs and warfarin, but notably also among individual DOACs, reflecting rapid clinical practice adaptation to evolving DOAC safety and effectiveness evidence. Continued research and ongoing updates to guidelines are needed to facilitate the

optimal selection of anticoagulation therapy, particularly among individual DOACs, and in patients with complex comorbidities

3 Chapter 3: Data access, data sources, and data management

This chapter describes the Scottish national healthcare data sources, data access procedures, data management processes and available variables used in this study. It outlines the national healthcare datasets linked to identify the study population, as well as the governance, ethical approvals, and data cleaning steps undertaken to prepare the data for analysis. These procedures ensured the secure handling and accurate linkage of routinely collected health data used in subsequent analyses.

3.1 Data sources

Multiple national administrative healthcare datasets are available in Scotland and, when linked, provide comprehensive information on medical history, baseline characteristics, treatments, laboratory results, hospitalisations, and mortality data for all patients registered with NHS Scotland. Data linkage is facilitated through the Community Health Index (CHI) (187), a unique identifier allocated to all residents registered with NHS Scotland health services. Its usage is mandatory in all clinical communications within NHS Scotland.

For this study, the following linked datasets were accessed and used to address the objectives presented in subsequent chapters:

The Scottish National Prescribing Information System (PIS) is the national repository of all NHS prescriptions prescribed, dispensed, and reimbursed in primary care in Scotland covering a total population of 5.3 million residents (188). It is widely regarded as a high-quality dataset because it is derived directly from electronic prescribing and dispensing records, reducing the potential for manual data entry errors. Comprehensive quality assurance protocols are embedded throughout the data collection process, ensuring accuracy and reliability (188).

Additionally, PIS was originally developed for processing prescriptions for payment reimbursement, providing a strong incentive for healthcare providers to submit complete and accurate prescription data. Consequently, the dataset exhibits a high overall level of completeness. Patient-level data have been available since 2009 following the incorporation of CHI numbers into digital systems across primary care (189). All drugs prescribed during the study period were classified according to the British National Formulary (BNF) code system as implemented at the time the data were extracted and the study was developed. Each medication was assigned a

structured BNF code reflecting its therapeutic classification, based on the BNF structure in use prior to version 70. Although the BNF classification system was updated in 2015 (188), these changes had not yet been fully implemented in prescribing and dispensing data during the period covered by this study. Accordingly, BNF codes corresponding to the pre–version 70 structure were used for analyses.

PIS records provided details on prescribed drugs, prescription dates for OACs, prescribed doses, and concomitant medications for other conditions such as antiplatelets and NSAIDs. The PIS dataset also provides information on prescribing history and patterns, as well as sociodemographic information, including Scottish Index of Multiple Deprivation (SIMD) quintiles, urban–rural classification, and health board of residence at the time of prescription.

The Community Health Index (CHI) registry is the national population register for people who use NHS Scotland services. It is maintained by NHS Scotland and contains a record for every individual registered with a GP or otherwise receiving NHS care in Scotland (190). The CHI registry holds core demographic information, including date of birth and sex, which is used routinely across NHS Scotland datasets and enables consistent identification and linkage of individuals across health records.

NRS (National Records for Scotland) is the Scottish government department responsible for collecting, maintaining, and publishing Scotland's civil registration records and population statistics, including legally registered deaths (191). NRS death records contain detailed mortality information, including date of death and underlying cause of death, coded using the Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). In this study, NRS death records were used as the authoritative source of mortality information to ascertain all-cause and cardiovascular disease (CVD)-related mortality outcomes.

The Scottish Morbidity Record (SMR) are a series of routinely collected national administrative datasets in Scotland that capture information on hospital activity across NHS Scotland, including patients' diagnoses, health conditions, and healthcare episodes recorded during interactions with NHS services. There are five main SMR datasets covering outpatient care, acute care, maternity, mental health, and geriatric long-stay admissions (192).

For this study, two SMR datasets were used: SMR00 and SMR01. SMR00 (Outpatient Attendance) records outpatient attendances, including visits to consultant-led clinics, other medical clinics, and arranged consultations conducted by consultants or senior clinical team members outside formal clinic settings. SMR01 (General/Acute Inpatient and Day Case) captures episodes of secondary care involving inpatient admissions or planned day-case treatments requiring hospital bed utilisation. Within SMR01, admissions are classified as emergency admissions, elective admissions, or inter-hospital transfers (193).

Since 1996, diagnostic information within both SMR00 and SMR01 datasets has been systematically coded using the ICD-10, while surgical procedures have been classified according to the Office of Population Censuses and Surveys (OPCS-4, version 4.10) Classification of Surgical Operations and Procedures (194).

The SMR00 and SMR01 datasets serve as primary data sources for extracting comprehensive patient information, including chronic comorbid conditions, admission classifications, and surgical operations. These data facilitated baseline patient characterisation and enabled the evaluation of both effectiveness and safety outcomes. Additionally, as comorbidities have an impact on treatment outcomes, this information was incorporated into analytical models as adjustment variables. Furthermore, surgical procedures and hospital admission data were utilised to assess the effectiveness and safety profile of the treatment interventions under investigation (e.g., bleeding, stroke, or thrombosis).

The SSCA (Scottish Stroke Care Audit) dataset is a national clinical audit that collects detailed, patient-level information on the care and outcomes of people admitted to hospital in Scotland with stroke or transient ischaemic attack (TIA). The audit is used to monitor and improve the quality of stroke care provided by hospitals across NHS Scotland, with data submitted by NHS boards through regional stroke managed clinical networks (195). In this study, SSCA data were used to complement and validate diagnoses of stroke and TIA, including both ischaemic and haemorrhagic subtypes, as well as AF. These diagnoses were originally identified from the SMR01 hospital admissions dataset, and the SSCA data were linked to capture any additional or confirmatory records.

Laboratory data from the Scottish Care Information (SCI) Store, a data repository that captures routinely collected laboratory test results generated at individual NHS health board level rather than as a single national dataset. The SCI

Store contains patient-level results from biochemistry, haematology, pathology and other laboratory types and is widely used for clinical monitoring and health research (196). In this study, SCI laboratory data were used specifically to obtain renal function measurements and, to identify and characterise renal function at baseline. For patients with available laboratory investigations, renal function was assessed using eGFR measurements and related renal function tests. Given that these laboratory parameters play a key role in anticoagulant prescribing decisions, they were analysed to examine the relationship between renal function status and OAC selection. However, the availability of laboratory data was limited to patients within the NHS Greater Glasgow and Clyde (NHS GGC) health board area, reflecting the health board level implementation of SCI systems and the scope of data approvals in place at the time of data extraction.

3.2 Study data overview

The availability of records varied by data source and reflects the datasets approved for use in this study. PIS were available annually from January 2009 to May 2021, covering more than twelve years of primary care prescribing activity across Scotland. NRS death registrations covered the same period. Laboratory data from the SCI Store were available from January 2009 to December 2022.

Hospital activity data from the (SMR00 and SMR01) records were available from January 1997 to May 2021. Extended look-back periods were applied to SMR00 and SMR01 only to capture prior hospital diagnoses and procedures for baseline characterisation and identification of factors potentially influencing treatment decisions or outcomes. Stroke events were additionally identified using the SSCA Audit, with records covering strokes occurring between January 2005 and December 2021.

The data used to conduct the study objectives included multiple categories: demographic variables (e.g., age and sex), clinical information (e.g., comorbidities and disease history), mortality data (date of death and underlying cause coded using ICD-10), sociodemographic indicators (e.g., urban–rural classification, SIMD quintile, and health board), prescription records, and laboratory measurements such as eGFR.

The datasets available for this study were restricted to individuals who met one or more predefined cohort definitions, as specified in the data access application.

These included all patients with a diagnosis of AF confirmed in hospital between January 1997 and May 2021, and patients with at least one prescription for any OAC issued between January 2009 and May 2021. For this defined cohort, all available linked records relating to hospital diagnoses and admissions (SMR00/SMR01), prescribing data from primary care (including all OAC prescriptions as well as other medications prescribed and dispensed), healthcare encounters, mortality records (NRS), and core demographic characteristics were supplied. As the initial datasets therefore contained records for a broad range of clinical activity within this cohort, the number of observations in each dataset was substantially reduced during data preparation after retaining only records relevant to the specific study objectives and removing duplicate entries.

Additionally, not all variables supplied in the initially provided datasets were retained for analysis. Variables were removed during data preparation to reduce dataset size and analytical complexity where they were not relevant to the study objectives, or duplicated information available from other sources.

Area of residence was classified according to the Scottish Government's urban–rural categorisation (197), which is determined by population size and accessibility as shown in **Table 3.1.**

Table 3.1: Scottish Government urban–rural classification categories

Class	Class Name	Description
1	Large Urban Areas	population of 125,000 people and over
2	Other Urban Areas	population of 10,000 to 124,999 people
3	Accessible Small Towns	population of 3,000 to 9,999 people & within a 30-minute drive time to an urban area
4	Remote Small Towns	Population 3,000 to 9,999 people & within a 30-minute drive to an urban area
5	Very Remote Small Towns	Population 3,000 to 9,999 people & > 60 min drive time to an urban area
6	Accessible Rural Areas	Population less than 3,000 people & within 30 min drive time to an urban area
7	Remote Rural Areas	Population less than 3,000 people & 30-60 min drive time to an urban area
8	Very Remote Rural Areas	Population less than 3,000 people& over 60 min drive time to an urban area

In addition to urban–rural classification, socioeconomic context was captured using the SIMD. The SIMD incorporates multiple aspects of deprivation by analysing data

across seven key areas: income levels, employment opportunities, educational attainment, health outcomes, service accessibility, crime rates, and housing quality (198). The methodology involves dividing Scotland into small geographic units called data zones, each of which assigned a deprivation score based on the combined indicators. These scores are used to create a national ranking system that orders all data zones from most to least disadvantaged. For analytical purposes, these ranks were grouped into quintiles, with quintile 1 representing the most deprived and quintile 5 the least deprived, with quintiles 2, 3, and 4 representing varying degrees of deprivation between these extremes. This standardized framework provides policymakers, researchers, and public services with a reliable method for identifying priority areas, allocating resources effectively, and making meaningful comparisons of socioeconomic conditions across Scotland's diverse geographic regions.

Health board of Residence refers to the regional administrative unit within NHS Scotland responsible for planning and delivering health services to the population in a defined geographical area. Scotland is divided into 14 territorial health boards, each covering a specific region (for example, NHS Greater Glasgow and Clyde or NHS Ayrshire and Arran), which are responsible for protecting and improving the health of their resident populations and for delivering frontline healthcare services. A full list of health board codes and names is provided in **Table 3.2**.

Table 3.2: NHS Scotland health boards and codes

Health board code	Health board
S08000015	Ayrshire and Arran
S08000016	Borders
S08000017	Dumfries and Galloway
S08000019	Forth Valley
S08000020	Grampian
S08000022	Highland
S08000024	Lothian
S08000025	Orkney
S08000026	Shetland
S08000028	Western Isles
S08000029	Fife
S08000030	Tayside
S08000031	Greater Glasgow and Clyde
S08000032	Lanarkshire

3.3 Data management

3.3.1. Data access

In Scotland, routinely collected health data are generated as part of the delivery and administration of healthcare services, including clinical care, service planning, and reimbursement (199). These data are systematically recorded through electronic health record systems and national administrative processes, capturing information on prescribing (200), hospital admissions, outpatient attendances, and disease-specific audits (201). Although these datasets are primarily collected to support patient care and health system administration, they can also be repurposed for approved health research following appropriate governance approvals. Since 2009, the availability of the CHI number has enabled robust individual-level data linkage across multiple healthcare datasets.

For research purposes, access to these routinely collected health data is provided through the National Safe Haven (202), a secure analytic environment managed by NHS National Services Scotland. Access to, and linkage of, specific administrative datasets for this study were coordinated by the electronic Data Research and Innovation Service (eDRIS) (203). Such access is subject to completion of mandatory governance training and approval of study protocols in accordance with NHS Scotland information governance requirements.

Through eDRIS, researchers may request access to multiple national administrative datasets for approved research projects; however, availability and coverage depend on governance approvals and the specific data requested.

Throughout the study, the data remained under the ownership and control of the data provider (NHS Scotland), and all analyses were conducted within the secure National Safe Haven environment (202). Using university-based PCs with three-level password protection, the researcher was able to access data through a virtual private network (VPN) connection. Within the Safe Haven, raw data were provided as read-only .csv files stored in a “Linked Data” folder. Editable working copies of the files were stored in a research folder named "Research/Hanan," providing the ability to edit and work with the data. Research outputs were required to be stored in a distinct folder named "Result/Hanan" and release was made available only upon request following a thorough review of the results conducted according to a statistical disclosure protocol (204). All data management and analytical procedures were conducted using R software, initially commencing with version R 4.3.3, and

subsequently updated in accordance with version releases and methodological requirements throughout the study period.

3.3.2. Data cleaning and preparation

In this project, multiple steps of data cleaning and preparation were carried out on the seven included datasets (PIS, CHI, SMR00, SMR01, NRS, SSCA and SCI-lab data) before proceeding with the analyses to ensure optimal formatting for subsequent statistical analysis.

Data preparation and cleaning procedures varied by dataset. Laboratory data required additional processing and are therefore described in detail within the renal impairment chapter. Cohort identification, variable definitions, and dataset selection are reported within the methods sections of the relevant analytical chapters.

Data cleaning and preparation comprised the following key steps:

Data validation and cleaning: For the PIS dataset, duplicate prescription records, records with missing or invalid patient identifiers, and entries not corresponding to OACs of interest were identified and removed to ensure accuracy and reliability. In addition, variables not required for the study objectives were also excluded. For all other datasets, only variables relevant to the study were extracted and linked to the PIS cohort based on patient identifiers.

Variable standardisation: Renaming variables using consistent, descriptive nomenclature to facilitate cross-dataset linkage and improve clarity in subsequent analyses.

Missing data handling: Data completeness was assessed for all linked datasets (e.g. PIS records). Missingness was minimal and restricted to sociodemographic variables (health board, SIMD, and urban–rural classification). Where possible, missing values were retrieved from SMR datasets; if no information was available, records were retained as a separate category labelled “NA/Unknown.”

Data type optimisation: Converting variables to appropriate formats, including transformation of numeric codes to categorical factors and standardisation of date formats to enable temporal analysis.

Quality assurance: Data integrity and consistency were assessed by verifying unique patient identifiers, confirming correct linkage across datasets using CHI

numbers, and performing range and plausibility checks on key demographic and clinical variables (e.g. age, dates, eGFR values)

3.3.2.1. Prescribing Information System (PIS)

For this project, annual PIS datasets were obtained for the years 2009–2021. Each annual dataset was cleaned individually before being merged into a single consolidated dataset. Each dataset contained a complete record of all prescriptions prescribed and dispensed in primary care in Scotland for the respective calendar year. The only exception was the 2021 dataset, which included only OAC prescriptions issued between 1 January 2021 and 2 June 2021, representing approximately six months of prescribing data.

Each annual dataset was received as a separate CSV file and cleaned individually before merging into a single consolidated dataset. The data processing workflow followed a systematic approach for each annual dataset. Initially, the BNF code variable was processed to retain only numeric characters (0–9) and subsequently converted to numeric format. Records containing a BNF code of 208020- corresponding to OACs – were extracted to identify the comprehensive range of OAC formulations prescribed in Scotland. However, due to missing values within the BNF code classification, the final OAC cohort was created using the approved drug name variable, which demonstrated complete data coverage.

Each file originally contained 33 variables. The total number of observations per year ranged from 7,583,949 in 2021 to 23,357,543 in 2014. As an initial data cleaning step, duplicate rows (defined as records identical across all 33 variables) were removed. The number of duplicates removed within the OAC subset ranged from 2,818 records in 2021 to 11,322 records in 2009 (**Table 3.3**).

Table 3.3: Annual prescribing information system (PIS) dataset summary: total observations, OAC prescriptions, and duplicates removed (2009–2021)

PIS year	Number of observations	Number of OAC prescriptions before removing duplicates	Duplicates removed (number of observations)
PIS 2009	20,822,632	641,622	11,322
PIS 2010	22,437,102	704,883	6,850
PIS 2011	22,611,136	728,355	7,649
PIS 2012	23,072,109	793,424	6,234
PIS 2013	23,287,743	866,746	6,500
PIS 2014	23,357,543	946,818	6,690
PIS 2015	23,135,350	1,022,228	6,671
PIS 2016	22,755,722	1,075,032	7,167
PIS 2017	22,122,898	1,113,585	7,672
PIS 2018	21,447,622	1,158,581	8,140
PIS 2019	20,710,653	1,191,889	8,308
PIS 2020	19,817,842	1,220,613	9,070
PIS 2021	7,583,949	471,398	2,818

Next, only the variables relevant to this study were retained, including patient identifiers, prescription and dispensing details, drug information, as detailed in **Table 3.4.** A unique patient identifier (ID) was generated by extracting a substring from the original Index NO variable. Prescription and dispensing dates were converted from integer to date format. Finally, data were grouped by ID and ordered by prescription date to establish a chronological record of OAC exposure for each patient.

Table 3.4: Subset of variables retained from each annual PIS dataset, with data types and missing value counts

Variable Name	Data Type	NA count	Description
ID	Character	0	Unique patient identifier
Prescribed date	Integer to date	0	Date the prescription was issued
Dispensed date	Integer to date	0	Date the medication was dispensed
Disp quantity	Numeric	3949 (0.033%)	Quantity of medication dispensed
Presc quantity	Numeric	17 (0.00014%)	Quantity of medication prescribed
Approved name	Character	0	Generic drug name
Item strength	Numeric	12 (0.00010%)	Strength of medication (mg)
Simd 2016 quintile	Integer to factor	44175 (0.37%)	Scottish Index of Multiple Deprivation quintile
Urban rural 2016	Integer to factor	51346 (0.43%)	Urban–rural classification
Patient health board	Character to factor	50156 (0.42%)	Health board of patient residence

Abbreviation: SIMD 2016 quintile: Scottish index of multiple deprivation-quantile

After merging all annual PIS datasets, the final combined dataset comprised 11,834,784 prescriptions. The prescribed date variable was used in this study, with no missing values, as it captures the exact date the prescription was issued to the patient and more accurately reflects prescribing behaviour compared to dispensed or paid dates.

Additional data transformations were performed to optimize variables for analysis. The health board variable was converted from character to a categorical (factor) variable with 15 levels, 14 corresponding to individual health boards and one representing unknown values. The SIMD quintile was utilized instead of the SIMD decile due to its five levels facilitating easier interpretation and classification; it was converted from integer to a categorical variable with an additional level for unknown

values. Similarly, the urban–rural indicator was converted from integer to a categorical variable with eight levels, plus an additional level for unknown values.

A new variable, drug type, was created to classify OACs as DOAC or VKA and was stored as a character variable. The approved name variable was retained to allow analysis of specific individual drugs. Date of birth and sex variables were merged from the demographic's dataset into the prescribing dataset. A new age variable was then derived, calculated at the time of each patient's first OAC prescription. Patients who initiated OAC therapy before the age of 18 were excluded from the cohort, resulting in the removal of 19,555 observations across 616 patients.

Empty string values in the dataset were systematically replaced with NA to ensure consistent representation of missing data across all variables and facilitate accurate downstream analysis. **Table 3.5** summarises the key variables retained for analysis, their data types after cleaning, and the number of missing values (NA count) in each variable. While variables such as patient ID, prescribed date, and approved name were complete, some variables contained missing entries, and were coded as NA.

Table 3.5: Summary of variables in the final OAC prescribing dataset

Variable Name	NA Count	Description
ID	0	Numeric
Date of birth	0	Date
sex	0	Factor
Prescribed date	0	Date
Dispensed date	0	Date
Disp quantity	3,949	numeric
Presc quantity	17	numeric
Approved name	0	character
Item strength	12	Numeric
Simd2016 quintile	44,175	Factor
Urban rural 2016	51,346	Factor
Drug type	0	Character
Patient health board	50,156	Factor
Age at prescription	0	numeric

Abbreviation: SIMD 2016 quintile: Scottish index of multiple deprivation-quantile

Health board, SIMD quintile, and urban–rural classification were cleaned and harmonized prior to analysis by comparing information across the PIS and SMR01

datasets. Variable formats were standardized; codes were cleaned and missing or “unknown” values in PIS were supplemented with corresponding values from SMR01 where available. This process reduced the proportion of missing entries and improved consistency across datasets. The final merged PIS dataset comprised all OAC prescriptions, ready for linkage with other datasets via the CHI number.

3.3.2.2. Community Health Index (CHI) dataset

The CHI dataset was imported from a CSV file, with relevant demographic variables retained for analysis, including Index number, date of birth, sex, and date of death (**Table 3.6**). A unique patient identifier (ID) was generated by extracting a substring from the Index number variable, and all date variables were reformatted to a standardized YYYY-MM-DD format. The sex variable was converted from an integer to a factor with two levels (1 = male, 2 = female).

Date of birth, which contained only year and month, were completed by appending a placeholder day value of "15" (e.g., "YYYY-MM" → "YYYY-MM-15") to minimize bias when exact dates were unknown and then converted to Date objects. Date of death, already in full date format, were converted directly to Date objects.

The CHI dataset was not used as the primary source of mortality information. Mortality ascertainment was based primarily on NRS death registrations. The final demographics dataset contained 637,150 observations. The cleaned demographics data were merged with prescription dataset.

Table 3.6: CHI dataset: variables, missing data, and type transformations

Variable	NA Count	Variable type
Date of birth	0	Change from integer to Date
Sex	0	Change from integer to factor of levels
Date of death	298,024	Change from integer to Date
ID	0	Change from character to numeric

3.3.2.3. NRS (National Records for Scotland) death records

The death records dataset was cleaned to retain only variables relevant to the study, including patient ID, date of death, underlying cause of death (ICD-10), and up to ten coded causes of death (ICD-10). Irrelevant variables, including place of occurrence, were excluded.

Patient identifiers were standardized by extracting unique ID substrings from the original index numbers and converting them to a numeric format to ensure consistency for data linkage. Date of death variables were reformatted to a standardized "YYYY-MM-DD" date format to ensure temporal consistency across the dataset. Variables representing additional contributing causes of death (cause of death 1–9) contained NA values. These might reflect the absence of additional recorded causes of death rather than missing data. A summary of variable completeness is provided in **Table 3.7**. The final dataset comprised 237,351 observations and 13 variables.

Table 3.7: Death records: variables, missing data, and type transformation

Column	NA Count	Type
ID	0	Change from character to numeric
Date of death	0	Change from character to Date
Underlying cause of death	0	Character
Cause of death code 0	0	Character
Cause of death code 1	28766	Character
Cause of death code 2	80111	Character
Cause of death code 3	141208	Character
Cause of death code 4	190238	Character
Cause of death code 5	217429	Character
Cause of death code 6	229690	Character
Cause of death code 7	234490	Character
Cause of death code 8	236342	Character
Cause of death code 9	236990	Character

Death information was obtained primarily from NRS, which was treated as the authoritative source for date of death. Demographics data were used to supplement mortality information where NRS data were unavailable. Death dates and underlying causes of death were standardised and merged with the primary prescription dataset using a unique patient identifier. Patients without a recorded death date in either source were assumed to be alive at the end of follow-up.

3.3.2.4. Scottish Morbidity Record 01 (SMR01) and Scottish Morbidity Record 00 (SMR00) datasets

The SMR01 dataset originally contained 38 variables and 8,599,716 observations. For this study, only the columns required for analysis were retained. The primary diagnosis for admission (main condition variable) demonstrated high data completeness with only three missing values out of 8,599,716 observations. Additional diagnosis fields (other condition 1–5) were also used to identify comorbidities. These fields contained varying proportions of empty entries, which are most likely attributable to the absence of additional recorded diagnoses rather than missing data, as only conditions relevant to the admission or clinical episode are typically coded (**Table 3.8**).

Surgical intervention data were captured through the main operation variable and supplementary operation fields (other operations 1–3) with their corresponding date variables. A substantial proportion of these fields contained empty entries, which likely also reflect the absence of additional recorded surgical procedures rather than incomplete data capture.

Medical conditions of interest were identified using ICD-10 diagnostic codes. Demographic and socioeconomic variables, including SIMD quintile, urban–rural classification, and health board codes, were retained where available to enable comprehensive patient characterization.

Standardized data cleaning procedures were applied to both SMR00 and SMR01 datasets to ensure consistent formatting and extract relevant variables. Patient identifiers were systematically extracted from the Index No field across all datasets, to support accurate linkage across datasets.

Date variables, including admission dates, operation dates, and clinic dates, were standardized by converting from their original character or numeric formats to a uniform date format (YYYY-MM-DD).

Table 3.8: Data completeness assessment of key SMR01 variables

Column Name	NA Count
ID	0
Urban rural 2016	85,101
Simd 2016 quintile	81,335
Health board of residence current date	0
Admission date	0
Admission reason	4,681,594
Admission transfer from	48,286
Discharge date	0
Speciality	0
Main condition	3
Other condition 1	1,920,020
Other condition 2	3,420,263
Other condition 3	4,593,383
Other condition 3.1	4,593,383
Other condition 4	5,615,872
Other condition 5	6,513,134
Main operation	4,939,722
Other operation 1	7,819,694
Other operation 2	8,399,716
Other operation 3	8,536,586
Date of main operation	4,939,720
Date of main operation 1	7,825,377
Date of main operation 2	8,399,715
Date of main operation 3	8,536,584

Note: SIMD 2016 quintile: Scottish index of multiple deprivation-quantile

The SMR00 dataset contained 17,789,643 outpatient attendance records with 26 variables in total. For this study, only variables relating to attendance date, primary and secondary diagnoses, operations, and health board of residence at the time of attendance were retained.

The SMR00 dataset contained a high proportion of missing values across most clinical condition and operation variables (**Table 3.9**), with over 90% of records having no entries for these fields. Given this, the overall contribution of SMR00 data to the study was limited. Most of the linked clinical information originated from the

SMR01 (inpatient/day case) dataset, which had more complete diagnostic and procedural records.

Table 3.9: Summary of selected variables and missing data in the SMR00 (outpatient) dataset

Column Name	NA Count
ID	0
Main condition	17,764,636
Other condition 1	17,784,194
Other condition 2	17,788,754
Other condition 3	17,789,410
Other condition 4	17,789,569
Other condition 5	17,789,611
Main operation	16,667,868
Other operation 1	17,653,891
Other operation 2	17,765,845
Other operation 3	17,783,744
Health board of residence current date	0

3.3.2.5. Scottish Stroke Care Audit (SSCA)

The SSCA dataset contained 266,609 observations with 82 variables, of which only those relevant to the study were retained. Selected variables included AF history and confirmation, anticoagulant use at stroke onset and discharge, final diagnoses of stroke and TIA, and stroke pathology classification. All retained variables had complete data.

AF diagnoses were identified in the SMR00, SMR01, and SSCA datasets using ICD-10 code I48, and combined to form a unified AF cohort, with diagnosis status recorded as present or absent. This cohort was subsequently linked to the PIS. A binary indicator was also created to denote a history of stroke or TIA. **Table 3.10** shows variables retained from the SSCA dataset, with descriptions and completeness.

The SSCA dataset does not reliably capture the date of AF diagnosis or the precise timing of stroke or TIA events in a form suitable for longitudinal analysis. As a result, indication for anticoagulant prescribing and outcome timing could not be determined using SSCA data alone. Stroke outcomes and event timing were therefore

ascertained using SMR records, where admission dates are available. **Table 3.10** summarises the SSCA variables retained for analysis, along with their descriptions and completeness.

Table 3.10: Selected variables from the Scottish Stroke Care Audit (SSCA) dataset and data completeness

Variable Name	Description	NA Count
ID	Unique patient identifier	0
History of atrial fibrillation or flutter	Indicates whether the patient had a prior diagnosis of AF or atrial flutter	0
Confirmed atrial fibrillation or flutter	Confirmation of atrial fibrillation/flutter diagnosis	0
History of atrial fibrillation or flutter	Patient history of atrial fibrillation/flutter (duplicate/alternative field)	0
Confirmed atrial fibrillation at operation	Confirmation of AF diagnosis at operation	0
Anticoagulant use at onset	Patient on anticoagulant therapy at onset	0
Final diagnosis: stroke	Final diagnosis of stroke	0
Final diagnosis: TIA	Final diagnosis of transient ischemic attack	0
Diagnosis stroke	Diagnosis of stroke (alternative field)	0
Anticoagulant use at onset (alternative field)	Anticoagulant use at onset (alternative)	0
Anticoagulant therapy at discharge	Anticoagulant therapy on discharge	0
Index stroke pathology	Pathology classification of index stroke	0

3.4 Ethical consideration

Although this study did not involve direct patient contact or intervention, ethical considerations remained essential aspects that should be protected and ensured in this type of research. While the potential for direct harm to individuals was minimal, risks associated with inappropriate data access, handling, or disclosure were

recognised. Accordingly, data security, confidentiality, and protection of patient privacy were central considerations throughout the study.

This research relied on routinely collected health data that were pseudonymized prior to researcher access and analyzed within a secure trusted research environment, in accordance with NHS Scotland information governance requirements and relevant data protection legislation. Access to the data was approved by the Public Benefit and Privacy Panel (PBPP) for Health and Social Care (Application No. eDRIS-2021-0217), which includes ethical review of the study proposal to ensure that data access requests are justified, reasonable, and aligned with ethical and public benefit standards (205). As ethical review is embedded within the PBPP approval process for studies using routinely collected health data in Scotland, separate formal university ethical approval was not required under the applicable governance frameworks.

The scoping review component of this study synthesized existing published literature and did not involve primary data collection from human participants or animals. Ethical approval and informed consent were therefore not required for this component.

4 Chapter 4: Prescribing pattern of direct oral anticoagulant drugs across Scotland from 2010 to 2020

4.1 Introduction

Since their introduction in 2008, DOACs have been marketed internationally for the prevention of thromboembolic events. In Scotland, these agents were approved for stroke prevention in patients with AF from 2011 onwards (206–209). The availability of these treatment options prompted significant changes to national and international guidelines on OAC selection.

Current clinical guidelines, including those issued by the ESC in 2020 and the NICE in 2021, recommend DOACs as first-line therapy for most non-valvular indications, notably AF and VTE (5,6,172). However, these guidelines do not specify preferred individual DOACs, potentially resulting in variability in prescribing practices both nationally and across different regions.

Prescribing decisions are further influenced by national and local policy considerations, as well as evolving clinical evidence (166). While major clinical guidelines do not prioritise specific DOAC agents, policy-level recommendations may favour particular drugs based on cost-effectiveness. For example, in January 2024, NHS England and NHS Improvement updated their commissioning recommendations to prioritise generic apixaban as the first-choice DOAC where clinically appropriate, owing to its comparable efficacy and lower cost relative to other DOACs (210). If apixaban is not suitable, edoxaban is recommended next, followed by rivaroxaban, and finally dabigatran.

In addition to policy influences, the choice of a specific DOAC is shaped by patient-level and clinical factors. The scoping review (Chapter 2) identified age, sex, renal impairment, prior stroke, thromboembolic risk, bleeding history, bleeding risk, and comorbidities as key determinants influencing DOAC selection, both in comparison with warfarin and between individual DOACs.

Prescribing patterns for anticoagulants have also evolved over time (211,212), reflecting the continuous publication of evidence evaluating the comparative efficacy and safety profiles of individual DOAC agents.

While previous studies have demonstrated increasing adoption of DOACs in clinical practice (166,213,214), most have focused on broad national trends across countries such as the United States, Belgium, France, Germany, and the UK (212–

214), with limited stratification by patient demographics or geographic region. In England, DOAC prescribing increased substantially over time, with an early preference for dabigatran and rivaroxaban shifting toward apixaban by 2019 (66).

However, the existing literature offers limited insight into detailed regional variations and differences in DOAC prescribing patterns across patient-level characteristics at a national scale in Scotland. To date, no comprehensive study has examined longitudinal annual prescribing trends of OACs across the decade from 2011 to 2020, a period encompassing the availability and widespread use of all four DOACs. Moreover, previous research has not evaluated differences in prescribing choices stratified by patient demographics, regional health boards, and urban-rural classification. Such analysis is essential to understand real-world prescribing behaviour, assess guideline adherence, and inform health policy aimed at equitable and evidence-based patient care.

4.1.1. Aims and objectives

This study aimed to report real-world OAC prescribing trends in Scotland, describing changes in OAC use across all indications. This included analysis of overall prescribing patterns by drug class (DOAC vs VKA) and individual DOAC types.

The objectives of this study were:

1. To describe trends in in the prevalence of OAC use in Scotland from January 2009 to December 2020.
2. To evaluate annual incidence rates of new OAC prescribing (per 100,000 population) in Scotland from January 2011 to December 2020.
3. To assess prescribing trends over time by drug class, comparing VKAs and DOACs, and by individual DOAC types (dabigatran, rivaroxaban, apixaban, edoxaban).
4. Among incident users of OAC therapy, to examine variation in prescribing patterns by patient demographics (age group and sex) and geographic factors (regional health board and urban–rural classification).

4.2 Methods

4.2.1. Study design and study timeline

This study used a retrospective population-based cohort design and electronic healthcare administrative data from primary care in Scotland to examine OAC prescribing patterns. Prescribing data were available from 1 January 2009 onwards;

analyses of prevalence and total prescription volume were therefore conducted from January 2009 to December 2020 (**Figure 4.1**). To allow an adequate look-back period for the identification of new users, analyses of incident OAC use were restricted to patients initiating therapy between January 2011 and December 2020.

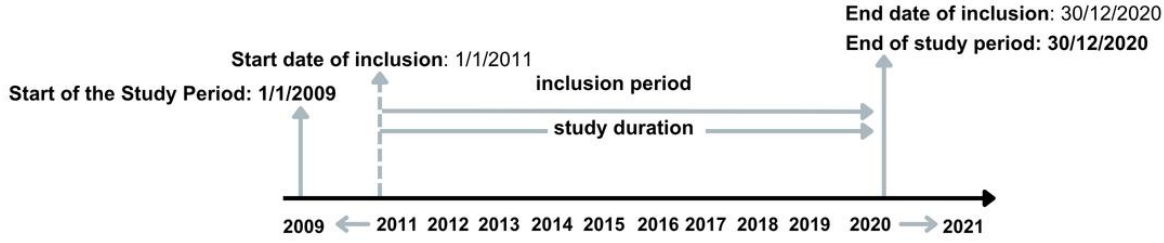

Figure 4.1: Study timeline

4.2.2. Study outcomes and analytic cohorts

The primary outcomes of this study were the changes in prescribing trends of OAC in Scotland, assessed in terms of incidence and prevalence overall, by drug class (DOACs and VKA), and by individual DOAC agents.

Two analytic cohorts were defined and used throughout this study.

- **The prevalent cohort** included all adults with at least one recorded OAC prescription in a given calendar year between January 2009 and December 2020, including both new and existing users. This cohort was used to examine trends in OAC prevalence and total prescription volume over time.
- **The incident cohort** comprised adults initiating OAC therapy for the first time between January 2011 and December 2020, with no prior recorded OAC use. This cohort was used to examine patterns of treatment initiation, baseline patient characteristics, and stratified analyses by demographic, socioeconomic, and geographic factors. For each incident user, the index date corresponded to the date of the first recorded OAC prescription.

4.2.3. Study cohort identification and selection

The overall study population comprised all adults (≥18 years) in Scotland with at least one recorded prescription for an OAC including VKA (warfarin, acenocoumarol, and phenindione) and DOACs (edoxaban, apixaban, rivaroxaban, and dabigatran) in the Prescribing Information System (PIS; described in Chapter 3). Eligibility criteria for inclusion in the study are summarised in **Table 4.1**. Patients were restricted to

those aged ≥18 years at first OAC prescription, as not all DOACs are approved for use in paediatrics and clinical trials evaluating their use in children and adolescents are ongoing (215).

Due to very low prescribing frequency, phenindione and acenocoumarol were excluded from individual drug–level analyses and baseline stratifications but were retained within the overall VKA category.

Table 4.1: Inclusion and exclusion criteria for the study cohort

Criteria	Inclusion	Exclusion
Prescription	All oral anticoagulant (OAC) drugs (by specific drug names) prescribed during the study period	No record of OAC prescription or prescriptions outside the study period
Study period	January 2009 – December 2020	Any OAC prescription before January 2009 or after December 2020
Patient age	≥ 18 years at index date (date of first OAC prescription)	< 18 years at index date

4.2.4. Cohort identification from the data source

Multiple national databases were linked to conduct this nationwide cohort study. Primary care prescribing data were obtained from the PIS. Other baseline data such as the patient's date of birth and patient sex were retrieved from the demographic dataset (described in Chapter 3). Information on comorbid conditions was identified using hospital inpatient records (SMR01), outpatient records (SMR00), and the Scottish Stroke Care Audit (SSCA), as described in detail in Chapter 3. Dataset linkage was performed using the CHI number. **Figure 4.2** illustrates the identification of the study cohort and the derivation of associated patient characteristics from linked national healthcare datasets.

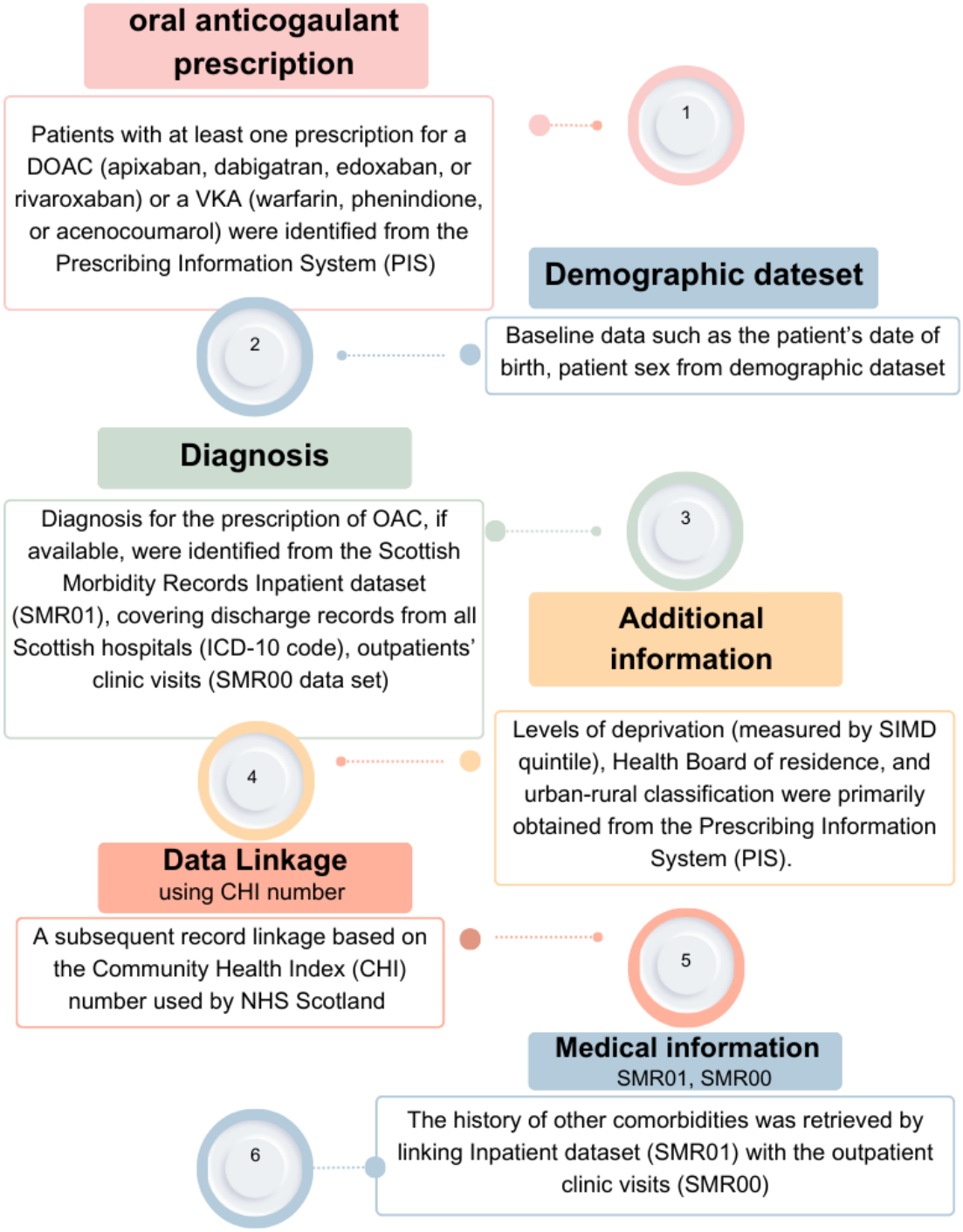

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Figure 4.2: Cohort identification and derivation of patient characteristics.

4.2.5. Baseline characteristics and stratified analyses

Analyses of baseline characteristics and stratified prescribing patterns by age, sex, health board, deprivation (SIMD quintile), and urban–rural classification were restricted to incident OAC users, as defined previously.

Selection of covariates was informed by the scoping review described in Chapter 2 and included demographic factors (age and sex), clinical factors (comorbid conditions and concomitant medications), and socioeconomic and geographic factors (SIMD quintile, health board of residence, and urban–rural classification). Definitions and data sources for all covariates used in the analyses are summarised in **Table 4.2**.

Comorbid conditions of interest included AF, DVT or PE, HF, prior stroke, ischemic heart disease (IHD), MI, HTN, DM, renal impairment, liver disease, previous bleeding, valvular AF (VAF). Concomitant medications were limited to recent aspirin or NSAID use, as these are clinically relevant modifiers of bleeding risk at the time of OAC initiation. Stroke and bleeding risk were assessed using the CHA_2DS_2-VASc and HAS-BLED scores, respectively, (as described in **Chapter 1, section 1.5**). For incident users, age and sex were determined at the index date. Concomitant medication use was defined as receipt of at least one prescription within the six months preceding the index date, reflecting concurrent or recent medication use at the time of OAC initiation. Comorbid conditions were identified from all available secondary care records prior to cohort entry, capturing diagnoses recorded during any previous hospital admissions before the index date, as the aim was to capture as much information as possible for the baseline table. This approach aligns with prior studies that have used complete historical hospital and prescribing records to define comorbidities at the time of OAC initiation (216,217). Baseline characteristics were first described for the overall incident cohort and subsequently stratified by anticoagulant group (DOAC or VKA) and by individual OAC agent.

Table 4.2: The definition of covariates identified in the relevant datasets

covariate	Definition	Data source
Age at the time of OAC prescription (Prescribed date)	Age was calculated at the date of the first OAC prescription (index date). It was assessed as a continuous variable and categorized into four categories (< 65 and 65-74, 75-84,>=85 years).	Demographic dataset
Sex	It was assessed as a binary variable, Male or female.	Demographic dataset
Comorbidities	The individual co-existing disease of interest was defined as a binary indicating the presence of a disease (yes/no).	SMR01, SMR00, SSCA dataset
Deprivation level	The Scottish Index of Multiple Deprivation (SIMD) (218)- quintile was used as a measurement of deprivation and presented as five categories. SIMD- quantile: 1 (the most deprived) to 5 (the least deprived).	PIS dataset, SMR01
Geographic area (Urban rural)	Geographic area (urban-rural) was classified using the eight-fold Scottish Government Urban Rural Classification (2016) (197), based on settlement size and drive-time accessibility.	PIS dataset, SMR01
Health board of patient residence	Patient residence was mapped to one of the 14 health boards in Scotland, following geography codes and labels defined by the Scottish Government (2006) (219).	PIS dataset, SMR01, SMR00
Concomitant medications	Each concomitant medication was recorded as binary variable (yes or no) indicate if the patient had a received a prescription for the drug within the last 6 months before the index date	PIS dataset

4.2.6. Statistical analyses

Descriptive analyses were conducted to summarise annual prescribing patterns of OACs in Scotland. Analyses were performed separately for incident and prevalent OAC users, in line with the cohort definitions described above. Annual prescribing patterns were examined overall, by anticoagulant class (DOACs and VKAs), and by individual agents.

4.2.6.1. Overall incidence and prevalence

Incidence and prevalence of OAC use were estimated on a calendar-year basis and expressed as rates per 100,000 population. Mid-year population estimates for

Scotland from 2009 to 2020 were obtained from National Records of Scotland and used as denominators (220), as presented in **Table 4.3**.

- **Prevalence** was defined as the number of individuals who received at least one OAC prescription during a given calendar year, divided by the mid-year population and multiplied by 100,000.
- **Incidence** was defined as the number of individuals initiating OAC therapy for the first time within a calendar year (with no prior recorded OAC use), divided by the mid-year population and multiplied by 100,000.

Class-level and drug-level prescribing patterns

Annual prescribing patterns were examined at both the drug-class and individual-drug levels.

Class level: The number of patients prescribed each drug class (DOAC and VKA) was calculated per calendar year. These proportions were expressed relative to the total number of patients prescribed any OAC in that year, allowing assessment of shifts in prescribing preferences between anticoagulant classes over time.

Drug level: Prescribing trends for individual DOAC agents (apixaban, rivaroxaban, dabigatran, and edoxaban) were examined separately to characterise changes in uptake and relative use of specific agents across the study period.

Incident and prevalent cohort analyses

- **Incident users**: The percentage of patients initiating a specific OAC class each year was calculated by dividing the number of patients who started that class by the total number of incident OAC users in the corresponding year. Similar calculations were performed for individual OAC agents.
- **Prevalent users**: Similarly, the percentage of patients receiving each OAC class and individual agent was calculated among all OAC users in that calendar year. Trends in total prescription volume (total number of OAC prescriptions issued per year) were assessed using the prevalent cohort.

Stratified analyses

Stratified analyses were conducted among incident OAC users only. Annual initiation patterns were examined by age group, sex, health board of residence,

SIMD quintile, and urban–rural classification to explore demographic, socioeconomic, and geographic variation in prescribing trends.
In addition, annual prescription volume was quantified by counting the total number of OAC prescription items issued per calendar year, stratified by anticoagulant class and individual drug. These counts were used to describe changes in overall prescribing volume over time.

Table 4.3: Mid-year population estimates for Scotland from 2011 to 2020 (220)

Year	Mid-year population estimate
2009	5231900
2010	5262200
2011	5299900
2012	5308500
2013	5317300
2014	5332200
2015	5351700
2016	5374900
2017	5389900
2018	5394300
2019	5414400
2020	5413100

4.2.6.2. Baseline characteristics

Baseline characteristics of the incident OAC user cohort were summarised using frequencies and percentages for categorical variables. Continuous variables were summarised using mean and standard deviation to facilitate comparability with existing literature. Age, CHA_2DS_2-VASc score, and HAS-BLED score were additionally presented using clinically relevant categories. Given the large sample size, descriptive summaries using mean and standard deviation were considered appropriate despite deviations from normality (221).

Data analyses were conducted in RStudio using the following packages: dplyr, lubridate, tidyverse, gtsummary, ggplot2, RcolorBrewer, tableone, and others.

4.3 Results

After removing duplicates and records with missing sex or date of birth (88 observations across 3 patient IDs) and excluding 616 patients who were under 18 years old at the time of their first OAC prescription, the final prevalent study cohort

included 277,947 adult patients with at least one OAC prescription between 1 January 2009 and 31 December 2020 (**Figure 4.3**).

- Over the study period, a total of 11,391,228 OAC prescriptions were issued: 2,918,743 for DOACs and 8,472,485 for VKAs.
- Of the total study population, 160,380 patients received at least one prescription for a VKA (warfarin, acenocoumarol, or phenindione), and 164,805 received at least one prescription for a DOAC. A subset of 47,238 patients (17%) was prescribed both VKAs and DOACs during the study period.
- The number of incident users (new initiators of OAC therapy) from 01.2011 to 12.2020 was 196,924. **Figure 4.3** provides an overview of the study population, the derivation of the incident and prevalent cohorts, and the distribution of OAC prescriptions over the study period.

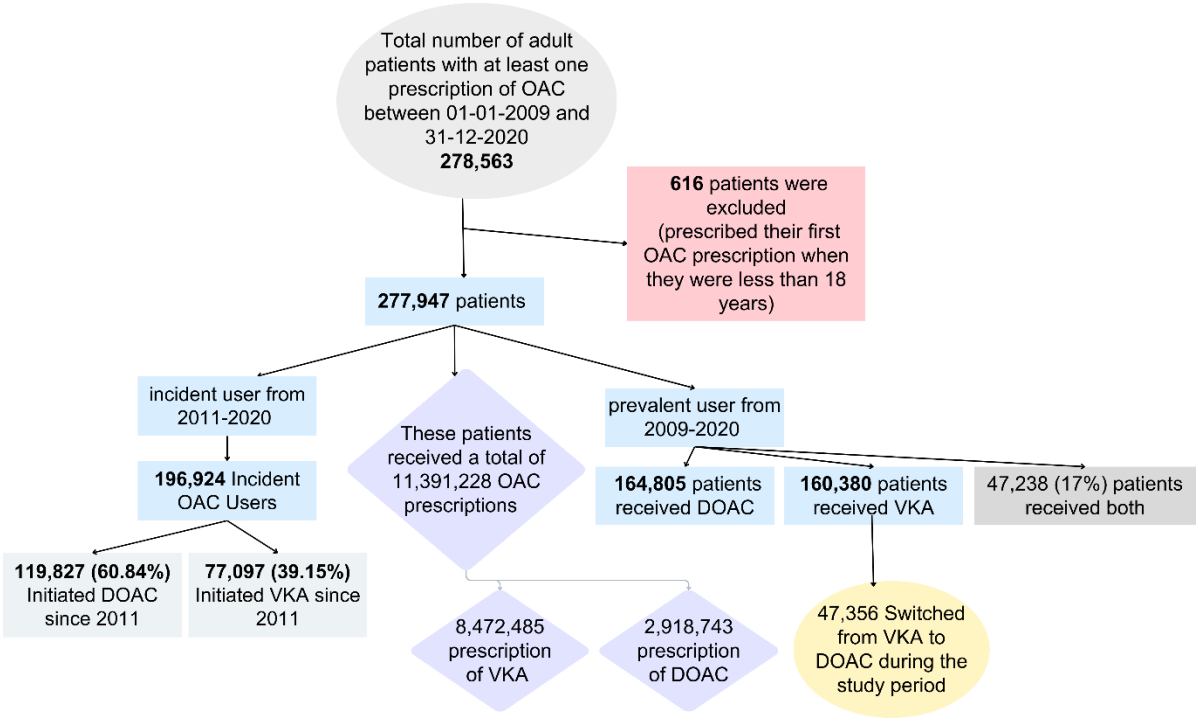

Figure 4.3: Overview of the study population, analytic cohorts (incident and prevalent), and oral anticoagulant prescriptions in Scotland, 2009–2020.

4.3.1. Total number of prescriptions dispensed in Scotland over time

The number of OAC prescriptions dispensed annually in Scotland increased steadily over the study period, rising from 637,636 prescriptions in 2009 to 1,016,342 in 2015, and reaching 1,206,003 in 2020.

The number of VKA prescriptions, primarily warfarin, decreased for the first time between 2014 and 2015 by approximately 1%, declining from 856,581 to 846,468 prescriptions, as shown in **Figure 4.4**. This downward trend in VKA prescribing continued in subsequent years. By 2020, the total number of VKA prescriptions had fallen by approximately 52% compared to 2014 levels. In contrast, DOAC prescriptions increased sharply over the same period. Between 2010 and 2020, DOAC prescribing rose by approximately 137%, reflecting a marked shift in prescribing patterns toward newer anticoagulant agents.

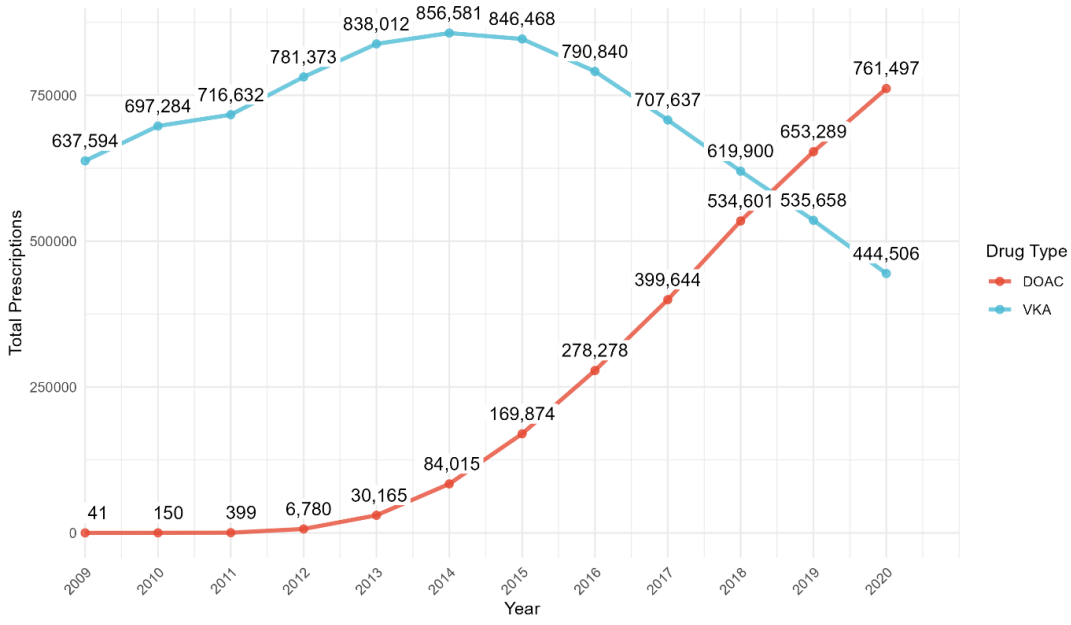

Figure 4.4: Number of OAC prescriptions prescribed in Scotland 2009-Jun 2020, by calendar year

Of the four DOACs, apixaban showed the highest increase in the number of prescriptions, reaching 389,792 by 2020, and it is the most prescribed DOAC. Even though edoxaban was approved in Scotland in 2015, results show a sharp increase

starting around 2017, reaching 218,960 prescriptions by 2020. Overall prescription numbers were much lower for both rivaroxaban and dabigatran as shown in **Figure 4.5**.

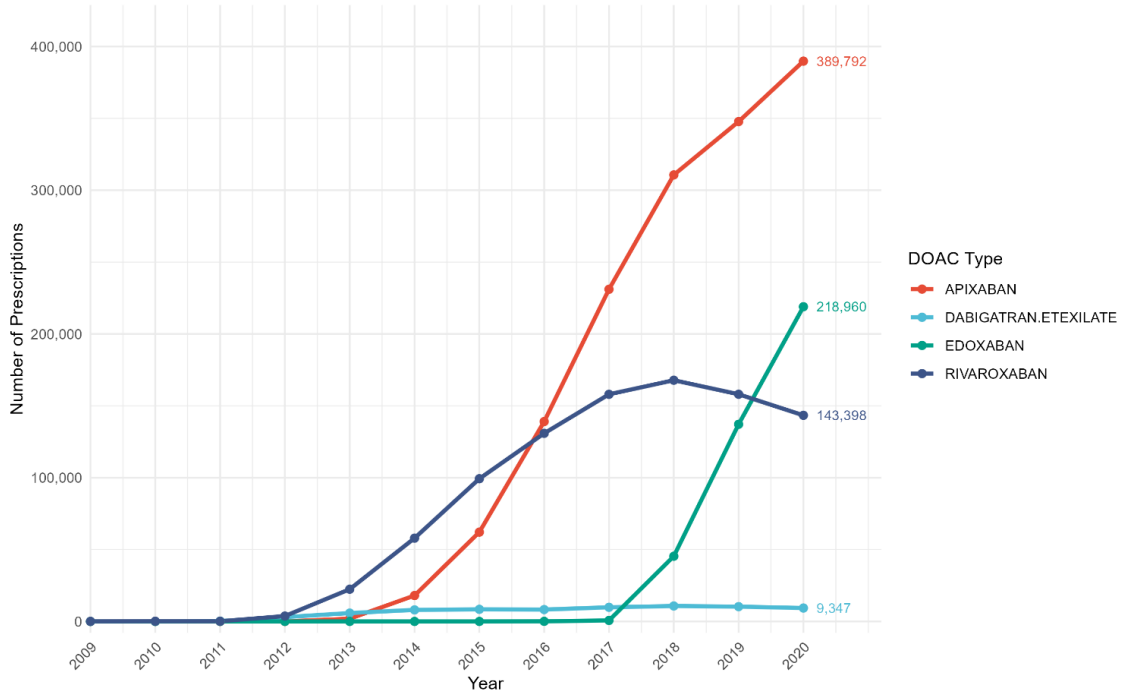

Figure 4.5: Number of DOAC prescriptions prescribed in Scotland 2009-2020, by drug and calendar year.

Note: Prescriptions for dabigatran in 2009–2010 were non-zero but excluded from the total here due to very low counts.

4.3.2. The number of prevalent OAC users per calendar year

The number of prevalent OAC users increased steadily over the study period (**Figure 4.6**), rising from 1,306.7 per 100,000 population in 2009 to 2,634.9 in 2020, representing an approximate doubling of prevalence. The most pronounced year-on-year increases occurred between 2012 and 2015. In 2013, prevalence reached 1,590.9 per 100,000 population, corresponding to an 8.23% increase compared with 2012. This was followed by further increases in 2014 (1,739.5 per 100,000; 9.35% increase) and 2015, when the growth rate peaked at 10%, reaching 1,915.4 per 100,000 population. Thereafter, the rate of increase moderated, with prevalence rising by 8.43% to 2,076.6 per 100,000 in 2016 and by 7.88% to 2,240.3 per 100,000 in 2017. By 2020, the annual increase had slowed to 3.57%, with prevalence reaching 2,634.9 per 100,000 population.

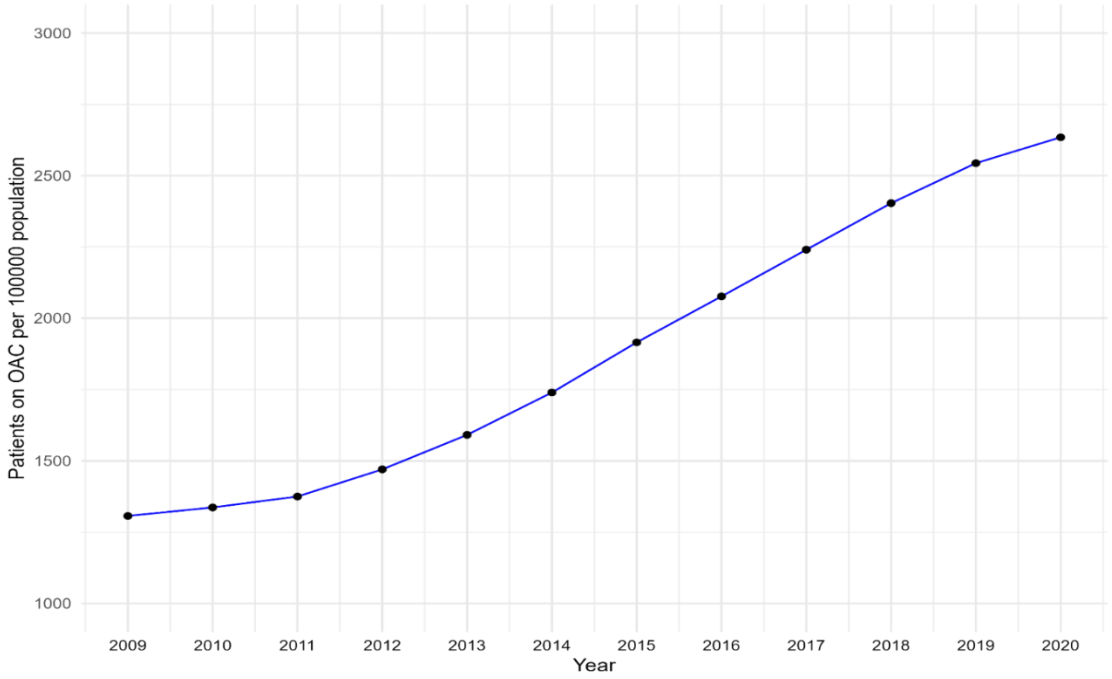

Figure 4.6: The total number of patients prescribed Oral Anticoagulants (OAC) per 100,000 population by year, from 2009 to 2020.

In 2017, 51.3% of prevalent users were on VKA, while 48.7 % were on DOAC. However, after 2017, the number of prevalent users of DOACs surpassed those of VKAs (**Figure 4.7**). By 2020, a substantial shift can be seen, with 72.1% of prevalent users taking DOACs as their OAC, while only 27.9% were on VKA therapy. The total number of patients prescribed OAC per 100,000 population by year, from 2009 to 2020.

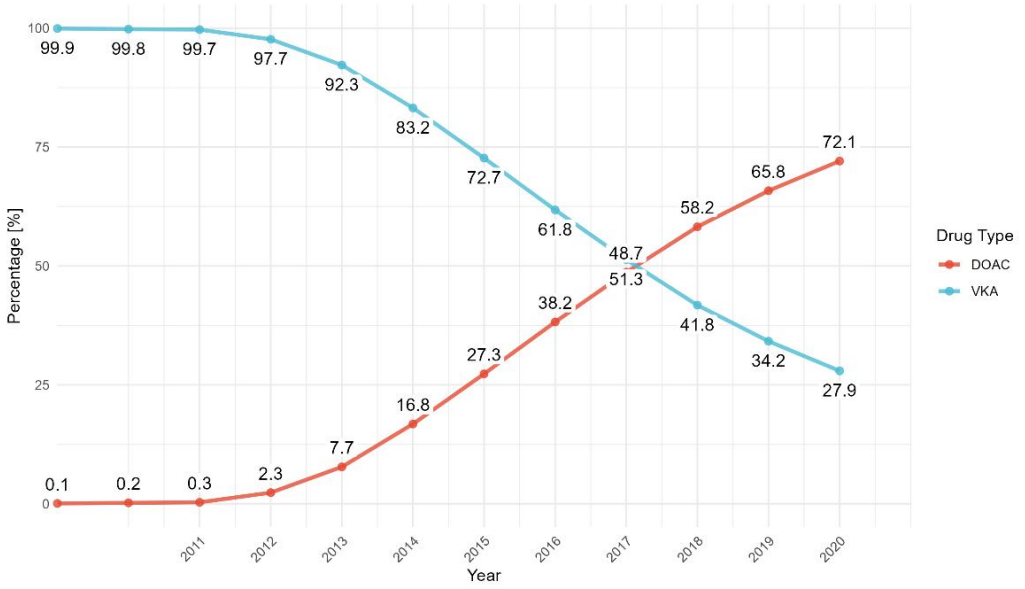

Figure 4.7: Percentage of patients on OAC per calendar year, 2009 to 2020

Warfarin was the predominant OAC until 2013. Thereafter, DOACs progressively replaced warfarin as the preferred therapy. Initially, dabigatran and rivaroxaban were the most commonly prescribed DOACs up to 2013. Between 2013 and 2016, apixaban usage began to rise markedly alongside rivaroxaban. Despite this growth, warfarin continued to hold the largest market share in 2016 at 50%, while apixaban had become the leading DOAC at 28.1%, rivaroxaban accounted for 19.5%, and edoxaban use remained minimal at 0.2%.

By 2018, warfarin's dominance declined to 40%, with rivaroxaban at 19% and edoxaban growing to 7.4%. Subsequently, edoxaban usage rose substantially, and gradually displacing rivaroxaban. By 2020, apixaban had become the most prescribed anticoagulant, accounting for 37.8% of OAC users, followed by edoxaban at 22.4%. In contrast, rivaroxaban usage declined to 13.1%, and warfarin prescriptions dropped to 25.7% of all patients on OAC, as shown in **Figure 4.8**.

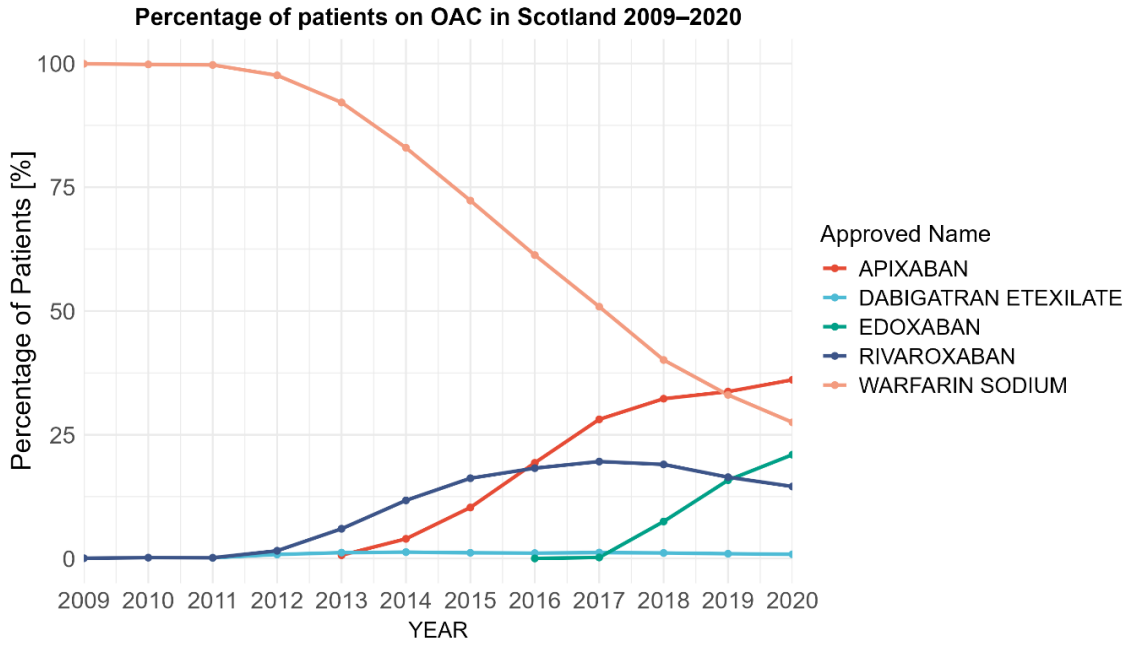

Figure 4.8: Percentage of prevalent users in each year by approved name (DOACs and warfarin)

4.3.3. Annual number of incident oral anticoagulant users (2011–2020)

When examining treatment initiation among all patients who were OAC naïve, there has been a consistent rise in OAC incident use. OAC incidence increased markedly by 72.3%, from 250.6 per 100,000 population in 2011 to 431.8 in 2019, before slightly declining by 7.9 % to 397.6 in 2020. Between 2012 and 2015, the incidence rose steadily by approximately 10% annually. However, this growth began to slow in subsequent years: from 2015 to 2016, the increase was 2.5%, followed by a 4.1% rise from 2017 to 2018, and a minimal increase of 0.3% from 2018 to 2019. Notably, from 2019 to 2020, there was a 7.9% decrease in the number of new patients starting on OACs (**Figure 4.9**).

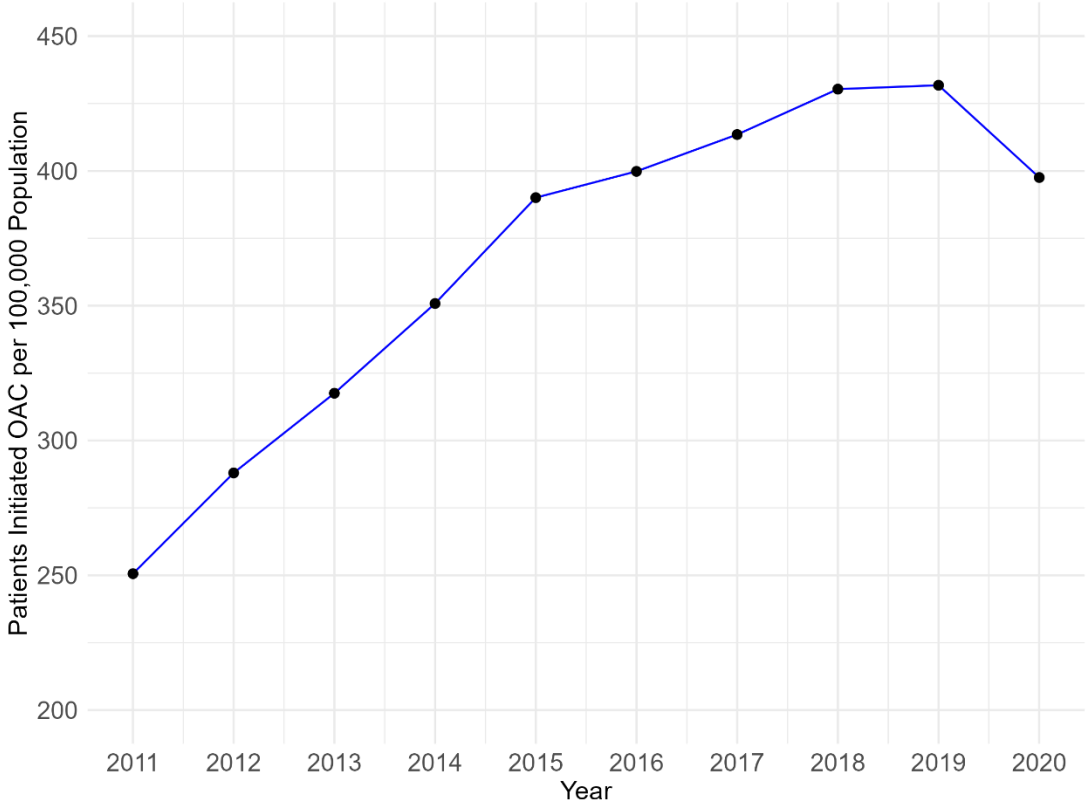

Figure 4.9: OAC incidence in Scotland 2011 – 2020, by calendar year [number patients per 100,000 population]

Additionally, a pronounced shift in the prescribing patterns for OAC is clear, with a marked increase in the share of patients initiating DOACs and a corresponding decline in those starting VKA over the past decade. In 2011, most patients (98.9%; n=13,133) initiated VKA therapy, with only 1.1% (n=148) starting DOACs.

A pivotal transformation occurred in 2015, when DOAC initiation (n=11,889; 57%) surpassed VKA initiation (n=8,987; 43.1%) for the first time. Since then, the percentage of incident users starting DOACs has consistently exceeded those starting VKAs, as illustrated in **Figure 4.10**. This trend accelerated substantially; by 2020, DOAC initiation reached 94.2% (n=20,282) of incident users, while warfarin initiation had declined dramatically to just 5.8% (n=1,232).

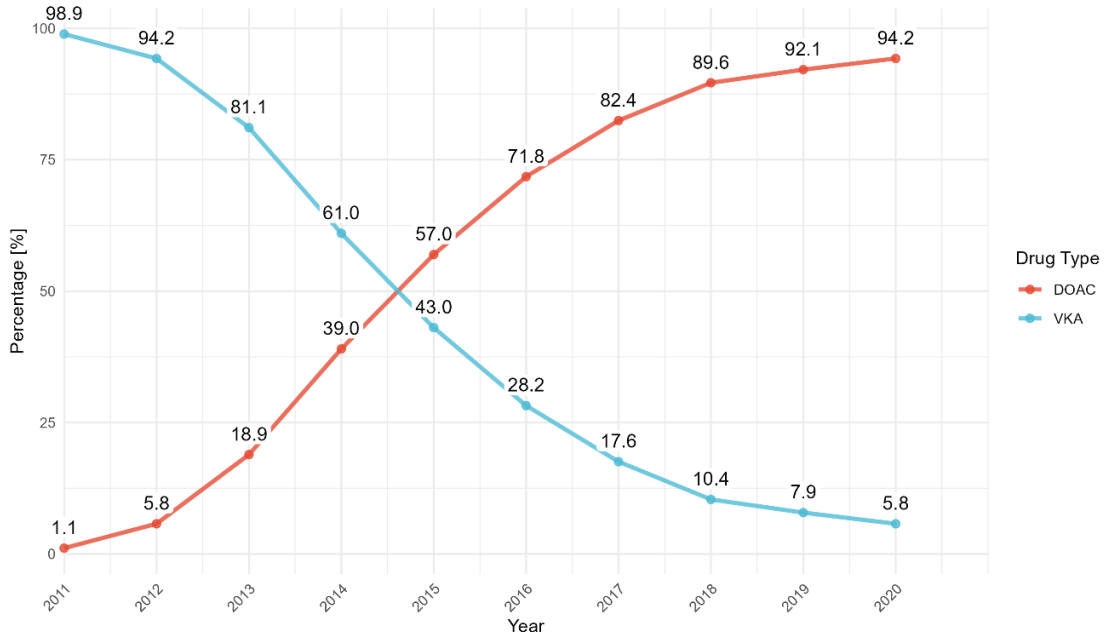

Figure 4.10: Share of patients initiating OAC with VKAs or DOAC 2011 – 2020, by calendar year [%].

Until 2015, rivaroxaban was the most prescribed DOAC for patients initiating OAC. However, from 2016 until 2021, apixaban became the most prescribed DOAC for incident OAC users in Scotland, followed by edoxaban, rivaroxaban, and lastly dabigatran. Warfarin showed a steady decline in its use from 2011 to 2020. Additionally, considerable changes over time have been observed; there was a rapid increase in patients initiating apixaban starting from 2014, peaking in 2017 and 2018, as shown in **Figure 4.11**. By 2017, apixaban was the first choice for 50% of new OAC patients. In contrast, rivaroxaban showed a steady increase from 2010 until 2016, after which its usage slightly declined from 2017 onwards. There was rapid growth for edoxaban between 2016 and 2018, with a pronounced increase in 2019. By 2020, edoxaban was the first choice for 30% of patients initiating OAC and apixaban was the first choice in 44.8% of patients initiating OAC, rivaroxaban at 19%, and warfarin at 5.7%. Dabigatran remained the least prescribed DOAC, with less than 2% of all patients initiated on any OAC being prescribed dabigatran across all years. The share of patients initiating DOAC treatment is shown in **Figure 4.11**.

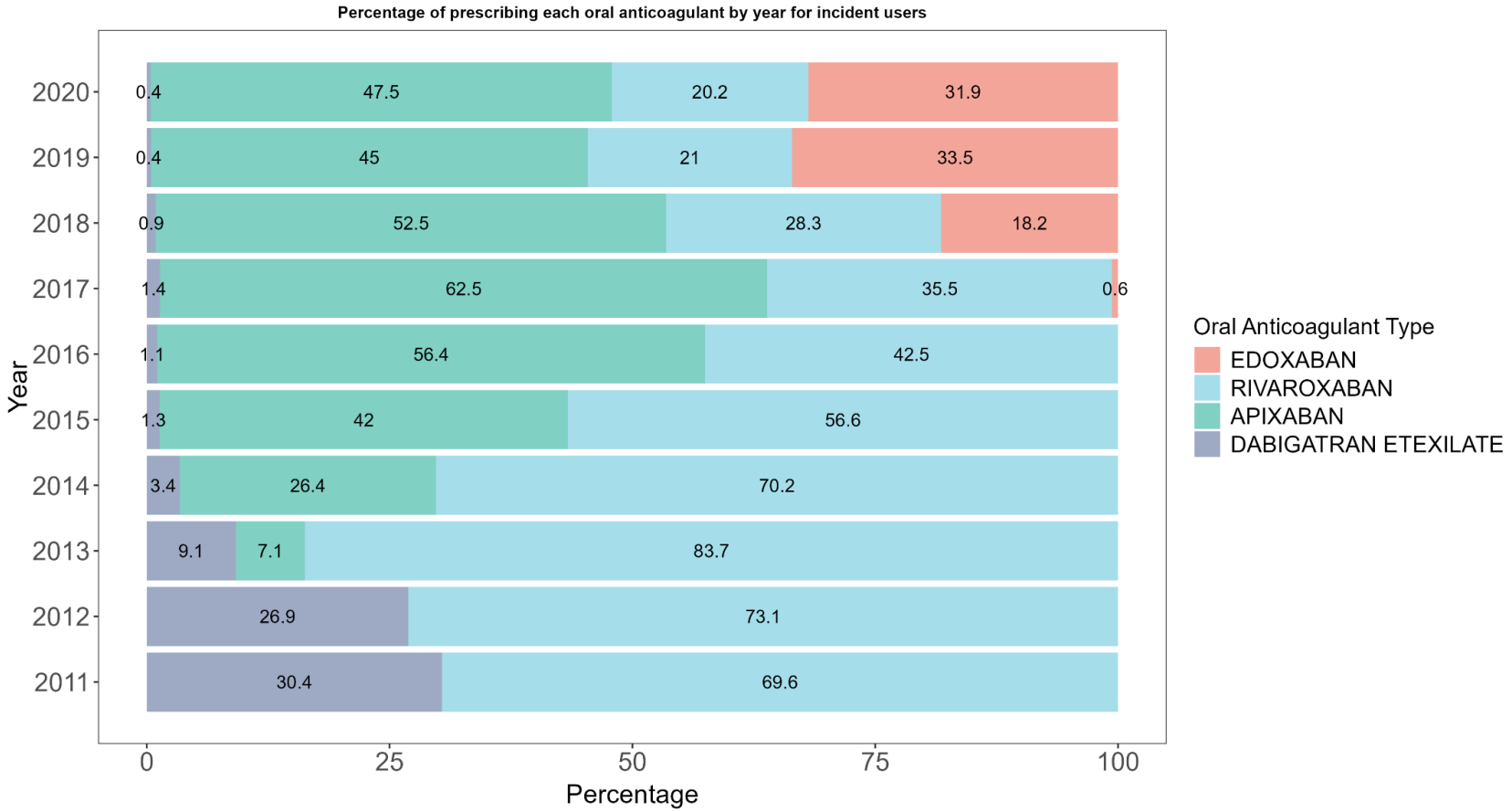

Figure 4.11: Percentage of patients initiated on each DOAC compared to other DOAC 2010-2020, by calendar year

4.3.4. Baseline characteristics of patients initiating OAC therapy

Baseline characteristics of patients who initiated OACs during the study period (n = 196,924) are presented in **Table 4.4**, stratified by anticoagulant type: (DOACs; n = 119,827) and (VKAs; n = 77,097).

Female patients comprised 47.1% of the overall incident cohort, with a slightly higher proportion among those initiating DOAC therapy compared with VKAs (47.6% vs. 46.3%). Mean age at OAC initiation was 69.5 years (SD 14.3), with patients initiating VKA therapy being slightly younger than those initiating DOACs (68.9 vs 69.9 years). Both groups demonstrated similar age distributions, with the largest proportion aged 75–84 years (29.3% DOACs, 31.2% VKAs), followed by <65 years (29.2% DOACs, 30.1% VKAs) and 65–74 years (27.6% DOACs, 29.4% VKAs). Fewer patients were aged ≥85 years, particularly among VKA initiators (13.9% DOACs vs. 9.3% VKAs).

Geographic variation in prescribing was observed. Patients initiating DOACs were more likely to reside in large urban areas compared with those initiating VKAs (32.7% vs 27.4%) and less likely to reside in other urban areas (33.5% vs. 38.2%) or very remote areas. Health boards differences were also observed, with DOAC initiators concentrated in Greater Glasgow and Clyde (23.1% vs. 16.7%), whereas VKA initiators accounted for a higher proportion of initiations in Lanarkshire (15.5% vs 8.1%) and Lothian (14.8% vs. 12.6%).

Socioeconomic status, measured by SIMD quintiles, also varied between groups. DOAC users were more evenly distributed across quintiles, while VKA users were slightly overrepresented in more deprived quintiles (e.g., quintile 2: 22.2% vs. 20.0%).

Regarding clinical characteristics, CHF, HTN, vascular disease, MI, IHD, and VAF were more prevalent among VKA users. In contrast, renal disease, history of bleeding, recent hip/knee surgery, and recent NSAID use were more common in the DOAC group. AF rates were comparable between groups (35.8% DOAC vs. 36.1% VKA), as were rates of DM (12.9% vs. 13.0%), prior stroke (10.2% vs. 10.1%), and DVT/PE history (19.6% vs. 19.7%).

Mean CHA_2DS_2-VASc scores were similar, though slightly lower in DOAC users (2.63 vs. 2.69), with fewer patients scoring ≥2 (69.5% vs. 71.7%). However, mean

HAS-BLED scores were marginally higher among DOAC users (1.83 vs. 1.78), with a greater proportion in the high-risk category (≥3: 28.8% vs. 26.7%). Complete baseline characteristics are detailed in **Table 4.4**.

Table 4.4: Baseline characteristics of the overall incident users and stratified by OAC type.

Characteristics	Overall (N= 196,924)	DOAC (N= 119,827)	VKA (N = 77,097)
Female sex, n (%)	92692 (47.1)	57009 (47.6)	35683 (46.3)
Age at prescription, mean (SD)	69.51 (14.33)	69.87 (14.55)	68.95 (13.98)
Age Category n (%)			
<65	58,167 (29.5%)	34,985 (29.2%)	23,182 (30.1%)
65-74	55,734 (28.3%)	33,090 (27.6%)	22,644 (29.4%)
75-84	59,173 (30%)	35,102 (29.3%)	24,071 (3 1.2%)
≥85	23,850 (12.1%)	16,650 (13.9%)	7,200 (9.3%)
Urban/rural n (%)			
1 large urban areas	60278 (30.6)	39175 (32.7)	21103 (27.4)
2 other urban areas	69680 (35.4)	40191 (33.5)	29489 (38.2)
3 accessible small towns	17519 (8.9)	10434 (8.7)	7085 (9.2)
4 remote small towns	5490 (2.8)	3302 (2.8)	2188 (2.8)
5 very remote small towns	3113 (1.6)	2036 (1.7)	1077 (1.4)
6 accessible rural areas	24279 (12.3)	14491 (12.1)	9788 (12.7)
7 remote rural areas	8160 (4.1)	4802 (4.0)	3358 (4.4)
8 very remote rural areas	8076 (4.1)	5206 (4.3)	2870 (3.7)
Unknown	329 (0.2)	190 (0.2)	139 (0.2)
Patient health board, n (%)			
Ayrshire and Arran	13843 (7.0)	7758 (6.5)	6085 (7.9)
Borders	5377 (2.7)	3534 (2.9)	1843 (2.4)
Dumfries and Galloway	7652 (3.9)	3239 (2.7)	4413 (5.7)
Fife	13331 (6.8)	7834 (6.5)	5497 (7.1)
Forth Valley	10246 (5.2)	6640 (5.5)	3606 (4.7)
Grampian	20056 (10.2)	12300 (10.3)	7756 (10.1)
Greater Glasgow and Clyde	40575 (20.6)	27699 (23.1)	12876 (16.7)
Highland	14894 (7.6)	10572 (8.8)	4322 (5.6)
Lanarkshire	21644 (11.0)	9714 (8.1)	11930 (15.5)
Lothian	26536 (13.5)	15119 (12.6)	11417 (14.8)
Orkney	888 (0.5)	537 (0.4)	351 (0.5)
Shetland	949 (0.5)	518 (0.4)	431 (0.6)
Tayside	17842 (9.1)	12422 (10.4)	5420 (7.0)

Characteristics	Overall (N= 196,924)	DOAC (N= 119,827)	VKA (N = 77,097)
Western Isles	1331 (0.7)	715 (0.6)	616 (0.8)
Unknown	1760 (0.9)	1226 (1.0)	534 (0.7)
Scottish index of multiple deprivation- quantile, n (%)			
1	38678 (19.6)	23454 (19.6)	15224 (19.7)
2	41150 (20.9)	24023 (20.0)	17127 (22.2)
3	42342 (21.5)	25458 (21.2)	16884 (21.9)
4	39207 (19.9)	24548 (20.5)	14659 (19.0)
5	35259 (17.9)	22186 (18.5)	13073 (17.0)
Unknown	288 (0.1)	158 (0.1)	130 (0.2)
Clinical comorbidities, n (%)			
Heart failure	21383 (10.9)	12008 (10.0)	9375 (12.2)
Hypertension	68603 (34.8)	40841 (34.1)	27762 (36.0)
Diabetes	25488 (12.9)	15431 (12.9)	10057 (13.0)
Prior stroke	20012 (10.2)	12193 (10.2)	7819 (10.1)
Vascular disease	40368 (20.5)	23460 (19.6)	16908 (21.9)
Renal disease	26652 (13.5)	17123 (14.3)	9529 (12.4)
Liver disease	893 (0.5)	492 (0.4)	401 (0.5)
History of bleeding	30713 (15.6)	19246 (16.1)	11467 (14.9)
Deep venous thrombosis/ pulmonary embolism	38665 (19.6)	23504 (19.6)	15161 (19.7)
Atrial fibrillation	70699 (35.9)	42879 (35.8)	27820 (36.1)
Valvular atrial fibrillation	17257 (8.8)	8986 (7.5)	8271 (10.7)
Myocardial infarction	17252 (8.8)	10242 (8.5)	7010 (9.1)
Ischemic heart disease	40187 (20.4)	22936 (19.1)	17251 (22.4)
Concomitant procedures and medications, n (%)			
Hip/knee surgery	22198 (11.3)	14351 (12.0)	7847 (10.2)
NSAID use	14514 (7.4)	9965 (8.3)	4549 (5.9)
Antiplatelet use	47537 (24.1)	28748 (24.0)	18789 (24.4)
Stroke risk score (CHA_2DS_2-VASc)			
CHA_2DS_2-VASc, mean (SD)	2.65 (1.78)	2.63 (1.80)	2.69 (1.76)
CHA_2DS_2-VASc category, n (%)			
0	21980 (11.2)	14097 (11.8)	7883 (10.2)
1	36389 (18.5)	22485 (18.8)	13904 (18.0)
≥2	138555 (70.4)	83245 (69.5)	55310 (71.7)
Bleeding risk score (HAS-BLED)			
HAS-BLED, mean (SD)	1.81 (1.29)	1.83 (1.31)	1.78 (1.24)
HAS-BLED category, n (%)			
0-1	89226 (45.3)	54071 (45.1)	35155 (45.6)
2	52636 (26.7)	31274 (26.1)	21362 (27.7)
≥3	55062 (28.0)	34482 (28.8)	20580 (26.7)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, prior Stroke/transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (age >65 years), Drugs or alcohol. Note: Data are presented as n (%) unless otherwise stated; continuous variables are presented as mean (SD).

4.3.5. Baseline characteristics stratified by individual oral anticoagulant

Table 4.5 describes the baseline characteristics of patients who were started on OAC, stratified by specific drug name. Among the incident patients, apixaban (n = 57,585) and warfarin (n = 76,953) were the most commonly prescribed OAC, followed by rivaroxaban (n = 42,868), edoxaban (n = 17,601), and dabigatran (n = 1,773).

The proportion of female patients ranged from 40.6% (dabigatran) to 49.1% (rivaroxaban). Mean age at prescription varied substantially, with edoxaban users being the oldest (mean 73.5 years, SD 11.2) and rivaroxaban users the youngest (66.9 years, SD 16.1). Additionally, the age distribution of patients varied across the different OACs. Among patients aged ≥85 years, edoxaban and apixaban were the most frequently initiated DOACs, with 15.8% and 15.0% of users in this age group, respectively. Dabigatran was initiated in 13.6% of patients aged ≥85 years, followed by rivaroxaban at 11.6%. Warfarin had the lowest proportion of users in the oldest age group, at only 9.3%. In contrast, a greater proportion of younger patients (<65 years) were initiated on rivaroxaban, with 37.0% of its users falling into this category, the highest among all anticoagulants. In contrast, edoxaban had the lowest proportion of younger users, with only 18.8% of patients initiated on this agent being under 65 years of age.

The majority of patients across all OACs predominantly resided in urban settings. Among warfarin users, 27.4% lived in large urban areas and 38.3% in other urban areas. For apixaban users, 39.9% were from large urban areas and 33.0% from other urban areas. This urban concentration was consistent across all DOACs, with large urban areas accounting for 22.5–39.9% of users and other urban areas for 20.1–35.5%. Conversely, rural and remote areas had minimal representation, with very remote small towns and rural areas each comprising less than 5% of users across all anticoagulant groups. This distribution is consistent with Scotland's predominantly urban population structure.

At baseline, the distribution of patients across Scottish health boards varied by anticoagulant group and largely reflected underlying health board population size. Across all anticoagulants, the largest proportions of patients were from Greater Glasgow and Clyde and Lothian, while smaller health boards, including Orkney, Shetland, and the Western Isles, contributed less than 1% of patients in each anticoagulant group. Differences in health board representation between anticoagulant groups reflect the geographic distribution of patients rather than prescribing patterns within individual health boards.

Patients with more comorbidities, including CHF, HTN, DM, renal disease, prior stroke, vascular disease, previous bleeding events, and higher thromboembolic (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED), were initiated more frequently on apixaban and edoxaban. Conversely, initiation of rivaroxaban, dabigatran, and warfarin was less common in these groups. An exception was observed for patients with a diagnosis of DVT/PE, who represented a larger proportion of rivaroxaban initiators compared with apixaban, dabigatran, and edoxaban (**Table 4.5**). Additionally, among patients with AF, initiation of rivaroxaban was comparatively lower than that of other anticoagulants.

Table 4.5: Baseline characteristics of incident oral anticoagulant users, stratified by individual oral anticoagulant

	Apixaban (N=57585)	Dabigatran (N=1773)	Edoxaban (N=17601)	Rivaroxaban (N=42868)	Warfarin (N=76953)
Female sex, n (%)	27278 (47.4)	720 (40.6)	7976 (45.3)	21035 (49.1)	35620 (46.3)
Age at prescription Maen (SD)	70.97 (13.87)	70.68 (13.05)	73.49 (11.20)	66.88 (16.07)	68.97 (13.97)
Age Category n (%)					
<65	15313 (26.6%)	485 (27.3%)	3316 (18.8%)	15871 (37%)	23106 (30.0%)
65-74	15953 (27.7%)	553 (31.2%)	5383 (30.6%)	11201 (26.1%)	22605 (29.4%)
75-84	17671 (30.7%)	494 (27.9%)	6120 (34.8%)	10817 (25.2%)	24048 (31.2%)
≥85	8648 (15.0%)	241 (13.6%)	2782 (15.8%)	4979 (11.6%)	7194 (9.3%)
Urban/rural, n (%)					
1 large urban area	22973 (39.9)	691 (39.0)	5867 (33.3)	9644 (22.5)	21050 (27.4)
2 other urban areas	18978 (33.0)	357 (20.1)	5632 (32.0)	15224 (35.5)	29437 (38.3)
3 accessible small towns	4758 (8.3)	122 (6.9)	1573 (8.9)	3981 (9.3)	7077 (9.2)
4 remote small towns	1264 (2.2)	55 (3.1)	486 (2.8)	1497 (3.5)	2186 (2.8)
5 very remote small towns	668 (1.2)	31 (1.7)	262 (1.5)	1075 (2.5)	1072 (1.4)
6 accessible rural areas	5830 (10.1)	194 (10.9)	2277 (12.9)	6190 (14.4)	9778 (12.7)
7 remote rural areas	1656 (2.9)	135 (7.6)	839 (4.8)	2172 (5.1)	3349 (4.4)
8 very remote rural areas	1355 (2.4)	181 (10.2)	647 (3.7)	3023 (7.1)	2868 (3.7)
Unknown	103 (0.2)	7 (0.4)	18 (0.1)	62 (0.1)	136 (0.2)
Patient health board, n (%)					
Ayrshire and Arran	4712 (8.2)	37 (2.1)	1650 (9.4)	1359 (3.2)	6074 (7.9)
Borders	2875 (5.0)	59 (3.3)	77 (0.4)	523 (1.2)	1841 (2.4)
Dumfries and Galloway	1698 (2.9)	108 (6.1)	956 (5.4)	477 (1.1)	4409 (5.7)
Fife	562 (1.0)	28 (1.6)	1261 (7.2)	5983 (14.0)	5493 (7.1)
Forth Valley	828 (1.4)	24 (1.4)	1124 (6.4)	4664 (10.9)	3602 (4.7)

	Apixaban (N=57585)	Dabigatran (N=1773)	Edoxaban (N=17601)	Rivaroxaban (N=42868)	Warfarin (N=76953)
Grampian	3158 (5.5)	308 (17.4)	1173 (6.7)	7661 (17.9)	7741 (10.1)
Greater Glasgow and Clyde	17298 (30.0)	481 (27.1)	5301 (30.1)	4619 (10.8)	12842 (16.7)
Highland	2075 (3.6)	366 (20.6)	1633 (9.3)	6498 (15.2)	4310 (5.6)
Lanarkshire	7573 (13.2)	112 (6.3)	955 (5.4)	1074 (2.5)	11915 (15.5)
Lothian	13490 (23.4)	93 (5.2)	448 (2.5)	1088 (2.5)	11396 (14.8)
Orkney	192 (0.3)	12 (0.7)	24 (0.1)	309 (0.7)	351 (0.5)
Shetland	129 (0.2)	10 (0.6)	124 (0.7)	255 (0.6)	431 (0.6)
Tayside	2046 (3.6)	65 (3.7)	2730 (15.5)	7581 (17.7)	5412 (7.0)
Western Isles	374 (0.6)	14 (0.8)	22 (0.1)	305 (0.7)	616 (0.8)
Unknown	575 (1.0)	56 (3.2)	123 (0.7)	472 (1.1)	520 (0.7)
Scottish index of multiple deprivation- quantile, n (%)					
1	12607 (21.9)	245 (13.8)	3559 (20.2)	7043 (16.4)	15187 (19.7)
2	12014 (20.9)	308 (17.4)	3370 (19.1)	8331 (19.4)	17095 (22.2)
3	11368 (19.7)	424 (23.9)	3711 (21.1)	9955 (23.2)	16851 (21.9)
4	10442 (18.1)	395 (22.3)	3780 (21.5)	9931 (23.2)	14634 (19.0)
5	11069 (19.2)	394 (22.2)	3169 (18.0)	7554 (17.6)	13059 (17.0)
Unknown	85 (0.1)	7 (0.4)	12 (0.1)	54 (0.1)	127 (0.2)
Clinical comorbidities, n (%)					
Heart failure	6740 (11.7)	162 (9.1)	2167 (12.3)	2939 (6.9)	9368 (12.2)
Hypertension	20417 (35.5)	606 (34.2)	7049 (40.0)	12769 (29.8)	27746 (36.1)
Diabetes	7745 (13.4)	221 (12.5)	2545 (14.5)	4920 (11.5)	10048 (13.1)
Prior stroke	7065 (12.3)	295 (16.6)	1983 (11.3)	2850 (6.6)	7815 (10.2)
Vascular disease	12358 (21.5)	331 (18.7)	3847 (21.9)	6924 (16.2)	16896 (22.0)
Renal disease	9285 (16.1)	174 (9.8)	2629 (14.9)	5035 (11.7)	9523 (12.4)

	Apixaban (N=57585)	Dabigatran (N=1773)	Edoxaban (N=17601)	Rivaroxaban (N=42868)	Warfarin (N=76953)
Liver disease	265 (0.5)	14 (0.8)	71 (0.4)	142 (0.3)	399 (0.5)
History of bleeding	9979 (17.3)	319 (18.0)	3088 (17.5)	5860 (13.7)	11452 (14.9)
DVT/ PE	10932 (19.0)	112 (6.3)	850 (4.8)	11610 (27.1)	15153 (19.7)
Atrial fibrillation	24483 (42.5)	760 (42.9)	8812 (50.1)	8824 (20.6)	27807 (36.1)
Valvular atrial fibrillation	5077 (8.8)	124 (7.0)	1725 (9.8)	2060 (4.8)	8265 (10.7)
Myocardial infarction	5726 (9.9)	143 (8.1)	1765 (10.0)	2608 (6.1)	7005 (9.1)
Ischemic heart disease	12376 (21.5)	359 (20.2)	3847 (21.9)	6354 (14.8)	17238 (22.4)
Concomitant procedures and medications, n (%)					
Hip/knee surgery	6557 (11.4)	156 (8.8)	2128 (12.1)	5510 (12.9)	7845 (10.2)
NSAID use	4772 (8.3)	90 (5.1)	1751 (9.9)	3352 (7.8)	4545 (5.9)
Antiplatelet use	16054 (27.9)	515 (29.0)	5240 (29.8)	6939 (16.2)	18784 (24.4)
Stroke risk score (CHA_2DS_2-VASc)					
CHA_2DS_2-VASc, mean (SD)	2.78 (1.81)	2.61 (1.77)	2.94 (1.73)	2.30 (1.76)	2.69 (1.76)
CHA_2DS_2-VASc category, n (%)					
0	5835 (10.1)	217 (12.2)	1181 (6.7)	6864 (16.0)	7843 (10.2)
1	9879 (17.2)	319 (18.0)	2510 (14.3)	9777 (22.8)	13853 (18.0)
≥2	41871 (72.7)	1237 (69.8)	13910 (79.0)	26227 (61.2)	55257 (71.8)
Bleeding risk score (HAS-BLED)					
HAS-BLED, mean (SD)	1.96 (1.32)	1.90 (1.34)	2.08 (1.27)	1.55 (1.26)	1.78 (1.24)
HAS-BLED category, n (%)					
0-1	23500 (40.8)	773 (43.6)	6434 (36.6)	23364 (54.5)	35042 (45.5)
2	15538 (27.0)	482 (27.2)	5102 (29.0)	10152 (23.7)	21343 (27.7)
≥3	18547 (32.2)	518 (29.2)	6065 (34.5)	9352 (21.8)	20568 (26.7)

Abbreviations: DVT/PE, deep vein thrombosis/pulmonary embolism; NSAID, non-steroidal anti-inflammatory drug; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, prior Stroke/transient ischaemic attack (2 points), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (age >65 years), Drugs or alcohol. Note: Data are presented as n (%) unless otherwise stated; continuous variables are presented as mean (SD).

4.3.6. Sociodemographic variation in prescribing among incident users

4.3.6.1. Prescribing patterns stratified by sex

There were minor disparities observed between patient sex regarding treatment initiation with DOAC or VKA, and their selection of the initial DOAC therapy. In 2018, 2019, and 2020, a slightly higher proportion of female patients newly initiating OAC treatment received a DOAC than male patients. Specifically, 90.4, 92.6% and 94.7% of all female patients newly initiating OAC treatment received a DOAC, while the share among male patients was 89, 91.7%, and 93.9%, respectively. The distribution of sex among patients initiating DOAC treatment between 2011 and 2020 is shown in **Figure 4.12**.

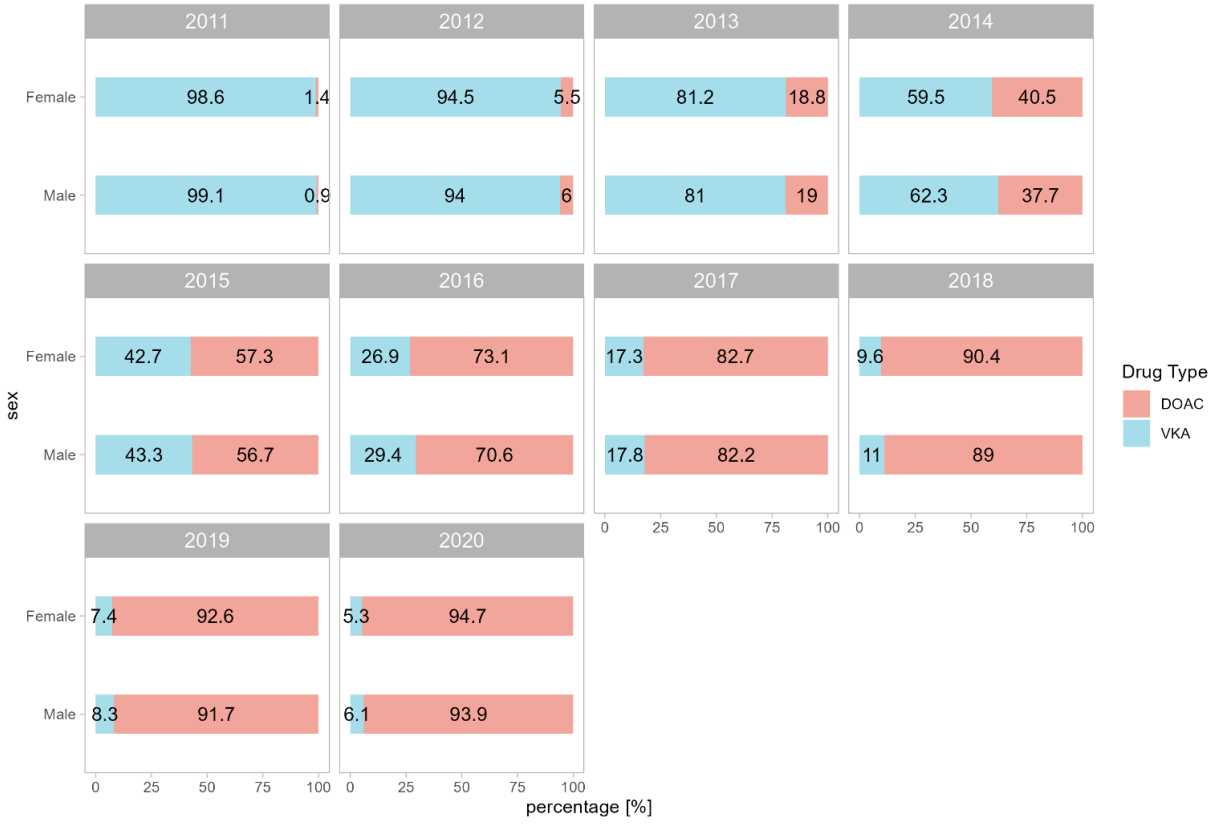

Figure 4.12: Share of patients initiating DOAC or VKA 2011-2020 by patient sex and calendar year [%]

As shown in **Figure 4.13**, from 2011 to 2020, both female and male patients demonstrated a clear shift from dabigatran and rivaroxaban toward apixaban and later edoxaban. Early in the study period, dabigatran and rivaroxaban predominated; however, from around 2014–2015 onward, apixaban rapidly became the most commonly initiated DOAC in both sexes. Edoxaban uptake increased in later years, particularly after 2017. By 2020, apixaban accounted for approximately half of DOAC initiations among both female (48%) and male (47%) patients.

In the early years (2011–2014), rivaroxaban accounted for a slightly higher proportion of initiations among female patients compared with males. From 2017 onward, edoxaban initiation increased in both sexes, with marginally higher proportions among male patients in later years; however, absolute differences between males and females were small. No consistent sex-based differences were observed for apixaban or dabigatran use.

Figure 4.13: Share of patients initiating each approved name 2011-2020 by patient sex and calendar year [%]

4.3.6.2. Prescribing patterns stratified by age at initiation

The proportion of patients initiating OAC treatment with DOACs increased across all age groups over time, with DOACs becoming the first choice for the majority of new patients by 2015. Initially, there were slight variations in adoption rates among age groups, with older age groups showing a higher proportion of DOAC initiation. For instance, in 2015, 54% of patients aged 75-84 received a DOAC as their first prescription compared to 66% of those aged 85 or older. Although this age-related disparity persisted, it diminished over time. By 2020, DOAC initiation rates had become more uniform and substantially higher across all age groups: 90% for patients <65 years, 95% for 65-74 years, 96% for 75-84 years, and 98% for those ≥85 years. See also **Figure 4.14**.

Figure 4.14: Prescribing patterns based on Age: from 2011-2020 % of patients starting DOAC

Across all years studied, rivaroxaban was consistently prescribed at higher rates among patients under 65 years of age compared to older age groups. Conversely, edoxaban was generally less frequently prescribed in the youngest age group (< 65 years) relative to all other age groups. Apixaban became the most commonly prescribed OAC across all age groups from 2016 onwards. It was particularly preferred in the oldest age groups (75-84 and ≥85 years) and less commonly prescribed in the youngest age group (< 65 years). However, this age-related disparity in apixaban prescription narrowed in 2019 and 2020. By 2020, apixaban had become the first choice OAC for over 40% of patients initiating any OAC treatment, regardless of age group. See **Figure 4.15**.

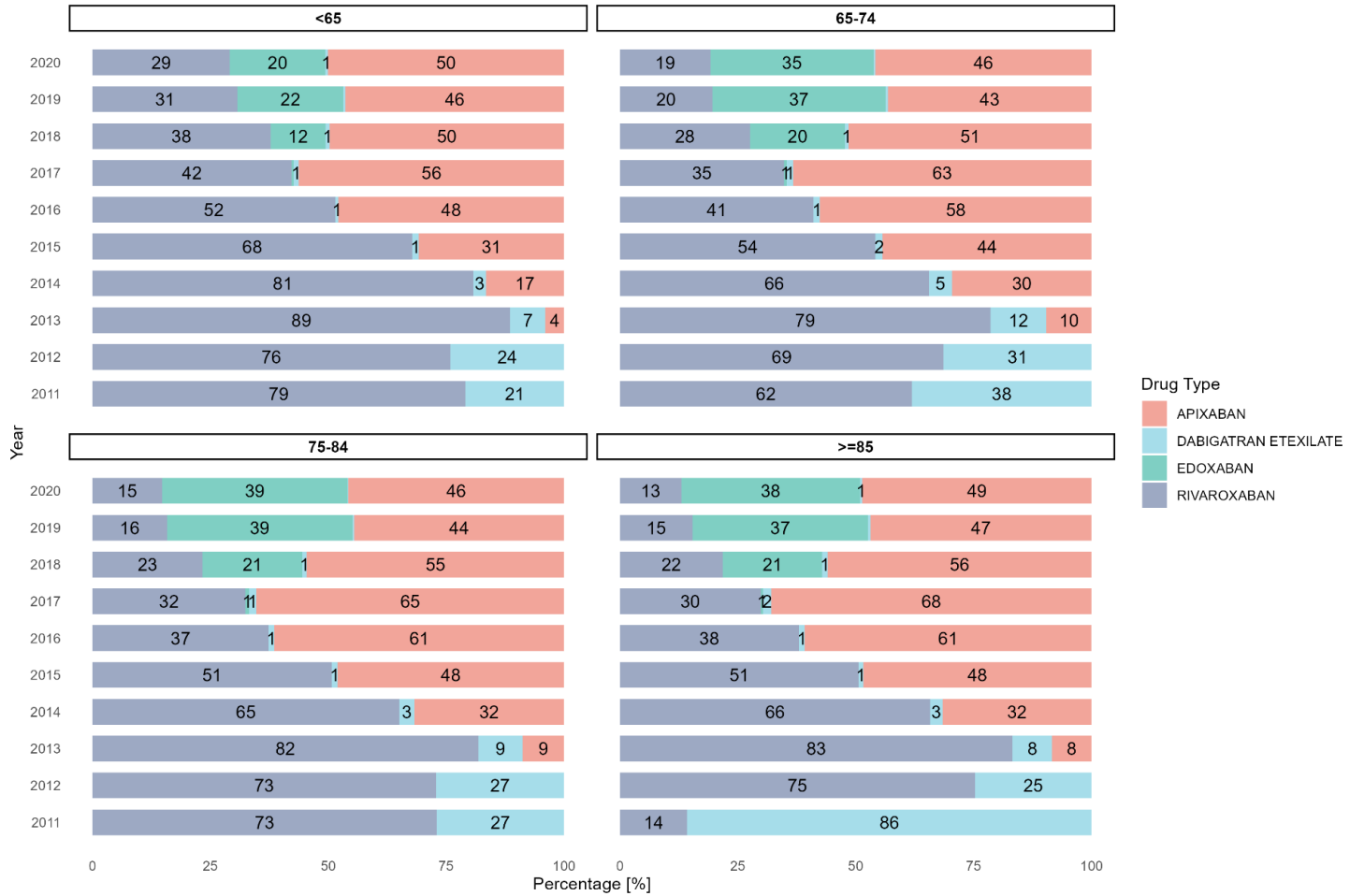

Figure 4.15: Share of patients initiating DOAC treatment with each drug 2011-2020, by patient age group at time of first prescription [%].

Note: Categories with proportions <1% are shown on the graph (coloured segments), but their percentage labels are not displayed for visual clarity.

4.3.6.3. Prescribing patterns stratified by socioeconomic and geographic factors

The choice between VKAs and DOACs for initiating oral anticoagulation showed minimal variation by socioeconomic deprivation, as measured by SIMD quintiles (**Figure 4.16**). By 2020, the proportion of patients initiated on a DOAC ranged from 91% to 96% across SIMD quintiles. Similarly, the distribution of specific DOAC agents varied minimally by deprivation level (**Figure 4.17**). From 2017 onwards, apixaban was the most frequently initiated DOAC in all quintiles, accounting for over 40% of initiations in each quintile, while edoxaban use increased across all deprivation categories, accounting for up to a third of new DOAC prescriptions in 2020.

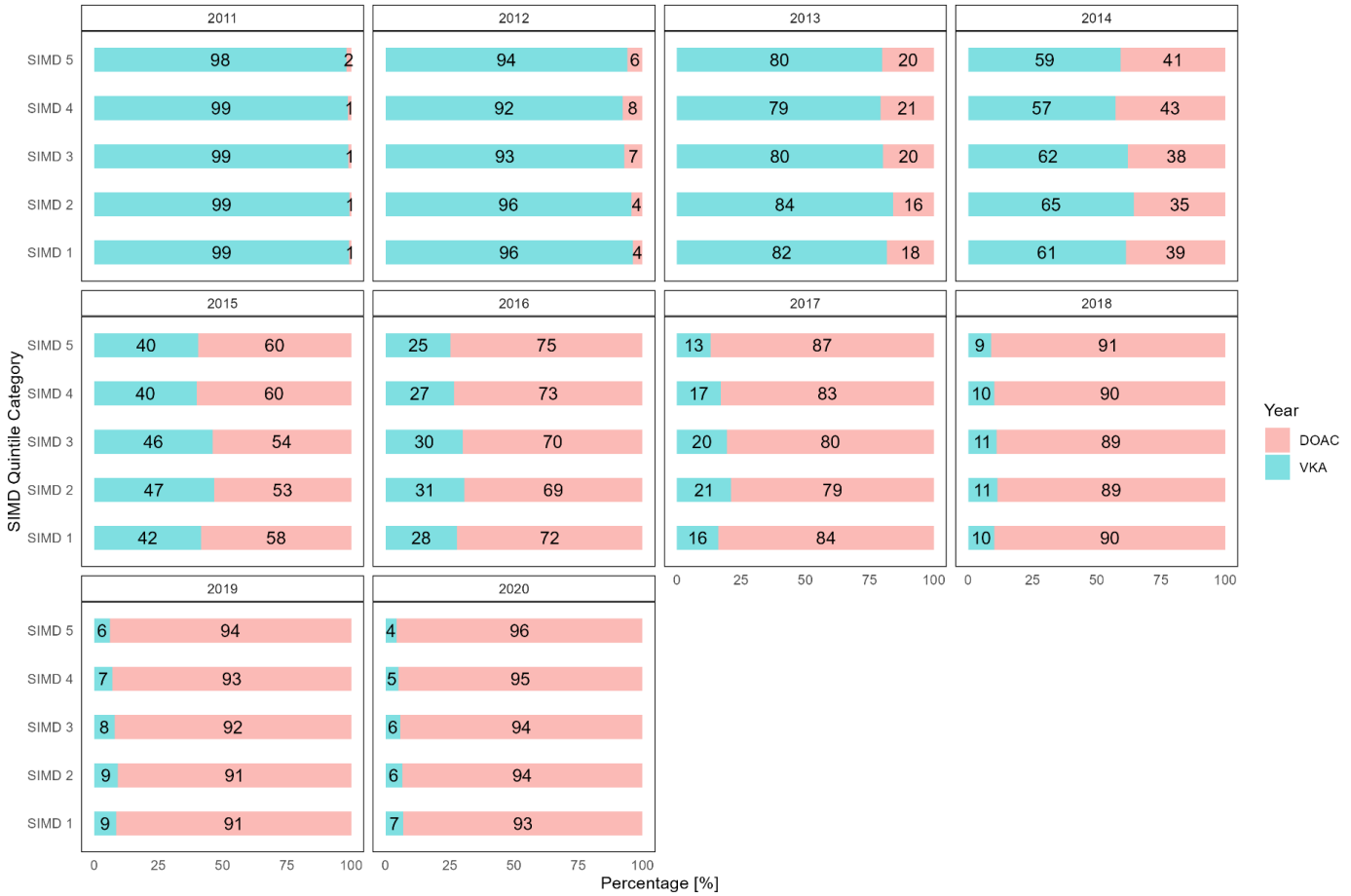

Figure 4.16: Share of patients initiating DOAC treatment with each drug 2010-2020, by level of deprivation [%].

Note: SIMD – Scottish Index of Multiple Deprivation; Category 1 represents the most deprived 20% of the population, while category 5 represents the least deprived 20%.

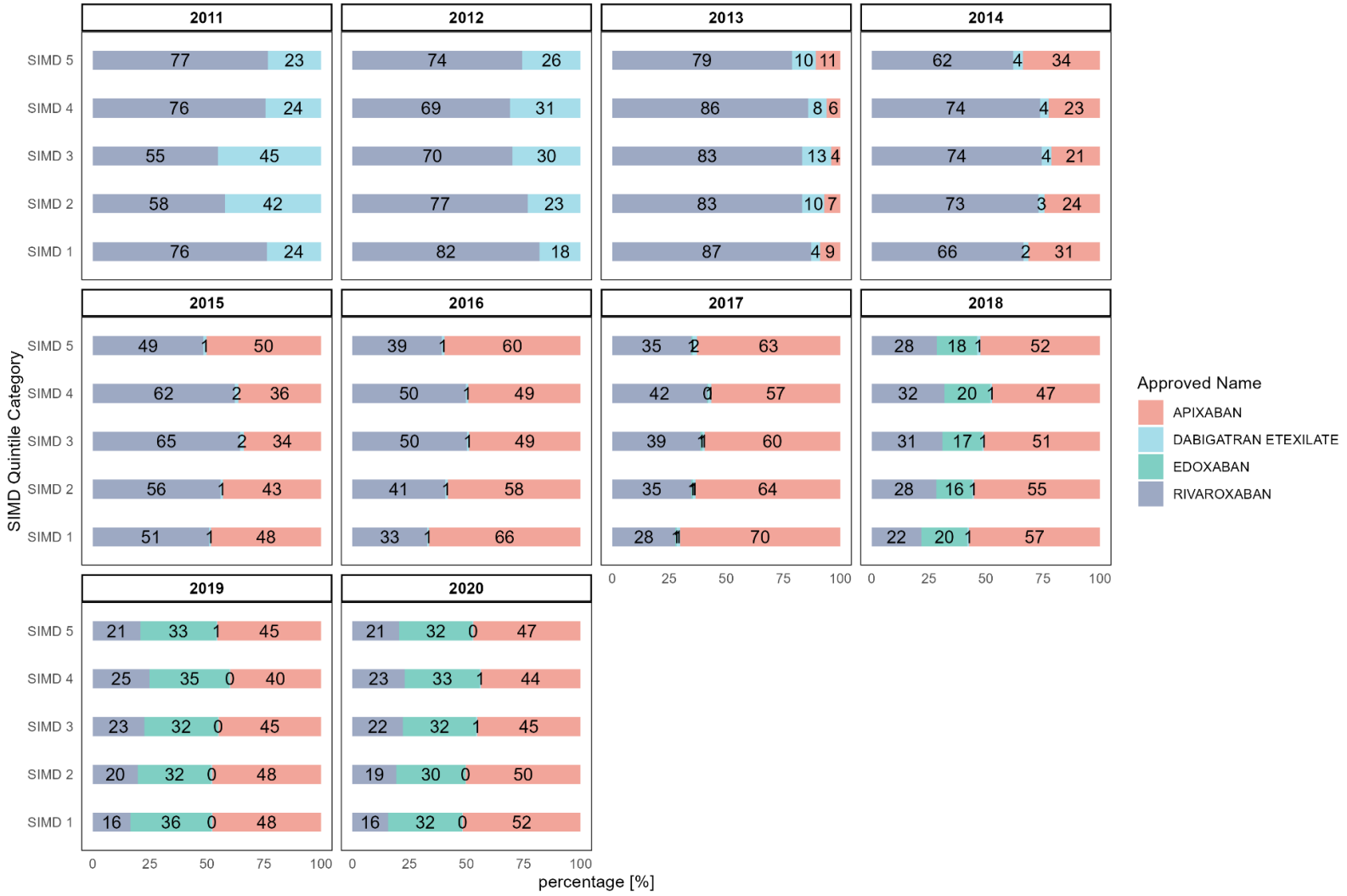

Figure 4.17: Percentage of patients initiating each DOAC compared to other DOAC stratified by SIMD quintile, 2011-2020.

In contrast, substantial geographic variation in OAC prescribing was observed in the early years (2012–2017), following DOAC approval, particularly across health boards (**Figure 4.18**). In 2015, Lanarkshire and Dumfries & Galloway reported the lowest proportions of DOAC initiation (56% and 42%, respectively), whereas Greater Glasgow and Clyde and the Highlands reported the highest proportions (93% and 91%, respectively). However, by 2020, DOAC initiation rates had increased markedly and became more uniform across all health boards. Lanarkshire and Dumfries & Galloway reported DOAC initiation rates of 91% and 93%, respectively, while Greater Glasgow and Clyde and the Highlands continued to show the highest rates, at 95% and 98%, respectively.

Additionally, there was clear geographic variation in the choice of first-line DOAC among patients initiating DOAC therapy across health boards. In 2020, apixaban was the most frequently initiated DOAC in many regions, particularly in the Western Isles (76%), Lothian (85%), Lanarkshire (76%), and Borders (91%). However, apixaban initiation remained relatively low in some health boards, including Fife (5%), Tayside (11%), and Forth Valley (14%). Additionally, in some regions, edoxaban accounted for a substantial share of DOAC initiations and was the most frequently initiated DOAC in Dumfries and Galloway (52%), Forth Valley (47%), Tayside (43%), and Shetland (37%), at the expense of apixaban, indicating a shift in the prescribing patterns in these regions.

Rivaroxaban initiation remained comparatively high in certain health boards, particularly Fife (46%), Tayside (43%), and Highland (39%). These findings indicate persistent regional variation in the choice of specific DOAC agents among patients initiating DOAC therapy (**Figure 4.19**, **Figure 4.20**).

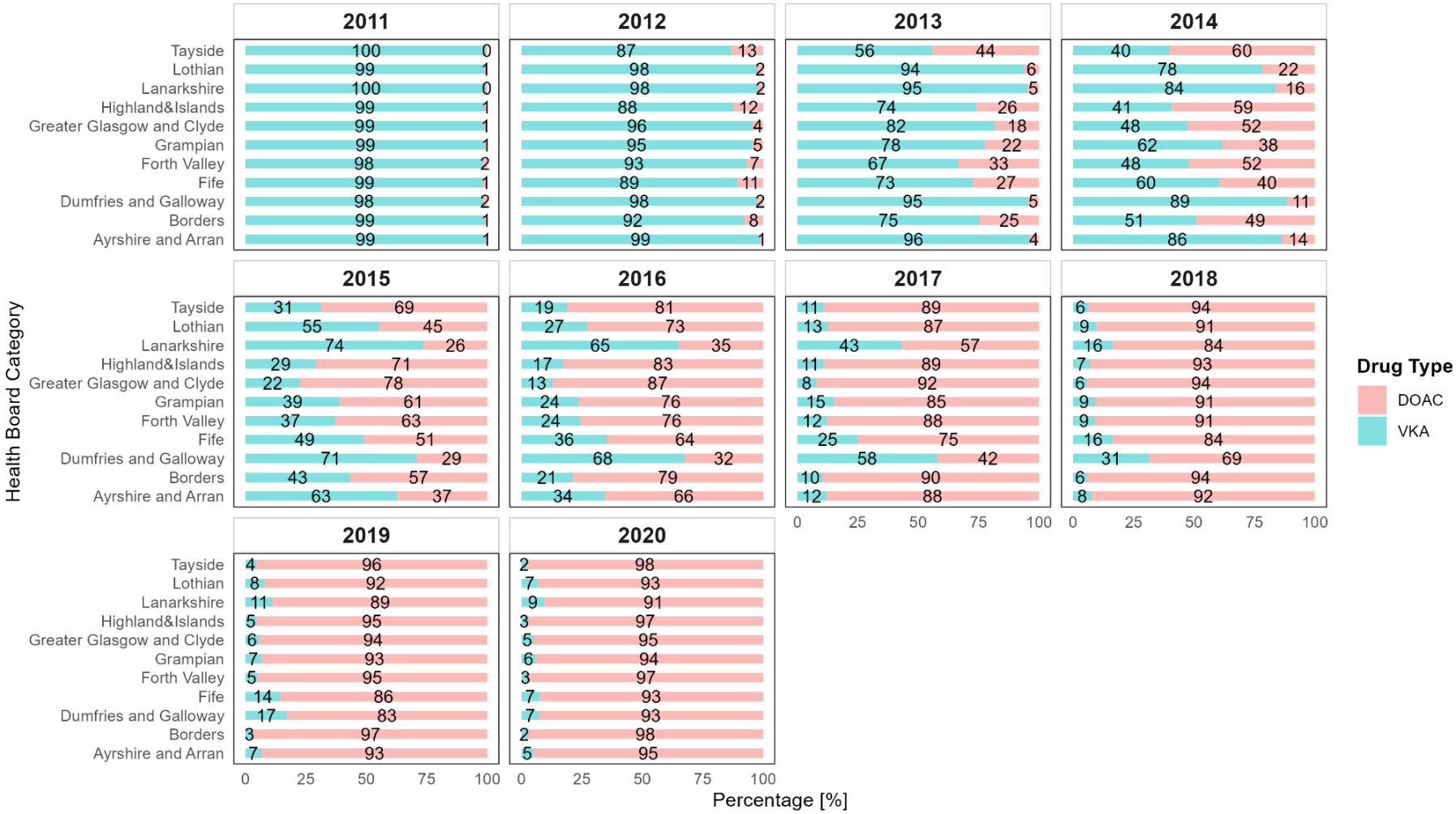

Figure 4.18: Percentage of patients initiating DOACs versus VKAs, stratified by health board and calendar year (2011–2020)

Figure 4.19: Percentage of patients initiating each OAC stratified by health board 2011-2015.

Note: To improve visual clarity given the number of health boards, anticoagulant agents, and calendar years included, results are presented separately for 2011–2015 and 2016–2020.

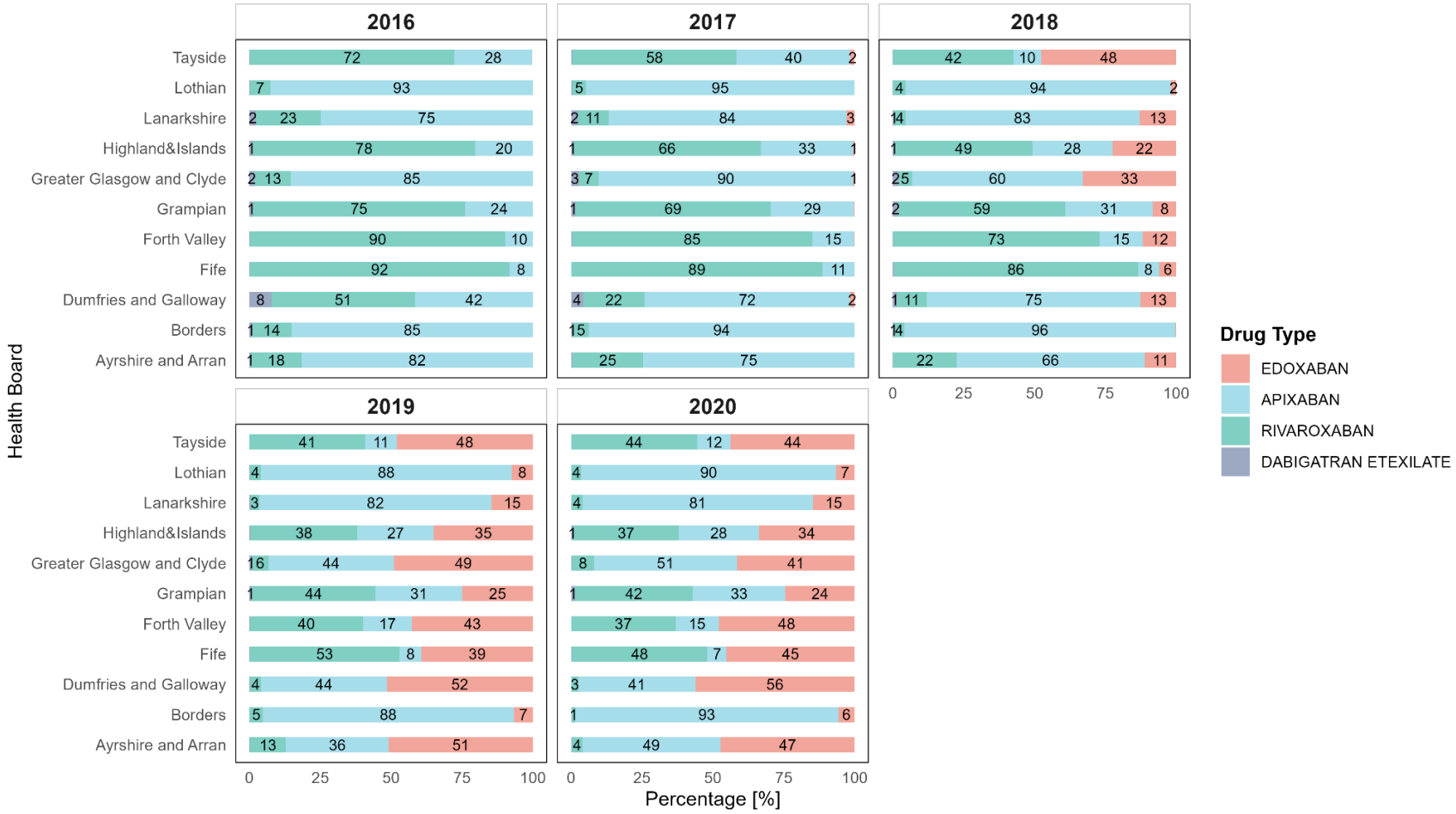

Figure 4.20: Percentage of patients initiating each OAC stratified by health board 2016-2020.

Note: To improve visual clarity given the number of health boards, anticoagulant agents, and calendar years included, results are presented separately for 2011–2015 and 2016–2020.

Patterns of OAC prescribing by urban–rural setting also demonstrated variation in the early years following DOAC approval (**Figure 4.21**, **Figure 4.22**). In 2015, the proportion of patients initiating treatment with a DOAC varied across area types, ranging from 49% to 68%, with relatively higher initiation observed at very remote rural areas, very remote small towns, and large urban areas. However, DOAC initiation rates increased across all areas over time. By 2020, DOAC initiation had become the preferred choice in all regions, with 94-97% of patients initiated on DOAC rather than VKA.

Preferences among DOACs differed across urban–rural area types and calendar years (**Figure 4.23**, **Figure 4.24**). Up to 2015, rivaroxaban was the most commonly used DOAC across most area types, except in large urban areas, where 39% of patients-initiated apixaban in 2015. However, since 2018, the percentage of patients receiving edoxaban as the first choice consistently increased over time; in 2020, there was considerable variation in the initiation patterns of anticoagulants urban–rural area types. Apixaban initiation ranged from 32% to 51% across area types. Edoxaban initiation ranged from 25% to 39%, rivaroxaban from 13% to 34%, and dabigatran had the lowest initiation proportions, with most area types showing 0–1% use.

Although prescribing guidance is issued at health board level, the present analysis was conducted by urban–rural classification. As most health boards encompass both urban and rural areas, observed differences likely reflect within-Board variation rather than differences between Boards.

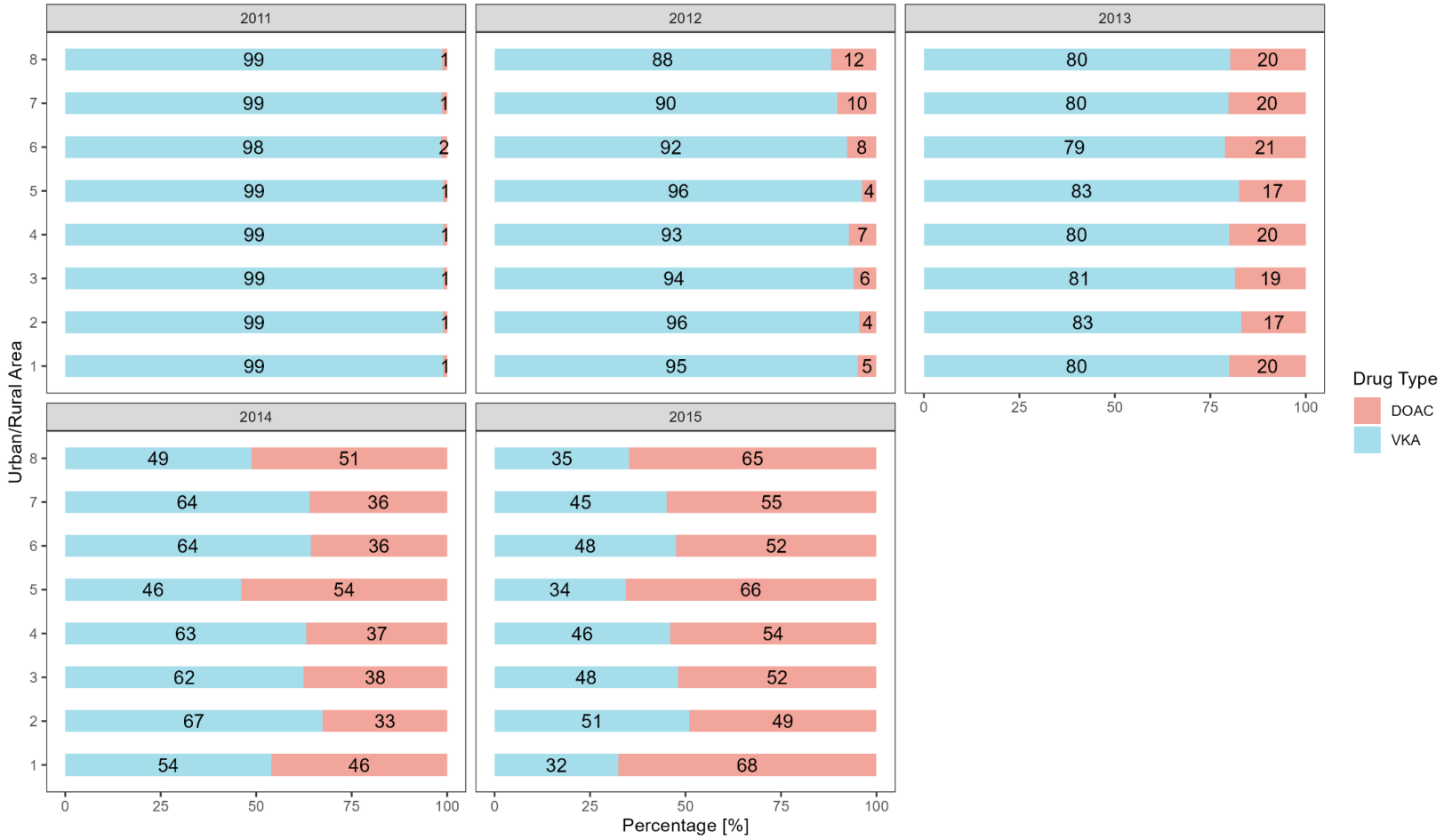

Figure 4.21: Percentage of patients initiating each drug type stratified by Rural/ Urban 2011-2015**.**

Note: To improve visual clarity given the number of urban–rural categories and anticoagulant agents, results are presented separately for 2011–2015 and 2016–2020.

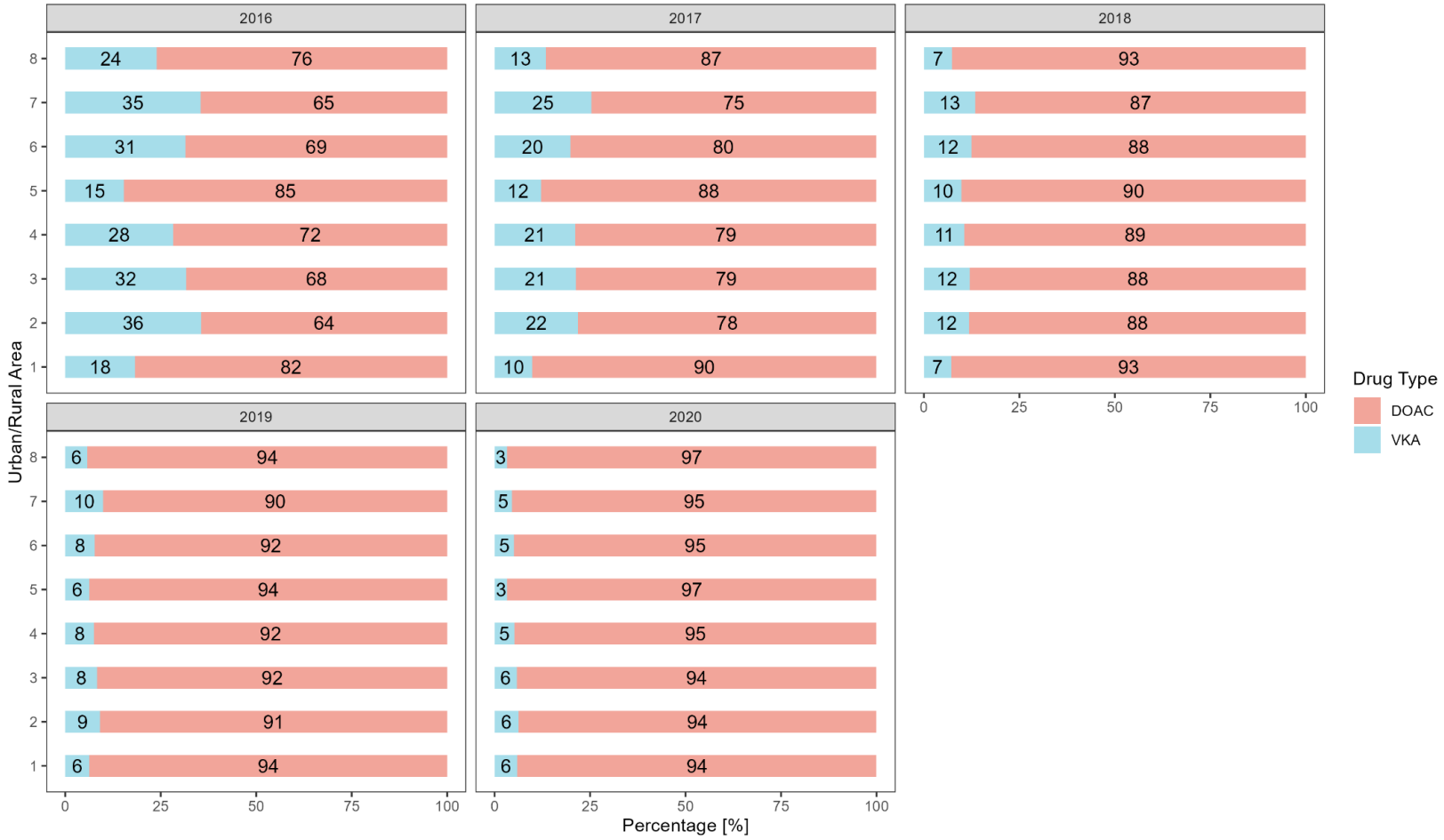

Figure 4.22: Percentage of patients initiating each drug type stratified by Rural/ Urban 2016-2020.

Note: To improve visual clarity given the number of urban–rural categories and anticoagulant agents, results are presented separately for 2011–2015 and 2016–2020.

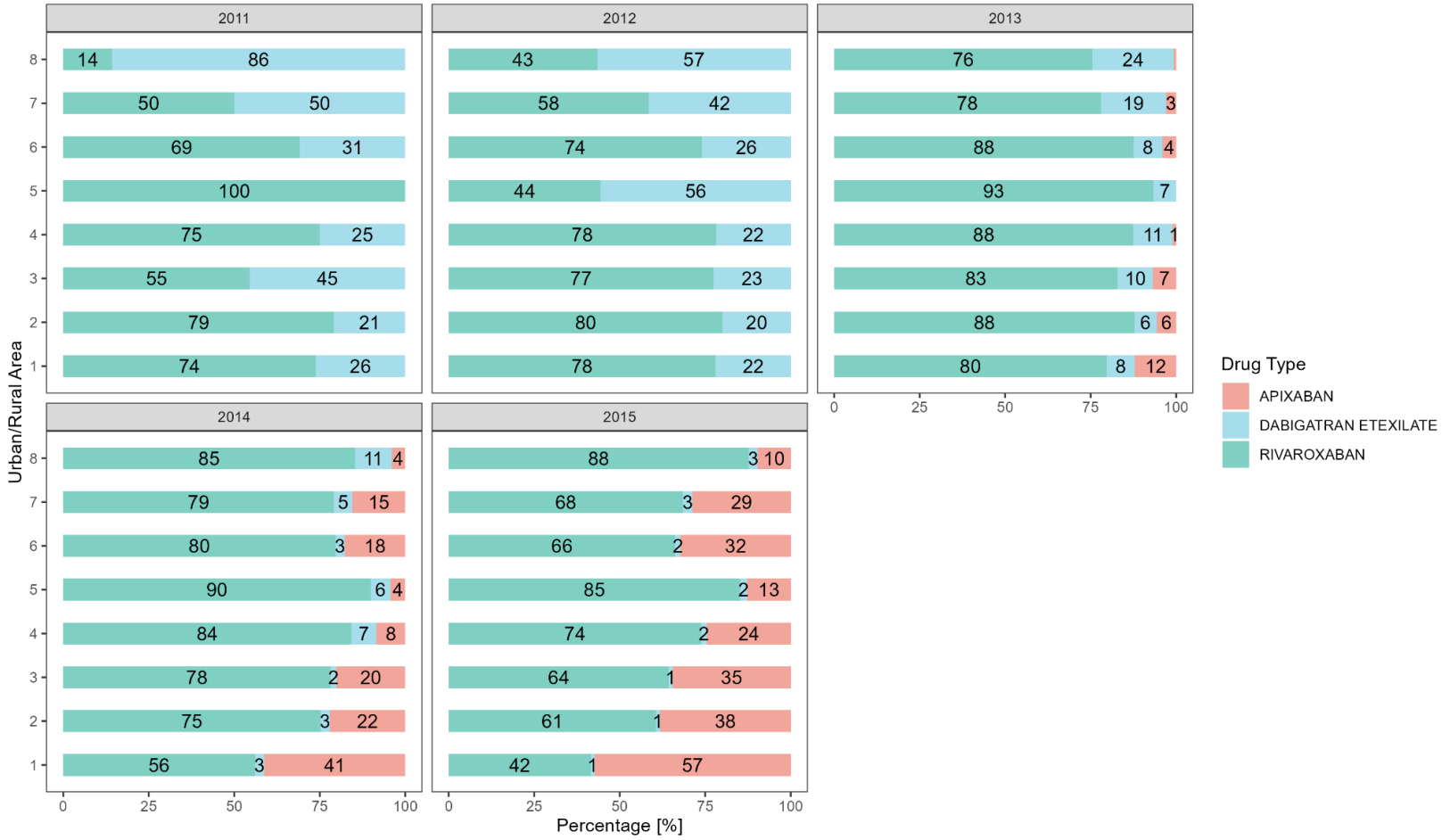

Figure 4.23: Percentage of patients initiating each DOAC compared to other DOACs stratified by Rural/ Urban 2011-2016**.**

Note: To improve visual clarity given the number of urban–rural categories and anticoagulant agents, results are presented separately for 2011–2015 and 2016–2020.

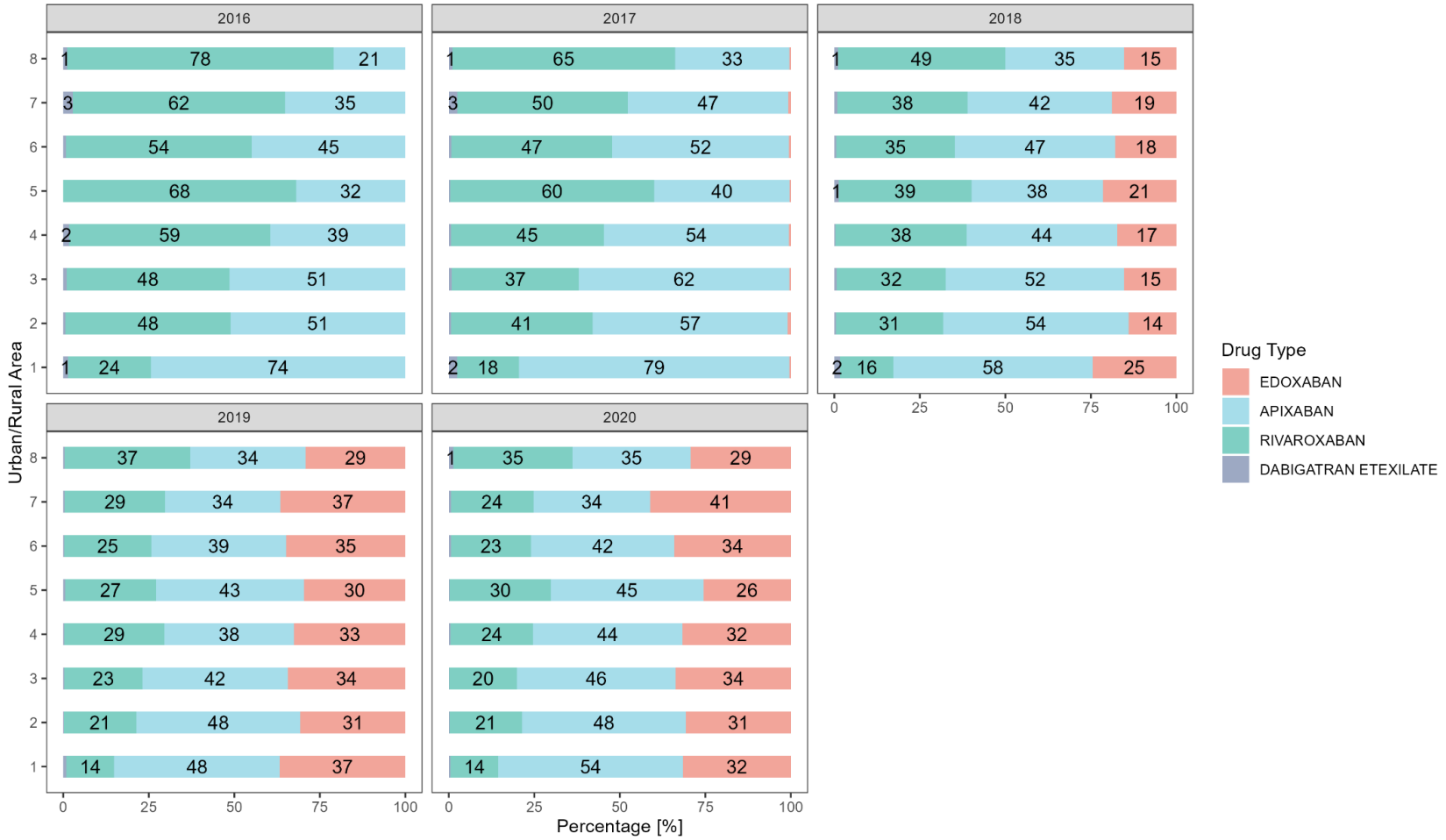

Figure 4.24: Percentage of patients initiating each DOAC compared to other DOACs stratified by Rural/ Urban 2016-2020.

Note: To improve visual clarity given the number of urban–rural categories and anticoagulant agents, results are presented separately for 2011–2015 and 2016–2020.

4.4 Discussion

This study describes the substantial changes in OAC prescribing practices across Scotland, characterized by a marked increases in both incident and prevalent utilization. The observed 72.3% increase in OAC incidence from 2011 to 2019 is consistent with trends reported in other UK settings. In particular, a previous English primary care study of OAC-naïve patients reported an approximately 58% increase in OAC initiation between 2009 and 2015, supporting a widespread shift toward greater anticoagulant utilisation following the introduction of DOACs (222).

In parallel, prevalent OAC use in Scotland more than doubled over the study period, increasing by approximately 102% between 2009 and 2020, reflecting both increased initiation and longer-term continuation of therapy. These results are consistent with broader international trends toward expanded anticoagulant use. For example, studies have reported an approximately 71% increase in overall OAC dispensing in the UK between 2012 and 2017 (223), as well as a 54% increase in the number of individuals receiving OACs in the United States over a similar period (223).

Studies restricted to patients with AF similarly report marked increases in anticoagulation coverage over the past decade. A global meta-analysis of observational studies likewise found that the proportion of OAC-treated AF patients nearly doubled between 2010 and 2018 (213).

The substantial increase in OAC prescribing can be attributed to factors such as an aging population, growing AF prevalence, and improved detection and treatment of thrombotic risk conditions. Moreover, the introduction of DOACs helped overcome certain barriers previously associated with OAC therapy in AF (66,147). The clinical evidence demonstrating superior safety profiles and enhanced convenience of DOACs relative to VKAs has enabled treatment of at-risk patients with AF who were previously unsuitable for anticoagulation, including those with advanced age, frailty, or complex comorbidities that historically contributed to therapeutic under-prescribing (224). This expansion of the treatable patient population has likely contributed substantially to the observed growth in new OAC users. This is evidenced by the substantial growth in OAC incidence during the early DOAC adoption period. Between 2012 and 2015, the incidence rose steadily by approximately 10% annually, reflecting the increasing confidence in prescribing DOACs to previously untreated patients. However, this growth began to slow in

subsequent years: in the period from 2015 to 2016, the increase was 2.5%, followed by a 4.1% rise from 2017 to 2018, and a minimal increase of 0.3% from 2018 to 2019. This deceleration in growth likely reflects the maturation of DOAC adoption, as the majority of eligible patients who were previously considered unsuitable for anticoagulation had been initiated on treatment. Notably, from 2019 to 2020, there was a 7.9% decrease in the number of new patients starting on OACs, which may reflect the impact of the COVID-19 pandemic on healthcare service delivery and patient access to care.

4.4.1. Prescribing pattern evolution

Findings showed that OAC prescribing patterns have shifted markedly over the study period, with DOACs increasingly replacing VKAs across all age groups, geographic areas, and socioeconomic levels. This change is consistent with clinical trial evidence and with clinical guideline updates such as those by ESC and NICE, which broadly recommend DOACs over VKAs for common indications such as AF and VTE, while recognizing certain scenarios where VKAs remain preferable. Moreover, these results are consistent with national and international studies reporting increased DOAC adoption since their introduction. A large, multi-country observational study comparing prescribing trends across the United States, Belgium, France, Germany, and the UK have similarly demonstrated rapid declines in warfarin use between 2010 and 2017, and a predominance of apixaban in recent years (213). However, the timing of this shift has varied by country and was often associated with key events such as guideline updates, reimbursement approvals, and formulary changes. In the UK the transition lagged behind other countries, with DOACs becoming the most common starting OAC in 2015, compared to 2012–2013 in the United States and European countries such as Belgium, France, and Germany (213).

This later transition is further supported by UK primary care evidence showing that DOACs accounted for approximately 56% of OAC prescriptions in 2015 for both DVT and AF treatment, with rivaroxaban being the most frequently prescribed, followed by apixaban and dabigatran (222). However, later evidence from England suggests that by 2019, overall DOAC use in AF patients had increased to at least 74%, with apixaban emerging as the most prescribed agent (166), while warfarin prescribing declined dramatically from 91% to 26% (166).

In Scotland specifically, previous research has shown that the proportion of patients hospitalised with newly diagnosed NVAF who prescribed OAC therapy were increased from 36.2% in 2010 to 64.5% in 2019. By 2019, factor Xa inhibitors accounted for 83.6% of all OACs prescribed (144). However, it is important to note that most of these studies have focused specifically on AF patients and have often been restricted to selected populations or indications. In contrast, the present study examined incident OAC prescribing in primary care without stratification by clinical indication. By 2020, DOAC initiation reached 94.2% among all new OAC users, regardless of clinical indication. This broader inclusion may partly explain the higher proportion of DOAC use observed compared with earlier studies. Overall, these results indicate that Scotland has now achieved a broad and consistent transition from warfarin to DOAC therapy in eligible patient populations.

4.4.2. Individual DOAC prescribing patterns

The changes in DOAC prescribing patterns over the study period appear to coincide with DOAC availability and updates to clinical guidelines in Scotland and Europe more broadly. The approvals of dabigatran and rivaroxaban were quickly reflected in increasing prescription rates from 2013 onwards, with rivaroxaban initially becoming the most commonly prescribed DOAC among new users until 2015.

A pronounced shift occurred from 2014 with the rapid rise in apixaban use, likely influenced by updated SIGN guidelines recommending DOACs as alternatives to VKAs (9), and accumulating evidence of apixaban's favourable bleeding profile in older adults (225). From 2016 onward, apixaban became the predominant choice, with a rapid increase in initiation between 2014 and 2018, peaking in 2017 when it accounted for approximately half of all new OAC initiations in Scotland. This trend mirrors national patterns reported in England, where apixaban became the most prescribed DOAC by 2019 (212).

Meanwhile, the introduction of edoxaban in 2016 marked a new phase of DOAC adoption, with prescriptions increasing rapidly while replacing some rivaroxaban use. By 2020, edoxaban had become the second most prescribed DOAC, and together with apixaban, these two agents accounted for nearly 75% of new OAC starts. The most current prescribing landscape as available for this study, in 2020, showed apixaban as the first choice for 44.8% of patients initiating OAC, edoxaban for 30%, rivaroxaban for 19%, and warfarin for only 5.7%. Dabigatran consistently remained the least used DOAC throughout the study period.

This evolution demonstrates that apixaban's dominance by 2020 likely reflects accumulating real-world evidence of its favourable risk-benefit profile, particularly in older adults, those at higher bleeding risk, and patients with renal impairment. The initially rapid adoption of rivaroxaban and dabigatran, followed by a plateau or decline, may relate to differences in side-effect profiles and evolving clinical experience with these agents. For example, early post-marketing reports raised concerns regarding bleeding risk with dabigatran, including serious GIB, which likely contributed to more cautious prescribing over time (226–228).

4.4.3. Evolving patient characteristics and prescribing considerations

The benefits and risks of DOAC treatment depend on the population treated, with important differences between patients included in clinical trials and those treated in real-world clinical practice (229). From 2009 to the present, the baseline characteristics of DOAC users have changed and varied among different DOACs (222). In the UK, analyses of CPRD primary care data showed that after DOACs entered the market, patients with cancer or CKD were less likely to be prescribed these drugs instead of warfarin, while by 2015, these conditions were no longer associated with OAC class selection (222). In the same study, compared to VKA users, patients initiated on DOACs were less likely to have CHF, CAD, or peripheral vascular disease, and more likely to have a history of ischaemic stroke (222).

In contrast, in the present Scottish cohort of patients newly initiating oral anticoagulation, DOAC users exhibited higher prevalences of renal disease, prior bleeding, recent hip or knee surgery, and recent NSAID use, suggesting that prescribing practices may have further evolved to favour DOACs in patients with higher bleeding risk and certain surgical contexts. Interestingly, unlike earlier UK studies, no meaningful difference in prior stroke prevalence was observed between DOAC and VKA initiators in this incident cohort (10.2% vs. 10.1%).

The risk stratification profiles in this study also demonstrated evolving prescribing patterns. Patients initiating DOAC therapy had a very similar stroke risk profile to those initiating VKAs, with only a slightly lower mean CHA_2DS_2-VASc score (2.69 vs. 2.63). In contrast, DOAC users exhibited a slightly higher bleeding risk, with a higher mean HAS-BLED score (1.83 vs. 1.78) and a greater proportion classified as high bleeding risk (HAS-BLED ≥3: 28.8% vs. 26.7%). This suggests that prescribers may have become more comfortable prescribing DOACs in patients with elevated bleeding risk, possibly reflecting growing confidence in the overall safety profile of

these agents. Particularly given the evidence indicating a lower risk of ICH compared with warfarin (230). Similar patterns have been reported in other real-world studies (127). Collectively, this highlights that DOAC prescribing in practice may involve a broader and more complex risk profile than typically represented in clinical trials (229,231) and highlight the importance of real-world data in understanding how DOACs are used across diverse clinical populations.

Age and sex

This study's findings reveal that DOAC initiation was highest among both the youngest (<65 years) and oldest (≥85 years) age groups during the early years following their approval in Scotland (2011–2015). This pattern likely reflects distinct clinical rationales: younger patients may have been prioritized due to fewer comorbidities, while the very elderly were possibly favoured due to DOACs' practical advantages, including reduced monitoring requirements and lower ICH risk compared to VKAs. By 2015, DOAC uptake had reached 66% in patients aged ≥85; the highest across all age groups, compared to 46% in those aged 75–84 and 41% in those under 65. This trend contrasts with patterns reported in other countries, where DOAC prescribing has often been lower in the very elderly, especially in the first years following DOAC approval, possibly due to concerns about frailty and renal impairment (224). In Scotland, the widening uptake of DOACs among older patients may reflect growing prescriber confidence in their use in this population, alongside the accumulation of real-world safety data supporting their use in older and higher-risk populations (232–234). This trend may also be influenced by evidence indicating that older age is a risk factor for higher stroke rates among patients receiving warfarin, alongside factors such as previous stroke or TIA, renal impairment, and higher $CHADS_2$ scores (235). However, whether these risk factors apply to DOACs remain uncertain (235).

Over time, age-related variation in prescribing diminished, and by 2020 more than 90% of patients in all age groups were initiated on DOAC therapy.

Additionally, individual DOAC selection showed age-related preferences that persisted throughout the study period. Rivaroxaban was consistently prescribed at higher rates among patients under 65 years compared to older age groups, while edoxaban was generally less frequently prescribed in the youngest age group relative to all other age groups. These patterns may reflect a combination of age-specific clinical considerations and differences in treatment indications across age

groups. For example, AF is more prevalent in older adults, whereas VTE and peri-operative prophylaxis, indications for which rivaroxaban is commonly used, are more frequent in younger populations.

Pharmacological factors may also contribute, as apixaban and edoxaban have lower renal dependence than dabigatran and rivaroxaban, potentially making them more suitable for older patients with age-related declines in renal function. In addition, local formularies and prescribing guidance may recommend different first-line DOACs for specific indications, further shaping age-related prescribing patterns.

When examining prescribing patterns among patients who initiated OACs, findings suggest that the overall distribution between sexes was broadly similar. However, a slightly higher proportion of female patients initiating OAC therapy between 2014 and 2020 were prescribed a DOAC compared to male patients. Rivaroxaban was the most prescribed DOAC until 2015, after which apixaban became the preferred agent across both sexes. Interestingly, a slightly higher percentage of men were prescribed edoxaban, while women were more likely to receive rivaroxaban. These differences were minimal and may reflect changes in drug availability and prescribing preferences over time rather than systematic sex-based variation. Overall, these results suggest a positive trend toward equity in DOAC prescribing between men and women. The shift toward DOACs appears to have narrowed previously reported sex disparities in anticoagulant prescribing, particularly those associated with VKA use (144).

Regional variations and healthcare policy implications

By 2020, DOACs had become the predominant first-line anticoagulant therapy across Scotland, with initiation rates ranging from 91% to 96% across socioeconomic deprivation quintiles, suggesting that socioeconomic status had minimal influence on the choice between DOACs and VKAs. Likewise, variation in specific DOAC selection by deprivation level was limited, indicating equitable access to newer anticoagulants.

However, notable regional differences were observed in DOAC prescribing trends, particularly during the early adoption phase (2012–2017). In 2015, DOAC initiation rates varied substantially across health boards, from 42% in Dumfries & Galloway to 93% in Greater Glasgow and Clyde, reflecting differences in local adoption policies or clinical practice preferences. These disparities narrowed over time, and by 2020,

DOAC use became highly uniform across regions. Similarly, early DOAC uptake varied across urban–rural classifications, with higher adoption rates initially observed in very remote rural areas and large urban centres, though by 2020, initiation rates exceeded 94% in all areas.

Despite this growing uniformity in the choice between DOACs and VKAs, variability persisted in the specific DOACs chosen, with apixaban favoured in many areas (e.g., Borders, Lothian), while edoxaban and rivaroxaban were preferred in others, such as Dumfries & Galloway and Fife.

These findings align with evidence from England, where substantial geographical variation in DOAC prescribing was observed in primary care. The study reported wide variation in DOAC use across geographical regions, with DOACs accounting for between 53% and 99% of all OAC prescriptions, reflecting differences in local prescribing policies and formulary recommendations rather than patient-level characteristics (166). Importantly, that study found that, in the absence of a nationally recommended first-line anticoagulant, local prescribing policies were associated with variation in the choice of individual DOACs but had little influence on the broader decision between DOACs and VKAs (166).

Moreover, as highlighted in previous studies, such progress is not universal across all healthcare systems. While DOAC use has increased globally, the choice between DOACs and VKAs may be influenced by healthcare system factors such as healthcare financing, reimbursement policies, and national prescribing guidance, particularly in settings where medication cost or insurance coverage varies (142,236,237).

The use of nationwide electronic prescribing databases, such as those employed in this study, offers valuable insight into real-world prescribing behaviour and helps identify regions where guideline uptake may lag. By continuously monitoring trends through these systems, policymakers and healthcare leaders can better address residual disparities and ensure equitable, evidence-based care across all regions and patient populations.

strengths and limitations

This study has several important strengths. First, it is based on a large, population-level dataset capturing prescribing information across Scotland, allowing for comprehensive evaluation of real-world OAC use with enhanced generalizability and

reduced selection bias. Second, the longitudinal design spanning over a decade (2009–2020) enables detailed assessment of temporal trends following the introduction and widespread uptake of DOACs, providing an opportunity to evaluate changes in clinical practice as evidence and guidelines evolved. Third, the focus on incident use allows assessment of prescribing choices at treatment initiation, examining patterns at multiple levels including drug class (DOAC versus VKA) and individual DOAC agents. Fourth, the inclusion of patient-level characteristics such as age and sex, alongside geographic factors including health boards and urban–rural classification, enables examination of variation in prescribing patterns. Finally, this study contributes important national-level data from Scotland's unified healthcare system, providing valuable evidence for international comparisons, particularly in understanding how healthcare system structure and policy influence medication use.

However, several limitations should be acknowledged. First, the identification of incident OAC users was based on the first recorded prescription during the study period, using all available historical prescribing data from January 2009 onwards to exclude prior users rather than applying a fixed washout period. While this means patients had variable lengths of prior observation time, this approach maximized data utilization and minimized misclassification of prevalent users as incident cases, the variable lengths of prior observation time may affect the comparability of incidence estimates across individuals and over time.

Second, the ascertainment of comorbidities and clinical covariates was based on secondary care data using all available historical records prior to OAC initiation to maximise capture of previous clinical conditions. However, this might result in unequal lookback periods across patients, with individuals entering the cohort later in the study having longer available clinical histories compared to those initiating treatment earlier. While this may have led to some differential capture of comorbidities, major conditions requiring hospital care are likely to have been captured even with shorter lookback periods.

Third, the use of routinely collected administrative data limits the availability of detailed clinical information, such as laboratory measurements (e.g., renal function at the time of prescribing), lifestyle factors, and prescriber rationale for treatment selection; thus, prescribing variations that could be driven by these factors were not investigated.

Fourth, variation in prescribing patterns across regional health boards may reflect differences in local policies, healthcare access, or population characteristics; however, these administrative regions may not be directly comparable to healthcare structures in other countries. Although the inclusion of urban–rural classification improves interpretability, caution is required when generalising these findings internationally.

Finally, although this study captures a comprehensive period of DOAC uptake through 2020, prescribing patterns may have continued to evolve since then due to new evidence, updated guidelines, or policy changes, which are not captured in this analysis.

4.5 Conclusion

During the study period, the incidence of OAC initiation increased by 72.3%, from 250.6 per 100,000 population in 2011 to 431.8 in 2019, before slightly declining by 7.9 % to 397.6 in 2020- likely reflecting the impact of the COVID-19 pandemic on healthcare utilization. OAC prescribing patterns have shifted markedly over the study period, with DOACs replacing VKAs as the preferred choice across all age groups, geographic areas, and socioeconomic levels. This trend aligns closely with updated clinical guidelines recommending DOACs over VKAs for most indications.

While disparities in DOAC uptake were evident in the early years following their introduction, these variations diminished over time. By the end of the study period, apixaban and edoxaban together accounted for 79.4% of all new OAC prescriptions, and 94% of patients initiating anticoagulation therapy were prescribed a DOAC

5 Chapter 5: Impact of the COVID-19 pandemic on the prescribing patterns of oral anticoagulants in the Scottish primary care setting: a population-based segmented interrupted time-series analysis

5.1 Introduction

The COVID-19 pandemic has affected healthcare systems globally (238). Prior to the pandemic, there was a clear trend of increasing OAC use across many countries, including Scotland, as shown in the preceding chapter. However, the marked 7.9% decline in new OAC initiations between 2019 and 2020 represents a substantial deviation from prior trends and is likely attributable to the widespread disruptions in healthcare delivery caused by the pandemic (Chapter 4). This decline may reflect several interrelated factors, including reduced patient access to healthcare services, deferred routine medical care, modified clinical practice patterns, and patient reluctance to seek medical attention during periods of elevated infection risk (239,240). Furthermore, in the early stages of the pandemic, hospitalisations for acute cardiovascular events may have been postponed or delayed (241). Changes in the availability of drugs, diagnostic tests, and treatments may have raised the burden of CVD (242).

As discussed in Chapter 4, prescribing patterns at the onset of the pandemic indicate that DOACs had largely replaced VKAs as the anticoagulant of choice for most new patients, although many established patients were still maintained on warfarin therapy.

The onset of COVID-19 in early 2020 brought remarkable disruptions to healthcare delivery, which extended to anticoagulation services. Pandemic related lockdowns and social distancing measures limited face-to-face medical visits, making routine warfarin monitoring (which in the UK typically requires frequent clinic or laboratory visits for INR testing rather than patient self-monitoring) considerably more difficult. Moreover, COVID-19 itself has been linked to myocarditis, thrombotic events, and multisystem vascular disorders (242), leading to increased risks of thromboembolic complications in infected patients. Furthermore, people with COVID-19 have a worse prognosis when they have established CVD and atherosclerotic CVD risk factors (242). The administration of COVID-19 vaccines highlighted the emergence of a rare but serious complication known as vaccine-induced immune thrombotic

thrombocytopenia (VITT), emphasizing the complicated interaction between the pandemic and coagulation disorders (243). These factors prompted health authorities to re-evaluate anticoagulation management strategies during the pandemic.

National clinical guidance and expert recommendations were published on the management of anticoagulation services during the pandemic (244), recommending the use of DOACs over warfarin when possible, in order to minimize patients' exposure to healthcare settings for INR checks. Moreover, early in the pandemic, the NHS in the UK issued guidance that appropriate patients stable on warfarin should be switched to a DOAC to reduce the need for frequent blood tests and therefore reduce the danger of viral transmission (244,245). DOAC therapy can be managed with predictable periodic renal function monitoring (e.g., every few months) instead of the continuous INR adjustments required by warfarin. By switching suitable warfarin patients to DOACs, clinicians aimed to maintain anticoagulation control while keeping patients safe at home and reducing clinical service demands.

As a result of these switching strategies, the COVID-19 pandemic is likely to have influenced switching from VKAs to DOACs, and large-scale changes in anticoagulant prescribing were subsequently reported (245). Many factors, such as advanced age, a higher number of recent INR tests, the new diagnosis of AF, normal renal function, and residence in a care facility, were linked to switching from warfarin to DOACs (245).

In Scotland, it is reasonable to expect similar shifts occurred, but robust patient level data and evidence specific to the Scottish population are required to confirm and quantify these changes. The present study used comprehensive, patient-level data from Scotland to examine changes in OAC prescribing over an extended period encompassing both the pre-pandemic and pandemic eras. Specifically, it investigated how the incidence and prevalence of OAC use evolved during the pandemic and the extent to which patients were switched from warfarin to DOACs.

To evaluate the impact of these disruptions on prescribing behaviour, the study employed an interrupted time series (ITS) design. ITS represents a robust quasi-experimental approach for assessing the longitudinal effects of interventions at specific time points (246). In the study context, the lockdowns serve as natural experimental intervention points affecting prescribing behaviour. The ITS design

examines data before and after the intervention to test for both immediate changes and gradual changes in the outcome following the intervention (246).

By comparing the post-intervention trend in OAC prescribing to the extrapolated pre-intervention trend, it is possible to isolate the lockdowns' effect on prescribing while accounting for the baseline trend (246). This strengthens causal inference about the lockdown impact, as opposed to a simple pre-post comparison which would ignore prior trends (247). This methodology is commonly employed in health services research for evaluating the effect of policy interventions or external disruptions such as COVID-19 (243).

Most prior studies examining COVID-19's impact on anticoagulant prescribing have used aggregated data (243) or have been limited to short term. To address this evidence gap, the present study examines changes in OAC prescribing in Scotland before and during the COVID-19 pandemic using linked, patient-level healthcare data.

Aims and objectives

This study aimed to investigate changes in the incidence and prevalence of OAC use, as well as the rate of switching from VKAs to DOACs, comparing the period before the pandemic to the period during the pandemic. The analysis covered the time period of January 2018 through April 2021, capturing trends leading up to COVID-19 and during the first year of the pandemic. The specific objectives were to quantify changes in the following outcomes over time:

1. Prevalent OAC use – the overall number of patients on oral anticoagulation, from January 2018 to April 2021.
2. Incident OAC use – the rate of new OAC initiations, from January 2018 to December 2020 (to assess the pandemic’s effect on starting anticoagulation therapy).
3. Switching from VKA to DOAC – the frequency and pattern of switching from warfarin (or other VKAs) to DOACs, from January 2018 to April 2021.

By quantitatively analysing these metrics, the study sought to characterize how prescribing behaviours evolved in the Scottish context, and to what extent COVID-19 may have accelerated pre-existing trends or introduced new shifts in OAC use.

5.2 Methods

5.2.1. Study design

An interrupted time-series analysis was conducted using primary care data from Scotland covering the study period January 1, 2018, to April 30, 2021. Two breakpoints were defined: the first aligned with the onset of the COVID-19 pandemic in March 2020 (the first national lockdown), and the second represented the second national lockdown in November 2020. The study timeline is shown in **Figure 5.1**.

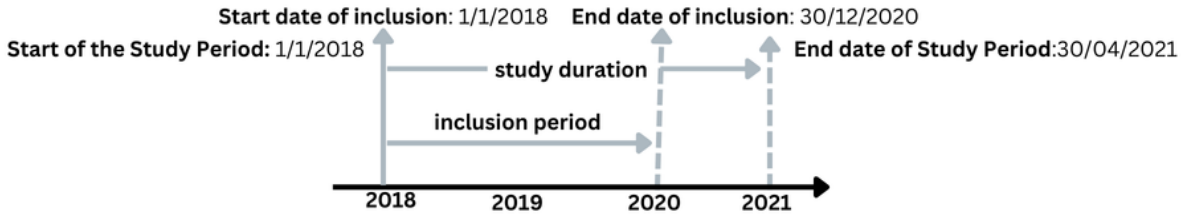

Figure 5.1: Timeline of the study period and inclusion period used in the interrupted time-series analysis.

OAC prescriptions were measured over a total duration of 40 consecutive months. The study period was divided into three distinct phases based on national COVID-19 lockdowns in Scotland:

- Pre-COVID-19 period: 26 months, from January 2018 to February 2020
- Post–first lockdown period: 8 months, from March 2020 to October 2020
- Post–second lockdown period: 6 months, from November 2020 to April 2021

These time segments allowed for the assessment of changes in prescribing patterns in relation to the timing of the national lockdowns.

5.2.2. Participants and procedures

All individuals aged 18 years and older who received at least one prescription for an OAC during the study period were included. The analysis examined overall OAC prescribing patterns, irrespective of treatment indication.

Procedures:

OACs were defined as any prescription for the following medications, based on their BNF codes: apixaban, rivaroxaban, edoxaban, dabigatran etexilate, warfarin sodium, acenocoumarol, or phenindione.

The monthly number of OAC prescriptions was calculated by counting all

prescriptions issued for these agents in each calendar month during the study period.

Acenocoumarol and phenindione were included in the total OAC counts and in group-level analyses (i.e., DOAC vs. VKA) but excluded from individual drug-level results due to very low prescription numbers.

5.2.3. Population identification, classification and outcomes

The study population comprised all individuals identified as receiving OAC therapy in primary care during the study period. Multiple national databases were linked to conduct this study. Cohort groups were determined using the PIS dataset (188) based on prescribed items, previous prescriptions, and prescription dates, irrespective of diagnosis or indication for OAC therapy.

All prescribed and dispensed items in primary care were included, capturing quantity and drug-approved names, excluding hospital prescriptions and private prescriptions. Additional variables including deprivation level (SIMD quintile), concomitant medications, health board of residence, and urban-rural classification were retrieved from PIS for the identified population. PIS records were linked to the demographic's dataset (described in chapter 3) to obtain baseline data of patients, including date of birth and sex.

Further clinical information about the identified population, including possible OAC indications and comorbid conditions, was extracted from previous inpatient episodes (SMR01 dataset, complemented with SSCA data), hospital procedures (SMR01 dataset), outpatient clinic visits (SMR00 dataset), and drug prescribing data (PIS dataset). Full details of data sources and linkage procedures are described in Chapter 3.

Record linkage was performed using the CHI number, the unique patient identifier used by NHS Scotland.

The identified cohort was subsequently divided into three groups:

- The prevalent cohort included all individuals with at least one recorded OAC prescription during a given calendar month.
- The incident cohort comprised individuals receiving their first recorded OAC prescription during the inclusion period, with no prior OAC use.

- The switcher cohort included patients who switched from a VKA to a DOAC within the study period, as defined in **5.2.4**.

The prescription and demographic data for the four DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) and VKAs (warfarin, acenocoumarol, phenindione) were uploaded into the R software from the linked data folder as comma-separated values (CSV) files.

These cohorts were used to define monthly prevalence, incidence of new OAC use, and switching patterns, respectively.

The primary outcomes were:

1) Monthly prevalence of OAC prescribing
   Defined as the total number of individuals prescribed any OAC (including patients receiving both initial and follow-up prescriptions) during each calendar month within the study period.
2) Incidence of new OAC prescribing
   Defined as the monthly number of individuals who received their first recorded OAC prescription during the inclusion period. These patients were extracted from the incident user's cohort previously defined in Chapter 4.
3) Treatment switch from VKA to DOACs
   Defined as the proportion of patients who switched from VKA to a DOAC within 90 days of their last recorded VKA prescription during the study period. The identification of switching events is described in detail in Section 2.4. The monthly switching rate was calculated as:

$$\left(\frac{\text{Number of patients who switched from VKA to DOAC}}{\text{Total number of patients on VKA}}\right) \times 100\%$$

5.2.4. Identification of patients switching from VKA to DOACs

While the identification of incident and prevalent OAC users is described in Section **5.2.3**, this section focuses specifically on the definition and identification of treatment switching from VKAs to DOACs.

Patients were included if they received a DOAC prescription following a VKA prescription within the study period (January 2018 to May 2021). Prescription records were first chronologically ordered by patient ID and prescription date. A switching event was defined as a patient whose current drug type was a DOAC and

who's immediately preceding prescription was a VKA. The number of days between the last VKA prescription and the first DOAC prescription was calculated. The workflow used to identify patients switching from VKA to DOACs is detailed **Figure 5.2**. The time interval between the last VKA prescription and the first DOAC prescription was calculated. Switching was defined by a gap of 90 days or fewer between these prescriptions.

The 90-day gap was selected based on median quantity of OACs dispensed per prescription was 56 tablets (interquartile range [IQR]: 56–112), corresponding to approximately one to two months of therapy. This median dispensing quantity was consistent both before the pandemic (January 2018 to February 2020) and during the pandemic (March 2020 to April 2021).

When examined by individual agents, the median dispensed quantity for rivaroxaban increased from 28 to 56 tablets, while quantities for other OACs remained unchanged (Table 5.1). Although the data capture the number of tablets dispensed rather than days' supply, these quantities align with common DOAC dosing regimens (e.g., once-daily dosing where 28 or 56 tablets approximate 28 or 56 days, and twice-daily dosing where 56 or 112 tablets approximate 28 or 56 days). Because the gap was measured from the last prescription date rather than from the end of medication supply, the actual time without medication is expected to be shorter (approximately 30 days for patients receiving a two-month supply and 60 days for those receiving a one-month supply). Together, these findings support the use of a 90-day window to capture true treatment switches while allowing for variation in prescription duration, stockpiling and refill timing.

A sensitivity analysis using a stricter 60-day gap was conducted to assess the robustness of the switching definition under a more conservative assumption regarding prescription duration and refill behaviour, approximating a one-month supply of medication.

To avoid counting multiple switches by the same individual, only the first observed switch from a VKA to a DOAC per patient was included in the switching cohort by selecting distinct patient identifiers. The number and type of DOAC agents to which patients switched were also summarised.

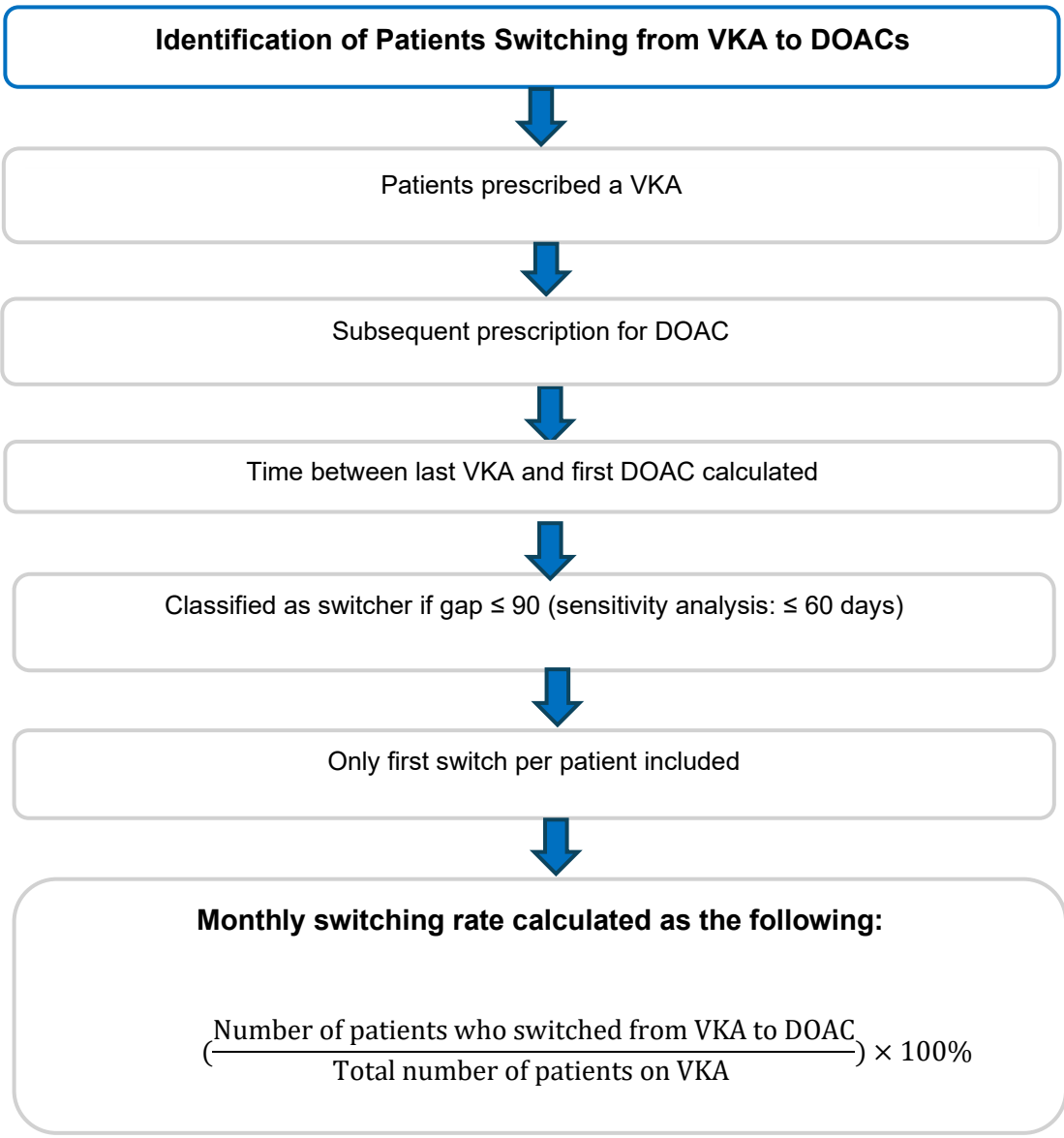

Figure 5.2: Identification of patients switching from VKAs to DOACs.

Note: Patients with a gap >90 days between the last VKA and first DOAC prescription were not classified as switchers. Patients with prior DOAC use before VKA therapy were excluded from the switching cohort.

Table 5.1: Median (interquartile range) number of anticoagulant tablets dispensed before (Jan 2018–Feb 2020) and during (March 2020–Apr 2021) the COVID-19 pandemic.

	Pre-pandemic (Jan 2018–Feb 2020)	During pandemic (March 2020 - April 2021)
Apixaban	56 (56–112)	60 (56–112)
Edoxaban	28 (28–56)	28 (28–56)
Rivaroxaban	28 (28–56)	56 (28–56)
Dabigatran	60 (56–120)	60 (56–120)
Warfarin	56 (56–56)	56 (56–56)

5.2.5. Statistical analysis

5.2.5.1. Interrupted time series and segmented regression analysis

To quantify changes in prescribing trends at the time of the lockdowns, segmented regression analysis was applied to the monthly prescription counts. Segmented regression represents a modification of standard linear regression that allows the slope and intercept to change at defined breakpoints (the intervention points). Linear regression was used to identify baseline trends over time to obtain the monthly changes in utilization before the pandemic. A segmented linear regression analysis of the interrupted time series was performed to assess the impact of the first and second lockdown.

A continuous time variable (months since study start) captured the baseline trend. Binary indicator variables were created for each lockdown, coded 0 before the intervention and 1 thereafter. Interaction terms between time and each indicator defined the post-intervention slopes. This structure enabled estimation of both immediate changes in level and changes in the ongoing trend associated with each lockdown.

For outcomes with data available through April 2021 (total prescriptions, prevalent OAC use, and switching from VKA to DOAC), a two-breakpoint model was specified, corresponding to the first national lockdown (March 2020) and subsequent restrictions (November 2020). The time series was therefore divided into three segments: (1) pre-lockdown, (2) between the first and second lockdown, and (3) post-second lockdown. Each segment has its own linear trend (intercept and slope), enabling estimation of how the lockdowns altered the level and trend of the outcome relative to the pre-intervention baseline.

For incident OAC use, data were only available through December 2020. Due to the limited number of observations following the November 2020 lockdown, a single-breakpoint model was specified with a breakpoint at March 2020.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the findings to alternative model specifications and to the handling of March 2020, which corresponded to the onset of lockdown and a period of abrupt disruption in healthcare utilisation that may not reflect the underlying trend. In addition, given the limited number of observations following November 2020 lockdown, sensitivity analyses using a single-breakpoint model were performed to evaluate whether inclusion of a second breakpoint influenced the results.

For incident OAC use, two sensitivity analyses were performed:

1. Excluding the March 2020 data point.
2. Retaining March 2020 while including a dummy variable to account for its transient effect.

For outcomes with extended follow-up (total prescriptions, prevalent use, and VKA-to-DOAC switching), additional sensitivity analyses were conducted to evaluate the impact of model specification:

1. A single-breakpoint model including all observations.
2. A single-breakpoint model excluding March 2020.
3. A single-breakpoint model including a dummy variable for March 2020.

Key parameters (β_1–β_5) and interpretation

The pandemic impact was described by a range of regression coefficient estimates obtained from the analysis (for both level and trend), that summarize the lockdown effects on prescribing:

- β_1 – Baseline trend: The underlying pre-lockdown slope (monthly change) in OAC prescribing. This represents the existing trend in the outcome per month before any lockdown occurred. It represents the baseline trend that would continue if no lockdown had occurred.

- β_2 – Immediate level change after first lockdown: The instant change in the outcome level immediately after the first lockdown in March 2020 (243). This coefficient captures any abrupt jump or drop in outcome attributable to the first lockdown, representing the difference between the observed level just after lockdown and the predicted level based on the pre-lockdown trend. A statistically significant β_2 indicates an immediate effect of the first lockdown on prescribing (a "step" change).
- β_3 – Slope change after first lockdown: The change in the monthly trend (slope) in the period following the first lockdown compared to the prior trend (243). This coefficient represents how the trend of prescribing was changed in the post-first-lockdown segment. A significant β_3 suggests a gradual or sustained intervention effect (e.g., a change in the rate of increase or decrease in prescriptions over time after the first lockdown).
- β_4 – Immediate level change after second lockdown: The instant level change after the second national lockdown in November 2020 (243). Similar to β_2, this coefficient captures any immediate jump or drop in the outcome right after the second lockdown, above or below what the extrapolated trend from the earlier segment would have predicted. It reflects the immediate impact of the second lockdown on the outcome.
- β_5 – Slope change after second lockdown: The change in trend (slope) in the post-second-lockdown period relative to the prior segment's trend (243). This coefficient indicates whether the second lockdown led to a further change in the trend of prescribing.

Each of these parameters is estimated with its 95% confidence interval and p-value to assess statistical significance. In practical terms, β_2 and β_4 test for immediate "step" effects of each lockdown, while β_3 and β_5 test for changes in the ongoing trend attributable to the interventions.

5.2.5.2. Detecting autocorrelation between values of the outcome over time

Ordinary linear regression model assumes that residuals are uncorrelated; however, in segmented regression analysis, time is the predictor, and consecutive observations are frequently correlated (246). Correction of autocorrelation is essential to prevent underestimation of standard errors and overestimation of statistical significance (248).

Autocorrelation assessment

Initial assessment involved visual inspection of residuals plotted against time from the segmented model. The results showed randomly scattered residuals without a specific pattern, suggesting the absence of systematic autocorrelation. Subsequently, formal statistical testing was conducted to confirm this preliminary assessment.

The Durbin-Watson test was employed to assess serial autocorrelation in the residuals of the segmented regression model. The Durbin–Watson (DW) test is a statistical diagnostic designed to detect first-order (lag-1) autocorrelation in the residuals of a regression model. First-order autocorrelation measures the correlation between a variable and its immediately preceding value in a time series (249).

The Durbin-Watson test statistic ranges from 0 to 4, with values approximating 2 indicating no serious autocorrelation. Values less than 2 and approaching 0 suggest positive serial autocorrelation, which underestimates standard errors and can create false significance. Conversely, values greater than 2 and approaching 4 indicate negative autocorrelation, which can lead to overestimation of standard errors (250).

Additional model assumptions

In addition to autocorrelation, other model assumptions and potential confounders were evaluated. Seasonality was considered, as certain medication use outcomes exhibit seasonal patterns (e.g., higher utilisation in winter versus summer) which, if present, should be modelled to avoid confounding the intervention effect (246). Inspection of the monthly OAC prescription data revealed no consistent or recurring seasonal pattern across years, which is reasonable given OACs are chronic medications (less tied to seasonal illness patterns). Thus, no seasonal dummy variables were included into the model.

5.2.5.3. Additional descriptive analyses

In addition to the segmented regression analyses, descriptive absolute and relative percentage changes were calculated for selected outcomes by comparing values between defined time periods or between consecutive months, where appropriate.

Statistical software and tools

Data analysis was conducted using R (initially version 4.3.3, later updated to version 4.4.1 following its release in June 2024). I verified all code to ensure consistency

across software versions. Segmented regression was performed using the lm () function, and diagnostic testing was conducted using the lmtest package, including the dwtest () function.

5.3 Results

This section presents the results of the study. Results are first presented for overall OAC prescribing trends over time, followed by stratified analyses by drug class (DOACs versus VKAs) and by individual DOAC agents.

5.3.1. OAC prescriptions

5.3.1.1. Overall OAC prescriptions

During the first national lockdown in March 2020, the total number of OAC prescriptions in Scotland increased sharply from approximately 93,000 in February to a peak of 122,000 in March (**Figure 5.3**), followed by a clear decline in April 2020 to around 95,000 prescriptions, returning to pre-lockdown baseline levels. In contrast, no comparable rise in prescription volume was observed preceding the second national lockdown, during which OAC prescribing remained relatively stable or began to decline. A rise in OAC prescriptions occurred in December 2020; however, this likely reflects holiday-related fluctuations rather than any lockdown effect.

The segmented regression analysis showed no significant impact of COVID-19 on the number of prescriptions following the first or second lockdown (**Table 1.1** and **Figure 5.3**).

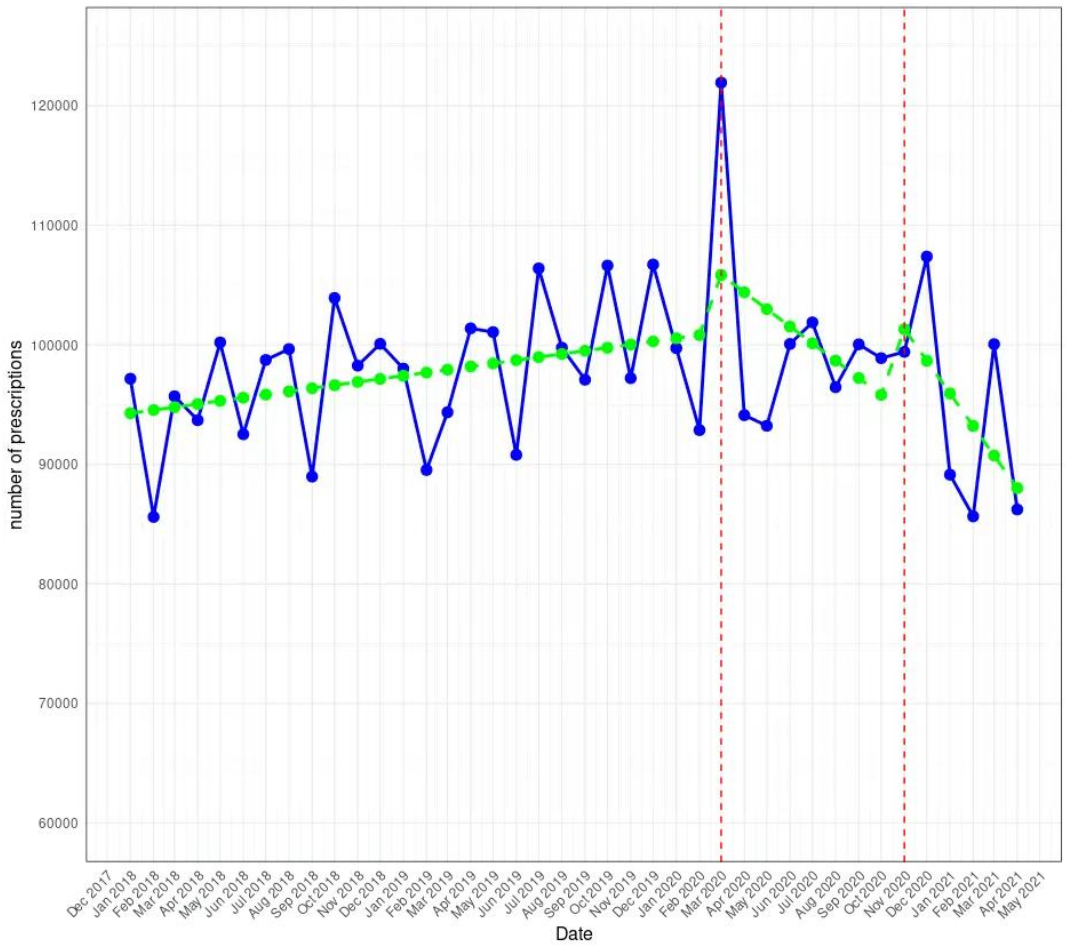

Figure 5.3: Monthly number of oral anticoagulant (OAC) prescriptions in Scotland from January 2018 to April 2021, with segmented regression showing the impact of the first (March 2020) and second (November 2020) COVID-19 lockdowns.

Note: The blue line represents time series. The green dashed lines indicate fitted segmented regression trends before and after the breakpoints. The red dashed vertical lines denote the break point(s).

Table 5.2: Segmented regression model results with two breakpoints (March 2020 and November 2020) for monthly OAC prescriptions, January 2018–April 2021

	Baseline trend (β1)	Level change after first lockdown (β2)	Time trend after first lockdown (β3)	Level change after second lockdown (β4)	Time trend after second lockdown (β5)
Estimate (95% CI)	261.4 (-80.2, 602.9)	6,390.9 (-4,864.4, 17,646.3)	-1,688.2 (-3723.0, 346.7)	8220.1 (-6,652.1, 23,092.3)	-1,253.2 (-4,987.5, 2,481.1)
P-value	0.129	0.257	0.101	0.269	0.5

Sensitivity analyses using a one-breakpoint approach showed that the direction of effects was consistent across models, with similar baseline trends and level changes observed. A decline in trend following the first lockdown was observed in all models; however, this reached statistical significance only in the single-breakpoint model including all observations. This effect was attenuated and no longer statistically significant when March 2020 was excluded or when a dummy variable was included to account for its effect. Detailed results are presented in **Appendix S.5.2**.

5.3.1.2. Prescribing by drug class (DOAC vs VKA)

The divergent prescribing trends for DOACs and VKAs are illustrated in **Figure 5.4**, which presents monthly prescription trends for DOACs and VKAs from January 2018 to April 2021. Over the study period, a steady increase in DOAC prescribing was observed, while VKA prescriptions showed a progressive decline.

The pronounced spike in total OAC prescriptions observed in March 2020 (as described in **Figure 5.3**) is reflected here as a simultaneous spike in both DOAC and VKA prescribing.

Following this peak, however, VKA prescriptions declined sharply, while DOAC prescribing remained relatively stable and high, maintaining its upward trend.

The second national lockdown in November 2020 did not result in another spike; instead, VKA prescriptions continued to decline, and DOAC prescribing exhibited a modest plateau or slight decline.

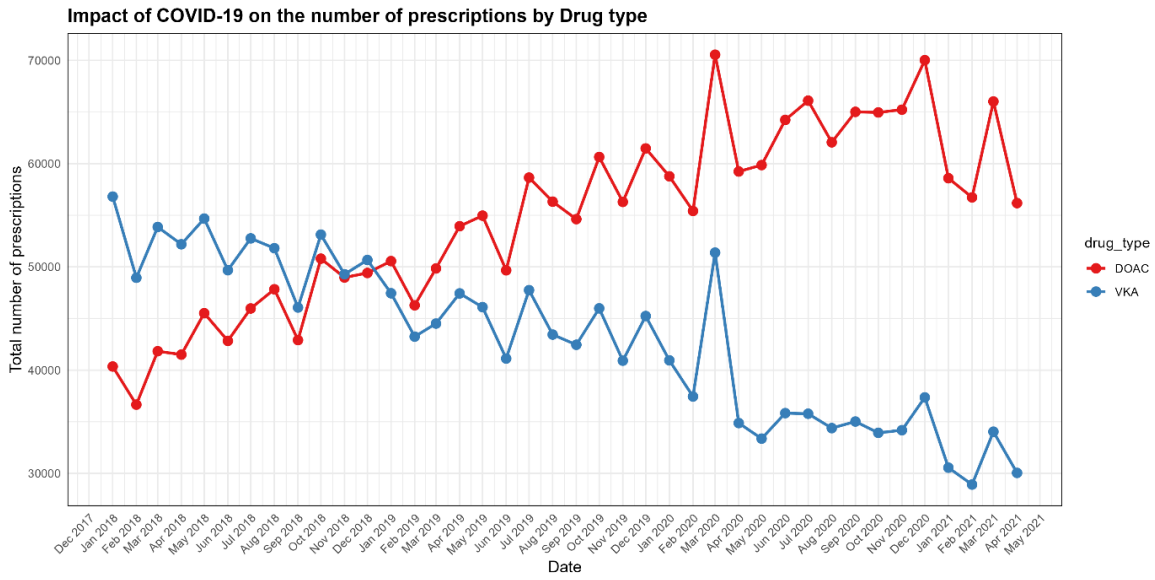

Figure 5.4: Time series analysis pf the total number of prescriptions by drug type, Jan 2018 to April 2021

5.3.1.3. Prescribing trends by Individual agents

Analysis of individual OAC agents revealed that the most pronounced peak was observed for warfarin, followed by apixaban, with more modest increases noted for edoxaban and rivaroxaban (**Figure 5.5**). There was no observable change in the total number of prescriptions for dabigatran.

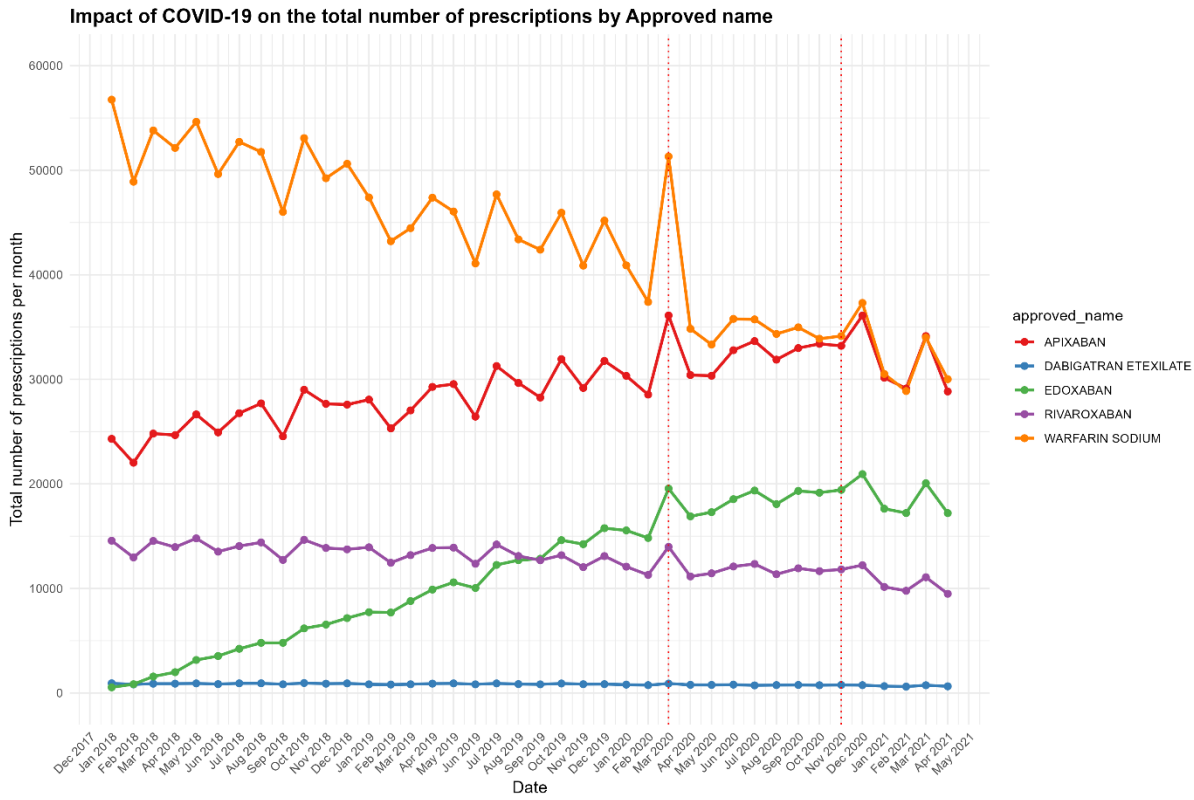

Figure 5.5: Time series analysis of the total number of prescriptions of OAC grouped by approved name, Jan 2018 to April 2021

5.3.2. Prevalent use of OACs

5.3.2.1. Overall prevalent use of OACs

Prior to the first lockdown, the number of prevalent users showed a general upward trend, with noticeable fluctuations month to month but with an overall increase in OAC use (**Figure 5.6**). Segmented regression analysis confirmed this pattern, estimating an average monthly incease of 380.35 users (95% CI: 197.36 to 563.33) (**Table 5.3**).

Immediately after the first lockdown, there was an abrupt increase of 2,627.79 users (95% CI: –3,401.56 to 8,657.13), although this jump was not statistically significant (p = 0.382). This means that although the model detects a rise in user numbers at that point, the uncertainty around this estimate is large, and we cannot conclude that a true level change occurred.

The post-first-lockdown period showed evidence of trend modification in the number of prevalent OAC users. The monthly growth rate declined by –778.74 users per month (95% CI: –1,868.77 to 311.29). While this change in slope was not

statistically significant (p = 0.156), it suggests a decline in growth relative to the pre-lockdown trend. The results indicate that prevalent use stabilised but at a lower level than the pre-lockdown trend, with continued fluctuation but no significant recovery to the previous growth pattern.

After the second lockdown, there was a further increase in the number of 4,569.85 prevalent users (95% CI: –3,397.01 to 12,536.70), although this immediate level change was also not statistically significant (p = 0.252).

Following this point, the monthly trend in OAC use decreased further, with the slope changing by –1,138.20 users per month (95% CI: –3,138.60 to 862.21). Although this change was also not statistically significant (p = 0.256).

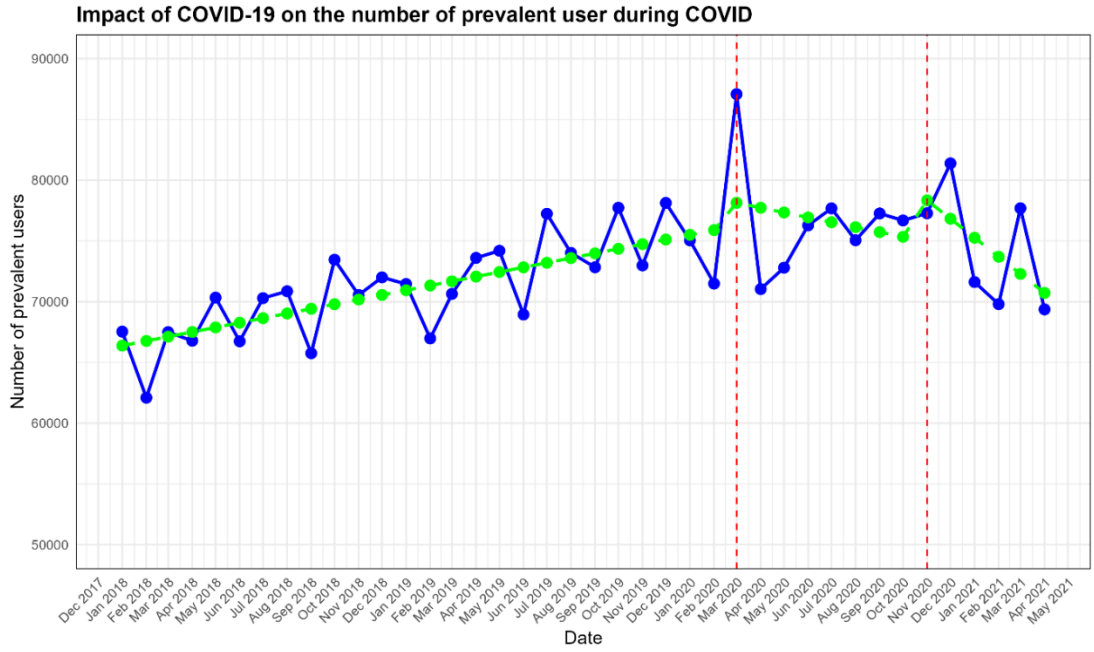

Figure 5.6: Monthly number of prevalent oral anticoagulant (OAC) users in Scotland from January 2018 to April 2021, with segmented regression showing the impact of the first (March 2020) and second (November 2020) COVID-19 lockdowns.

Table 5.3: Segmented regression model with two breakpoints (March and November 2020) for total number of prevalent OAC users (Jan 2018–Apr 2021)

	Baseline trend (β1)	Level change after 1st lockdown (β2)	Trend change after 1st lockdown (β3)	Level change after 2nd lockdown (β4)	Trend change after 2nd lockdown (β5)
Estimate (95% CI)	380.35 (197.36-563.33)	2627.79 (-3,401.56, 8,657.14)	-778.74 (-18,68.77, 311.29)	4,569.85 (-3,397.01, 12,536.70)	-1138.20 (-3,138.60, 862.21)
P-value	**< 0.001**	0.382	0.156	0.252	0.256

Sensitivity analyses using one-breakpoint demonstrated that the overall pattern of results was consistent with the primary two-breakpoint model. Baseline trends and level changes remained similar across all model specifications, with no statistically significant level change observed following the first lockdown. A decline in trend after the first lockdown was observed in all models; however, this reached statistical significance only in the single-breakpoint model including all observations. When March 2020 was excluded or adjusted for using a dummy variable, the trend change was attenuated and no longer statistically significant. Detailed results are presented in **Appendix S.5.3**.

Together, these findings suggest a continued slowing in the growth of prevalent OAC use after the second lockdown, indicating a potentially longer-term impact on prescribing patterns.

5.3.2.2. Prevalent OAC users by drug type (DOAC vs VKA)

The number of prevalent DOAC users demonstrated consistent growth throughout the study period, with a particularly pronounced increase during early 2020 following the first lockdown as shown in **Figure 5.7**. In contrast, prevalent VKA users exhibited gradual decline from 2018 onwards, with this downward trend accelerating after the first lockdown.

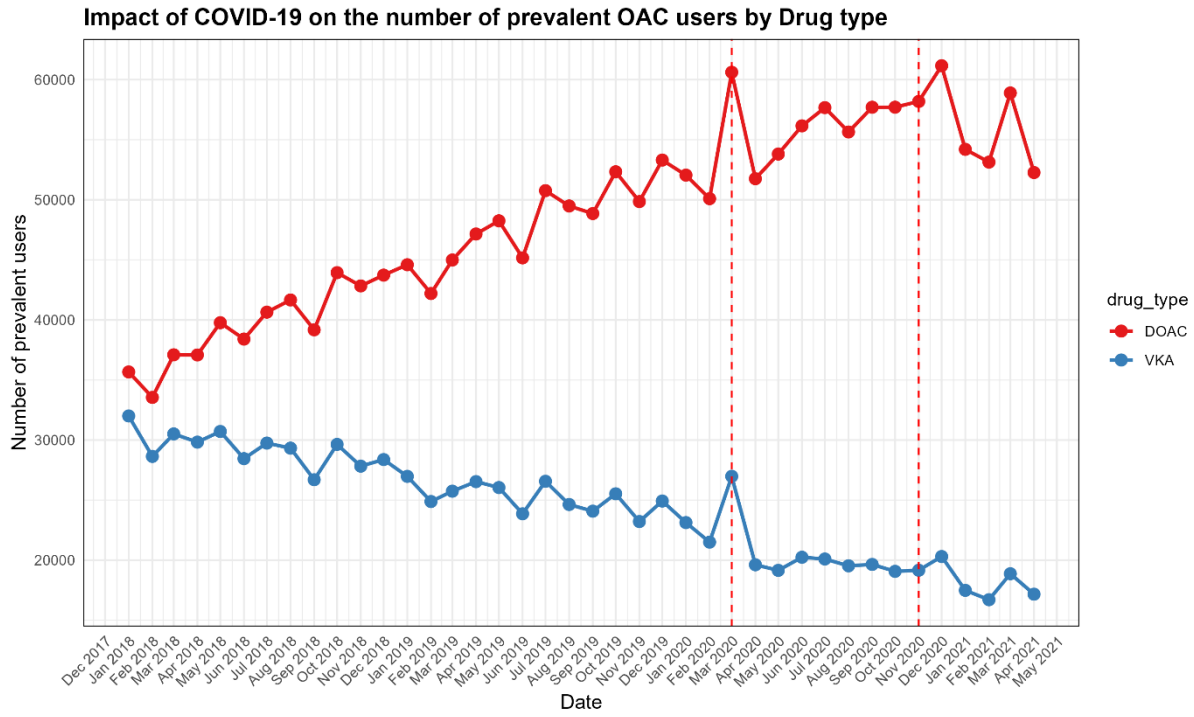

Figure 5.7: Time series analysis for the number of prevalent users per month by drug type, Jan 2018 to April 2021

5.3.2.3. Trends in prevalent OAC use by approved name

Figure 5.8 displays the monthly number of prevalent users for individual OACs from January 2018 to April 2021. Throughout the study period, apixaban use increased steadily, becoming the most commonly used DOAC by the end of the period. In March 2020, apixaban experienced a substantial increase in use, with the number of prevalent users rising by approximately 19.9% compared to February (from 26,233 to 31,460). This spike marked a significant step-change, after which usage remained consistently high, with only moderate monthly fluctuations.

Edoxaban also experienced a substantial increase in March 2020, with the number of prevalent users rising by 25.3% (from 13,157 to 16,495). Unlike some other DOACs, edoxaban usage continued to increase steadily after March 2020, eventually becoming the second most used DOAC after apixaban. However, the rate of increase appeared to slow slightly after November 2020. In contrast, warfarin exhibited a gradual decline throughout the study period, which accelerated markedly following the initial lockdown.

Rivaroxaban usage remained relatively stable with a slight downward trend post-lockdown, while dabigatran maintained consistently low usage across the entire timeframe, showing minimal variation in response to the pandemic.

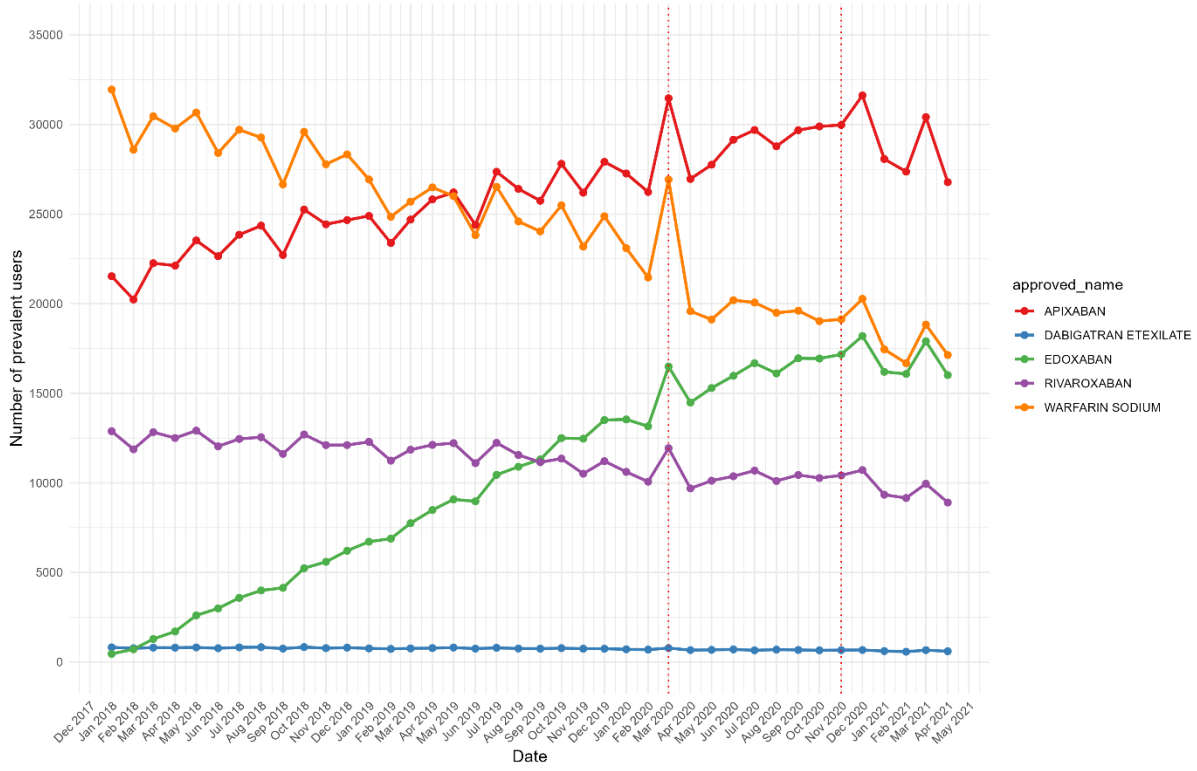

Figure 5.8: Monthly number of prevalent users of individual oral anticoagulants from January 2018 to April 2021, with reference lines marking the first (March 2020) and second (November 2020) COVID-19 lockdowns in Scotland.

5.3.3. Trends for incident OAC users

5.3.3.1. Overall incident use of OACs

The analysis of incident OAC prescribing revealed a significant immediate decline in the number of new patients initiating therapy following the onset of the COVID-19 pandemic. As shown in **Figure 5.9**, there was a pronounced drop immediately after the implementation of the first national lockdown in March 2020. Segmented regression analysis quantified this immediate reduction, estimating a monthly decrease of approximately 423 new incident OAC users (95% CI: –633.8 to –212.3, $p < 0.001$) compared to pre-lockdown trends. Following this sharp decline, a statistically significant gradual recovery was observed, characterized by an upward shift in the monthly number of incident users ($\beta_3 = 38.7$, $p = 0.015$), ultimately returning to pre-pandemic levels by November 2020 (**Figure 5.9** and **Table 5.4**).

Only one breakpoint was included in the segmented regression analysis for incident users because the inclusion period ended in December 2020. Consequently, there were insufficient data points after the second lockdown to include a second breakpoint in the analysis.

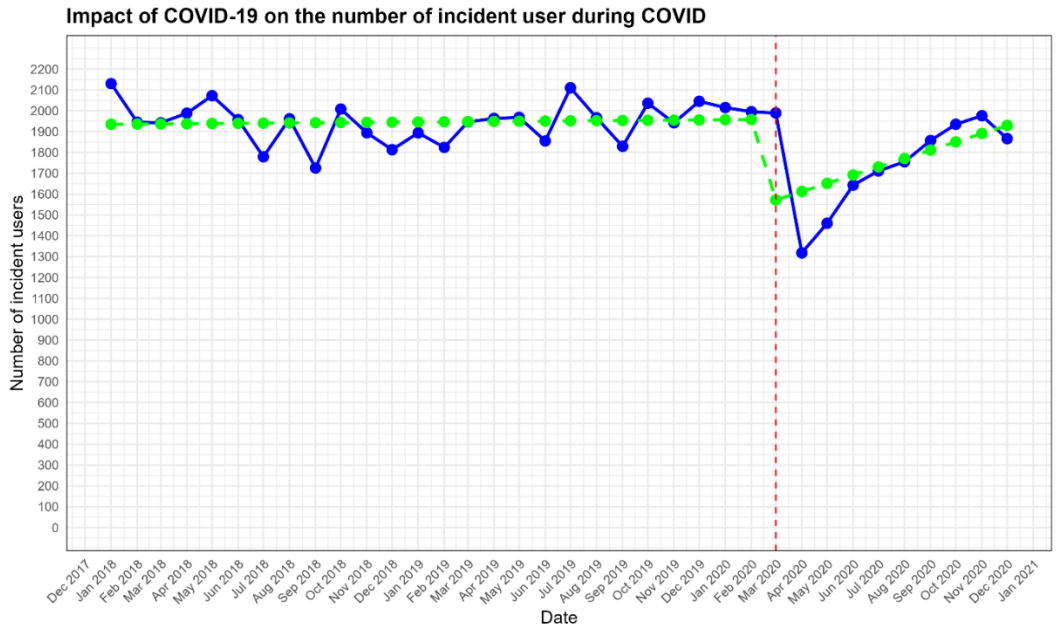

Figure 5.9: Monthly incident OAC users, one break point, from Jan 2018 to Dec 2020

Note: OAC includes both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). The red dashed line indicates the first COVID-19 lockdown (March 2020).

Table 5.4: Segmented regression results for incident oral anticoagulant users (Jan 2018 – Dec 2020)

	Baseline trend (β1)	**Level change after first lockdown (β2)**	**Time trend after first lockdown (β3)**
Incident OAC users (total)	0.89 (-6.18, 7.97)	-423.08 (-633.83, -212.31)	38.67 (8.17, 69.17)
P-value	0.799	**< 0.001**	**0.015**
Incident DOAC users	4.61 (- 1.81, 11.03)	-379.53 (-570.72, -188.33)	32.33 (4.66, 60.01)
P-value	0.1534	**< 0.001**	**0.023**
Incident VKA users	-3.72	-43.55	6.34
P-value	**< 0.001**	**0.005**	**0.004**

Sensitivity analyses models excluding March 2020 or adjusting for March using a dummy variable showed that the overall pattern of results was consistent across model specifications. The baseline trend remained stable and non-significant in all models. A statistically significant reduction in incident OAC use immediately following the first lockdown was observed across all analyses, with similar magnitude of effect. In addition, a positive trend in incident use after the first lockdown was observed in all models and was statistically significant. Detailed results are presented in **Appendix S.5.4** .

5.3.3.2. Incident OAC users by drug type (DOAC vs VKA)

Further stratification by anticoagulant type revealed distinct patterns of pandemic impact on OAC initiation rates. Prior to the pandemic, DOACs showed consistently high utilization, with monthly incident users ranging between 1,500-2,000 patients from January 2018 through early 2020, while VKA incident use remained at relatively stable but substantially lower levels of fewer than 500 patients per month throughout the study period (**Figure 5.10**).

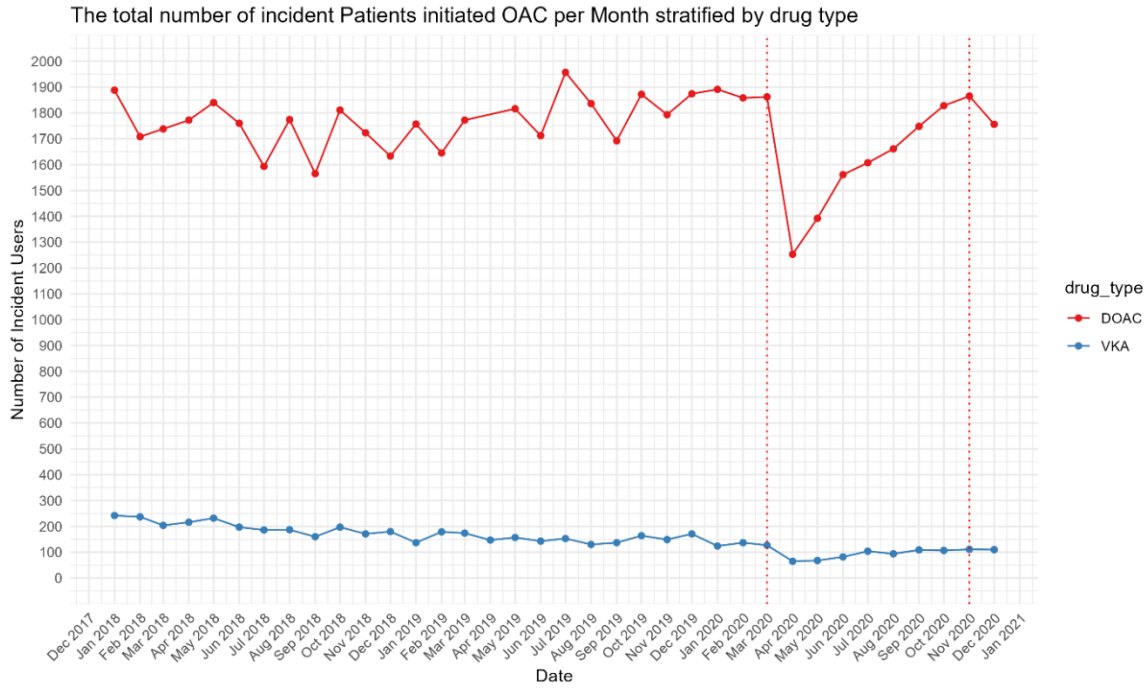

Figure 5.10: Time series analysis for the number of incident users per month by drug type, from Jan 2018 to Dec 2020

The pandemic period was characterized by differential reductions in new anticoagulant initiations across OAC subtypes. Monthly average DOAC initiations showed a modest decrease during the pandemic compared to pre-pandemic levels (1,653 vs. 1,773 patients), representing a 6.8% reduction. In contrast, VKA initiations experienced a more substantial decline (98 vs. 174 patients), corresponding to a 43.9% decrease. For the incident user analysis, absolute and relative percentage changes were computed by comparing mean monthly prescribing levels in the pre-COVID period (January 2018–February 2020) with those during the pandemic (March–December 2020), as shown in **Table 5.5**.

Table 5.5: Comparison of mean monthly incident DOAC and VKA users before (Jan 2018–Feb 2020) and during (Mar–Dec 2020) the COVID-19 pandemic, including absolute and relative changes.

Period	Drug type	Mean count of incident users (95% CI)	Absolute change	Relative change
During COVID (03/2020-12/2020)	**DOAC**	1653 (1507-1800)	120	-6.76 %
Pre-COVID (1/2018-02/2020)	**DOAC**	1773 (1734-1812)		
During COVID (03/2020-12/2020)	**VKA**	98 (83- 112)	76.3	-43.85
Pre-Covid (1/2018-02/2020)	**VKA**	174 (160-187)		

5.3.3.3. Segmented regression analysis of incident DOAC users

Segmented regression analysis of individual anticoagulant subtypes further elucidated the temporal dynamics of pandemic impact. For DOAC initiations, the analysis revealed a statistically significant immediate level drop of approximately 380 users following the first lockdown (β_2, 95% CI: –570.7 to –188.3, $p < 0.001$), followed by a significant increase in monthly trend ($\beta_3 = 32.3$, $p = 0.023$), indicating rapid recovery and resumption in DOAC initiation patterns (**Figure 5.11** and **Table 5.4**).

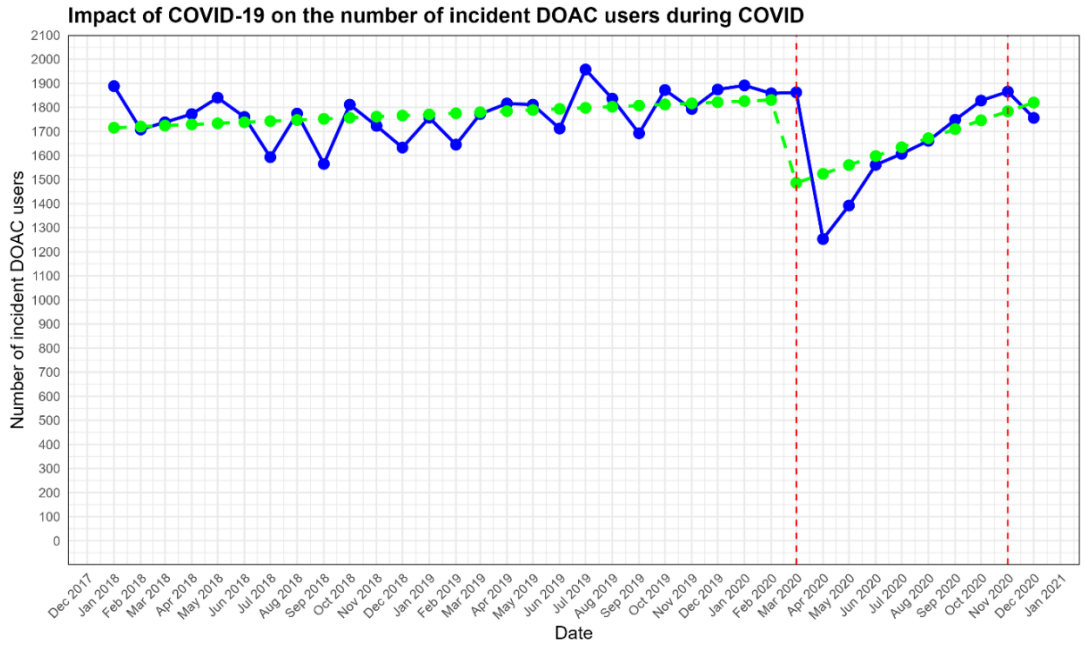

Figure 5.11: The impact of COVID 19 on the number of patients initiating DOACs, Jan 2018 to Dec 2020

5.3.3.4. Segmented regression analysis of incident VKA users

In contrast, VKA initiations demonstrated a more complex temporal pattern characterized by a pre-existing declining trend that preceded the pandemic (β_1 = –3.72, p < 0.001). This baseline decline was further exacerbated by a modest but statistically significant level drop after the first lockdown (β_2 = –43.6, p = 0.005), accompanied by a small but significant positive trend shift (β_3 = 6.34, p = 0.004) (**Figure 5.12** and **Table 5.4**).

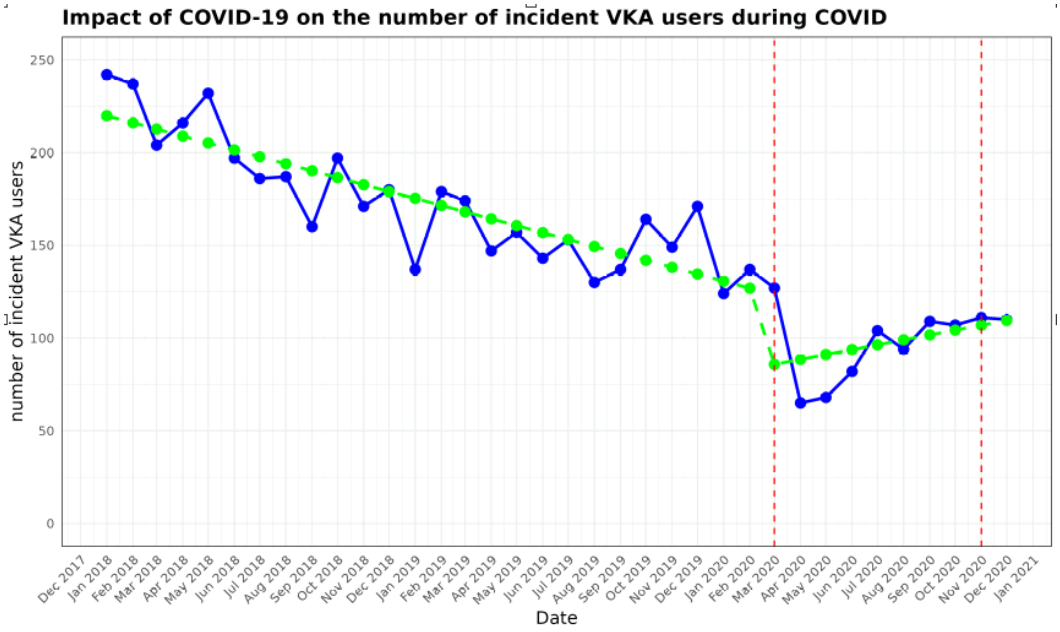

Figure 5.12: The impact of COVID 19 on the number of patients initiating VKA, Jan 2018 to Dec 2020

5.3.3.5. Incident OAC users by individual DOAC agents

Before COVID-19, monthly initiations averaged 750–1,175 for apixaban and fewer than 250 for warfarin (**Figure 5.13**). A sharp decline occurred in April 2020 (to approximately 620 apixaban initiations) coinciding with the first lockdown, followed by a gradual but strong recovery to pre-pandemic levels by late 2020 (August 2020: ≈ 820, November: ≈920 initiators).

Edoxaban showed rapid pre-pandemic growth, with incidence rising markedly from approximately 100 per month in 2018 to ≈ 650-700 just before lockdown. Usage decreased during April 2020 (approximately 370 initiations) before recovering to 575–600 initiations per month in Sep 2020. Incident warfarin use continued its long-term decline, dropping below 100 initiations per month throughout the period. These trends are illustrated in **Figure 5.13**.

The combined incident use of rivaroxaban and dabigatran (grouped together due to low dabigatran numbers) showed a gradual decline from the observation period's start, becoming more pronounced around April 2020 with the first COVID-19 lockdown. At this point, incident use dropped to approximately 250 initiations per month, the lowest observed level. Following this decline, there was gradual resumption reaching around 400 initiations per month by November 2020. However,

the overall trend change was less pronounced compared to other DOACs, particularly apixaban, which demonstrated sharper recovery and growth patterns. These data indicate a temporary disruption in DOAC initiation during the early pandemic period, followed by gradual recovery and a sustained shift away from warfarin among new incident users.

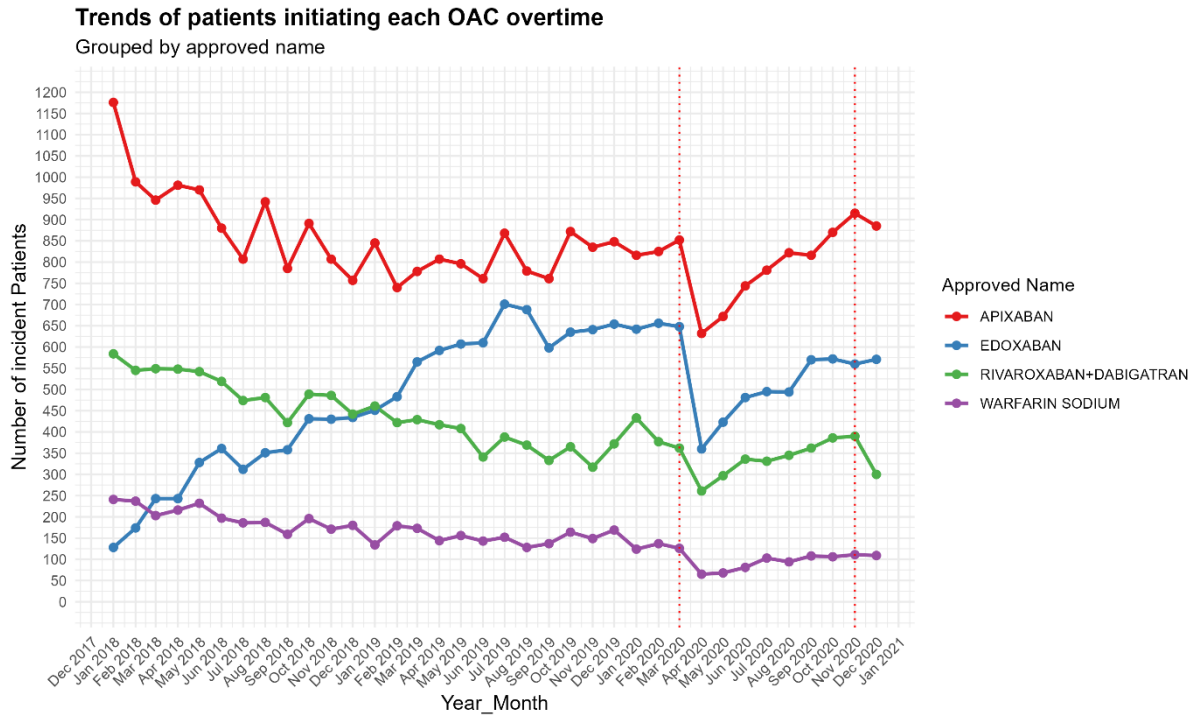

Figure 5.13: Time series analysis for the number of incident users per month grouped by approved name, from Jan 2018 to Dec 2020.

Note: Due to very low numbers of dabigatran initiations, dabigatran and rivaroxaban were grouped together for the incident user analysis to ensure model stability. This grouping was applied solely for incident ITS models and does not reflect pharmacological similarity between the two agents.

5.3.4. Switching from VKA to DOAC during the pandemic

5.3.4.1. Descriptive trends in switching

The switching rate was relatively stable in the pre-COVID-19 period (before March 2020), with minor fluctuations. The percentage of patients switching each month ranged from 1.3% to 1.8% (340-550 patients) of the total patients on VKA **(Figure 14)**.

A substantial increase in the percentage of patients switching to DOAC was observed with the onset of the pandemic. Following the first lockdown in March 2020, the switching rate increased to 4.0% (~1,095 patients), reaching its peak at

8.13% (~1,596 patients) in April 2020, the highest recorded rate during the study period (**Figure 5.14**).

The switching rate subsequently declined in May 2020 to 4.0% (~772 patients), followed by a gradual decrease to 1.9% and 1.4% in subsequent months. By October 2020, the rate had returned to pre-pandemic levels of approximately 1.3-1.8% of the total VKA patient population. Notably, the second lockdown in November 2020 did not appear to influence the switching rate, which remained consistent with pre-pandemic averages. The relative increase is significant; there has been a 141% increase in the percentage of patients switched in March 2020 (4%) when COVID started compared to the rate before the COVID-19 pandemic in Feb 2020 (1.66%). The absolute change was 2.34%.

5.3.4.2. Segmented regression results

The segmented regression model revealed a statistically significant immediate increase in the percentage of patients switching to DOACs following the first national lockdown in March 2020. This was reflected by a level change of $\beta_2 = 4.6542$ (95% CI: 3.437 to 5.870, $p = 4.80 \times 10^{-9}$), as shown in **Figure 5.14**.

In the post-lockdown period leading up to the second lockdown, the trend in switching rates declined significantly, with a negative slope change of $\beta_3 = -0.6683$ (95% CI: -0.8883 to -0.4484, $p = 5.11 \times 10^{-7}$). This indicates that although the initial level of switching increased sharply after the first lockdown, the rate of increase slowed in subsequent months.

There was no statistically significant immediate level change associated with the second national lockdown. However, the slope following the second lockdown showed a significant positive change, with $\beta_5 = 0.7034$ (95% CI: 0.2997 to 1.1071, $p = 0.0012$), indicating a renewed upward trend in switching rates over time after the second lockdown (**Table 5.6**).

These results demonstrate that the first lockdown had a profound immediate impact on switching behaviour, while the second lockdown's effect was primarily reflected in longer-term trend changes rather than immediate level shifts.

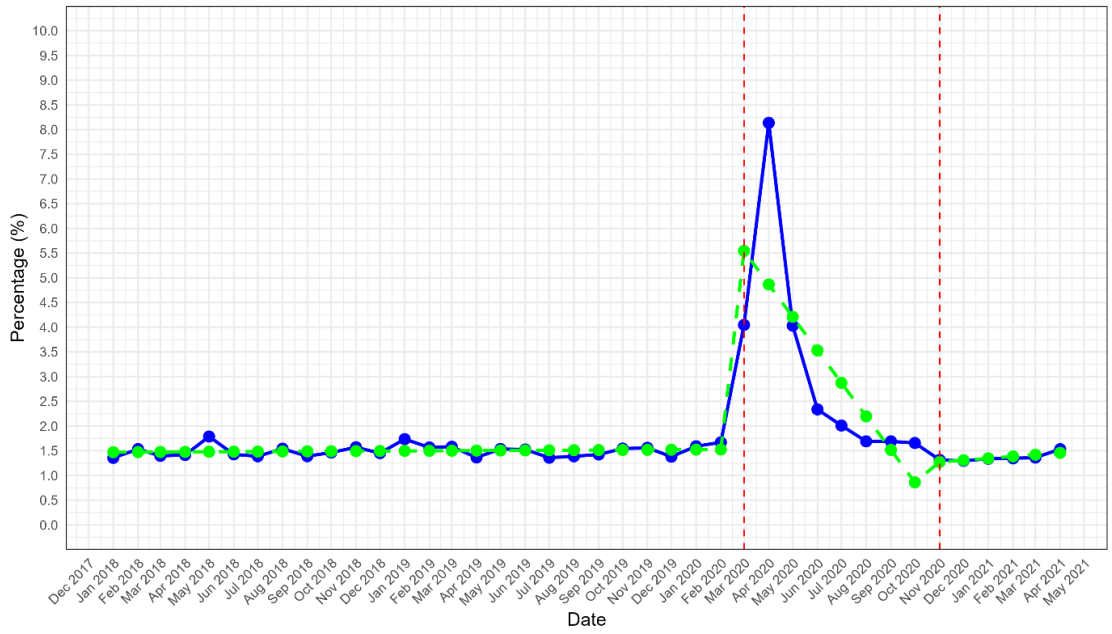

Figure 5.14: Impact of COVID-19 on the percentage of patients switching from VKA to DOAC: a segmented regression model with two breakpoints and a 90-day gap

Table 5.6: Segmented regression model with two breakpoints (March 2020 and November 2020) estimating the monthly percentage of patients switching from vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs), using 90-day and 60-day prescription gap (Jan 2018 – Apr 2021)

Switching Definition	Baseline trend (β1)	Level change after first lockdown (β2)	Time trend after first lockdown (β3)	Level change after second lockdown (β4)	Time trend after second lockdown (β5)
90-day gap	0.0022 (0.0347, 0.0390)	4.654 (3.438, 5.871)	-0.668 (-0.888, -0.448)	0.374 (-1.234, 1.981)	0.703 (0.299, 1.107)
P-value	0.906	**<0.001**	**<0.001**	0.640	**0.0012**
60-day gap	0.00332(-0.03146, 0.0381)	4.212259 (3.0661, 5.358)	-0.612913 (-0.82011, -0.4057)	0.381164 (-1.1332, -0.4057)	0.640937 (0.2606, -1.0211)
P-value	0.847	**<0.001**	**<0.001**	0.612	**0.0016**

Note: CI = Confidence Interval. Significant p-values are marked: $p < 0.05$. Model coefficients represent changes in level and trend after each lockdown period.

5.3.4.3. Sensitivity analysis results

The sensitivity analysis demonstrates the robustness of the primary findings. Specifically, using a 60-day gap to define switching yielded a statistically significant coefficient consistent in direction and magnitude with the primary (90-day gap) analysis. This suggests that the observed lockdown-related effects on switching from VKA to DOAC are not sensitive to the specific gap definition used, as shown in **Figure 5.15** and **Table 5.6**.

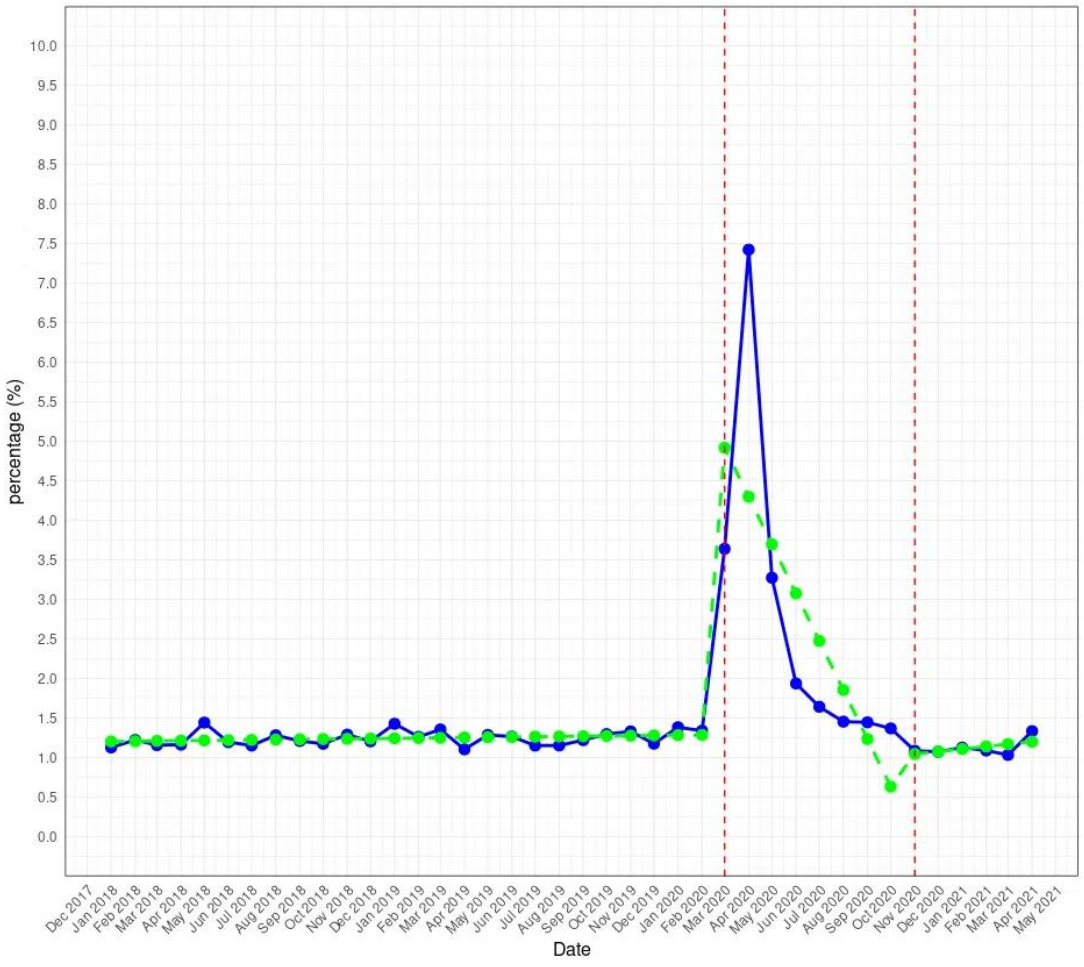

Figure 5.15: Impact of COVID-19 on the percentage of patients switching from VKA to DOAC: a segmented regression model with two breakpoints and a 60-day gap

Additionally, results from single-breakpoint models, as well as models excluding March 2020 or including a dummy variable for March, were consistent with the primary analysis. A statistically significant increase in switching immediately following the first lockdown and a subsequent decline in trend were observed across all models, with similar magnitude and direction of effects. Although the estimates

were slightly attenuated when March 2020 was excluded or adjusted for, statistical significance was maintained. These findings suggest that the results are robust to both model specification and handling of short-term disruption (**Appendix S.5.5**).

5.3.4.4. Distribution of first DOAC agent after switching from VKA

Table 5.7 presents the distribution of patients switching from VKAs to specific DOAC agents, stratified by time period. This analysis refers specifically to the first DOAC prescribed following a switch from VKA and should not be confused with the incident prescribing of DOACs in the overall population.

Of the 16,690 total switchers identified, apixaban was the most common DOAC, accounting for 45.8% of switches overall, followed closely by edoxaban (42.0%).

However, a notable shift in prescribing preference occurred during the pandemic. Apixaban use declined from 48.9% before COVID to 39.3% during COVID, while edoxaban increased substantially from 35.3% to 54.8%. Rivaroxaban demonstrated a moderate decline from 15.1% to 5.7%, while dabigatran remained extremely limited throughout both periods.

Table 5.7: Distribution of patients who switched from vitamin K antagonists (VKAs) to specific direct oral anticoagulants (DOACs) from January 2018 to May 2021, including pre-COVID and during-COVID periods.

Medication	Count (N/%)	Before COVID (N/%)	During COVID (N/%)
Apixaban	7735 (45.79%)	4768 (48.85%)	2193 (39.30%)
Dabigatran	89 (0.52%)	71 (0.72%)	8 (0.143%)
Edoxaban	7099 (42.03%)	3449 (35.34%)	3059 (54.83%)
Rivaroxaban	1967 (11.64%)	1471 (15.07%)	319 (5.71%)

5.3.5. Autocorrelation diagnostics

Initial analysis using a simple linear model indicated potential autocorrelation in the residuals (e.g., DW = 1.5701, p = 0.0577). However, after applying the segmented regression model, no significant autocorrelation was observed across any of the models. For example, in the model assessing total prescriptions, the Durbin–Watson statistic improved to DW = 2.5405, p = 0.8457), as shown in **Table 5.8**.

These findings were further supported by inspection of the autocorrelation function (ACF) plots of the residuals, which were used to visually assess the correlation between different values in a time series at various time lags. In all cohorts, the ACF

plots showed that fewer than 5% of time lags exceeded the 95% confidence bounds, indicating no strong serial autocorrelation **(Appendix S.5.1**).

Table 5.8: Durbin–Watson test statistics and p-values for autocorrelation in simple and segmented regression models.

	DW (Simple model)	DW (Segmented model)
Incident users (Jan 2018–Dec 2020)	1.19 (p = 0.003) **	2.11 (p = 0.429)
Prevalent users (until Apr 2021)	2.20 (p = 0.678)	2.82 (p = 0.976)
Total prescriptions	1.57 (p = 0.058)	2.54 (p = 0.846)
% Switched (VKA → DOAC, 90-day gap)	0.82 (p = <0.001) **	2.48 (p = 0.787)
% Switched (VKA → DOAC, 60-day gap)	0.89 (p = <0.001) **	2.49 (p = 0.794)

Note: Durbin–Watson values closer to 2 indicate no autocorrelation. Values substantially below 2 suggest positive autocorrelation

5.4 Discussion

The COVID-19 pandemic significantly disrupted OAC prescribing patterns in Scotland, revealing three key changes: altered overall usage trends, reduced new treatment initiations, and accelerated switching from VKAs to DOACs. These findings align with broader international evidence while highlighting the pandemic's profound impact on chronic cardiovascular care delivery. Scottish patient-level data provides comprehensive understanding of these trends, revealing not only the slowdown in new OAC initiations but also highlighting how existing users were generally maintained on therapy.

The initial increase in OAC prevalence observed during the first lockdown is unlikely to represent a true rise in anticoagulation uptake. Instead, it likely reflects temporary stockpiling behaviour or a surge in prescriptions issued immediately prior to the implementation of pandemic-related restrictions. This interpretation is supported by the marked spike in prescription volume observed in March 2020, suggesting that prescribers may have issued early or additional supplies in anticipation of disrupted access to healthcare services. The subsequent return to baseline prescribing levels further supports the concept of a temporary modification in prescribing patterns rather than a sustained change in treatment uptake. Similarly, the prescription surge across DOACs reflects both genuine prescribing shifts driven by national guidance

favouring DOAC switching and stockpiling behaviour as clinicians and patients anticipated reduced healthcare access. Similar patterns were documented across various medication classes during early pandemic phases, reflecting widespread concerns about medication access (240,251–253). The absence of comparable spikes before subsequent lockdowns suggests improved system preparedness and adapted clinical workflows.

The longer-term slowing of OAC prevalence growth, resulting in lower total OAC usage by 2021 relative to pre-pandemic trends, is likely attributable to a combination of reduced new initiations and possible discontinuation or adherence challenges among existing users during healthcare system disruptions. This pattern mirrors findings from England, where similar deviations from expected growth rates indicated potential care gaps (254).

An important observation was the immediate monthly decline in new OAC initiations following the March 2020 lockdown ($\beta 2 = -423$, 95% CI –633.8 to –212.3; $p < 0.001$). Following the first lockdown, there was a significant positive change in the prescribing trend, with a β_3 estimate of 38.67 (95% CI: 8.17–69.17; $p = 0.0146$), indicating a sustained increase in the number of incident users over time. However, prescribing rates took approximately eight months to fully recover to pre-pandemic levels. This substantial reduction corresponds with broader healthcare utilization patterns, where overall healthcare access fell by roughly one-third during early 2020 (255).

The clinical significance of this gap extends beyond numerical deficits, as delayed anticoagulation exposes high-risk patients to preventable thromboembolic events. Nationwide studies reported a 35% decrease in new AF diagnoses during 2020, with authors warning of potential increases in stroke, HF, and mortality due to delayed diagnosis and treatment (256). Given that untreated AF increases stroke risk five-fold and oral anticoagulation reduces this risk by over 60% (256), the observed initiation deficit represents a serious public health concern with implications for preventable adverse outcomes. While patient outcomes were not directly measured in this analysis, supporting evidence in the literature suggests negative consequences of interrupted anticoagulation care during COVID-19, with some studies reporting higher stroke severity among patients during the pandemic and raising concerns that disruptions in chronic care could contribute to these patterns (257).

The pandemic's impact varied significantly between anticoagulant types. While new DOAC initiations decreased modestly (from 1,773 to 1,653 monthly), VKA initiations were approximately halved (from 174 to 98 monthly). This disparity likely reflects both pandemic-related disruption to routine care and national guidance recommending DOAC initiation in preference to VKAs (244). The practical challenges of managing warfarin during lockdowns, given its requirement for regular INR monitoring and dose adjustments, led clinicians to avoid treatments necessitating intensive in-person monitoring, instead favouring DOACs with their fixed dosing and minimal monitoring requirements. These findings align with comprehensive English data from over 53 million individuals, which demonstrated significant changes in anticoagulant utilization patterns, including notable increases in DOAC prescribing concurrent with warfarin decline (243).

This shift was further supported by national guidance in England recommending switching suitable warfarin patients to DOACs to minimize clinic visits. Following this guidance, approximately 20,000 of 164,000 warfarin patients (around 12%) in England were switched to DOAC therapy between March and May 2020 (245). Although Scotland did not issue a single national directive identical to England's, similar recommendations were provided through local NHS boards and anticoagulation services (258,259), encouraging switching from VKAs to DOACs, which likely contributed to similar patterns observed in Scotland.

Analysis of Scottish data revealed a substantial increase in switching from VKAs to DOACs during the early phase of the COVID-19 pandemic. Pre-pandemic switching rates remained relatively stable at 1.3-1.8% monthly (340-550 patients) but increased sharply to 4.0% (~1,095 patients) in March 2020, peaking at 8.13% (~1,596 patients) in April 2020, representing a 141% relative increase compared to February 2020 levels. Segmented regression analysis confirmed a statistically significant immediate level change following the first lockdown ($\beta_2 = 4.6542$, 95% CI: 3.437 to 5.870, $p = 4.80\times10^{-9}$), followed by a declining trend in subsequent months ($\beta_3 = -0.6683$, 95% CI: -0.8883 to -0.4484, $p = 5.11\times10^{-7}$). By October 2020, switching rates had returned to pre-pandemic levels. Notably, the second lockdown did not trigger comparable switching behaviour, likely because most eligible patients had already switched during the initial surge. The pandemic effectively accelerated what may have otherwise been a gradual transition, resulting in a rapid shift toward the predominance of DOAC prescribing.

Among DOACs, apixaban exhibited the most pronounced response to the pandemic, with a marked increase in use observed during the initial lockdown period, maintaining its position as the most commonly prescribed OAC throughout the study period while showing marked acceleration following COVID-19 onset. The data reveal a substantial 19.9% increase in prevalent apixaban users and a 25.5% increase in apixaban prescriptions between February and March 2020, representing the largest step-change among all anticoagulants during this period. This preference likely reflects apixaban's favourable safety and efficacy profile, particularly advantageous during periods of limited healthcare access.

Edoxaban similarly showed substantial growth, with prevalent users increasing by 25.3% and prescriptions rising by 48.6% in March 2020, eventually emerging as the second most used DOAC. Among patients switching from VKAs, the shift in DOAC agent selection observed during the pandemic, particularly the increased use of edoxaban, may reflect the practical advantages during healthcare disruption. Edoxaban’s once-daily dosing regimen may have facilitated treatment initiation and continuation when routine monitoring and follow-up were limited. However, this shift may also reflect pre-existing prescribing trend; since its regulatory approval, edoxaban use had been rising rapidly, possibly contributing to a natural transition away from rivaroxaban and gradually displacing part of its market share. Concurrently, apixaban and edoxaban appear to be increasingly preferred overall, confirming an ongoing evolution in DOAC prescribing patterns that extends beyond the pandemic period. Together, these findings suggest that while the pandemic may have accelerated certain prescribing changes, the underlying shift towards newer DOAC agents represents a broader transformation in anticoagulation management practices.

Supporting this interpretation, evidence from Spain demonstrated that patients on DOACs experienced fewer adverse events, better persistence, and reduced healthcare resource utilization compared to VKA users during the pandemic (260). In contrast, warfarin-treated patients had significantly higher rates of stroke, thromboembolism, major bleeding, mortality, and healthcare resource consumption compared to DOAC users during the pandemic period (260).

International comparisons

In contrast to the significant decline in new OAC initiations observed in Scotland, a large Swedish population-based interrupted time series study found no significant

overall reduction in anticoagulant initiation following pandemic onset (261). This difference likely reflects variations in national pandemic response strategies, as Sweden did not implement strict national lockdowns during early 2020 and instead relied on voluntary measures, potentially preserving access to routine cardiovascular care compared with many other countries (262).

Despite these differences in overall initiation rates, warfarin exhibited a negative pre-pandemic trend that was attenuated following COVID-19 onset in both studies. In Scotland this attenuation occurred after a marked immediate reduction in initiation accompanied by accelerated switching from VKAs to DOACs, whereas in Sweden the change was primarily expressed as a modification of the pre-existing declining trend without a pronounced level change, suggesting less abrupt service disruption and fewer policy-driven prescribing shifts than observed in Scotland.

Age-stratified analyses further strengthen the comparability between the two settings. In Sweden, individuals aged ≥65 years experienced immediate decline in anticoagulant and DOAC initiation followed by recovery trends, while younger adults showed numerical increases in initiation. When restricted specifically to DOAC initiation among older adults, the Swedish pattern closely resembled that observed in Scotland, although the post-pandemic trend change did not reach statistical significance. These findings suggest that older, higher-risk populations were disproportionately affected by early pandemic-related disruptions across healthcare systems, even in settings with less restrictive public health measures.

Several methodological differences may also explain the more modest overall effects observed in the Swedish study. Anticoagulant use was defined more broadly, including heparins in the overall category, whereas the present study focused exclusively on OACs. Given the distinct clinical indications and care pathways for heparins, which are predominantly administered in hospital settings, their inclusion may partially attenuate observed population-level changes in anticoagulant initiation. During COVID-19 pandemic, increased hospitalisation rates and widespread use of heparins for thromboprophylaxis among hospitalised patients may have further contributed to this attenuation.

Findings from other international settings provide additional comparative context. An interrupted time series analysis from Tuscany, Italy, demonstrated patterns highly consistent with the Scottish results, with substantial immediate declines in initiation of both DOACs and VKAs during lockdown, followed by recovery for DOACs but

more limited recovery for VKAs (263). Across both settings, VKAs were more severely and persistently affected.

In contrast, a large US cohort study examining anticoagulation initiation among patients with newly diagnosed AF reported no significant changes in initiation of oral anticoagulation or DOAC therapy within 30 days of diagnosis following the onset of COVID-19, although non-pharmacological interventions such as electrical cardioversion declined markedly (264). This contrasts with the substantial initiation deficits observed in Scotland and parts of Europe and may reflect differences in healthcare system organisation and access to outpatient prescribing, as well as important methodological differences. The US study assessed treatment initiation conditional on diagnosis within a short time window, rather than population-level initiation rates that also capture disruptions in diagnosis and delayed care.

Taken together, these cross-national findings indicate that while the magnitude of disruption to anticoagulation initiation varied between countries, the pandemic consistently accelerated existing clinical trends away from warfarin and toward DOACs rather than introducing entirely new prescribing behaviours. The Scottish data extend this evidence by demonstrating a more pronounced initiation deficit and rapid switching behaviour, likely driven by stricter lockdown measures and national guidance.

Implications and future directions

While the reduction in new anticoagulant initiations represents a concerning care gap requiring attention, the shift toward DOACs may confer long-term benefits given their improved management profile under constrained healthcare conditions. Future research should focus on quantifying the clinical consequences of delayed anticoagulation initiation and developing strategies to maintain therapeutic continuity during healthcare system disruptions, ensuring that the lessons learned from this pandemic inform more resilient chronic disease management approaches. This study provides a more detailed and population-specific understanding of the pandemic's impact on anticoagulation management in Scotland, filling an important evidence gap and offering insights to inform future public health planning and guideline development.

Strength and limitations

Strength:

A major strength of this study is the use of patient-level data to examine incidence of new initiations, prevalence of ongoing treatment, switching between anticoagulant classes, and overall prescribing volume. This comprehensive approach provides a detailed assessment of the pandemic's impact on anticoagulation management that extends beyond initiation alone.

Additionally, the use of 40 consecutive months of monthly data enabled detailed capture of both short- and long-term temporal changes.

Limitations:

This study has several methodological limitations that should be acknowledged. First, switching from VKA to DOAC was defined as a 90-day gap between the last VKA and first DOAC prescription, based on observed dispensing patterns. While a sensitivity analysis using a 60-day gap yielded consistent results, the optimal threshold for defining switching remains uncertain, and some degree of misclassification of switching events cannot be excluded.

Second, the washout period used to identify incident OAC users may have influenced the composition of the study cohort over time. Patients initiating therapy earlier in the study period had shorter available lookback periods to exclude prior use compared to those initiating later. This may have resulted in some misclassification of prevalent users as incident users in the earlier study years.

Third, this study focused on prescribing patterns and did not assess clinical indications or patient outcomes; consequently, it was not possible to determine whether observed changes in anticoagulant initiation translated into differences in thromboembolic or bleeding events. In addition, although interrupted time series analysis accounts for underlying trends, residual confounding from concurrent changes in healthcare delivery and patient behaviour during the pandemic cannot be excluded.

Fourth, post-intervention observation windows were limited across all models. For incident use, only one breakpoint (March 2020) was included, with data extending only to December 2020. For switching, prevalent use, and overall prescribing, two breakpoints were used (March 2020 and November 2020), with data available through April 2021. Even with the extended follow-up period, the time available after each lockdown remained limited, with 7 months after the first lockdown and 5 months after the second lockdown in the two-breakpoint models. This is below the

commonly recommended 12 post-intervention observations for interrupted time series analysis using monthly data (246,265), which may have reduced the precision of estimated trend changes, particularly for the second lockdown period. Nevertheless, sensitivity analyses using alternative model specifications, including one-breakpoint models across key outcomes, demonstrated consistent findings, supporting the robustness of the results.

Finally, due to the small number of dabigatran initiations, dabigatran and rivaroxaban were grouped for time-series analysis. Although dabigatran is a direct thrombin inhibitor and rivaroxaban is a Factor Xa inhibitor, separate modelling was not feasible because of limited dabigatran data. This should be considered when interpreting results for this combined group. This grouping applies only to the incident user analysis.

5.5 Conclusion

This chapter demonstrates the significant impact of the COVID-19 pandemic on oral anticoagulant prescribing patterns in Scotland. While the early pandemic phase prompted a prescription surge driven by anticipatory prescribing, overall OAC utilization ultimately fell below anticipated levels by 2021, indicating a care gap arising from reduced healthcare access and delayed diagnosis. The marked decline in new OAC initiations, particularly following the first lockdown, highlights broader disruption to cardiovascular care pathways. However, the pandemic also accelerated an ongoing clinical shift from VKA to DOACs, a transition supported by evidence and contemporary guidelines favouring DOACs for their safety, efficacy, and ease of use.

These findings highlight the dual impact of the pandemic as both a disruptor of chronic care delivery and an accelerator of evidence-based clinical change. Although the pandemic revealed systemic vulnerabilities in chronic care delivery, it may have also catalysed lasting improvements in anticoagulation practice, particularly through the broader adoption of DOAC therapy. They also highlight the importance of strengthening health system resilience and developing strategies to maintain therapeutic continuity during future public health emergencies.

6 Chapter 6: Factors associated with switching from VKA to DOAC before and during the COVID-19 pandemic

6.1 Introduction

Switching from VKAs to DOACs represents a major shift in the management of patients requiring long-term anticoagulation. Unlike treatment initiation, where prescribing guidelines and clinical trial evidence provide relatively clear direction, switching decisions involve balancing multiple clinical and practical considerations. It requires weighing the risks and benefits of moving a patient who is already stable on one therapy to another, while considering patient characteristics, treatment history, and wider healthcare system factors (266,267).

Even before the COVID-19 pandemic, switching from VKAs to DOACs was commonly reported in routine clinical practice across multiple countries, including the United States, the UK, and Nordic healthcare systems (267). Switching decisions were individualized and typically driven by clinical challenges with warfarin management. A scoping review identified unstable INR control as the primary clinical trigger in 60% of studies (266), alongside other factors including frequent monitoring requirements, bleeding events, poor time in therapeutic range, drug interactions, recent cardiovascular events (such as stroke or TIA) (266,267), and patient dissatisfaction (268). Clinical features that made DOAC therapy more suitable for some patients, such as convenience of fixed dosing and elimination of frequent monitoring, also influenced switching decisions.

The COVID-19 pandemic, however, fundamentally affected switching practices. As demonstrated in the previous chapter (Chapter 5), the COVID-19 pandemic accelerated switching from a VKA to DOACs in Scotland on a large scale, with national guidance actively encouraged switching to reduce face-to-face monitoring visits during periods of restricted healthcare access (244). This external pressure led to a sharp increase in switching (269), particularly in settings with lockdowns and strained medical services (270).

Internationally, the COVID-19 pandemic prompted variable responses in anticoagulation management. The UK implemented large-scale reviews of warfarin patients to identify suitable candidates for DOAC switching and reduce the need for INR monitoring (270). In contrast, countries such as the United States and Australia observed more modest, clinician-driven changes and had temporary upticks in switching when COVID-19 first hit (270). European data revealed a gradual

transition toward DOACs that appeared to be predominantly influenced by long-standing healthcare policies and infrastructural capabilities rather than immediate pandemic related urgency (270). While the pandemic did not precipitate a fundamental shift in anticoagulation management, it magnified pre-existing treatment preferences (270). The UK's experience stands out for both its scale and lasting impact, characterized by an abrupt and large-scale switch that led to sustained changes in anticoagulation practice (270,271).

Prior studies have identified several potential factors associated with switching (266). However, most evidence originates from international cohorts, with limited evidence from Scotland. Given differences in prescribing policies, healthcare delivery, and patient demographics, it is essential to evaluate these associations within Scotland to provide locally relevant insights. Furthermore, previous research has largely been conducted in non-pandemic settings, and understanding the factors that drive this switching, is crucial for optimizing patient care, particularly in the context of evolving guidelines and external influences such as the COVID-19 pandemic.

This chapter investigates the demographic, clinical, and geographic factors associated with switching from VKAs to DOACs among patients in Scotland between 2018 and 2021. A key hypothesis of this investigation is that switching patterns during the COVID-19 pandemic were systematically different from those in the pre-pandemic period, potentially driven by non-clinical factors such as the practical and logistical considerations emphasized in COVID-19-specific NICE guidance, rather than primarily clinical indications. By comparing patterns in the pre-pandemic and pandemic periods, it provides insight into the evolving factors of anticoagulant switching, complementing the preceding analysis of prescribing trends and setting the stage for the next chapter, which examines outcomes after switching.

6.1.1. Objectives

The primary objective was to evaluate whether there were significant variations in factors associated with switching from VKAs to DOACs before and during the COVID-19 pandemic.

6.2 Methods

6.2.1. Study design

This retrospective cohort study examined factors associated with switching from a VKA to a DOAC in adult patients between January 1, 2018, and April 30, 2021.

The study period was divided into two intervals; these periods were selected to capture potential changes in prescribing behaviour following the onset of the COVID-19 pandemic and the implementation of national guidance recommending switching during this time:

- **Pre-COVID**: January 1, 2018 – February 29, 2020 (26 months)
- **During COVID**: March 1, 2020 – April 30, 2021 (14 months)

6.2.2. Index date and follow-up period

- **Pre-COVID cohort (Follow-up: January 1, 2018 - February 29, 2020)**

Patients were followed from the latest of either January 1, 2018 (for patients already on VKA before this date), or their actual VKA start date during this period (for those who began VKA afterwards).
Follow-up ended at the earliest of switching from VKA to DOAC, last prescription date, death, or February 29, 2020, which marked the end of the pre-pandemic follow-up window. Patients who remained on VKA therapy at the end of the pre-COVID period were subsequently included in the post-COVID analysis, with new follow-up starting from March 1, 2020, specific to that period.

- **Post-COVID cohort (Follow-up: March 1, 2020- April 30, 2021)**

Patients were followed from the latest of either March 1, 2020 (for patients already on VKA before this date), or their actual VKA start date (for those who began VKA afterwards).
Follow-up ended at the earliest of switching from VKA to DOAC, last prescription date, death, or the end of the post-COVID study period (April 30, 2021).

A minimum of one day of follow-up was required for inclusion in the analysis.

6.2.3. Study population

6.2.3.1. Cohort definition and inclusion criteria

The study cohort comprised patients who were either on VKA therapy at the beginning of the study period or initiated VKA during the study period. Specifically:

1. Patients who initiated VKA therapy at any point since January 1, 2009, and remained on VKA as of January 1, 2018
2. Patients who newly initiated VKA therapy between January 1, 2018, and April 30, 2021

Patients whose first OAC was a DOAC were excluded.

6.2.3.2. Handling of left truncation

Time-to-event data in this study were subject to left truncation (delayed entry), which occurs when patients enter the study only after surviving some period from a defined starting point (272). As some patients initiated VKA therapy before the start of the study period, the analysis accounted for delayed entry to ensure that individuals contributed person-time only once they became observable in the study period. Left truncation can introduce selection bias if not appropriately handled, as only those who survived and remained on VKA until cohort entry were eligible for inclusion (273,274).

To address left truncation, delayed-entry Cox proportional hazards models were used (274). Patients were considered at risk from their cohort entry date, January 1, 2018, for the pre-COVID period, or March 1, 2020, for the post-COVID period, rather than from their original VKA initiation date. Entry time was set as the cohort entry date when the patient became at risk, and exit time was defined as the date of switching to DOAC or censoring (due to death, end of study period, or administrative censoring). This approach ensured that patients contributed risk time only from their date of cohort entry, thereby enabling valid estimation of hazard ratios (272,274).

6.2.4. Exposures, covariates, and outcome definitions

This section defines the study exposure, outcome, and covariates, including demographic, clinical, and treatment-related characteristics evaluated as potential factors influencing switching from VKA to DOAC therapy.

Exposure definition

In this analysis, exposure refers to OAC therapy, specifically VKAs and DOACs.

Exposure to VKA or DOAC was defined using prescription data from the PIS. Patients were considered exposed to VKA if they had a prescribed data for warfarin during the study period, and exposed to DOACs if they were prescribed apixaban, rivaroxaban, dabigatran, or edoxaban.

Outcome definition

The primary outcome was time to first switch from VKA to DOAC therapy, defined as the first DOAC prescription occurring within 90 days of the last VKA prescription, consistent with the switching definition described in Chapter 5 and with previous real-world studies of OAC switching (275). This 90-day threshold was chosen to capture clinically meaningful switching behaviour and to exclude cases where a DOAC may have been initiated independently or long after VKA discontinuation. Patients whose first DOAC prescription occurred more than 90 days after their last VKA prescription were excluded from the main analysis, as these cases were considered indicative of treatment discontinuation or new initiation rather than a direct switch. However, a sensitivity analysis was conducted including all patients who switched from VKA to DOAC regardless of the gap between prescriptions to assess the robustness of the findings.

Covariates

Covariates were measured at baseline, defined as the patient's cohort entry date for each analysis period. Accordingly, for the pre-COVID analysis, covariates were captured up to 1 January 2018 (or the actual entry date for patients who initiated VKA during follow-up), and for the post-COVID cohort, up to 1 March 2020 (or the VKA start date if initiated later). All available secondary care data prior to the baseline were used to identify comorbidities to maximise capture of relevant clinical conditions. This approach was chosen because most of these conditions are chronic, and a single recorded diagnosis is likely to remain clinically relevant and influence anticoagulant management decisions, consistent with previous studies using similar methods (217,276). However, as primary care diagnostic data were not available, AF diagnoses managed exclusively in primary care may not have been captured, and the prevalence of AF in this study is therefore likely to be underestimated.

This approach allowed for the consideration of the potential influence of prior clinical events on the decision to switch.

Demographics:

- **Age at index date:** Included as a categorical variable (<65 as the reference category, 65–74, 75–84, and ≥85 years). These categories were selected to reflect clinically meaningful age bands commonly used in anticoagulation studies and to ensure sufficient sample size within each group (126,141,143).
- **Sex:** Included as factor (0 Male and 1 Female).

Clinical characteristics:

- Clinical comorbidities (including AF, VAF, CHF, stroke, VTE, bleeding history, renal disease, liver disease, DM, MI, IHD, HTN) were coded as binary factors based on secondary care data up to entry.
- **Socio-demographic factors:**
- **Health board of residence:** A 10-level factor. (Reference: Greater Glasgow and Clyde, largest board). While there are 14 health boards in Scotland, for the purposes of this analysis, smaller island boards – Orkney, Shetland, and the Western Isles – were combined with NHS Highland due to small population sizes.
- **Scottish Index of Multiple Deprivation (SIMD) quintile** (218): A 5-level factor based on area-level deprivation (reference: SIMD quintile 1, most deprived).
- **Urban-rural classification** (277)**:** An 8-level factor (reference: Large urban areas, largest group).

All data were retrieved from hospital and PIS records at baseline and included as categorical factors in the analysis.

Prior VKA exposure (Time on VKA prior to 2018):

- Calculated as the duration (in days) from first VKA initiation to the cohort index date (January 1, 2018, for pre-COVID; March 1, 2020, for COVID). Negative values (i.e., VKA initiation after the index date) were set to zero. The resulting exposure (in days) was converted to years and categorized into three groups: <2 years, 2–5 years, and >5 years to reflect early, established, and long-term therapy phases, while ensuring adequate sample sizes and model stability. This variable was included as a categorical

covariate in all analyses to capture the potential influence of prior treatment duration on switching behaviour, and to adjust for potential confounding related to pre-index treatment duration.

6.2.5. Statistical analyses

Time-to-event analyses were performed using Cox proportional hazards models. Each patient contributed person-time from their cohort entry date until either switching to DOAC or being censored (**Table 6.1**). Separate multivariable Cox models were fitted for the pre-COVID and COVID periods to compare covariate effects and assess potential shifts in clinical decision-making. Both models included the same covariate set, measured using period-specific baseline windows defined at each cohort's index date. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Table 6.1: Definition of time-to-event variables for Cox proportional hazards models

Variable	Definition
Cohort index date	Pre-COVID: 2018-01-01; COVID: 2020-03-01
Entry time	- If VKA was before the cohort index date → cohort index date was used. If VKA began on/after the cohort index date → actual VKA start date was used.
End date	If the patient switches to a DOAC: date of DOAC initiation. If the patient does not switch(censored): earliest of last prescription date, date of death, or study end.
Event Indicator	1 = switched to DOAC. 0 = censored (death, last follow-up, or study end).
Time at risk	Length of follow-up (Number of days between entry time and end date).

VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; pre-COVID cohort = cohort with index date 1 Jan 2018; COVID cohort (post-COVID) = cohort with index date 1 Mar 2020; Entry time (start of follow-up) = when a patient begins contributing risk time; End date = event or censoring date; Time at risk (stop time)

6.2.5.1. Model diagnostics and proportional hazards assumption

The proportional hazards (PH) assumption was assessed for all covariates using Schoenfeld residuals ($p > 0.05$ indicating no meaningful violation) and

complementary graphical diagnostics, as well as visual inspection of scaled Schoenfeld residual plots to identify any time-varying effects.

6.2.5.2. Handling of non-proportional hazards

Pre-COVID cohort: most covariates satisfied the PH assumption. However, two covariates, (health board and age group) demonstrated evidence of time-varying effects. Examination of the Schoenfeld residual plots revealed that the effects of these covariates on the hazard changed notably after approximately 400 days (~1 year of follow-up). To address this violation, follow-up time was split at 400 days, creating two intervals (0–400 days and >400 days). A binary time indicator was generated to distinguish these periods, and interaction terms between this indicator and the two non-proportional covariates were included in the Cox model, allowing their effects to vary across time intervals (278).

In the COVID cohort, most covariates again satisfied the PH assumption, except for health board and urban–rural classification, which showed clear time-varying effects. Schoenfeld residual plots indicated that the hazard ratios for these covariates changed significantly after approximately 100 days. A similar time-splitting approach was applied at 100 days, with corresponding interaction terms incorporated into the model.

Other covariates were modelled with constant hazard ratios. Although some demonstrated statistically significant departures from proportionality, these deviations were clinically minor. When hazard ratios vary in magnitude but not in direction, this typically represents a minor violation of the PH assumption (279). The Cox model is recognized as robust to such minor violations, with the overall hazard ratio interpretable as an average effect over time (279). In large datasets such as those used for this study (>50,000 patients), even minimal departures from the PH assumption can yield statistically significant test results. Visual inspection of Schoenfeld residual plots showed no clear temporal trends or systematic patterns, supporting the proportional hazards assumption for retained covariates (280).

Additionally, the relatively short follow-up duration in this study further minimizes concerns about non-proportionality, as violations are less likely to substantially affect estimates over shorter time intervals (280). Therefore, these covariates were retained with time-constant effects, given the large sample size, stable effect directions, and absence of clinically meaningful temporal patterns. This approach

aligns with established recommendations that emphasize considering both statistical and clinical significance when evaluating PH violations (279,280).

6.2.5.3. Additional and sensitivity analyses

Two additional analyses were conducted:

1. CHA_2DS_2-VASc and HAS-BLED scores were not included in the primary models because most of their individual components were already incorporated as separate covariates, which could introduce multicollinearity. Instead, they were evaluated in separate models to examine their overall association with switching
2. As a sensitivity analysis, models were repeated without the 90-day gap requirement (including all switchers).

All analyses were conducted in R (version 4.5.1) using the *survival* and *survminer* packages.
Differences in the direction and magnitude of associations across periods were assessed descriptively by comparing hazard ratio estimates and their 95% confidence intervals.

6.3 Results

6.3.1. Study population and switching patterns

A total of 54,551 unique patients were included in the final study cohort (**Figure 6.1**). Of these, 15,403 (28.2%) switched from a VKA to a DOAC between Jan 2018 and April 2021, while 39,148 (71.8%) remained on VKA therapy throughout follow-up, regardless of whether VKA treatment was initiated prior to 2018 or during the study period.

For the pre-COVID period (January 2018–February 2020), 53,671 patients were at risk at the start of follow-up (**Figure 6.1**). During this period, 9,152 patients (17.0%) switched to DOAC therapy, while 44,519 were censored due to death, discontinuation of VKA therapy, or remaining on VKA treatment at the end of the pre-COVID period.

For the post-COVID period (March 2020–April 30, 2021), 37,632 patients contributed follow-up time (**Figure 6.1**). Of these, 6,251 patients (16.6%) switched to

DOAC therapy, while 31,381 were censored due to death, VKA discontinuation, or remaining on VKA therapy at the end of the study period.

In the sensitivity analysis which included all patients who switched without applying the 90-day gap criterion, the total number of patients who switched increased to 10,759 (19.1%) in the pre-COVID period (with 45,565 censored), and 7,301(18.9%) in the post-COVID period (with 31,381 censored).

The duration of follow-up differed between the pre-COVID and post-COVID periods (approximately two years versus one year); therefore, the crude proportions of patients who switched are not directly comparable and are presented for descriptive purposes only. Formal comparisons of switching rates over time were addressed using interrupted time series methods in Chapter 5.

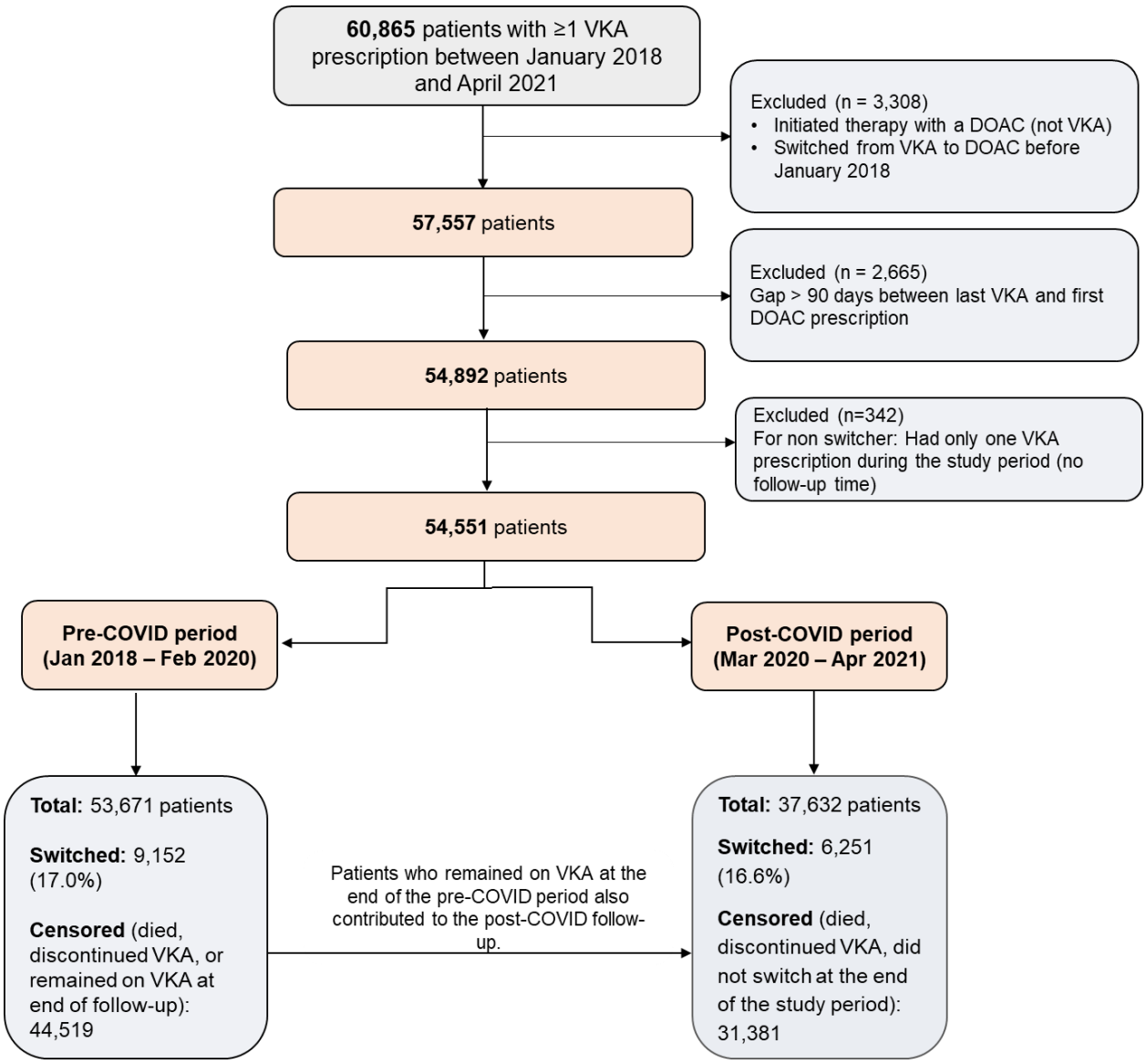

Figure 6.1: Flowchart of patient selection and cohort distribution for pre- and post-COVID periods.

Note: "Censored" refers to patients who did not switch to DOAC before death, treatment discontinuation, or end of follow-up in each period. Differences in total numbers between periods reflect new VKA initiations during the post-COVID period, as patients entered the cohort at different times.

6.3.2. DOAC agent selection

The choice of specific DOAC agents differed between the two periods. In the pre-COVID cohort, apixaban was the most frequently prescribed agent (4,485 patients, 49.0%), followed by edoxaban (3,269 patients, 35.7%), rivaroxaban (1,336 patients, 14.6%), and dabigatran (62 patients, 0.67%). However, the post-COVID period demonstrated a notable shift in prescribing patterns, with edoxaban becoming the

most prescribed DOAC (n=3,388, 54.2%), while apixaban decreased to 40.3% (n=2,523), rivaroxaban declined substantially to 5.3% (n=331), and dabigatran to 0.1% (n=9).

6.3.3. Baseline characteristics

Baseline characteristics of patients who switched from VKA to DOAC therapy and those who did not switch during the pre- and post-COVID periods are presented in **Table 6.2** and **Table 6.3**. Females comprised a similar proportion of the overall VKA-treated population in both periods (42.9% pre-COVID and 41.9% post-COVID). In each period, the proportion of females was modestly higher among patients who switched from VKA to DOAC compared with those who did not switch, with this difference being more pronounced in the pre-COVID period.

Table 6.2: Baseline characteristics of patients receiving VKA therapy before and after the COVID-19 pandemic, stratified by switching status

	Overall cohort		**Pre-COVID**		**Post- covid**	
	Pre-COVID	**Post-covid**	**Non switched**	**Switched**	**Non switched**	**switched**
N	53671	37632	44519	9090	31381	6242
Female, n (%)	23027 (42.9)	15,776 (41.9)	18771 (42.2)	4227 (46.5)	13096 (41.7)	2,675 (42.9)
Age, mean (SD)	73.04 (12.30)	73.35 (12.40)	72.44 (12.50)	76.02 (10.79)	72.48 (12.63)	77.71 (10.06)
Age group, n (%)						
<65	10500 (19.6)	7540 (20.0)	9367 (21.0)	1122 (12.3)	6953 (22.2)	584 (9.4)
65–74	14225 (26.5)	9435 (25.1)	12052 (27.1)	2158 (23.7)	8153 (26.0)	1,281 (20.5)
75–84	19772 (36.8)	13589 (36.1)	16063 (36.1)	3681 (40.5)	10953 (34.9)	2,632 (42.2)
≥85	9174 (17.1)	7068 (18.8)	7037 (15.8)	2129 (23.4)	5322 (17.0)	1,745 (28.0)
Prior VKA exposure, n (%)						
>5 years	30874 (57.5)	28,475 (75.7)	25848 (58.1)	4993 (54.9)	23681 (75.5)	4787 (76.7)
2–5 years	13350 (24.9)	3,050 (8.1)	10826 (24.3)	2508 (27.6)	5038 (16.1)	1,069 (17.1)
<2 years	9447 (17.6)	6,107 (16.2)	7845 (17.6)	1589 (17.5)	2662 (8.5)	386 (6.2)
Urban–rural classification, n (%)						
Large urban areas	14498 (27.0)	10127 (26.9)	11980 (26.9)	2483 (27.3)	8712 (27.8)	1412 (22.6)
Other urban areas	20976 (39.1)	15062 (40.0)	17735 (39.8)	3229 (35.5)	12916 (41.2)	2145 (34.4)

	Overall cohort		Pre-COVID		Post- covid	
	Pre-COVID	Post-covid	Non switched	Switched	Non switched	switched
Accessible small towns	5070 (9.4)	3571 (9.5)	4212 (9.5)	856 (9.4)	2973 (9.5)	597 (9.6)
Remote small towns	1461 (2.7)	983 (2.6)	1204 (2.7)	257 (2.8)	753 (2.4)	229 (3.7)
Very remote small towns	708 (1.3)	452 (1.2)	545 (1.2)	160 (1.8)	351 (1.1)	101 (1.6)
Accessible rural areas	6813 (12.7)	4716 (12.5)	5604 (12.6)	1205 (13.3)	3645 (11.6)	1069 (17.1)
Remote rural areas	2342 (4.4)	1591 (4.2)	1912 (4.3)	428 (4.7)	1195 (3.8)	396 (6.3)
Very remote rural areas	1803 (3.4)	1130 (3.0)	1327 (3.0)	472 (5.2)	836 (2.7)	293 (4.7)
Health board, n (%)						
Ayrshire and Arran	4131 (7.7)	2880 (7.7)	3443 (7.7)	686 (7.5)	2222 (7.1)	658 (10.5)
Borders	1389 (2.6)	980 (2.6)	1166 (2.6)	<250	717 (2.3)	<300
Dumfries and Galloway	3060 (5.7)	2117 (5.6)	2579 (5.8)	479 (5.3)	1663 (5.3)	454 (7.3)
Fife	4387 (8.2)	3258 (8.7)	3839 (8.6)	548 (6.0)	2806 (8.9)	452 (7.2)
Forth Valley	2572 (4.8)	1704 (4.5)	2008 (4.5)	563 (6.2)	1471 (4.7)	233 (3.7)
Grampian	5344 (10.0)	3655 (9.7)	4357 (9.8)	978 (10.8)	2643 (8.4)	1008 (16.1)
Greater Glasgow and Clyde	9539 (17.8)	6751 (17.9)	8081 (18.2)	1429 (15.7)	5984 (19.1)	764 (12.2)
Highland	2879 (5.4)	1813 (4.8)	2175 (4.9)	700 (7.7)	1339 (4.3)	474 (7.6)
Lanarkshire	9249 (17.2)	6943 (18.4)	8133 (18.3)	1108 (12.2)	6356 (20.3)	587 (9.4)
Lothian	6529 (12.2)	4436 (11.8)	5062 (11.4)	1466 (16.1)	3673 (11.7)	763 (12.2)
Orkney	217 (0.4)	144 (0.4)	168 (0.4)	<50	114 (0.4)	<50
Shetland	289 (0.5)	191 (0.5)	224 (0.5)	62 (0.7)	168 (0.5)	23 (0.4)
Tayside	3742 (7.0)	2557 (6.8)	3053 (6.9)	689 (7.6)	2090 (6.7)	467 (7.5)
Western Isles	344 (0.6)	203 (0.5)	231 (0.5)	112 (1.2)	135 (0.4)	68 (1.1)
SIMD quintile, n (%)						
1	10589 (19.7)	7589 (20.2)	9030 (20.3)	1543 (17.0)	6609 (21.1)	978 (15.7)

	Overall cohort		Pre-COVID		Post- covid	
	Pre-COVID	Post-covid	Non switched	Switched	Non switched	switched
2	11921 (22.2)	8345 (22.2)	9981 (22.4)	1929 (21.2)	7061 (22.5)	1282 (20.5)
3	11589 (21.6)	8039 (21.4)	9477 (21.3)	2100 (23.1)	6600 (21.0)	1436 (23.0)
4	10199 (19.0)	7087 (18.8)	8381 (18.8)	1806 (19.9)	5711 (18.2)	1374 (22.0)
5	9373 (17.5)	6572 (17.5)	7650 (17.2)	1712 (18.8)	5400 (17.2)	1172 (18.8)
Comorbidities, n (%)						
Congestive heart failure	9296 (17.3)	6639 (17.6)	7732 (17.4)	1,552 (17.1)	5539 (17.7)	1098 (17.6)
Hypertension	22796 (42.5)	16027 (42.6)	18519 (41.6)	4,243 (46.7)	12993 (41.4)	3030 (48.5)
Diabetes mellitus	7907 (14.7)	5690 (15.1)	6427 (14.4)	1,469 (16.2)	4635 (14.8)	1055 (16.9)
Prior stroke/TIA	6457 (12.1)	4473 (11.9)	5295 (11.9)	1,148 (12.7)	3718 (11.8)	754 (12.1)
Renal disease	9165 (17.1)	6969 (18.5)	7552 (17.0)	1,603 (17.6)	5736 (18.3)	1230 (19.7)
Liver disease	288 (0.5)	249 (0.7)	255 (0.6)	30 (0.4)	226 (0.7)	23 (0.4)
Prior bleeding	12350 (23.0)	9423 (25.0)	10274 (23.1)	2,048 (23.4)	7985 (25.4)	1434 (23.0)
Haemorrhagic stroke	454 (0.8)	372 (1.0)	404 (0.9)	49 (0.5)	334 (1.1)	38 (0.6)
DVT/PE	8812 (16.4)	6637 (17.6)	7457 (16.8)	1,348 (14.8)	5780 (18.4)	856 (13.7)
Atrial fibrillation	29722 (55.4)	21062 (56.0)	24012 (53.9)	5,671 (62.2)	16919 (53.9)	4136 (66.3)
Valvular AF	10521 (19.6)	8374 (22.3)	9433 (21.2)	1,079 (11.9)	7638 (24.3)	736 (11.8)
Myocardial infarction	4495 (8.4)	3116 (8.3)	3720 (8.4)	769 (8.5)	2601 (8.3)	515 (8.3)
Ischaemic heart disease	14285 (26.6)	10057 (26.7)	11815 (26.5)	2,452 (27.0)	5780 (18.4)	1702 (27.3)
Vascular disease	12842 (23.9)	8873 (23.6)	10545 (23.7)	2280 (25.1)	7346 (23.4)	1527 (24.5)
Concomitant procedures and medications, n (%)						
Hip/knee replacement	6269 (11.7)	4460 (11.9)	4938 (11.1)	1,319 (14.5)	3542 (11.3)	917 (14.7)
NSAID use	1996 (3.7)	2070 (5.5)	1691 (5.4)	353 (3.9)	1691 (5.4)	379 (6.1)

	Overall cohort		Pre-COVID		Post- covid	
	Pre-COVID	Post-covid	Non switched	Switched	Non switched	switched
Antiplatelet use	1306 (2.4)	481 (1.3)	411 (1.3)	224 (2.5)	411 (1.3)	70 (1.1)
Stroke risk score (CHA_2DS_2-VASc)						
CHA_2DS_2-VASc score, mean (SD)	3.05 (1.56)	2.97 (1.57)	3.01 (1.56)	3.24 (1.54)	2.91 (1.57)	3.29 (1.49)
CHA_2DS_2-VASc category, n (%)						
0	2694 (5)	2105 (5.6)	2361 (5.3)	330 (3.6)	1917 (6.1)	187 (3.0)
1	6335 (11.8)	4851 (12.9)	5431 (12.2)	899 (9.9)	4315 (13.8)	534 (8.6)
≥2	44642 (83.2)	30676 (81.5)	36727 (82.5)	7861 (86.5)	25149 (80.1)	5521 (88.4)
Bleeding risk score (HAS-BLED)						
HAS-BLED score, mean (SD)	1.89 (1.13)	1.90 (1.16)	1.87 (1.14)	1.98 (1.11)	1.87 (1.17)	2.05 (1.11)
HAS-BLED score category, n (%)						
0-1	22073 (41.1)	15296 (40.6)	13124 (41.8)	3417 (37.6)	13124 (41.8)	2167 (34.7)
2	16640 (31.0)	11412 (30.3)	9347 (29.8)	2926 (32.2)	9347 (29.8)	2064 (33.1)
≥3	14958 (37.9)	10924 (29.0)	8910 (28.4)	2747 (30.2)	8910 (28.4)	2011 (32.2)

Note: Dabigatran was excluded from the total baseline and the stratified baseline because of the low numbers. Abbreviations; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke/transient ischaemic attack/thromboembolism (2 points), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), Drugs or alcohol. Statistical disclosure control was applied in line with Safe Haven requirements. Small cell counts (<10) were suppressed, and additional values were masked where necessary to prevent back-calculation and potential disclosure.

Table 6.3: Baseline characteristics of patients who switched from VKAs to DOACs before and after the COVID-19 pandemic, stratified by DOAC agent

	Pre-covid			Post-covid		
	Apixaban	**Edoxaban**	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Rivaroxaban**
n	4485 (49.0%)	3269 (35.7%)	1336 (14.6)	2523 (40.4)	3388 (54.2)	331 (5.3)
Female, n (%)	2122 (47.3)	1476 (45.2)	629 (47.1)	1,134 (44.9)	1,391 (41.1)	150 (45.3)
Age, mean (SD)	75.99 (10.94)	76.46 (9.95)	75.07 (12.08)	77.35 (10.0)	78.46 (8.94)	72.78 (12.47)
Age group, n (%)						
<65	572 (12.8)	337 (10.3)	213 (15.9)	271 (10.7)	233 (6.9)	80 (24.2)
65–74	1049 (23.4)	816 (25.0)	293 (21.9)	510 (20.2)	689 (20.3)	82 (24.8)
75–84	1818 (40.5)	1362 (41.7)	501 (37.5)	1,022 (40.5)	1,503 (44.4)	107 (32.3)
≥85	1046 (23.3)	754 (23.1)	329 (24.6)	720 (28.5)	963 (28.4)	62 (18.7)
Prior VKA exposure, n (%)						
>5 years	2395 (53.4)	1851 (56.6)	747 (55.9)	1914 (75.9)	2614 (77.2)	259 (78.2)
2–5 years	1289 (28.7)	893 (27.3)	326 (24.4)	442 (17.5)	584 (17.2)	43 (13.0)
<2 years	801 (17.9)	525 (16.1)	263 (19.7)	167 (6.6)	190 (5.6)	29 (8.8)
Urban–rural classification, n (%)						
Large urban areas	1338 (29.8)	945 (28.9)	200 (15.0)	693 (27.5)	667 (19.7)	52 (15.7)
Other urban areas	1683 (37.5)	1076 (32.9)	470 (35.2)	839 (33.3)	1180 (34.8)	126 (38.1)
Accessible small towns	404 (9.0)	288 (8.8)	164 (12.3)	299 (11.9)	277 (8.2)	21 (6.3)
Remote small towns	116 (2.6)	99 (3.0)	42 (3.1)	64 (2.5)	143 (4.2)	22 (6.6)
Very remote small towns	65 (1.4)	61 (1.9)	34 (2.5)	32 (1.3)	50 (1.5)	19 (5.7)
Accessible rural areas	522 (11.6)	469 (14.3)	214 (16.0)	376 (14.9)	658 (19.4)	35 (10.6)
Remote rural areas	173 (3.9)	171 (5.2)	84 (6.3)	107 (4.2)	262 (7.7)	27 (8.2)
Very remote rural areas	184 (4.1)	160 (4.9)	128 (9.6)	113 (4.5)	151 (4.5)	29 (8.8)
Health board, n (%)						
Ayrshire and Arran	359 (8.0)	292 (8.9)	35 (2.6)	135 (5.4)	506 (14.9)	17 (5.1)
Borders	<250	<10	<10	<250	<50	<10
Dumfries and Galloway	206 (4.6)	254 (7.8)	19 (1.42)	<50	406 (12.0)	<10
Fife	41 (0.9)	208 (6.4)	299 (22.4)	20 (0.8)	390 (11.5)	42 (12.7)

	Pre-covid			Post-covid		
	Apixaban	Edoxaban	Rivaroxaban	Apixaban	Edoxaban	Rivaroxaban
Forth Valley	62 (1.4)	279 (8.5)	222 (16.6)	21 (0.8)	183 (5.4)	29 (8.8)
Grampian	327 (7.3)	277 (8.5)	374 (28.0)	443 (17.6)	438 (12.9)	127 (38.4)
Greater Glasgow and Clyde	552 (12.3)	839 (25.7)	38 (2.8)	<250	533 (15.7)	<10
Highland	155 (3.5)	392 (12.0)	153 (11.5)	65 (2.6)	360 (10.6)	49 (14.8)
Lanarkshire	952 (21.2)	132 (4.0)	24 (1.8)	466 (18.5)	<200	<10
Lothian	1398 (31.2)	41 (1.3)	27 (2.0)	725 (28.7)	25 (0.7)	13 (3.9)
Orkney	<20	<10	<50	<20	<10	<10
Shetland	22 (0.5)	21 (0.6)	19 (1.4)	<10	11 (0.3)	<10
Tayside	100 (2.2)	520 (15.9)	69 (5.2)	87 (3.4)	356 (10.5)	24 (7.3)
Western Isles	82 (1.8)	<10	<50	61 (2.4)	<10	<10
SIMD quintile, n (%)						
1	781 (17.4)	603 (18.4)	159 (11.9)	411 (16.3)	516 (15.2)	51 (15.4)
2	1050 (23.4)	620 (19.0)	259 (19.4)	531 (21.0)	678 (20.0)	73 (22.1)
3	1002 (22.3)	754 (23.1)	344 (25.7)	550 (21.8)	800 (23.6)	86 (26.0)
4	809 (18.0)	694 (21.2)	303 (22.7)	535 (21.2)	768 (22.7)	71 (21.5)
5	843 (18.8)	598 (18.3)	271 (20.3)	496 (19.7)	626 (18.5)	50 (15.1)
Comorbidities, n (%)						
Congestive heart failure	823 (18.4)	530 (16.2)	199 (14.9)	459 (18.2)	594 (17.5)	45 (13.6)
Hypertension	2136 (47.6)	1496 (45.8)	611 (45.7)	1181 (46.8)	1699 (50.1)	150 (45.3)
Diabetes mellitus	771 (17.2)	506 (15.5)	192 (14.4)	424 (16.8)	573 (16.9)	58 (17.5)
Prior stroke/TIA	614 (13.7)	408 (12.2)	126 (9.4)	327 (13.0)	400 (11.8)	27 (8.2)
Renal disease	879 (19.6)	507 (15.5)	217 (16.2)	539 (21.4)	624 (18.4)	67 (20.2)
Liver disease	19 (0.4)	<20	<10	11 (0.4)	<10	<10
Prior bleeding	1048 (23.4)	717 (21.9)	283 (21.2)	593 (23.5)	760 (22.4)	81 (24.5)
Haemorrhagic stroke	28 (0.6)	<25	<10	<25	<25	<10
DVT/PE	751 (16.7)	328 (10.0)	269 (20.1)	455 (18.5)	285 (8.4)	116 (35.0)
Atrial fibrillation	2791 (62.2)	2152 (65.8)	728 (54.5)	1628 (64.5)	2364 (69.8)	144 (43.5)

	Pre-covid			Post-covid		
	Apixaban	**Edoxaban**	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Rivaroxaban**
Valvular AF	550 (12.3)	371 (11.3)	158 (11.8)	323 (12.8)	383 (11.3)	30 (9.1)
Myocardial infarction	418 (9.3)	262 (8.0)	89 (6.7)	211 (8.4)	277 (8.2)	27 (8.2)
Ischaemic heart disease	1244 (27.5)	860 (26.3)	348 (26.0)	693 (27.5)	932 (27.5)	77 (23.3)
Vascular disease	1153 (25.7)	811 (24.8)	316 (23.7)	622 (24.7)	832 (24.6)	73 (22.1)
Hip/knee replacement	653 (14.6)	466 (14.3)	200 (15.0)	370 (14.7)	513 (15.1)	34 (10.3)
CHA_2DS_2-VASc score, mean (SD)	3.30 (1.57)	3.23 (1.49)	3.09 (1.59)	3.29 (1.50)	3.34 (1.45)	2.82 (1.66)
CHA_2DS_2-VASc category, n (%)						
0	163 (3.6)	97 (3.0)	70 (5.2)	81 (3.2)	74 (2.2)	32 (9.7)
1	426 (9.5)	298 (9.1)	175 (13.1)	219 (8.7)	263 (7.8)	52 (15.7)
≥2	3986 (86.9)	2874 (87.9)	1091 (81.7)	2223 (88.1)	3051 (90.1)	247 (74.6)
HAS-BLED score, mean (SD)	2.03 (1.13)	1.97 (1.08)	1.87 (1.14)	2.06 (1.12)	2.06 (1.07)	1.90 (1.31)
HAS-BLED category (%)						
0-1	1626 (36.3)	1235 (37.8)	556 (41.6)	884 (35.0)	1144 (33.8)	139 (42.0)
2	1427 (31.8)	1093 (33.4)	406 (30.4)	804 (31.9)	1172 (34.6)	88 (26.6)
≥3	1432 (31.9)	941 (28.8)	374 (28.0)	835 (33.1)	1072 (31.6)	104 (31.4)
NSAID use, n (%)	173 (3.9)	132 (4.0)	48 (3.6)	154 (6.1)	201 (5.9)	24 (7.3)
Antiplatelet use, n (%)	104 (2.3)	82 (2.5)	38 (2.8)	<50	<50	<10

Note: Dabigatran was excluded from both the overall analysis and the specific DOAC analysis due to the low number of patients. Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke/transient ischaemic attack/thromboembolism (2 points), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal or liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), Drugs or alcohol. Statistical disclosure control was applied in line with Safe Haven requirements. Small cell counts (<10) were suppressed, and additional values were masked where necessary to prevent back-calculation and potential disclosure.

In both periods, patients who switched from VKA to DOAC therapy were older than non-switchers (**Table 6.2**). In the pre-COVID period, the mean age of switchers was 76 years (SD 10.8), compared with 72 (SD 12.5) years in the non-switchers. This age difference persisted in the post-COVID period, with switchers having a mean age of 77.7 years (SD 10.1) compared with 72.5 years (SD 12.6) in non-switchers. While switching was more frequent among older age groups, this largely reflects the underlying age distribution of the VKA-treated population, in which older patients constituted the majority of the cohort in both periods.

Among individual DOACs, patients switching to edoxaban were the oldest in both periods (**Table 6.3**). In the pre-COVID period, mean age was 76.5 years for edoxaban, 76.0 years for apixaban, and 75.1 years for rivaroxaban. This pattern became more pronounced in the post-COVID period, with edoxaban switchers averaging 78.5 years and apixaban switchers 77.4 years. Patients switching to rivaroxaban in the post-COVID period were younger on average (mean 72.8 years), although this group represented a relatively small proportion of overall switches.

Prior VKA exposure differed between the two study periods, reflecting the timing of cohort entry and accumulated treatment duration. Overall, a higher proportion of patients in the post-COVID period had more than five years of prior VKA use compared with the pre-COVID period (75.5% vs 57.5%).

In the pre-COVID period, switchers had shorter prior VKA exposure than non-switchers. Among switchers, 54.9% had more than five years of VKA use, 27.6% had two to five years, and 17.5% had less than two years of exposure, whereas 58.1% of non-switchers had more than five years of prior VKA use.

In the post-COVID period, both groups were more likely to have long-term VKA exposure. Among switchers, 76.7% had more than five years of prior VKA use, comparable to non-switchers (75.5%). Shorter durations (<2 years) were uncommon in this period, occurring in 6.2% of switchers and 8.5% of non-switchers. This higher proportion of long-term VKA users in the post-COVID period reflects the later study period and longer cumulative exposure time, rather than changes in switching behavior alone.

Regional variation in DOAC switching reflected the distribution of patients across health boards in Scotland. The largest health boards, Greater Glasgow and Clyde

(~18%), Lanarkshire (~18%), Lothian (~12%), and Grampian (~10%), represented the majority of the overall study cohort across both periods and consequently contributed the highest numbers of switchers. These proportions reflect each board's share of all VKA-treated patients and their roles as major population centers in Scotland. Socioeconomic distribution, based on SIMD 2016, was broadly similar across both periods.

Baseline comorbidities were largely similar between switchers and non-switchers in both study periods. However, AF was more prevalent among switchers than non-switchers in both the pre-COVID period (62.2% vs 53.9%) and the post-COVID period (66.3% vs 53.9%). Conversely, VAF was less common among switchers in both periods (11.9% vs 21.2% pre-COVID; 11.8% vs 24.3% post-COVID). It should be noted that these proportions reflect only secondary care diagnoses and likely underestimate the true AF prevalence, as AF is the primary indication for oral anticoagulation and many patients are likely diagnosed and managed exclusively in primary care. Other comorbid conditions were broadly comparable between groups.

Patients who switched from VKA to DOAC therapy had consistently higher baseline stroke and bleeding risk compared with non-switchers across both periods. Mean CHA_2DS_2-VASc scores were higher among switchers in the pre-COVID period (3.24 vs 3.01) and the post-COVID period (3.29 vs 2.91). The majority of switchers were at high risk for stroke, with 86.5% having scores ≥2 in the pre-COVID period and 88.4% in the post-COVID period, compared with 82.5% and 80.1% among non-switchers, respectively.

Mean HAS-BLED scores were also modestly higher among switchers in both periods. In the pre-COVID period, switchers had a mean score of 1.98 compared with 1.87 among non-switchers, with 30.2% versus 28.4% classified as high bleeding risk (score ≥3). This difference was more pronounced in the post-COVID period, with mean scores of 2.05 versus 1.87, and 32.2% versus 28.4% at high bleeding risk. Concomitant NSAID and antiplatelet use was uncommon and similar between switchers and non-switchers in both periods.

6.3.4. Changes in switching behaviour during the COVID-19 pandemic

Switching patterns from VKA to DOAC exhibited apparent changes following the onset of COVID-19, with several demographic, clinical, and geographic factors showing evolving associations with switching likelihood across the two study periods.

Demographic factors

Across both pre- and post-COVID periods, demographic factors were associated with switching behaviour (**Figure 6.2** and **Figure 6.3**). Female patients were more likely to switch compared with males in both periods (pre-COVID HR: 1.16, 95% CI 1.11–1.21; post-COVID HR: 1.06, 95% CI 1.00–1.11). Although the post-COVID point estimate was lower, the confidence intervals overlapped, indicating no clear evidence of a change in this association during the pandemic.

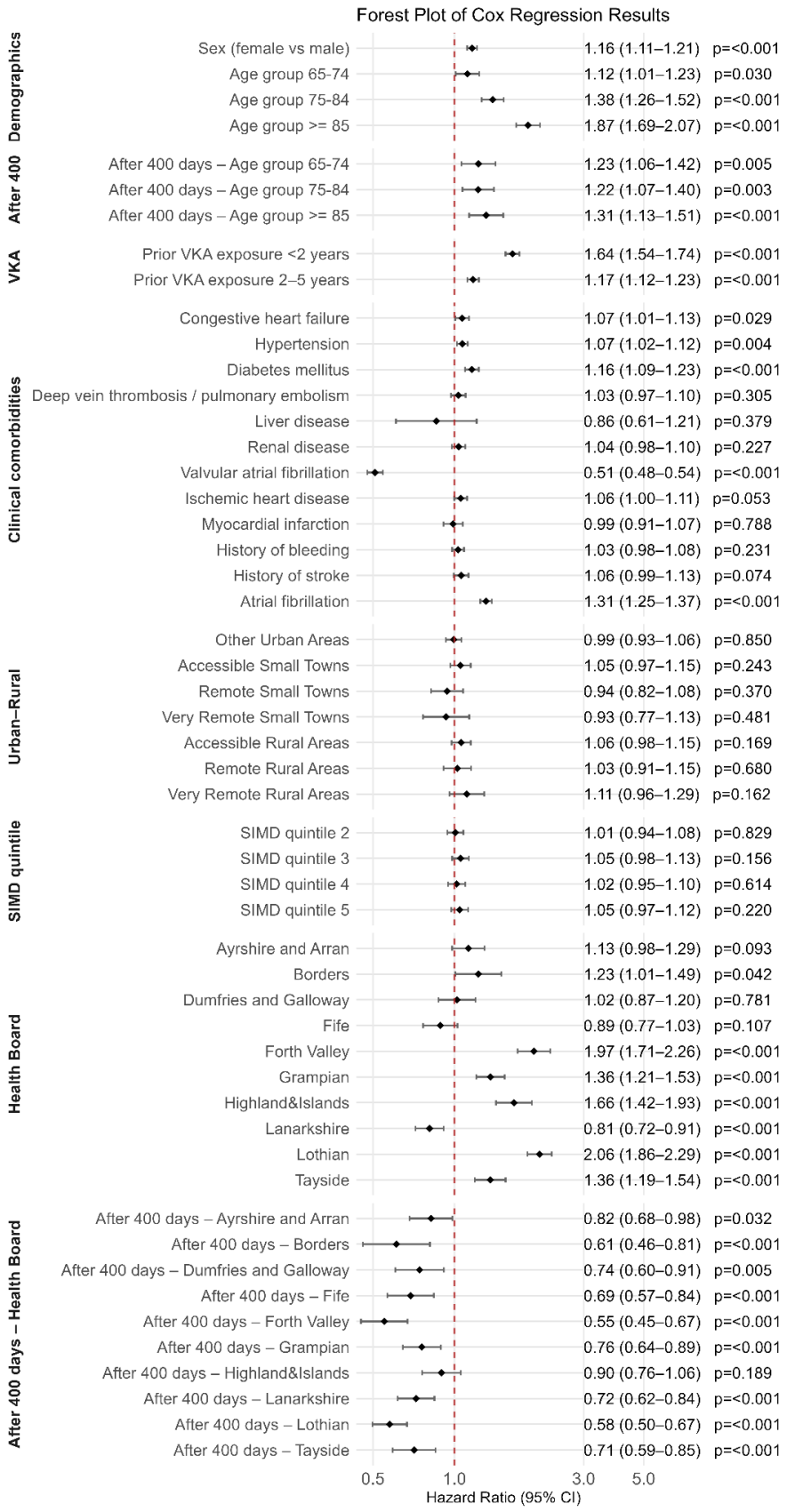

Figure 6.2: Forest Plot of Pre-COVID VKA→DOAC Switching (90-Day Gap)

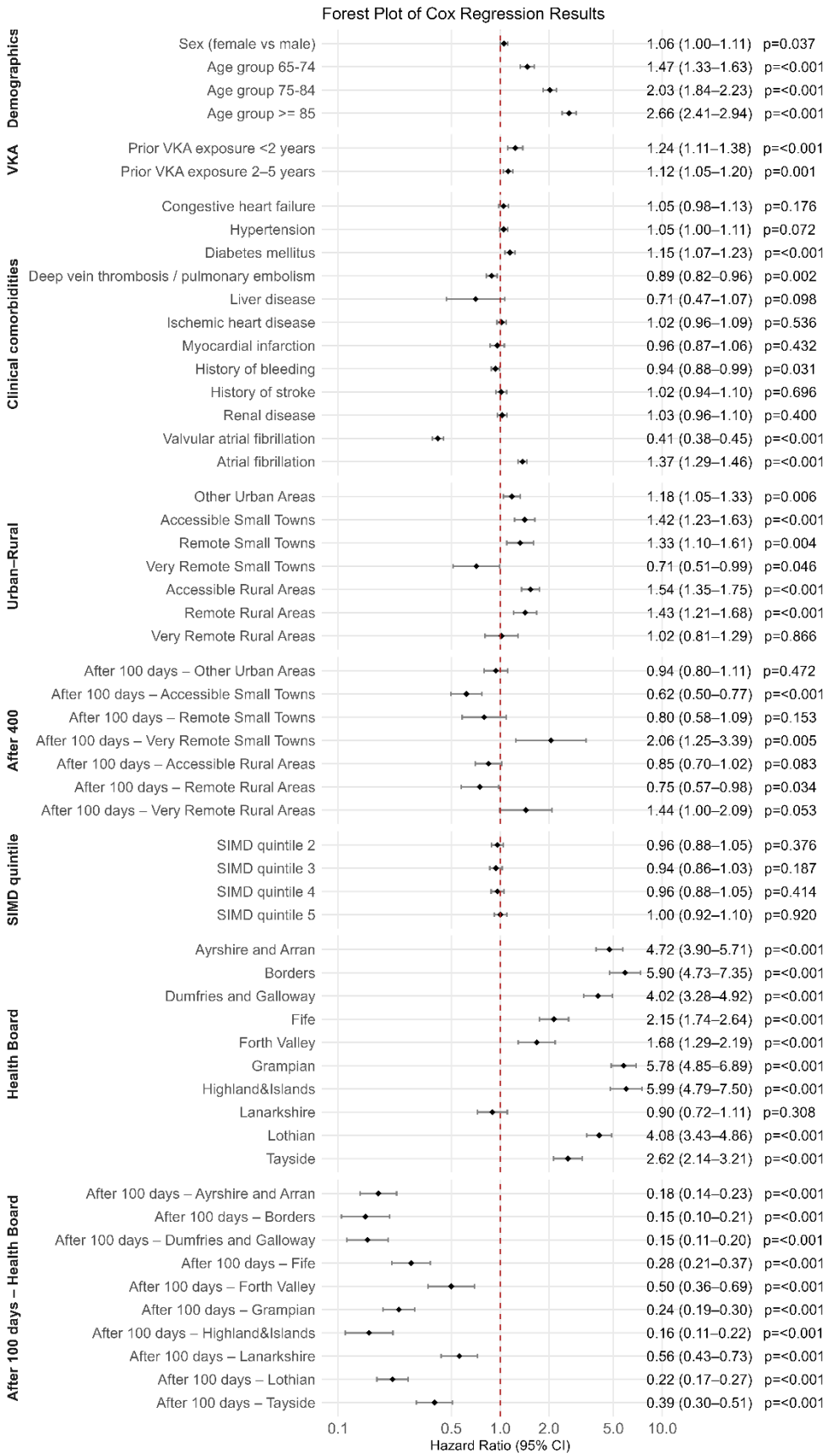

Figure 6.3: Forest Plot of Post-COVID VKA→DOAC Switching (90-Day Gap)

Age showed a pronounced and time-varying association with switching. The likelihood of switching increased markedly with age, and this relationship strengthened in the post-COVID period. In the early pre-COVID period (January 2018 to January 2019), compared with patients aged <65 years, those aged 65–74, 75–84, and ≥85 years had progressively higher hazards of switching (HR 1.12, 1.38, and 1.87, respectively; all $p < 0.05$). However, this age-related effect attenuated after approximately one year of follow-up (January 2019 to February 2020), with lower hazard ratios observed in the later pre-COVID period (HR 1.23, 1.22, and 1.31 for ages 65–74, 75–84, and ≥85 years, respectively). This suggests that age-related differences in switching behaviour were strongest early in the pre-COVID period and diminished over time prior to the onset of the pandemic.

In the post-COVID cohort, the effect of age on switching became markedly more pronounced. For example, compared with younger patients (aged <65 years), hazard ratios were higher post-COVID than pre-COVID among those aged 65–74 years (pre-COVID HR: 1.12, 95% CI 1.01–1.23; post-COVID HR: 1.47, 95% CI 1.33–1.63), 75–84 years (1.38, 95% CI 1.26–1.52 vs 2.03, 95% CI 1.84–2.23), and ≥85 years (1.87, 95% CI 1.69–2.07 vs 2.66, 95% CI 2.41–2.94). The non-overlapping confidence intervals suggest a potential increase in the strength of the association between age and switching during the pandemic.

Clinical characteristics associated with switching

Clinical characteristics were also associated with switching from VKA to DOAC, although the magnitude of these associations varied between periods. Compared with patients with longer prior VKA exposure (>5 years), those with shorter duration of VKA therapy were more likely to switch in both periods, with stronger associations observed before the pandemic.

In the pre-COVID period, patients with less than two years of prior VKA therapy had a substantially higher likelihood of switching (HR: 1.64, 95% CI 1.54–1.74), while those with two to five years of exposure also demonstrated increased switching, albeit to a lesser extent (HR: 1.17, 95% CI 1.12–1.23). Following the onset of COVID-19, the same pattern persisted, but with lower hazard ratios (HR: 1.24, 95% CI 1.11–1.38 for <2 years; HR: 1.12, 95% CI 1.05–1.20 for 2–5 years). The non-overlapping confidence intervals for the <2-year exposure group suggest a potential attenuation of the association during the pandemic, whereas overlapping confidence intervals for the 2–5-year group indicate no clear evidence of change.

Several comorbidities were associated with switching behaviour. Patients with confirmed AF consistently showed a higher likelihood of switching (pre-COVID HR 1.31, 95% CI 1.25–1.37; post-COVID HR 1.37, 95% CI 1.29–1.46; both $p < 0.001$). Similarly, DM was significantly positively associated with switching in both periods (pre-COVID HR 1.16; post-COVID HR 1.15; both $p < 0.001$). For both conditions, confidence intervals overlapped between periods, indicating stable associations over time.

In contrast, patients with a history of DVT or PE showed no significant association in switching pre-COVID but were slightly less likely to switch post-COVID (HR: 0.89; 95% CI: 0.82–0.96; $p = 0.0023$). Likewise, a history of bleeding was not associated with switching before COVID but was linked to a modestly lower likelihood post-COVID (HR 0.94, 95% CI 0.88–0.99; $p = 0.031$). For both conditions, the non-overlapping confidence intervals suggest a potential change in the direction of association during the pandemic.

HTN and CHF showed weak positive associations with switching in the pre-COVID period, with lower point estimates post-COVID; however, confidence intervals overlapped across periods, indicating no clear evidence of a change in association. VAF was strongly and consistently associated with reduced hazard of switching in both periods (HR 0.51 pre-COVID; HR 0.41 post-COVID; both $p < 0.001$), with overlapping confidence intervals.

Other comorbidities, including IHD, history of stroke or TIA, liver disease, renal disease, and MI, were not clearly associated with switching in either period, and showed overlapping confidence intervals between periods, suggesting stable associations.

Geographic and socioeconomic variation in switching behaviour

Geographic and socioeconomic variation in switching behaviour was observed, with evidence of time-dependent effects, particularly during the COVID-19 period (Figure 3). In the pre-COVID period, no significant differences in switching were observed across urban–rural classifications. However, during the early post-COVID phase (~ first 3 months), patients residing in several urban and rural areas exhibited higher likelihoods of switching compared with those in large urban areas, with these differences attenuating over time. For example, the hazard ratio for Other Urban Areas (population of 10,000 to 124,999 people) was 1.18 (95% CI: 1.05–1.33; p =

0.006). In contrast, patients in very remote small towns (Population 3,000 to 9,999 people & > 60 min drive time to an urban area) were significantly less likely to switch (HR: 0.71; 95% CI: 0.51–1.00; p = 0.046). After the first three months post-COVID, the differences between most areas and large urban areas were no longer statistically significant, resembling the pre-COVID pattern.

Similar temporal variation was evident across health boards, with several boards showing higher switching rates early in follow-up that reversed in later periods, both before and after the onset of COVID-19. This apparent reversal may reflect a depletion effect, whereby health boards that had already switched a large proportion of eligible patients prior to COVID had fewer remaining patients available to switch during the pandemic. In contrast, boards with lower pre-COVID switching rates may have retained a larger pool of VKA-treated patients, resulting in a surge in switching once pandemic-related pressures intensified.

In contrast, socioeconomic deprivation, as measured by SIMD, was not significantly associated with switching in either period. There were no meaningful differences in switching rates between less deprived and most deprived quintiles.

Stroke and Bleeding Risk Scores

In the additional analyses incorporating the CHA_2DS_2-VASc and HAS-BLED scores as covariates (**Figure 6.4**), baseline bleeding and stroke risk were associated with the likelihood of switching from VKA to DOAC.

Stroke Risk (CHA_2DS_2-VASc)

Compared with patients at low thromboembolic risk (CHA_2DS_2-VASc score 0), the association between CHA_2DS_2-VASc ≥2 and switching was stronger during the pandemic (pre-COVID HR: 1.18, 95% CI 1.05–1.33; post-COVID HR: 1.53, 95% CI 1.31–1.78), with non-overlapping confidence intervals suggesting a potential increase in the strength of this association. For patients with CHA_2DS_2-VASc = 1, confidence intervals overlapped across periods (pre-COVID HR: 1.07, 95% CI 0.95–1.22; post-COVID HR: 1.11, 95% CI 0.94–1.32), indicating no clear evidence of change.

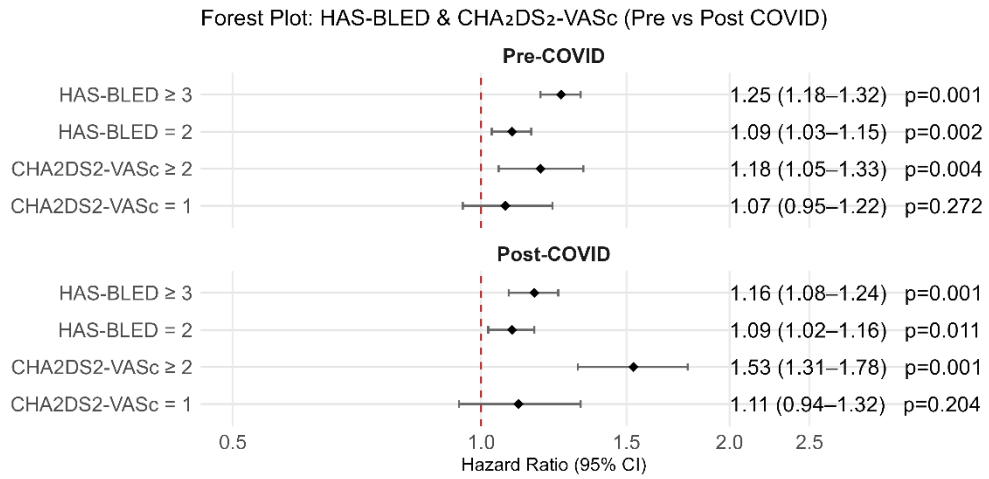

Figure 6.4: Forest Plot of HAS-BLED and CHA_2DS_2-VASc Scores: Pre- vs. Post-COVID Switching.

Note: This model was adjusted for all other covariates included in the above models, except for those variables that are components of the CHA_2DS_2-VASc or HAS-BLED scores.

Bleeding Risk (HAS-BLED)

Compared with patients at low bleeding risk (HAS-BLED score of 1), higher HAS-BLED scores were associated with increased switching rates in both periods; however, the magnitude of these associations appeared similar before and during the pandemic. For patients with HAS-BLED ≥3, hazard ratios were comparable between periods (pre-COVID HR: 1.25, 95% CI 1.18–1.32; post-COVID HR: 1.16, 95% CI 1.08–1.24), with overlapping confidence intervals. Similar overlap was observed for HAS-BLED = 2 (pre-COVID HR: 1.09, 95% CI 1.03–1.15, p = 0.002; post-COVID HR: 1.09, 95% CI 1.02–1.16, p = 0.011).

Sensitivity analysis

An additional sensitivity analysis that included all patients who switched from VKA to DOAC therapy at any time during the study period, irrespective of the interval between the last VKA and first DOAC prescription (**Figure 6.5** and **Figure 6.6**), showed results consistent with the primary analysis using a 90-day gap, both in direction and statistical significance across the pre- and post-COVID periods.

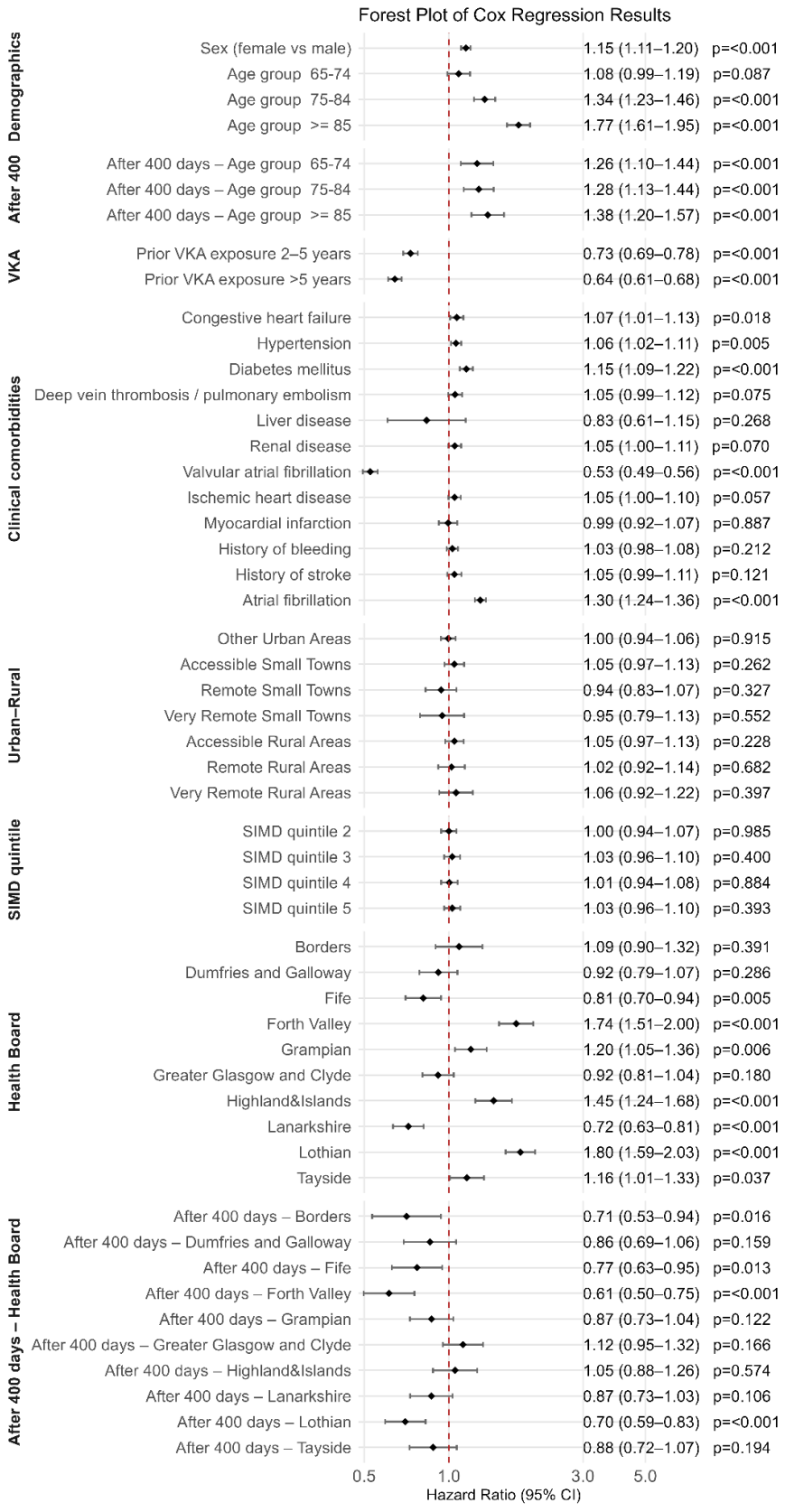

Figure 6.5: Forest Plot of Pre-COVID VKA→DOAC Switching (No Gap)

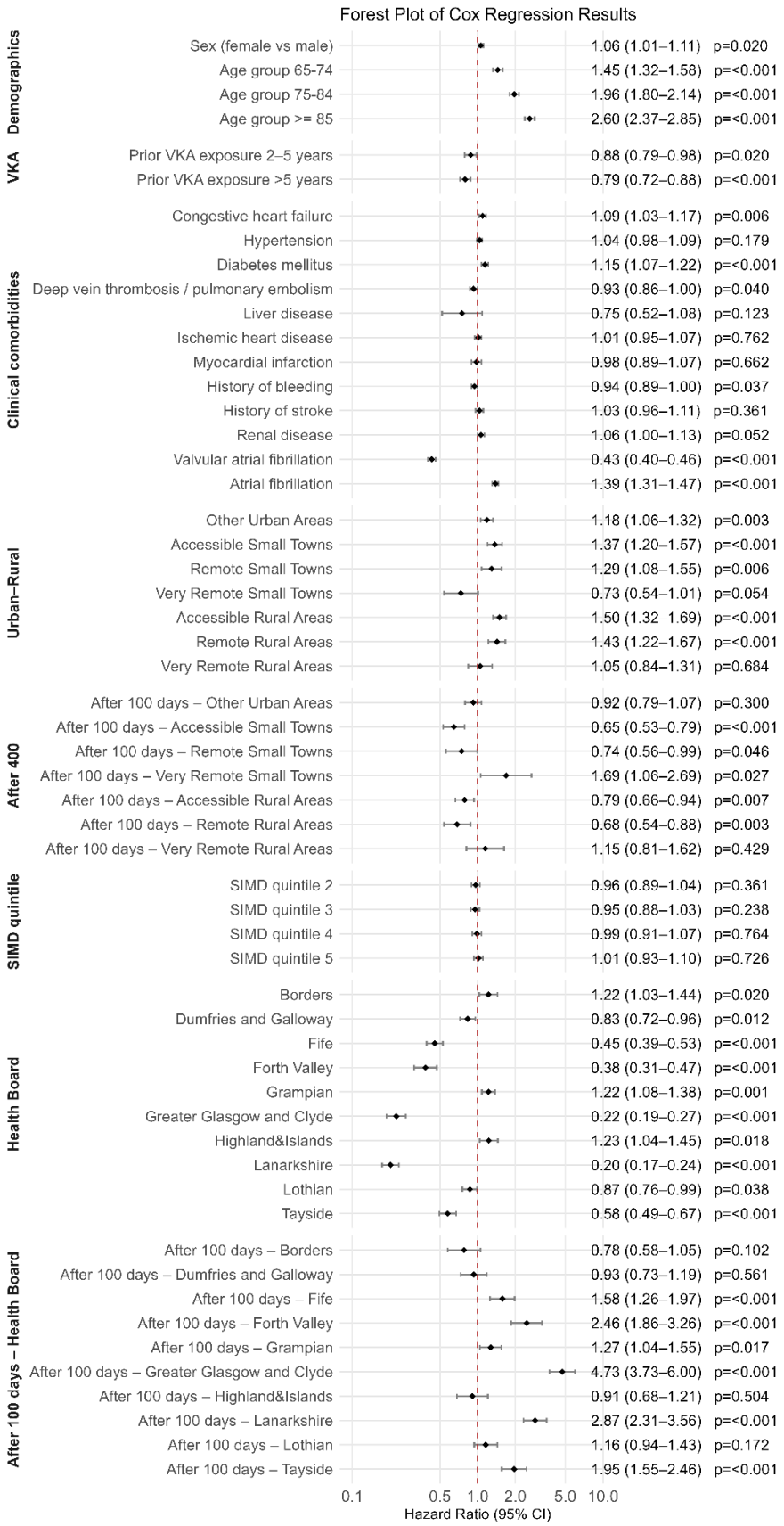

Figure 6.6: Forest Plot of Post-COVID VKA→DOAC Switching (No Gap)

6.4 Discussion

This study examined factors associated with switching from VKAs to DOACs before and during the COVID-19 pandemic in Scotland, providing new insights into how the pandemic influenced anticoagulation management practices. Findings revealed important changes in the associations between patient characteristics and switching behaviour across the two time periods. For example, the effect of age on switching strengthened post-COVID, with patients aged ≥85 years showing the highest relative hazard of switching. Similarly, the association between high stroke risk (CHA_2DS_2-VASc ≥2) and switching strengthened considerably during the pandemic (HR 1.18 to HR 1.53).

While the overall direction of most associations remained consistent, such as female sex, DM, and AF all being associated with higher switching likelihood in both periods, evident differences were noted in their magnitude and patterns. The associations with HTN and CHF that were significant pre-COVID were no longer significant post-COVID. These findings suggest that switching patterns during the pandemic increasingly reflected higher clinical risk profiles, with certain factors becoming more strongly associated with switching while others attenuated or lost significance.

Additionally, while patients with shorter prior VKA exposure remained consistently more likely to switch than long-term users in both periods, the magnitude of this association decreased in the COVID-19 period. This attenuation suggests that clinicians became more willing to switch long-term, stable VKA users to DOACs during the pandemic, particularly those at elevated thromboembolic and bleeding risk. These patterns indicate that under pandemic conditions, convenience and safety considerations may have further reinforced the preference for DOACs in clinically complex, high-risk populations.

6.4.1. Demographic factors

Female patients demonstrated persistently higher switching rates across both cohorts. Although the point estimate was lower during the pandemic (pre-COVID HR: 1.16, 95% CI 1.11–1.21; post-COVID HR: 1.05, 95% CI 1.00–1.11), the overlapping confidence intervals indicate no clear evidence of a change in the strength of this association. This positive association is consistent with findings from prior observational studies and a recent scoping review, which reported higher

likelihood of VKA-to-DOAC switching among women across diverse healthcare settings (266).

An important finding of this study was a potential strengthening of age-related switching patterns following the onset of COVID-19. While older patients were more likely to switch in both periods, the association appeared stronger post-COVID, with patients aged ≥85 years consistently showing the highest likelihood of switching.

In the pre-COVID period, increased switching among elderly patients (who are at higher risk of anticoagulation-related complications) may have been influenced by evidence showing that DOACs provide at least equivalent efficacy with a potentially lower risk of devastating bleeding events such as intracerebral haemorrhage (160). This evidence may have encouraged clinicians to preferentially switch older patients to DOACs.

However, this finding contrasts with some studies in the scoping review that found younger age associated with switching (266). This discrepancy may be attributable to the timing of those earlier studies. Many were conducted shortly after DOAC approval (between 2010–2015) (281), while the pre-COVID switching analysis in this study covered the post-2018 period. By this later period, DOACs were commonly prescribed across all adult age groups, with greater uptake among elderly patients with AF as clinicians became more confident in their safety profile.

Additionally, in the initial years following DOAC approval, switching from a VKA to a DOAC was not routinely recommended, particularly for patients with stable anticoagulation control. During this early adoption phase, patient values and preferences played a central role in switching decisions. European physicians tended to switch patients with lower baseline clinical risk, reflected by lower CHA_2DS_2-VASc scores and fewer comorbidities, compared with those who remained on VKAs (268). Patients who switched more frequently reported adverse experiences with VKA therapy, including bruising or bleeding episodes, dissatisfaction with their anticoagulant treatment, mobility limitations, and symptoms of anxiety or depression (268). These patient-reported concerns and quality-of-life considerations appeared to have been important drivers of the decision to switch from VKA to DOAC, reflecting a patient-centered approach to anticoagulation management in the early DOAC era (268). The convenience of DOACs (particularly the elimination of regular INR monitoring and dietary restrictions) likely appealed to patients experiencing these specific challenges with VKA therapy.

However, under pandemic conditions, the increase in switching among older adults, may reflect efforts to reduce exposure to INR monitoring visits and to simplify regimens particularly for patients with limited mobility, frailty, or increased vulnerability to COVID-19. Priority was often given to those at highest risk from COVID-19 including older patients, residents of nursing homes or care facilities, and patients requiring frequent INR testing. Supporting this interpretation, a large English cohort study identified older age, care home residence, AF, and frequent INR monitoring as independent factors of switching between March and May 2020 (269).

6.4.2. Duration of prior VKA use

The association between shorter duration of prior VKA use (<2 years and 2–5 years) and switching was evident in both periods. This indicates clinicians may have been more cautious about switching patients who had long-established VKA control (>5 years). However, the strength of this effect was attenuated following the onset of COVID-19, with lower hazard ratios observed post-COVID among patients with <2 years of prior VKA use (pre-COVID HR: 1.64, 95% CI 1.54–1.74 vs post-COVID HR: 1.24, 95% CI 1.11–1.38), likely reflecting pandemic-related pressures to reduce INR monitoring and simplify anticoagulation management, as well as growing clinical confidence in switching long-term VKA users during the pandemic.

6.4.3. Clinical comorbidities

Patients with AF consistently showed higher switching rates across both periods, consistent with previous reports linking AF to higher treatment changes (266,282). This association is expected, as AF is the main indication for long-term OAC therapy. However, the true prevalence of AF is likely underestimated because diagnoses recorded exclusively in primary care were not captured in the available data. Additionally, these findings reflect the robust evidence base and guideline preferences supporting DOAC use in AF, where the long-term anticoagulation requirement makes simplified dosing and monitoring particularly attractive.

While previous studies found that stroke, or TIA history increased switching likelihood (266,282,283), this study found only a weak, non-significant association pre-COVID and none post-COVID, with overlapping confidence interval. Similarly, while previous literature linked CHF, and kidney disease to switching decisions (266), this analysis did not identify renal impairment, or liver disease as significant factors in either period. These differences may reflect pandemic-era prioritization of practical and safety considerations over individual clinical history.

VAF was a significant negative factor of switching in in both periods, consistent with clinical guidelines that advise against DOAC use in patients with moderate-to-severe mitral stenosis or mechanical prosthetic heart valves. This recommendation is based on evidence of potential harm, including increased risk of valve thrombosis and bleeding, and the lack of robust trial data supporting DOAC efficacy in this subgroup. The observed pattern therefore reflects appropriate adherence to established anticoagulation guidance (284).

Patients with DVT/PE history were less likely to switch post-COVID (HR: 0.89; 95% CI: 0.82–0.96; p = 0.0023), and those with bleeding history also showed reduced switching post-COVID (HR 0.94, 95% CI 0.88–0.99; p = 0.031). This contrasts with earlier studies that identified bleeding history and , thromboembolism as a positive factors of switching (281,282,285). However, those studies were conducted during the early period following DOAC approval (2008–2016), when a history of bleeding was found to be positively associated with DOAC prescribing, but this association was not observed in later years (286). The shift may reflect increased prescriber caution in switching patients with a documented history of bleeding to newer therapies, particularly during a period of uncertainty such as the COVID-19 pandemic.

The discrepancy between this study's findings and existing literature regarding certain comorbidities is likely attributable to the reliance on secondary care data to define comorbidities. This approach captures diagnoses primarily at hospital admission and may underrepresent patients managed in primary or outpatient settings, thus underestimating the true prevalence of these comorbidities and reducing the likelihood of detecting significant associations. Additionally, from 2018 onwards, DOAC adoption was already widespread in the UK, potentially making baseline comorbidities less influential than in earlier years when treatment decisions reflected more cautious, selective approaches to DOAC prescribing.

6.4.4. Risk scores

The findings related to CHA_2DS_2-VASc scores revealed a distinct temporal pattern. Compared with patients at low thromboembolic risk (CHA_2DS_2-VASc score 0), those with a score of 1 showed no clear association with switching in either period. In contrast, patients with CHA_2DS_2-VASc scores ≥2 were modestly more likely to switch in the pre-COVID period (HR: 1.18, 95% CI 1.05–1.33), with a higher hazard ratio observed post-COVID (HR: 1.53, 95% CI 1.31–1.78). The non-overlapping

confidence intervals suggest a potential strengthening of this association following the onset of the pandemic. These findings partially align with previous research. Park et al. reported increased switching with each 1-point increase of the score (suggesting linearity) (283), while Fosbøl et al. described a U-shaped association (281). The threshold effect observed in the present study at CHA_2DS_2-VASc ≥2 aligns with guideline recommendations, as patients with scores at or above this level are generally indicated for initiation of long-term oral anticoagulation (5).

The strengthening of this association during COVID-19 may also reflect practical considerations. Patients with higher stroke risk scores often have greater comorbidity burdens and may require closer clinical follow-up when treated with VKA therapy. During the pandemic, when minimizing healthcare contact was a priority, these higher-risk patients may have been prioritized for switching to DOACs to reduce their exposure to healthcare settings while maintaining adequate thromboembolic protection. This interpretation is supported by the concurrent increase in age-related switching, as age is a key component of the CHA_2DS_2-VASc score and older patients were particularly vulnerable to COVID-19.

Furthermore, patients at higher clinical risk may have more frequent contact with healthcare services, including routine monitoring, hospitalisation, or specialist review. This increased clinical interaction may provide more opportunities for treatment reassessment and medication changes, thereby contributing to the higher observed rates of switching in these groups. As such, switching patterns may partly reflect healthcare utilisation rather than solely clinical need.

Higher HAS-BLED scores were consistently associated with increased switching likelihood in both periods, suggesting that bleeding risk remained a stable consideration in clinical decision-making regardless of the pandemic context. This aligns with Potpara et al. and others, who identified HAS-BLED ≥3 as a factor significantly associated with switching (153,283). Furthermore, the preference for switching high bleeding-risk patients may reflect the clinical rationale that DOACs' predictable pharmacological profiles and lack of routine monitoring requirements offer particular advantages for these patients.

However, the association magnitude for HAS-BLED ≥3 attenuated slightly post-COVID (HR 1.25 [95% CI 1.18–1.32] to 1.16 [95% CI 1.08–1.24]), possibly reflecting broader, more generalized switching driven by convenience and the need to

minimize in-person INR monitoring. This suggests that while bleeding risk continued to inform decisions, it may have been weighed differently amid pandemic-related healthcare pressures, with greater system-level emphasis on treatment convenience and safety, and potentially greater focus on stroke prevention even in patients with elevated bleeding risk.

6.4.5. Geographic and socioeconomic factors

Urban–rural disparities in switching behaviour were minimal pre-COVID, but notable geographic heterogeneity became evident post-COVID, particularly during the first three months of lockdown. Patients in other urban areas (population of 10,000 to 124,999 people) and some semi-rural locations (population less than 3,000 people and 30 to 60 minutes' drive time to an urban area) were significantly more likely to switch compared to those in large urban areas (population of 125,000 people and over), though these differences diminished over time, suggesting an initial pandemic response that subsequently converged.

Several factors may explain these findings. Large urban areas may have had higher baseline DOAC adoption rates prior to the pandemic (see chapter 4), leaving fewer VKA patients eligible for switching when COVID-19 began. Urban areas typically benefit from earlier access to new therapies, greater specialist density, and more established prescribing pathways. Consequently, the pool of suitable candidates for switching may have been substantially smaller in large urban areas compared to other urban and semi-rural locations. In contrast, other urban and semi-rural regions may have had greater scope for rapid changes in prescribing practices when minimizing healthcare contact became a priority. For many patients, switching from warfarin to a DOAC reduced the need for frequent clinic visits and laboratory monitoring, a benefit particularly relevant for rural populations with limited access to INR testing services. The initial surge in switching among patients outside large urban areas likely reflected both the rapid expansion of telemedicine and the reduced access to INR monitoring services, factors that made DOACs a more practical option.

This pattern of geographic variation extended beyond simple urban-rural distinctions to encompass broader regional differences across health boards. Several boards showed increased switching early in the pandemic followed by subsequent decline. While previous literature has noted that OAC switching varies between practices and providers, this study extends those findings by demonstrating how such

variation evolved following the onset of COVID-19. These patterns likely reflect a combination of local healthcare system responses, resource availability, baseline prescribing practices, and health board-specific formularies, which may influence both the proportion of patients eligible for switching and the choice of anticoagulant therapy. The subsequent stabilization of switching patterns across both urban-rural categories and health boards suggests that healthcare systems adapted to pandemic constraints, and that most eligible patients may have been switched during the first lockdown period.

Notably, despite these geographic variations, this study found no significant association between socioeconomic deprivation and switching. This finding contrasts with several international studies that reported associations between higher socioeconomic status, private insurance, and increased switching rates (266). The absence of socioeconomic effects in this study likely reflects Scotland's universal healthcare system, where patients do not face direct costs for anticoagulant therapy and therefore have limited financial incentive to remain on lower-cost treatments such as warfarin. In this context, access to DOACs is more strongly shaped by healthcare system organisation and local prescribing practices than by individual economic circumstances. In addition, SIMD is an area-level indicator and may not fully capture individual socioeconomic status, which could further attenuate observed associations between deprivation and switching behaviour. This interpretation is supported by pre-pandemic patterns reported in the international literature, where cost consistently emerged as a barrier to DOAC adoption (287).The higher expense of DOACs relative to warfarin led to delayed adoption in lower-resource areas and countries where insurance coverage was limited. Even in high-income countries such as the USA, substantial geographic disparities in prescribing persisted.

The international literature also reveals complex and sometimes contradictory geographic patterns. Existing evidence demonstrates urban–rural differences and geographical variations in DOAC prescribing across multiple healthcare systems (287). Additionally, Norby et al. found lower DOAC initiation among rural Medicare beneficiaries, particularly in isolated rural areas (288). However, by 2020, while 92% of U.S. clinicians prescribing anticoagulants used DOACs, rural prescribers displayed divergent practices. Some rural areas demonstrated high DOAC-only use, while others continued favouring warfarin (287). This variability suggests that local

practice culture and access to anticoagulation clinics or laboratory services shaped uptake, with some rural clinicians continuing to prescribe warfarin despite DOACs' potential to reduce patient travel for INR monitoring (287).

Together, these findings support the interpretation that the geographic patterns observed in our study reflect complex, system-level responses to the pandemic rather than persistent structural disparities between urban and rural settings or health board differences. The absence of socioeconomic associations in Scotland, combined with the temporal convergence of geographic differences, suggests that within a universal healthcare system, the pandemic served as a catalyst for accelerating DOAC adoption among eligible patients who had not previously been switched, with this effect being most pronounced in areas where baseline adoption was lower. This pattern differs markedly from international settings where financial and access barriers continue to shape anticoagulation prescribing independent of clinical need.

6.4.6. Overall interpretation

This study provides important evidence on how patterns of switching from VKA to DOAC therapy changed following the onset of COVID-19. The pandemic amplified certain existing trends, particularly age-related switching, while attenuating others, including associations with gender and prior VKA duration. The observed temporal dynamics, with pronounced changes during the first three months of the pandemic followed by stabilisation, suggest that clinical practice adapted in response to pandemic-related constraints. In Scotland, these changes are consistent with efforts to reduce reliance on frequent INR monitoring and minimise face-to-face contact, which may have facilitated increased uptake of DOACs. Taken together, these findings indicate that while core clinical decision-making factors remained stable, external system-level pressures influenced how and for whom switching occurred.

Strengths and Limitations

This study has several methodological strengths. First, the use of a large, population-based retrospective cohort enabled the examination of real-world anticoagulant switching patterns across a complete national healthcare system, enhancing internal validity and reducing selection bias related to healthcare access. The extended study period spanning both pre-pandemic and pandemic phases allowed for direct comparison of switching behaviour before and during COVID-19,

including the period following the introduction of national guidance encouraging switching.

Second, the application of time-to-event methods using Cox proportional hazards models allowed appropriate modelling of the timing of switching events while accounting for differences in follow-up duration between individuals. The use of delayed-entry Cox models explicitly addressed left truncation arising from heterogeneous VKA initiation dates, ensuring that patients contributed person-time only from when they became observable and at risk within each study period.

Finally, the study employed a clear and clinically informed outcome definition of switching from VKA to DOAC, using a prespecified 90-day window that has been applied in previous real-world studies. The inclusion of sensitivity analyses assessing alternative switching definitions further strengthened the robustness of the findings.

Several limitations should be considered when interpreting the results. First, the observational nature of the study limits causal inferences, and unmeasured confounding may have influenced the observed associations. Second, the specific context of the Scottish healthcare system may limit generalisability to other settings, particularly those with different healthcare financing models or organisational structures.

Third, comorbidities were ascertained using all available secondary care data prior to each patient's baseline date, without applying a fixed lookback window (e.g., 5 years). While this approach maximized capture of chronic conditions that remain clinically relevant over time, it resulted in systematically longer lookback periods for patients in the post-COVID cohort compared to the pre-COVID cohort. This may have led to differential ascertainment of comorbidities, with patients in the later cohort more likely to have prior conditions recorded simply due to longer observation time, potentially overestimating the comorbidity burden in the post-COVID group and affecting comparisons between periods.

Finally, the analysis could not account for some patient- and prescriber-related factors that may have influenced switching decisions. These include, e.g., patient preferences for convenience or reduced monitoring, dissatisfaction with current therapy, and prescriber attitudes or preferences. Other important but unmeasured factors, such as unstable INR control, prior bleeding episodes, or poor treatment

adherence, may also have contributed to switching behaviour beyond what was captured in the available data.

6.5 Conclusion

This study demonstrates that the COVID-19 pandemic influenced both the rate and pattern of switching from VKA to DOAC therapy in Scotland, while maintaining continuity in several clinical decision-making factors. Female sex, shorter duration of prior VKA use, and confirmed AF remained consistently associated with switching in both periods, while VAF consistently reduced switching likelihood.

However, the pandemic introduced important shifts in treatment patterns. Switching became more common among older patients and those with higher stroke risk, reflecting an expansion of DOAC use toward groups in whom treatment simplification and safety considerations were particularly relevant. Geographic variations exhibited temporal dynamics, with urban-rural and health board differences emerging early in the pandemic but subsequently diminishing, demonstrating healthcare system adaptation over time.

Overall, the COVID-19 pandemic was associated with broader and more rapid uptake of DOAC therapy. The accelerated switching toward DOACs was associated with greater treatment convenience and reduced monitoring requirements, particularly for high-risk and elderly patients and across geographic areas. These findings highlight how healthcare systems adapted anticoagulation management by reshaping clinical practice patterns while preserving core decision-making principles.

7 Chapter 7: Effectiveness and safety outcomes for patients who switched from Vitamin K Antagonists (VKA) to Direct Oral Anticoagulants (DOACs)

7.1 Introduction

DOACs have increasingly replaced VKAs such as warfarin for preventing and treating thromboembolic events. This shift in clinical practice has been supported by evidence from large RCTs and real-world studies demonstrating that DOACs are at least as effective as VKAs, with more favorable safety profiles, particularly for ICH (56,59). Consequently, current clinical guidelines recommend DOACs as first-line therapy for most patients with AF and VTE. These recommendations have contributed to a decline in warfarin use and a corresponding increase in DOAC prescribing. This increase has affected not only newly diagnosed/treated patients but also a significant proportion of patients switching from VKAs to DOACs.

Switching from VKAs to DOACs has become increasingly common in clinical practice. A large U.S.-based cohort study found that approximately one in six patients switched from VKAs to DOACs therapy following their availability (285). Furthermore, across published studies, switching frequencies varied widely between 2%–56%, depending on the DOAC switched to, the length of follow-up, the baseline population (incident versus prevalent OAC users), and the healthcare setting, with follow-up periods ranging from 0.3 to 5.5 years (266). Nevertheless, VKAs remain widely prescribed, with 30-40% of patients worldwide continuing on VKA therapy (214), including patients in Scotland as shown in previous findings (see Chapter 4). The decision to switch patients from a VKA to a DOAC involves multiple factors, including DOAC benefits such as improved safety profiles, fewer drug and food interactions, and elimination of routine INR monitoring (267,289). Additional important considerations include VKA intolerance, suboptimal INR control, patient preference, convenience and ease of use and care home residence (245,290).

The COVID-19 pandemic further accelerated this switching due to pandemic-related disruptions to face-to-face healthcare services, which limited access to routine INR monitoring in order to minimize the risk of virus transmission (245). Additionally, guidance issued by NHS England in early 2020 recommended switching from VKAs to DOACs where clinically appropriate (245). Previous research showed a marked increase in VKA-to-DOAC switching during the pandemic. Approximately 12% of patients in England switched between March and May 2020 alone, highlighting the

pandemic's impact on anticoagulation management (245). Similarly, findings from Chapter 5 of this thesis demonstrated that in Scotland, the proportion of VKA patients switched to DOACs increased from 1.3–1.8% prior to the pandemic to 8% during April 2020, further highlighting the pandemic's substantial impact on anticoagulation management.

Despite strong evidence supporting the overall safety and effectiveness of DOACs in clinical practice, most studies evaluating their clinical effectiveness and safety have focused on patients newly initiating DOAC therapy rather than those switching from VKA treatment. A 2021 narrative review reported that although switching between OACs is common in clinical practice, studies assessing clinical outcomes following switching are relatively limited and report inconsistent findings, with variability in the direction and magnitude of associations for outcomes such as bleeding and thromboembolic events (267). Many studies were characterised by relatively short follow-up periods and heterogeneity in study design and outcome definitions (267). More recently, a large scoping review published in 2023, similarly found conflicting results regarding clinical outcomes, with studies reporting higher, lower, or unchanged risks of ischaemic stroke, systemic embolism, and GI bleeding among patients who switched from VKA to DOAC, compared to those who remained on VKA (266).

Consequently, clinical outcomes following VKA-to-DOAC switching, particularly regarding stroke prevention, bleeding complications, and mortality, remain inadequately characterized, especially in the context of widespread switching during the COVID-19 pandemic. Whereas pre-pandemic switching was predominantly associated with clinical triggers such as poor INR control, bleeding events, or thromboembolic complications, switching during the pandemic occurred in a context increasingly shaped by practical and logistical considerations, including disruptions to INR monitoring services and the need to minimise face-to-face healthcare contact.

Aims and objectives

The present study aims to examine real-world effectiveness and safety outcomes of switching patients from VKAs to DOACs, using a large population-based cohort of OAC users in Scotland, including patients who switched both before and during the COVID-19 pandemic.

The specific objectives of this study were:

1. To compare clinical outcomes between patients who switched from VKAs to DOACs to those who continued VKA therapy.
2. To compare clinical outcomes of different DOACs among patients who switched from VKA therapy.

7.2 Methods

7.2.1. Study design

This retrospective cohort study was conducted using linked administrative healthcare datasets described in Chapter 3. In this analysis, outcomes among patients who switched from VKAs to DOACs were compared to those who continued VKA therapy (control group). The study covered the period from January 2018 to May 2021.

7.2.2. Study population

Patients were included if they were aged ≥18 years and had at least one VKA prescription during the study period (January 2018–April 2021). To ensure that all patients were DOAC-naïve at cohort entry, individuals with any recorded DOAC prescription prior to the start of their follow-up period were excluded. Prior anticoagulant exposure was assessed using prescribing data available from January 2009 up to cohort entry, which occurred between January 2018 and April 2021. This approach ensured a clean exposure definition, allowing comparison between patients receiving VKA therapy who either continued VKA treatment or switched to a DOAC during the study period, without any prior exposure to DOACs.

7.2.3. Exposure definition

The cohort of patients treated with VKAs was defined and categorized into two exposure groups based on treatment changes during follow-up: first, patients switching from VKA to DOAC (switching group); and second, patients continuing on VKA (control group).

7.2.3.1. Switching group (VKA to DOAC)

Patients who were receiving VKA therapy and subsequently switched to a DOAC (dabigatran, rivaroxaban, edoxaban, or apixaban) during the study period (January 2018–April 2021).

Switching was defined as discontinuation of VKA therapy followed by initiation of a DOAC, with a gap of ≤90 days between the last VKA prescription and the first DOAC prescription; patients with a gap >90 days were excluded. This exclusion criterion was applied to ensure that included patients represented true switches from VKA to DOAC therapy, rather than treatment discontinuation followed by later re-initiation, which could otherwise result in exposure misclassification and biased follow-up.

As mentioned in chapter 5, the 90-day switching window was informed by dispensing quantities observed in the study population (**Table 5.1**, Chapter 5). The 90-day window was therefore selected to allow for delayed refilling, stockpiling, variation in prescription duration and dosing regimens, and to minimize exposure misclassification. To ensure meaningful follow-up, patients were required to have at least one day of follow-up after the switch date.

7.2.3.2. Control group (continued VKA therapy)

The control group included patients receiving VKA therapy during the study period (January 2018–May 2021). To ensure comparability with the switching group and avoid inclusion of newly initiated VKA users, patients were eligible only if their first VKA prescription during the study period was preceded by another VKA prescription within the prior 90 days, indicating ongoing rather than newly initiated VKA use.

Index date and follow-up

For the switching group, the index date (entry date) was defined as the switch date, that is, the date of the first DOAC prescription recorded during the study period and within 90 days of the last VKA prescription. For the control group, the index date was defined as the first VKA prescription during the study period that was preceded by another VKA prescription within the prior 90 days, indicating continued VKA therapy.

Follow-up began at the index date (time zero) and continued until the earliest of the following: occurrence of the outcome of interest, last prescription date, death, or the end of the study period (May 2021).

To ensure meaningful follow-up, patients in the switching group were required to have at least one additional DOAC prescription following the index DOAC prescription (a minimum of two DOAC prescriptions, including the index prescription).

7.2.4. Outcome definitions

Outcomes were classified into two categories: effectiveness outcomes and safety outcomes.

- **Effectiveness outcomes**

The primary effectiveness outcome was a composite of all strokes (including both ischaemic and haemorrhagic stroke), ischaemic stroke separately, systemic embolism, and death due to cardiovascular reasons. Secondary effectiveness outcomes included: PE, TIA, MI, and all-cause mortality.

In addition, two composite endpoints were analyzed: (1) ischaemic stroke and systemic embolism, and (2) all stroke, systemic embolism, and TIA. These composite endpoints were selected to capture clinically related thromboembolic events commonly used in anticoagulation research, to increase statistical power for relatively infrequent outcomes, and to facilitate comparison with prior observational studies and RCTs evaluating anticoagulant effectiveness (85,291).

- **Safety outcomes**

The main bleeding outcome was haemorrhagic stroke (including intracranial and subarachnoid haemorrhage). Other major bleeding events included GI bleeding and non-traumatic ICH. A composite safety endpoint of all bleeds was also defined, comprising haemorrhagic stroke, GI bleeding, and other major bleeding events. This composite safety endpoint was chosen to capture overall clinically relevant bleeding risk and to increase statistical power for individual bleeding events, which occur relatively infrequently.

Outcome identification

All outcomes (except death) were identified from secondary care records (SMR01) using International Classification of Diseases, Tenth Revision (ICD-10) codes from hospital admissions (main condition plus up to six secondary diagnoses). Cardiovascular mortality was identified from the national death registry, using both main and underlying causes of death. The ICD-10 code lists used to define study outcomes were based primarily on a previously published Scottish real-world study of OACs (Mueller et al.) and were adapted where necessary for the present analysis (83), These definitions were also consistent with those used in the published

literature (292–294). The full list of ICD-10 codes used to define outcomes is provided in **Table 7.1**.

Table 7.1: ICD-10 codes used to identify study outcomes

Outcomes	Diagnostic codes
Clinical effectiveness outcomes	
Stroke, all	I60, I61, I63, I64
Ischaemic Stroke	I63, I64
Transient Ischaemic attack	G45.8, G45.9
Systemic Embolism	I74
Myocardial Infarction	I21, I22
Pulmonary Embolism	I26
Death, Cardiovascular	I11, I13, I20-I26, I46, I47, I49, I50, I60, I61, I63, I64, I67, I74
Safety outcomes	
Haemorrhagic stroke	I60, I61
Other major bleeds	D62, H11.3, H35.6, H43.1, I62, J94.2, N02, N95.0, R04, R31, R58
Gastrointestinal bleeding	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0 – 92.2

All outcomes were analyzed separately. Recurrent events of the same type (e.g., a second stroke after the first) were not included. However, patients who experienced different outcomes (e.g., both stroke and bleeding) were included in multiple analyses: for the stroke analysis, follow-up extended from the index date until the stroke event, and for the bleeding analysis, from the index date until the bleeding event. This approach ensured that each distinct outcome was evaluated independently while preserving the integrity of the time-to-event analyses for each outcome type.

Time to event was defined as the number of days between the index date and either the hospital admission date for the outcome of interest or the date of death (as appropriate). Patients were censored at the earliest of last prescription date or the end of the study period, whichever occurred first.

7.2.5. Additional criteria for outcome-specific analyses

For each analysis, patients were required to be free of the outcome of interest prior to the index date. In the switching group, this meant no record of the outcome before the switch date (index date). In the control group, patients were required to be outcome-free prior to their first VKA prescription during the study period. Outcome history was assessed using all available secondary care and hospital admission records prior to the index date. For example, in the ischaemic stroke survival analysis, patients with a documented ischaemic stroke before their index date were excluded, and only those naïve to ischaemic stroke were included. In addition, patients in each outcome-specific analysis were required to have a minimum of one day of follow-up to ensure that all event times were greater than zero (time to event >0).

These criteria ensured that analyses focused on events occurring after the index date. Excluding patients with a prior history of the outcome of interest avoided baseline differences in recurrence risk and reduced the potential for selection bias, as prior events may also influence clinical decisions to switch anticoagulant therapy, thereby confounding post-switch treatment comparisons. This approach ensured comparability of baseline event history across groups.

7.2.6. Covariates

Covariates were selected based on clinical relevance and prior evidence demonstrating their association with thromboembolic and bleeding outcomes among OAC users (295), as well as their inclusion in validated risk scores used in anticoagulation decision-making, such as CHA_2DS_2-VASc and HAS-BLED (295). For each outcome analysis, individuals with a documented history of the outcome of interest prior to the index date were excluded, while other comorbid conditions were retained as covariates.

Accordingly, covariates considered across the outcome-specific models included age, sex, AF, DM, HTN, CHF, liver disease, renal disease, MI, IHD, history of ischaemic stroke, history of haemorrhagic stroke, history of major bleeding, DVT or PE, and VAF. Variables representing a prior history of the outcome being modelled (e.g. prior ischaemic stroke in the stroke analysis or prior major bleeding in the bleeding analysis) were not included in the corresponding outcome-specific model, as such patients were excluded at baseline. An overview of variable sources and types is provided in **Table 7.2**.

Table 7.2: Variable source and type

Variable	Data source	Variable type
sex	Demographics	Factor, binary
Patient age at switch date or first VKA prescription during the study period	Demographics	Continuous
VKA start date	PIS	Date
DM	SMR01	Factor, binary
HTN	SMR01	Factor, binary
Renal disease	SMR01	Factor, binary
Liver disease	SMR01	Factor, binary
CHF	SMR01	Factor, binary
DVT or PE	SMR01	Factor, binary
MI	SMR01	Factor, binary
IHD	SMR01	Factor, binary
AF	SMR01	Factor, binary
Vascular disease	SMR01	Factor, binary
Prior stroke	SMR01	Factor, binary
Hemorrhagic stroke	SMR01	Factor, binary
Valvular AF	SMR01	Factor, binary
Antiplatelet use	PIS	Factor, binary
NSAID use	PIS	Factor, binary

Abbreviations: AF, atrial fibrillation; VAF, valvular atrial fibrillation; CHF, congestive heart failure; DVT, deep vein thrombosis; PE, pulmonary embolism; MI, myocardial infarction; IHD, ischemic heart disease; DM, diabetes mellitus; HTN, hypertension; NSAID, non-steroidal anti-inflammatory drug; PIS, Prescribing Information System; SMR01, Scottish Morbidity Record 01. SMR01 captures acute inpatient and day-case hospital admissions in Scotland, while PIS records community-dispensed prescriptions.

All covariates were fixed at the index date. Comorbidities were identified based on diagnoses recorded in secondary care data or hospital admission records within the five years preceding the index date. Diagnostic definitions were based on ICD-10 and OPCS-4 codes, as detailed in **Table 7.3**.

Additionally, duration of VKA use prior to the index date was included in the Cox proportional hazards models as a categorical variable (<2 years, 2–5 years, and >5 years) to adjust for differences in treatment history.

Table 7.3: ICD-10 and BNF code definitions for outcomes and covariates

Comorbidity	ICD10-code
AF	I48
Valvular disease or heart valve replacement	ICD-10: I05, I06, I08, I34, I35, Q23, Z95.2 – Z95.4 **OPCS-4 codes** K25.2 – K25.4, K26.2 – K26.4, K29.2 – K29.4
Liver disease	ICD-10: K70.2-70.4, k70.9, K72- K74, K71.1, K71.3-K71.7, K76.5-76.7
Prior major bleeding	ICD-10: D62, H11.3, H35.6, H43.1, I60 – I62, J94.2, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0 – K92.2, N02, N95.0, R04, R31, R58
Renal disease	ICD-10: I12, I13, N00 – N05, N07, N10, N11, N14, N17 – N19, Q61, Z99.2, Z49, Z94.0
Prior ischeamic stroke or TIA	ICD-10: I63, I64, G45, G46.3 – G46.7, I67.6, I169.4, I169.3
CHF	ICD-10: I11.0, I13.0, I13.2, I50
Hypertension	ICD-10: I10 – I15
Diabetes mellitus	ICD-10: E10, E11, E13, E14, G59.0, G63.2, H28.0, H36.0, M14.2, N08.3, O24.0, O24.1, O24.3
PE or DVT	ICD-10 codes I26, I67.6, I80.1 – I80.9, I81, I82.2-I82.9
Vascular disease	ICD-10: I20 – I22, I70, I73.1, I73.8, I73.9, I74
Alcohol usage	ICD-10: E52, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, T51, Z71.4, Z72.1 BNF: 04.10.01
MI	ICD-10: 121,122
IHD	ICD-10: I24, 125.0, 125.1, I25.5, I25.6, I25.8, I25.9
Haemorrhagic stroke	I60, I61, I62
concomitant medication	
Antiplatelet drugs	BNF: 02.09
NSAIDs	BNF: 10.01.01

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack; MI, myocardial infarction; IHD, ischemic heart disease; ICD-10, International Classification of Diseases, 10th Revision; OPCS-4, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision; BNF, British National Formulary; NSAIDs, non-steroidal anti-inflammatory drugs. ICD-10 and OPCS-4 codes were used to identify diagnoses and procedures recorded in secondary care, while BNF codes were used to identify concomitant medications dispensed in the community.

HAS-BLED and CHA_2DS_2-VASc Risk Scores

The HAS-BLED and CHA_2DS_2-VASc scores were calculated for each patient using secondary care data, based on comorbidities recorded within the five years preceding the index date. Age was defined at the index date, corresponding to the switch date for the switching group and the date of the first VKA prescription during the study period for the control group.

- HAS-BLED score components included HTN, abnormal renal/liver function, stroke, bleeding history, age ≥65, and concomitant use of drugs/alcohol.
    - Alcohol use was identified using ICD-10 codes from hospital records (**Table 7.3**).
    - NSAID and antiplatelet use were determined based on prescriptions within six months prior to the index date. Medication exposures, including NSAIDs and antiplatelet agents, were identified using BNF codes from prescribing records (**Table 7.3**).
- CHA_2DS_2-VASc score components included CHF, HTN, age ≥75 (2 points), DM, prior stroke/TIA/thromboembolism (2 points), vascular disease, age 65–74, and female sex.

The CHA_2DS_2-VASc score was categorised as 0, 1, and ≥2, reflecting low, intermediate, and elevated thromboembolic risk, respectively, consistent with guideline-based thresholds for considering anticoagulation (296). The HAS-BLED score was categorised as 0–1 (low risk), 2 (moderate risk), and ≥3 (high risk) bleeding risk, reflecting bleeding risk stratification widely used in the literature (296).

7.2.7. Outcome assessment and statistical analysis

Propensity score matching

Given the observational nature of the study, propensity score matching (PSM) was employed to reduce confounding and approximate the conditions of a RCT. Propensity score matching estimates the probability of receiving the treatment or exposure conditional on observed baseline covariates (297). By forming matched sets of treated and untreated individuals with similar propensity scores, PSM aims to balance observed baseline covariates between treatment groups, thereby improving the validity of treatment comparisons and reducing bias in the estimation of treatment effects (297).

Thus, to reduce confounding and enhance comparability between groups, 1:1 propensity score matching was performed using a nearest-neighbour algorithm with a caliper width of 0.2 standard deviations of the logit of the propensity score, without replacement (298,299). Under this approach, each treated individual was matched to a single control individual with the closest propensity score within the specified caliper. Matching without replacement ensured that each control individual was used only once. The choice of a 0.2 caliper width was intended to minimise poor-quality matches while maximising retention of treated patients (297).

Propensity scores were estimated using logistic regression to model the probability of switching treatment based on observed baseline covariates measured at the index date. Covariates included age at index date, sex, VKA initiation date, and a history of comorbidities including AF, VAF, DM, HTN, CHF, liver disease, renal disease, MI, IHD, prior stroke, haemorrhagic stroke, major bleeding, DVT or PE, HAS-BLED score, and CHA_2DS_2-VASc score. Composite risk scores were included as categorical variables in the propensity score model to ensure baseline balance in overall thromboembolic and bleeding risk between the switching and control groups.

In addition to inclusion in the propensity score model, matching was constrained to be exact on sex, such that treated and control individuals were matched only within the same sex, while nearest-neighbour matching was performed on the estimated propensity score. Balance between groups was evaluated using standardized mean differences (SMDs), with SMD <0.1 considered acceptable (300).

Unlike traditional p-values, SMDs are not affected by sample size and are thus a more stable and interpretable measure of balance in observational studies (301). Covariate balance was visually assessed using Love plots (300). These plots display the SMDs for each covariate both before and after matching, providing graphical representation of how well the matching procedure reduced imbalance (301). Love plots are a commonly used diagnostic tool in propensity score analyses, helping to evaluate the effectiveness of the matching strategy in achieving comparability between groups (300,301). Matching was implemented using the **MatchIt** package in R and love plots generated with the **cobalt** package.

Multiple analytical approaches were employed to assess outcomes:

7.2.7.1. Incidence rates

Incidence rates per 100 person-years were calculated for each outcome separately in the switching and control group. Within the switching groups, incidence rates were further stratified by specific DOAC type to identify differences between individual agents. Person-time at risk was measured from the index date until the end of follow-up. To prevent exposure misclassification, patients who switched to more than one DOAC types during the follow-up period were excluded from the drug-specific analyses.

7.2.7.2. Cox proportional hazards models

To evaluate the adjusted association between switching and clinical outcomes over time, Cox proportional hazards regression models were fitted to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), comparing the switching group with the control group.

These models estimate hazard ratios, reflecting the likelihood of an event occurring at any given time in the switching group compared with the control group. For outcomes with sufficient event counts, Cox proportional hazards models were adjusted for key baseline covariates to account for residual imbalance and improve statistical efficiency (297,302), including age, sex, AF, MI, IHD, CHF, VAF, prior stroke or TIA, DVT or PE, history of major bleeding, renal disease, HTN, DM and duration of VKA use prior to the index date, categorised as <2 years (reference), 2–5 years, and >5 years. Additionally, for each outcome, analyses were restricted to patients who were free of that outcome at the index date; accordingly, history of the outcome itself (e.g. prior stroke when modelling stroke) was not included as a covariate in the corresponding Cox model.

CHA_2DS_2-VASc and HAS-BLED scores were included in the propensity score model but were not included in the Cox outcome models, as their individual components were adjusted for instead to avoid collinearity and overadjustment. However, sensitivity analyses including the composite scores yielded similar results.

The proportional hazards assumption was assessed using Schoenfeld residuals and the global test (Cox.zph) in R. All covariates met the assumption ($p > 0.05$), except for cardiovascular death and all-cause mortality, where evidence of non-proportional hazards was observed. Visual inspection of Schoenfeld residual plots suggested

time-varying treatment effects, with a marked change in the hazard around 500 days of follow-up in the treatment group.

Accordingly, for CVD mortality and all-cause mortality outcomes, piecewise Cox proportional hazards models were fitted to accommodate non-proportional hazards (303). Follow-up time was divided into three intervals (0–500 days, 501–900 days, and >900 days) using the survSplit function in R. Cut-points were selected based on inspection of Schoenfeld residual plots and related diagnostic measures, which indicated changes in the treatment effect over time, with notable shifts around approximately 500 and 900 days (303). Interaction terms between treatment group and time interval were included to allow estimation of time-varying hazard ratios, consistent with established recommendations for modelling non-proportional hazards (303).

7.2.7.3. Time- varying and piecewise Cox proportional hazards modelling

To further evaluate whether the risks associated with switching from VKAs to DOACs varied over time, a time-dependent Cox regression analysis was applied using a prespecified 90-day cutoff, adjusting for relevant covariates. The choice of the 90-day cutoff was informed by prior observational studies indicating that clinical risks may differ shortly after switching OAC therapy compared with longer-term follow-up (304).

Follow-up time was divided into an early (≤90 days) and a late (>90 days) period using a piecewise Cox proportional hazards modelling framework to distinguish short-term from longer-term risks. Each patient contributed one or more observations corresponding to their time at risk within each interval. Interaction terms between treatment group (switching vs control) and time interval were included to estimate period-specific hazard ratios, thereby allowing the effect of switching to vary between the early and later follow-up periods.

Baseline hazards were stratified by time interval to permit the underlying hazard function to differ between the early and late periods, accommodating potential non-proportionality in the baseline hazard. Where necessary, additional stratification by covariates such as AF and CHF was applied to satisfy the proportional hazards assumption.

Separate Cox regression analyses were also conducted to compare outcome risks across individual DOAC types, excluding patients who switched to dabigatran

because of small sample size. DOAC type was modelled as a categorical variable (apixaban, rivaroxaban, and edoxaban), with apixaban as the reference group. This approach enabled the estimation of relative HRs for each DOAC, indicating whether risks differed between agents after adjustment for potential confounders.

$$coxph(Surv(time.to.event, outcome) \sim group + covariates)$$
$$coxph(Surv(time.to.event, outcome) \sim DOAC.type + covariates)$$

7.2.7.4. Kaplan–Meier survival analysis

Kaplan–Meier survival curves were generated to visually estimate event-free survival by group (switching vs. control) and separately by DOAC type among switchers. Differences between matched groups were compared using log-rank tests.

To investigate the timing of outcome occurrence post-switch, Kaplan–Meier survival estimates were calculated at predefined intervals: 60, 180, 365, and 1095 days. Estimates were stratified by group (switching vs. control) and DOAC type (apixaban, edoxaban, rivaroxaban). For each stratum, the number at risk, cumulative number of events, survival probability, standard error, and 95% confidence intervals were reported. These estimates were used descriptively to assess cumulative risk patterns across treatment groups and DOACs over time.

The occurrence of each outcome of interest was coded as a binary variable (0 indicated the absence of the event and 1 when the event occurred). Analyses were performed using R software (4.4.3 version).

7.2.7.5. Sensitivity analyses

An additional sensitivity analysis was performed by calculating the incidence rate for all patients who continued VKA therapy throughout the study period (January 2018 to April 2021) and who had a VKA prescription within the preceding 90 days, irrespective of matching status. This evaluated the robustness of the findings compared to the primary propensity score–matched cohort. However, the sensitivity analysis were limited to incidence rates; Cox regression and Kaplan–Meier survival analyses were not repeated using the stricter matching and were restricted to the primary propensity score–matched cohorts based on the predefined key covariates.

7.3 Results

Of the 15,488 patients who switched from a VKA to a DOAC during the study period, 505 patients were excluded because they had only one DOAC prescription, and their switch date was either their last follow-up date or date of death (**Figure 7.1**). This resulted in 14,983 patients eligible for analysis: 6,816 (45.49%) were treated with apixaban, 6,472 (43.19%) with edoxaban, 1,626 (10.85%) with rivaroxaban, and 69 (0.46%) with dabigatran.

An additional 939 patients were excluded from drug-specific outcome analyses due to switching between multiple DOAC types during the follow-up period. Thus, 14,004 patients who remained on a single DOAC type throughout follow-up were included in the drug-specific outcome analyses: 6,520 on apixaban, 6,119 on edoxaban, 1,357 on rivaroxaban, and 48 on dabigatran.

Among the 39,404 patients who continued VKA therapy and did not switch to a DOAC during the study period, 11,840 were excluded because they did not have a VKA prescription within 90 days prior to their first VKA prescription during the study period. This exclusion ensured that the continued-VKA group consisted of patients with established and continuous VKA use and avoided inclusion of new VKA initiators or patients with treatment gaps. This resulted in an unmatched continued-VKA group of 27,564 patients for the sensitivity analysis (**Figure 7.1**).

For comparative analyses, 14,977 patients from the VKA-to-DOAC switching group were propensity score–matched to 14,977 patients from the continued-VKA group, resulting in 1:1 matched pairs that were included in the main analysis.

The median follow-up time was 3.2 years (IQR: 2.5–3.3 years) for non-switchers and 1.2 years (IQR: 0.8–2.1 years) for switchers.

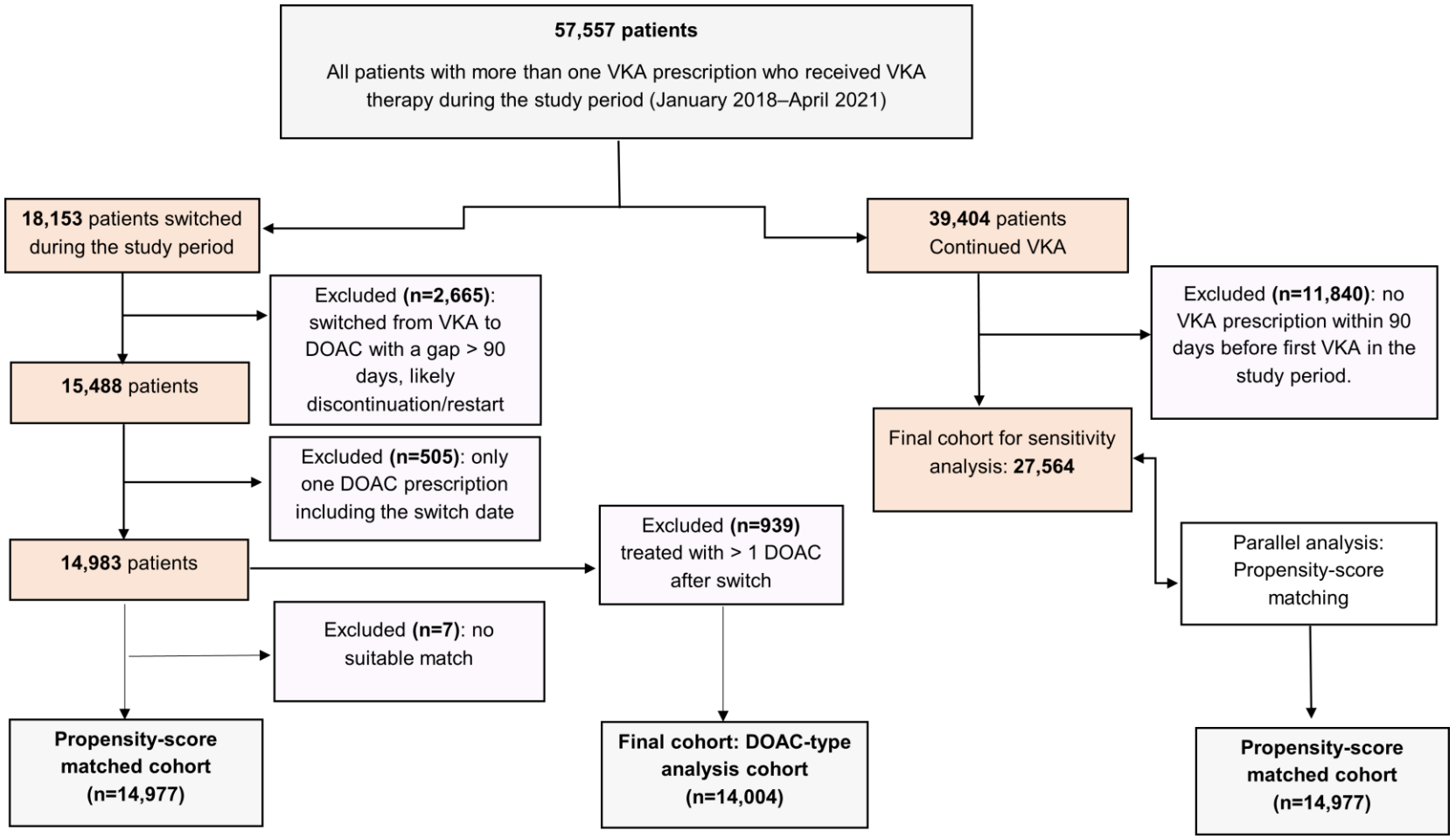

Figure 7.1: Flowchart of patient selection for the comparative effectiveness analysis of VKA to DOAC switchers and continued VKA users.

7.3.1. Baseline characteristics of the propensity score-matched cohorts

Following propensity score matching, a total of 29,954 patients were included in the analysis, with 14,977 in each group: those who continued VKA and those who switched to DOACs. After matching, baseline characteristics were well balanced between groups, with standardized mean differences (SMDs) below 0.1 for all covariates. A Love plot illustrating covariate balance before and after matching is shown in **Figure 7.2**, confirming successful matching with minimal residual confounding.

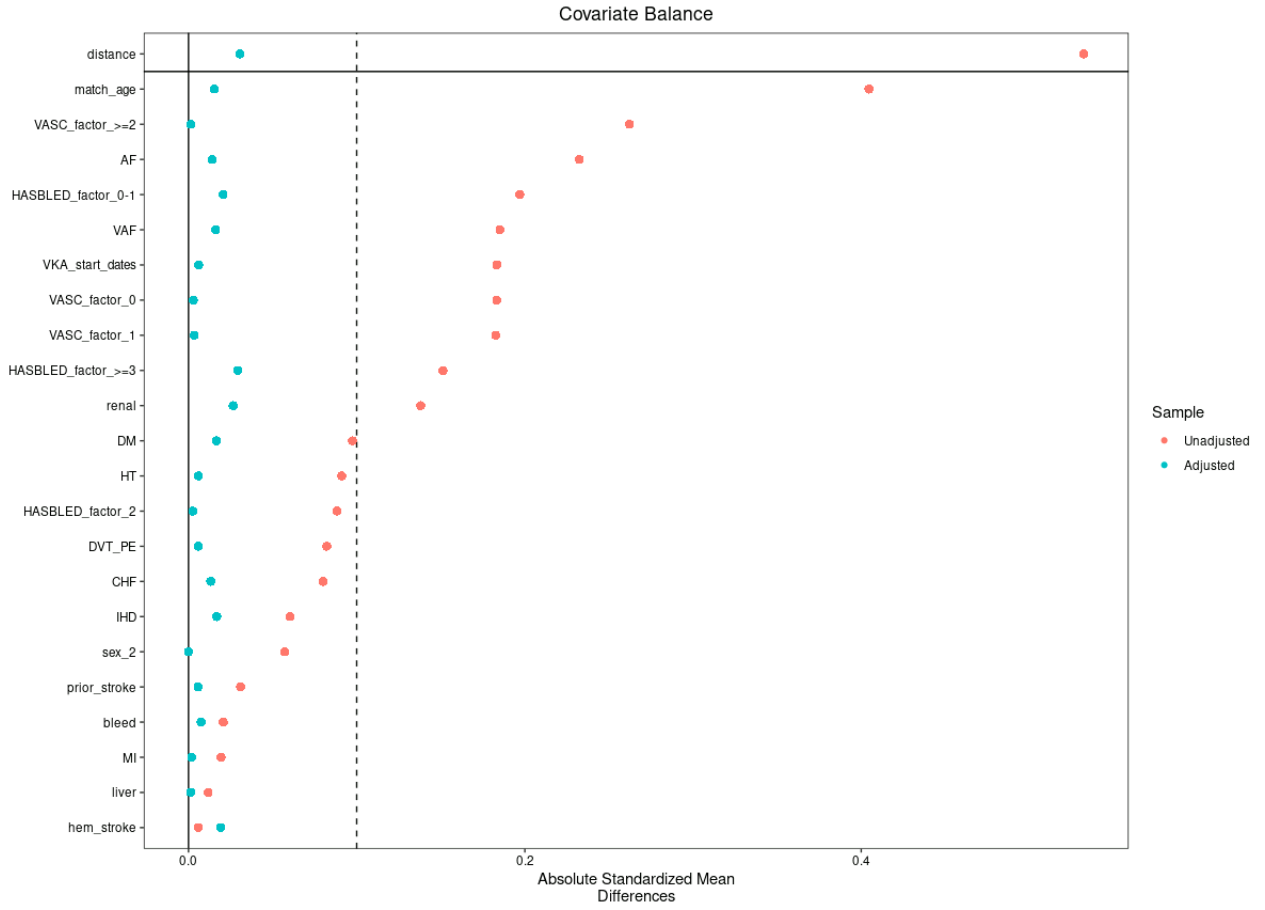

Figure 7.2: love plot: Standardized mean differences before and after propensity score matching.

Note: After matching (blue points): All variables moved very close to 0 on the x-axis. All variables have SMDs smaller than 0.1.

The mean age of the propensity score–matched cohort was approximately 77 years (mean ± SD: 77.1 ± 9.8 years in the continued VKA group and 77.3 ± 10.5 years in the switched DOAC group), and 45.1% of patients were female in both groups. Approximately half of patients had a history of AF, while HTN and DM were present in 27–28% and 14–15% of patients, respectively, with comparable proportions across treatment groups. Prior stroke or TIA was observed in 6.0% of the VKA group and 5.8% of the DOAC group, while CHF was present in 12.3% and 12.7%, respectively.

More than 50% of patients in both groups had received VKA therapy for more than five years prior to the index date. However, the distribution of prior VKA treatment duration differed slightly: long-term use (≥5 years) was more common in the DOAC group (71.1%) compared with the VKA group (52.6%), while shorter durations (<2 years or 2–5 years) were more frequent in the VKA group. Median HAS-BLED scores were similar (mean 1.59 VKA vs. 1.63 DOAC), as were CHA_2DS_2-VASc scores (mean 2.80 VKA vs. 2.82 DOAC).

Concomitant medication use during the six months prior to the index date was generally low, although antiplatelet use was slightly higher in the DOAC group (2.5% vs. 1.7%), as was NSAID use (6.5% vs. 4.3%). Complete baseline characteristics are shown in **Table 7.4**.

Table 7.4: Baseline characteristics of propensity score-matched switched and continued VKA therapy cohorts (n = 14,977 per group)

Variable	Total matched cohort	Continued VKA	Switched to DOAC
Number of patients (n)	29,954	14977	14977
Demographics			
Female (%)	13524 (45.1)	6762 (45.1)	6762 (45.1)
Mean age (SD)	77.20 (10.18)	77.12 (9.84)	77.29 (10.51)
Time on VKA, n (%)			
Short (<2y)	3671 (12.3)	2291 (15.3)	1380 (9.2)
Medium (2-5y)	7754 (25.9)	4801 (32.1)	2953 (19.7)
Long (≥5y)	18529 (61.9)	7885 (52.6)	10644 (71.1)
Comorbidities, n (%)			
CHF	3746 (12.5)	1840 (12.3)	1906 (12.7)
Hypertension	8308 (27.7)	4134 (27.6)	4174 (27.9)
Diabetes Mellitus	4288 (14.3)	2100 (14.0)	2188 (14.6)
Stroke	1766 (5.9)	893 (6.0)	873 (5.8)
Renal Disease	5463 (18.2)	2654 (17.7)	2809 (18.8)
Liver Disease	73 (0.2)	37 (0.2)	36 (0.2)
Bleeding History	3213 (10.7)	1589 (10.6)	1624 (10.8)
DVT/PE History	1348 (4.5)	683 (4.6)	665 (4.4)
AF	15077 (50.3)	7486 (50.0)	7591 (50.7)
VAF	2400 (8.0)	1167 (7.8)	1233 (8.2)
MI	963 (3.2)	479 (3.2)	484 (3.2)
IHD	5335 (17.8)	2619 (17.5)	2716 (18.1)
Haemorrhagic stroke	89 (0.3)	36 (0.2)	53 (0.4)
Vascular disease	3655 (12.2)	1771 (11.8)	1884 (12.6)
Fall-related conditions, n (%)			
Hip/Knee Fracture	1545 (5.2)	763 (5.1)	782 (5.2)
Risk scores			
CHA_2DS_2-VASc score, mean (SD)	2.81(1.42)	2.80(1.41)	2.82(1.42)
CHA_2DS_2-VASc score = 0 (%)	1381 (4.6)	695 (4.6)	686 (4.6)
CHA_2DS_2-VASc score = 1 (%)	3783 (12.6)	1883 (12.6)	1900 (12.7)
CHA_2DS_2-VASc score ≥2 (%)	24790 (82.8)	12399 (82.8)	12391 (82.7)

HAS-BLED, mean (SD)	1.61 (0.98)	1.59 (0.96)	1.63 (1.00)
HAS-BLED score = 0-1 (%)	16369 (54.6)	8261 (55.2)	8108 (54.1)
HAS-BLED score = 2 (%)	8201 (27.4)	4109 (27.4)	4092 (27.3)
HAS-BLED score ≥3 (%)	5384 (18.0)	2607 (17.4)	2777 (18.5)
Medication use, n (%)			
Antiplatelet use	628 (2.1)	251 (1.7)	377 (2.5)
NSAID Use	1613 (5.4)	640 (4.3)	973 (6.5)

Baseline characteristics of the 1:1 propensity-score matched cohorts. Balance between groups was assessed using standardized mean differences (SMDs). An SMD <0.1 was considered indicative of adequate balance.

Abbreviations: AF, atrial fibrillation; VAF, valvular atrial fibrillation; CHF, congestive heart failure; MI, myocardial infarction; IHD, ischaemic heart disease; DVT, deep vein thrombosis; PE, pulmonary embolism; NSAID, non-steroidal anti-inflammatory drug; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; SD, standard deviation; **CHA_2DS_2-VASc** = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, prior Stroke/transient ischaemic attack/systemic embolism (2 points), Vascular disease, Age 65–74 years, Sex category (female); **HAS-BLED** = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), Drugs/alcohol concomitantly.

Note: Antiplatelet use = Antiplatelet use within the last 6 months; NSAID use: NSAID use within the last 6 months before the index date; Time on VKA is the time between VKA start date and switch date or the first VKA prescription during the study period (The time on VKA before the index date); CHA_2DS_2-VASc and HAS-BLED denote standard stroke and bleeding risk scores, respectively. Values are n (%) unless otherwise stated; percentages are column percentages.

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7.3.2. Baseline characteristics of patients stratified by DOAC type

The mean age was highest in the edoxaban (78.1 ± 9.5 years), followed by apixaban (77.1 ± 10.9 years) and rivaroxaban (75.2 ± 12.2 years). The proportion of female patients ranged from 43.2% in the edoxaban group to 46.6% in the apixaban group, and 46.7% in the rivaroxaban group.

Duration of prior VKA use was longest among edoxaban users, with 74.5% having ≥5 years of use compared to 68.9% in apixaban users and 66.9% in rivaroxaban users. Shorter durations (<2 years) were more frequent in the rivaroxaban group (14.5%) than in apixaban (9.7%) or edoxaban (7.3%).

CHF ranged from 11.1% in rivaroxaban users to 13.5% in apixaban users, while HTN affected approximately 28% across all groups. Prior stroke prevalence was slightly higher in apixaban users (7.0%) compared with edoxaban (5.0%) and rivaroxaban (3.3%). Renal disease ranged from 16.1% in rivaroxaban users to 20.8% in apixaban users.

AF was highly prevalent across all DOAC types, with the highest frequency in edoxaban users (52.2%) and the lowest in rivaroxaban users (43.8%). VAF was present in approximately 8% of patients in all groups.

Regarding cardiovascular history, IHD was observed in 19.3% of apixaban users, 17.1% of edoxaban users, and 17.6% of rivaroxaban users. MI prevalence was relatively consistent across groups (2.6%–4.0%).

Risk scores were similarly distributed, with more than 75% of patients in each group having a CHA_2DS_2-VASc score ≥2. The mean HAS-BLED score was slightly higher in apixaban users (1.66) than in edoxaban (1.62) or rivaroxaban (1.52) users.

Use of concomitant medications within six months of the index date was relatively low. Antiplatelet use ranged from 2.1% (edoxaban) to 2.9% (apixaban), and NSAID use was highest in edoxaban users (6.9%) compared to apixaban (6.2%) and rivaroxaban (6.1%). Complete baseline characteristics of DOAC subgroups are presented in **Table 7.5**.

Table 7.5: Baseline characteristics of patients stratified by type of DOAC among switched cohort

Variable	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Number of patients (N)	6813	69	6469	1626
Demographics				
Female (%)	3173 (46.6)	34 (49.3)	2795 (43.2)	760 (46.7)
Mean age (SD)	77.05 (10.87)	73.82 (12.88)	78.10 (9.50)	75.18 (12.19)
Time on VKA, n (%)				
Short (<2y)	661 (9.7)	13 (18.8)	471 (7.3)	235 (14.5)
Medium (2-5y)	1460 (21.4)	11 (15.9)	1178 (18.2)	304 (18.7)
Long (≥5y)	4692 (68.9)	45 (65.2)	4820 (74.5)	1087 (66.9)
Comorbidities, n (%)				
CHF	919 (13.5)	12 (17.4)	795 (12.3)	180 (11.1)
Hypertension	1913 (28.1)	19 (27.5)	1773 (27.4)	469 (28.8)
Diabetes Mellitus	1046 (15.4)	9 (13.0)	908 (14.0)	225 (13.8)
Stroke	478 (7.0)	15 (21.7)	326 (5.0)	54 (3.3)
Renal Disease	1420 (20.8)	17 (24.6)	1110 (17.2)	262 (16.1)
Liver Disease	23 (0.3)	0 (0.0)	9 (0.1)	<5
Bleeding History	765 (11.2)	17 (24.6)	671 (10.4)	171 (10.5)
DVT/PE History	411 (6.0)	<5	137 (2.1)	114 (7.0)
AF	3459 (50.8)	40 (58.0)	3380 (52.2)	712 (43.8)
VAF	589 (8.6)	<5	515 (8.0)	124 (7.6)
MI	271 (4.0)	0 (0.0)	170 (2.6)	43 (2.6)
IHD	1312 (19.3)	15 (21.7)	1103 (17.1)	286 (17.6)
Haemorrhagic stroke	28 (0.4)	<5	18 (0.3)	<5
Vascular disease	924 (13.6)	<5	760 (11.7)	196 (12.1)
Fall-related conditions, n (%)				
Hip/Knee Fracture	351 (5.2)	<5	330 (5.1)	98 (6.0)
Risk scores				
CHA_2DS_2-VASc score, mean (SD)	2.87 (1.46)	2.84 (1.63)	2.82 (1.36)	2.66 (1.48)
CHA_2DS_2-VASc category, n (%)				
CHA_2DS_2-VASc score = 0	319 (4.7)	<5	244 (3.8)	118 (7.3)
CHA_2DS_2-VASc score = 1	856 (12.6)	7 (10.1)	780 (12.1)	257 (15.8)

CHA_2DS_2-VASc score ≥2	5638 (82.8)	57 (82.6)	5445 (84.2)	1251 (76.9)
HAS-BLED, mean (SD)	1.66 (1.03)	1.94 (1.29)	1.62 (0.95)	1.52 (1.04)
HAS-BLED category, n (%)				
HAS-BLED score = 0-1	3613 (53.0)	29 (42.0)	3524 (54.5)	942 (57.9)
HAS-BLED score = 2	1847 (27.1)	19 (27.5)	1831 (28.3)	395 (24.3)
HAS-BLED score ≥3	1353 (19.9)	21 (30.4)	1114 (17.2)	289 (17.8)
Medication use, n (%)				
Antiplatelet use	197 (2.9)	<5	134 (2.1)	43 (2.6)
NSAID Use	423 (6.2)	<5	447 (6.9)	99 (6.1)

Abbreviations: AF, atrial fibrillation; VAF, valvular atrial fibrillation; CHF, congestive heart failure; MI, myocardial infarction; IHD, ischaemic heart disease; DVT, deep vein thrombosis; PE, pulmonary embolism; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; **CHA_2DS_2-VASc** = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, prior Stroke/transient ischaemic attack/systemic embolism (2 points), Vascular disease, Age 65–74 years, Sex category (female); **HAS-BLED** = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), Drugs/alcohol concomitantly.

Note: Antiplatelet use = Antiplatelet use within the last 6 months; NSAID use: NSAID use within the last 6 months before the index date; Time on VKA is the time between VKA start date and switch date or the first VKA prescription during the study period (The time on VKA before the index date); CHA_2DS_2-VASc and HAS-BLED denote standard stroke and bleeding risk scores, respectively. Values are n (%) unless otherwise stated; percentages are column percentages. Cell counts <5 are suppressed in accordance with data disclosure control requirements.

7.3.3. Comparative effectiveness and safety outcomes between switchers and non-switchers

For each outcome, analyses were restricted to patients without a documented history of that specific event prior to the index date, such that reported incidence rates reflect incident events occurring during follow-up.

Overall, patients in the switching group exhibited higher incidence rates for several outcomes, particularly ischemic stroke, MI, and major bleeding (**Table 7.6**).

Effectiveness outcomes

Switchers experienced higher rates of thromboembolic events across multiple endpoints. The incidence rate for all stroke was 1.46 per 100 person-years (PY) in the switched group compared with 1.04 per 100 PY in the VKA group. Ischaemic stroke incidence was notably elevated among switchers (1.27 vs. 0.73 per 100 PY), as was MI (0.91 vs. 0.61 per 100 PY). Rates of PE and TIA were similarly elevated in the switched group (0.28 vs. 0.20 and 0.40 vs. 0.22 per 100 PY, respectively).

Composite effectiveness outcomes showed a similar pattern, with higher incidence rates observed among switchers compared with patients who continued VKA therapy (**Table 7.6**). Additionally, all-cause mortality was higher among switchers (11.71 vs. 10.16 per 100 PY), with a similar trend observed for cardiovascular mortality (6.43 vs. 5.77 per 100 PY).

Safety outcomes

Major bleeding events occurred more frequently in the switched group compared with the VKA group (3.36 vs. 3.11 per 100 PY). GI bleeding and other major bleeding rates were also elevated among switchers. In contrast, haemorrhagic stroke occurred less frequently in the switched group (0.24 vs. 0.36 per 100 PY), as did ICH (0.21 vs. 0.33 per 100 PY), consistent with the recognized intracranial safety advantage of DOACs.

Table 7.6: Incidence rates of clinical outcomes in matched cohorts of patients switched vs. continued VKA therapy (per 100 person-years).

Outcome	Group	No. of Events	Person-Time (Years)	Incidence Rate
All Stroke	Switched	275	18,809.07	1.462
	Continued VKA	373	35,741.91	1.044
Ischaemic Stroke	Switched	240	18,874.31	1.272
	Continued VKA	260	35,841.23	0.725
TIA	Switched	81	20,215.70	0.401
	Continued VKA	85	37,786.40	0.225
MI	Switched	174	18,874.31	0.905
	Continued VKA	221	35,973.90	0.614
PE	Switched	54	19,180.09	0.282
	Continued VKA	72	36,349.87	0.198
Systemic Embolism	Switched	29	20,895.67	0.139
	Continued VKA	50	38,781.70	0.129
Comp1	Switched	258	18,579.72	1.389
	Continued VKA	291	35,258.19	0.825
Comp2	Switched	323	17,769.63	1.818
	Continued VKA	433	33,939.64	1.276
Major Bleeding (All)	Switched	530	15,770.08	3.361
	Continued VKA	917	29,510.88	3.107
GI Bleeding	Switched	265	19,012.93	1.394
	Continued VKA	405	35,805.73	1.131
Other Bleeding	Switched	356	17,457.36	2.039
	Continued VKA	586	32,239.24	1.818
Haemorrhagic Stroke	Switched	50	21,143.03	0.237
	Continued VKA	143	39,261.87	0.364
ICH	Switched	44	21,173.80	0.208
	Continued VKA	128	39,313.89	0.326
SAH	Switched	7	21,207.52	0.033
	Continued VKA	18	39,369.78	0.046
All-Cause Death	Switched	2,537	21,661.58	11.712
	Continued VKA	4,116	40,493.65	10.165
Cardiovascular Death	Switched	1,393	21,661.58	6.431
	Continued VKA	2,336	40,493.65	5.769

Incidence rates are expressed per 1,00 person-years, with person-time representing the total time at risk accrued during follow-up. **Comp1** denotes a composite endpoint comprising ischaemic stroke and systemic embolism, and **Comp2** denotes a composite endpoint comprising all stroke, systemic embolism, and transient ischaemic attack. **Major bleeding (all)** represents a composite safety endpoint including haemorrhagic stroke, gastrointestinal bleeding, intracranial haemorrhage, subarachnoid haemorrhage, and other major bleeding events. **Abbreviations:** VKA, vitamin K antagonist; TIA, transient ischaemic attack; MI, myocardial infarction; PE, pulmonary embolism; ICH, intracranial haemorrhage; SAH, subarachnoid haemorrhage

Drug-Specific Effectiveness Outcomes

When stratified by drug, distinct differences were observed (**Table 7.7**). For all strokes, rivaroxaban users had a substantially lower incidence rate (0.65 per 100 PY) compared with edoxaban (1.37) and apixaban (1.36). This pattern was consistent for ischaemic stroke, with rates of 0.60 for rivaroxaban, 1.11 for apixaban, and 1.20 for edoxaban. TIA incidence was highest among apixaban users (0.48 per 100 PY), followed by rivaroxaban (0.31) and edoxaban (0.26).

MI incidence was comparable across the three DOACs: apixaban (0.92), edoxaban (0.89), and rivaroxaban (0.88 per 100 PY). Systemic embolism was rare overall, though slightly higher with edoxaban (0.15) and apixaban (0.14) compared with rivaroxaban (0.09). PE rates were low across all agents, ranging from 0.20 for rivaroxaban to 0.29 for apixaban. For composite outcomes, edoxaban showed slightly higher rates for COMP1 (1.34) and COMP2 (1.71) compared with apixaban (1.21 and 1.72 per 100 PY, respectively), whereas rivaroxaban consistently demonstrated lower rates (0.71 and 0.98).

All-cause mortality rates were somewhat higher for apixaban (12.25) and edoxaban (12.09) compared with rivaroxaban (11.33 per 100 PY). Cardiovascular mortality followed a similar pattern: apixaban (6.61), edoxaban (6.76), and rivaroxaban (6.33 per 100 PY).

Drug-Specific Safety Outcomes

Haemorrhagic stroke incidence was comparable between apixaban (0.27) and edoxaban (0.23 per 100 PY), but notably lower with rivaroxaban (0.09). However, GI bleeding was most frequent among rivaroxaban users (1.86 per 100 PY), followed by edoxaban (1.62) and apixaban (1.01). Other major bleeding events showed a similar pattern, with the highest incidence in rivaroxaban users (2.38), compared with edoxaban (2.05) and apixaban (1.93). Overall bleeding rates (all bleeding events) were highest with rivaroxaban (3.55), followed by edoxaban (3.47) and apixaban (3.05 per 100 PY).

ICH was more frequent with apixaban (0.24) and edoxaban (0.20) compared with rivaroxaban (0.04). SAH remained rare across all agents.

These findings highlight differences in the safety and effectiveness profiles of individual DOACs, with rivaroxaban generally associated with lower rates of

thromboembolic events but higher bleeding risk, particularly GI and major bleeding. Apixaban exhibited a more balanced profile with moderate risks across both thromboembolic and bleeding domains, while edoxaban showed a tendency toward higher stroke rates but comparable bleeding outcomes. Further details on the number of events and incidence rates by DOAC type are presented in **Table 7.7**.

Sensitivity analysis yielded incidence rate estimates that were consistent with those observed in the primary propensity score–matched analysis, with the same outcomes demonstrating higher incidence rates among switchers. This consistency suggests that the observed differences were robust to alternative cohort definitions and matching strategies.

Table 7.7: Number of events, person-time at risk, and incidence rates for the clinical outcomes in the switched group by DOAC type.

Outcome	Drug	N (14,004)	Events	Person-Time	Incidence Rate
All stroke	Apixaban	12,469	114	8377.7	1.360
	Edoxaban		91	6630.68	1.372
	Rivaroxaban		14	2159.15	0.648
Ischaemic Stroke	Apixaban	12,509	93	8408.81	1.105
	Edoxaban		80	6649.86	1.203
	Rivaroxaban		13	2165.81	0.600
Systemic embolism	Apixaban	13,829	13	9405.00	0.138
	Edoxaban		11	7331.06	0.150
	Rivaroxaban		<5	2281.51	0.088
PE	Apixaban	12691	24	8433.52	0.285
	Edoxaban		19	6972.85	0.272
	Rivaroxaban		<5	1986.95	0.201
TIA	Apixaban	13395	44	9084.09	0.484
	Edoxaban		18	7059.93	0.255
	Rivaroxaban		7	2275.15	0.308
MI	Apixaban	12712	79	8584.52	0.920
	Edoxaban		60	6770.60	0.886
	Rivaroxaban		19	2160.58	0.879
COMP1	Apixaban	12316	100	8246.90	1.212
	Edoxaban		88	6586.09	1.336
	Rivaroxaban		15	2114.79	0.709
COMP2	Apixaban	11787	135	7860.88	1.717
	Edoxaban		108	6307.17	1.712
	Rivaroxaban		20	2050.80	0.975
All bleed events	Apixaban	10613	217	7103.60	3.055
	Edoxaban		194	5588.52	3.471
	Rivaroxaban		64	1801.30	3.553
GI bleedings	Apixaban	12670	87	8571.60	1.015
	Edoxaban		108	6680.66	1.617
	Rivaroxaban		39	2099.66	1.857

Other major bleeding	Apixaban	11675	152	7879.44	1.929
	Edoxaban		126	6149.98	2.049
	Rivaroxaban		47	1977.59	2.377
Haemorrhagic stroke	Apixaban	13982	26	9549.59	0.272
	Edoxaban		17	7379.62	0.230
	Rivaroxaban		<5	2325.38	0.086
ICH	Apixaban	14000	23	9561.59	0.241
	Edoxaban		15	7387.95	0.203
	Rivaroxaban		<5	2334.81	0.043
SAH	Apixaban	14026	<5	9582.32	0.042
	Edoxaban		<5	7395.84	0.027
	Rivaroxaban		<5	2329.04	0.043
Death, cardiovascular	Apixaban	14004	647	9790.07	6.609
	Edoxaban		510	7542.97	6.761
	Rivaroxaban		152	2399.81	6.334
Death, all cause	Apixaban	14004	1199	9790.07	12.247
	Edoxaban		912	7542.97	12.091
	Rivaroxaban		272	2399.81	11.334

Incidence rates are expressed per 1,00 person-years, with person-time representing the total time at risk accrued during follow-up. Values shown as “<5” indicate suppressed counts due to small cell sizes in accordance with data governance requirements. **Abbreviations:** DOAC, direct oral anticoagulant; TIA, transient ischaemic attack; MI, myocardial infarction; PE, pulmonary embolism; ICH, intracranial haemorrhage; SAH, subarachnoid haemorrhage; GI, gastrointestinal. All strokes (including both ischaemic and haemorrhagic strokes), COMP1 denotes a composite endpoint comprising ischaemic stroke and systemic embolism, and COMP2 denotes a composite endpoint comprising all stroke, systemic embolism, and transient ischaemic attack. The composite safety endpoint “all bleed events” includes haemorrhagic stroke, gastrointestinal bleeding, and other major bleeding events

7.3.4. Time-to-event analyses: Kaplan–Meier estimates and adjusted hazard ratios

7.3.4.1. Clinical outcomes by treatment group

Table 7.8 presents adjusted hazard ratios for clinical outcomes comparing patients who switched from VKA to DOACs with those who remained on VKAs during follow-up.

Thromboembolic Outcomes

Patients who switched to DOACs demonstrated significantly increased risks of all strokes (HR 1.38; 95% CI 1.17–1.62; p = 0.00017), ischemic stroke (HR 1.67; 95% CI 1.38–2.02; p < 0.0001), and TIA (HR 1.67; 95% CI 1.21–2.32; p = 0.002) compared with those who remained on VKAs. Switching was also associated with increased risk of MI (HR 1.35; 95% CI 1.09–1.66; p = 0.0054). No statistically significant differences were observed for PE (HR 1.43; p = 0.062) or systemic embolism (HR 0.88; p = 0.600), although trends suggested possible increased PE risk among switchers.

Composite effectiveness outcomes

Switchers had an increased risk of composite events, including Comp1 (ischaemic stroke and systemic embolism; HR: 1.56; 95% CI: 1.30–1.86; p < 0.001) and Comp2 (all stroke, systemic embolism, and TIA; HR: 1.37; 95% CI: 1.18–1.60; p < 0.001).

Bleeding outcomes

The risk of haemorrhagic stroke was lower among switchers (HR 0.69; 95% CI 0.49–0.96; p = 0.030), as was ICH (HR 0.68; 95% CI 0.48–0.98; p = 0.037). No significant difference was observed for subarachnoid haemorrhage.

Although GIB hazard ratios were numerically higher among switchers, this did not reach statistical significance (HR 1.15; 95% CI 0.98–1.36; p = 0.090). No significant differences were observed for all bleeding or major bleeding events.

Cardiovascular and all-cause mortality

Mortality risk demonstrated clear time-dependent patterns. During the first 500 days of follow-up, no significant difference in cardiovascular death was observed between switchers and non-switchers (HR 0.95; 95% CI 0.87–1.04; p = 0.291). Between 500–900 days, CVD mortality risk increased among switchers, though this did not reach significance (HR 1.12; 95% CI 0.98–1.27; p = 0.095). Beyond 900 days, switchers experienced nearly double the risk of cardiovascular death (HR 1.98; 95% CI 1.57–2.48; p < 0.001).

A similar time-varying pattern was observed for all-cause mortality. No significant difference was detected during the first 500 days (HR 1.04; 95% CI 0.97–1.11; p = 0.279), but risk became significantly elevated during the 500–900-day interval (HR

1.16; 95% CI 1.05–1.27; p = 0.0031) and increased further beyond 900 days (HR 1.95; 95% CI 1.65–2.31; p < 0.001).

Table 7.8: HRs and p-values for clinical outcomes by treatment group (switched and control group) overall

	By treatment group (switched and control group)		
Outcome	**Time interval**	**HR (95% CI)**	**p-value**
All Stroke	Overall	1.378 (1.166–1.623)	**<0.001**
Ischaemic Stroke	Overall	1.67 (1.38–2.02)	**<0.001**
TIA	Overall	1.67 (1.21–2.32)	**0.0020**
MI	Overall	1.35 (1.09–1.66)	**0.0054**
PE	Overall	1.43 (0.98–2.09)	0.062
Systemic embolism	Overall	0.88 (0.55–1.42)	0.600
Comp1	Overall	1.56 (1.30–1.86)	**<0.001**
Comp2	Overall	1.37 (1.18–1.60)	**<0.001**
All bleed	Overall	0.87 (0.54–1.40)	0.572
Other major bleeding	Overall	1.12 (0.97–1.29)	0.109
GI bleeding	Overall	1.15 (0.98–1.36)	0.090
Haemorrhagac stroke	Overall	0.69 (0.49–0.96)	**0.030**
ICH	Overall	0.68 (0.48–0.98)	**0.037**
SAH	Overall	0.67 (0.26–1.70)	0.400
Death, cardiovascular	0–500 days	0.95 (0.87–1.04)	0.291
	500–900 days	1.12 (0.98–1.27)	0.095
	>900 days	1.98 (1.57–2.48)	**<0.001**
Death, all cause	0–500 days	1.04 (0.97–1.11)	0.279
	500–900 days	1.16 (1.05–1.27)	**0.0031**
	>900 days	1.95 (1.65–2.31)	**<0.001**

Hazard ratios (HRs) with 95% confidence intervals (CIs) compare patients who switched from vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs) with patients who continued VKA therapy (reference group). **Comp1** denotes a composite endpoint comprising ischaemic stroke and systemic embolism, and **Comp2** denotes a composite endpoint comprising all stroke, systemic embolism, and transient ischaemic attack. “All bleed” represents a composite safety endpoint including haemorrhagic stroke, gastrointestinal bleeding, intracranial haemorrhage, subarachnoid haemorrhage, and other major bleeding events. **Abbreviations:** HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack; MI, myocardial infarction; PE, pulmonary embolism; GI, gastrointestinal; ICH, intracranial haemorrhage; SAH, subarachnoid haemorrhage. **Note:** HRs not reported for certain time intervals due to low event counts or unstable estimates

7.3.4.1. Time-dependent hazard analysis using 90-day cut-off

Table 7.9 presents the time-dependent hazard ratios for clinical outcomes by treatment group (switched vs. continued VKA).

Thromboembolic Outcomes

For all stroke, the hazard was not significantly increased during the first 90 days post-switch (HR 1.08; 95% CI 0.71–1.66; p = 0.720) but became significantly elevated beyond 90 days (HR 1.44; 95% CI 1.20–1.72; p < 0.001). A similar pattern was observed for ischemic stroke, with the HR increasing from 1.55 (95% CI 0.95–2.53; p = 0.077) in the early period to 1.69 (95% CI 1.38–2.07; p < 0.001) after 90 days.

In contrast, TIA risk was elevated both in the short term (HR 3.13; 95% CI 1.02–9.61; p = 0.047) and beyond 90 days (HR 1.54; 95% CI 1.09–2.18; p = 0.013). Similarly, MI showed a non-significant increase within the first 90 days (HR 1.46; 95% CI 0.86–2.48; p = 0.156), with significant elevation thereafter (HR 1.33; 95% CI 1.06–1.68; p = 0.014).

Bleeding Outcomes

For hemorrhagic stroke, the protective effect of switching was concentrated in the first 90 days (HR 0.17; 95% CI 0.05–0.60; p = 0.005), with attenuation beyond 90 days (HR 0.82; 95% CI 0.57–1.16; p = 0.265), indicating that the overall association was driven primarily by early post-switch risk reduction. Other bleeding outcomes (GIB, all bleeding, and major bleeding) did not demonstrate statistically significant time-varying effects.

Composite Endpoints

Composite endpoints demonstrated time-varying patterns. For Comp1, the HR increased from 1.39 (95% CI 0.88–2.20; p = 0.157) within 90 days to 1.58 (95% CI 1.30–1.92; p < 0.001) thereafter. For Comp2, the HR rose from 1.22 (95% CI 0.81–1.83; p = 0.340) to 1.40 (95% CI 1.18–1.65; p < 0.001) after 90 days.

Mortality Outcomes

Mortality outcomes showed contrasting early effects. Switching was associated with significantly lower cardiovascular death risk within the first 90 days (HR 0.65; 95% CI 0.53–0.80; p < 0.001), which reversed beyond 90 days (HR 1.13; 95% CI 1.04–1.21; p = 0.0018). A similar pattern was observed for all-cause mortality, with

reduced early hazard (HR 0.79; 95% CI 0.67–0.92; p = 0.0031) followed by significant increase beyond 90 days (HR 1.19; 95% CI 1.12–1.25; p < 0.001).

Table 7.9: Time-dependent hazard ratios for clinical outcomes by treatment group (switched vs. continued VKA)

By treatment group (switched and control group)			
Outcome	**Time interval**	**HR (95% CI)**	**p-value**
All Stroke	0-90 days	1.08 (0.71–1.66)	0.720
	>90 days	1.44 (1.20–1.72)	**<0.001**
Ischemic Stroke	0-90 days	1.55 (0.95–2.53)	0.077
	>90 days	1.69 (1.38–2.07)	**<0.001**
TIA	0-90 days	3.13 (1.02–9.61)	**0.047**
	>90 days	1.54 (1.09–2.18)	**0.013**
MI	0-90 days	1.46 (0.86–2.48)	0.156
	>90 days	1.33 (1.06–1.68)	**0.014**
PE	0-90 days	1.19 (0.84–3.55)	0.754
	>90 days	1.47 (0.98–2.18)	0.060
Comp1	0-90 days	1.39 (0.88–2.20)	0.157
	>90 days	1.58 (1.30–1.92)	**<0.001**
Comp2	0-90 days	1.22 (0.81–1.83)	0.340
	>90 days	1.40 (1.18–1.65)	**<0.001**
All bleeding	0-90 days	1.17 (0.89–1.54)	0.250
	>90 days	1.06 (0.93–1.20)	0.367
GI bleeding	0-90 days	1.35 (0.89–2.05)	0.155
	>90 days	1.12 (0.93–1.34)	0.221
Other bleeding	0-90 days	1.37 (0.97–1.92)	0.072
	>90 days	1.08 (0.93–1.26)	0.308
Hemorrhagc stroke	0-90 days	0.17 (0.05–0.60)	**0.005**
	>90 days	0.82 (0.57–1.16)	0.265
Death, all cause	0-90 days	0.79 (0.67–0.92)	**0.0031**
	>90 days	1.19 (1.12–1.25)	**<0.001**
Death, cardiovascular	0-90 days	0.65 (0.53–0.80)	**<0.001**
	>90 days	1.13 (1.04–1.21)	**0.0018**

Note: Group (1: switchers, 0: non switchers)**.** HRs not reported for certain time intervals due to low event counts or unstable estimates. Systemic embolism, SAH and ICH were not done because of the low event number in the first 90 days. **Comp1** denotes a composite endpoint of ischaemic stroke and systemic embolism; **Comp2** denotes a composite endpoint of all stroke, systemic embolism, and transient ischaemic attack. All bleeding includes haemorrhagic stroke, gastrointestinal bleeding, and other major bleeding events. **Abbreviations:** HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack; MI, myocardial infarction; GI, gastrointestinal.

7.3.4.2. Comparative effectiveness by DOAC type (reference: apixaban)

Table 7.10 presents comparative effectiveness and safety outcomes for edoxaban and rivaroxaban relative to apixaban.

Thromboembolic Outcomes

Compared with apixaban, edoxaban showed no significant difference in all stroke risk (HR 1.02; 95% CI 0.77–1.35; p = 0.903), whereas rivaroxaban was associated with significantly lower risk (HR 0.53; 95% CI 0.31–0.93; p = 0.026). For ischemic stroke specifically, neither edoxaban (HR 1.11; 95% CI 0.82–1.51; p = 0.489) nor rivaroxaban (HR 0.60; 95% CI 0.34–1.08; p = 0.082) differed significantly from apixaban.

For TIA, edoxaban demonstrated significantly reduced risk compared with apixaban (HR 0.53; 95% CI 0.30–0.92; p = 0.025), while rivaroxaban showed no significant difference (HR 0.69; 95% CI 0.31–1.54; p = 0.362). Neither edoxaban (HR 1.15; 95% CI 0.51–2.58; p = 0.738) nor rivaroxaban (HR 0.60; 95% CI 0.14–2.69; p = 0.509) differed significantly from apixaban for systemic embolism.

Composite Outcomes

No statistically significant differences were observed for Comp1 when comparing either edoxaban or rivaroxaban with apixaban. For Comp2, edoxaban showed no difference (HR 1.00; 95% CI 0.77–1.29; p = 0.994), whereas rivaroxaban was associated with significantly lower hazard (HR 0.62; 95% CI 0.39–0.99; p = 0.047).

Bleeding Outcomes

Edoxaban did not differ significantly from apixaban for all bleeding (HR 1.12; 95% CI 0.92–1.36; p = 0.259), major bleeding (HR 1.06; 95% CI 0.83–1.35; p = 0.630), hemorrhagic stroke (HR 0.84; 95% CI 0.45–1.57; p = 0.591), or ICH (HR 0.86; 95% CI 0.44–1.66; p = 0.652). Rivaroxaban similarly showed no significant differences for these outcomes, although a non-significant trend toward higher other major bleeding risk was observed (HR 1.38; 95% CI 0.99–1.91; p = 0.058).

In contrast, both edoxaban (HR 1.55; 95% CI 1.16–2.06; p = 0.0027) and rivaroxaban (HR 1.91; 95% CI 1.31–2.80; p = 0.0009) were associated with significantly higher GI bleeding risk compared with apixaban.

Mortality Outcomes

No significant differences in CVD mortality were observed when comparing edoxaban (HR 1.09; 95% CI 0.97–1.23; p = 0.148) or rivaroxaban (HR 1.08; 95% CI 0.91–1.29; p = 0.386) with apixaban. Similarly, neither edoxaban nor rivaroxaban showed statistically significant differences in all-cause mortality compared with apixaban.

Table 7.10: Hazard ratios by approved DOAC name with apixaban as reference overall and across time intervals

By DOAC type (N=14,004)			
Outcome	**Comparator drug**	**HR (95% CI)**	**p-value**
All Stroke	Edoxaban	1.02 (0.77–1.35)	0.903
	Rivaroxaban	0.53 (0.31–0.93)	**0.026**
Ischaemic Stroke	Edoxaban	1.11 (0.82–1.51)	0.489
	Rivaroxaban	0.60 (0.34–1.08)	0.082
MI	Edoxaban	1.04 (0.74–1.46)	0.830
	Rivaroxaban	0.99 (0.60–1.65)	0.983
TIA	Edoxaban	0.53 (0.30–0.92)	**0.025**
	Rivaroxaban	0.69 (0.31–1.54)	0.362
PE	Edoxaban	1.02(0.56-1.89)	0.927
	Rivaroxaban	0.68(0.23-1.97)	0.478
Systemic embolism	Edoxaban	1.15 (0.51–2.58)	0.738
	Rivaroxaban	0.60 (0.14–2.69)	0.509
COMP1	Edoxaban	1.13 (0.84–1.51)	0.409
	Rivaroxaban	0.64 (0.37–1.10)	0.109
COMP2	Edoxaban	1.00 (0.77–1.29)	0.994
	Rivaroxaban	0.62 (0.39–0.99)	**0.047**
All bleed	Edoxaban	1.12 (0.92–1.36)	0.259
	Rivaroxaban	1.26 (0.95–1.67)	0.108
Other major bleeding	Edoxaban	1.06 (0.83–1.35)	0.630
	Rivaroxaban	1.38 (0.99–1.91)	0.058
GI bleeding	Edoxaban	1.55 (1.16–2.06)	**0.0027**
	Rivaroxaban	1.91 (1.31–2.80)	**<0.001**
Haemorrhagic Stroke	Edoxaban	0.84 (0.45–1.57)	0.591
	Rivaroxaban	0.36 (0.08–1.51)	0.162

ICH	Edoxaban	0.86 (0.44–1.66)	0.652
	Rivaroxaban	0.19 (0.03–1.44)	0.109
SAH	Edoxaban	Low numbers	
	Rivaroxaban	Low numbers	
Death, CVD	Edoxaban	1.09 (0.97–1.23)	0.148
	Rivaroxaban	1.08 (0.91–1.29)	0.386
All-cause mortality	Edoxaban	1.04 (0.96–1.14)	0.339
	Rivaroxaban	1.05 (0.92–1.20)	0.485

Note: HRs not reported for certain time intervals due to low event counts or unstable estimates. Composite endpoints were defined as follows: **Comp1** comprised ischaemic stroke and systemic embolism; **Comp2** comprised all stroke, systemic embolism, and transient ischaemic attack. **All bleed** represents a composite safety endpoint including haemorrhagic stroke, gastrointestinal bleeding, intracranial haemorrhage, subarachnoid haemorrhage, and other major bleeding events.
Abbreviations: DOAC, direct oral anticoagulant; HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack; MI, myocardial infarction; PE, pulmonary embolism; GI, gastrointestinal; ICH, intracranial haemorrhage; SAH, subarachnoid haemorrhage; CVD, cardiovascular disease.

7.3.4.3. Time-Stratified Comparison (<90 days vs >90 days)

When stratified by time since treatment switch (<90 days vs. >90 days), associations between DOAC type and clinical outcomes varied by outcome and agent **Table 7.11**. Time-varying analyses were performed only for outcomes with sufficient event counts to allow reliable estimation within each interval.

Thromboembolic Outcomes

For all stroke, edoxaban showed no statistically significant difference compared with apixaban in either time period. In contrast, rivaroxaban was associated with significantly lower risk beyond 90 days (HR 0.54; 95% CI 0.30–0.97; p = 0.039) but not within the first 90 days (HR 0.27; 95% CI 0.04–2.04; p = 0.205). For MI, neither edoxaban nor rivaroxaban differed significantly from apixaban in either time interval.

Bleeding Outcomes

No statistically significant differences in all bleeding events were observed for either DOAC in either period, although rivaroxaban demonstrated a non-significant trend toward increased risk beyond 90 days (HR 1.31; 95% CI 0.97–1.78; p = 0.082).

For GI bleeding, both edoxaban (HR 1.47; 95% CI 1.07–2.03; p = 0.018) and rivaroxaban (HR 1.95; 95% CI 1.29–2.94; p = 0.001) were associated with significantly increased risks after 90 days, but not within the initial 90 days.

Mortality Outcomes

Edoxaban was associated with significantly lower cardiovascular mortality during the first 90 days (HR 0.61; 95% CI 0.43–0.88; p = 0.008), with no significant association thereafter. A similar pattern emerged for all-cause mortality, with edoxaban showing reduced risk within the first 90 days (HR 0.72; 95% CI 0.56–0.94; p = 0.014) but no significant difference in the later period. Rivaroxaban showed no statistically significant differences in cardiovascular or all-cause mortality in either time interval.

Table 7.11: Time-dependent hazard ratios for clinical outcomes by approved DOAC name with apixaban as reference

By treatment group (switched and control group)				
Outcome	**Comparator drug**	**Time interval**	**HR (95% CI)**	**p-value**
All Stroke	Edoxaban	0-90 days	1.11 (0.58–2.11)	0.758
		>90 days	0.99 (0.73–1.36)	0.996
	Rivaroxaban	0-90 days	0.27 (0.04–2.04)	0.205
		>90 days	0.54 (0.30–0.97)	**0.039**
MI	Edoxaban	0-90 days	1.11 (0.54–2.28)	0.769
		>90 days	1.01 (0.69–1.49)	0.958
	Rivaroxaban	0-90 days	0.70 (0.16–3.08)	0.639
		>90 days	1.08 (0.63–1.84)	0.792
All bleeding	Edoxaban	0-90 days	1.08 (0.71–1.64)	0.720
		>90 days	1.13 (0.90–1.41)	0.288
	Rivaroxaban	0-90 days	1.07 (0.52–2.20)	0.855
		>90 days	1.31 (0.97–1.78)	0.082
GI bleeding	Edoxaban	0-90 days	1.76 (0.93–3.33)	0.081
		>90 days	1.47 (1.07–2.03)	**0.018**
	Rivaroxaban	0-90 days	1.67 (0.61–4.59)	0.322
		>90 days	1.95 (1.29–2.94)	**0.001**
Death, all cause	Edoxaban	0-90 days	0.72 (0.56–0.94)	**0.014**
		>90 days	1.08 (0.92–1.19)	0.103
	Rivaroxaban	0-90 days	1.05 (0.70–1.59)	0.807
		>90 days	1.07 (0.93–1.23)	0.340
Death, cardiovascular	Edoxaban	0-90 days	0.61 (0.43–0.88)	**0.008**
		>90 days	1.15 (0.87–1.31)	0.030

	Rivaroxaban	0-90 days	1.01 (0.58–1.75)	0.971
		>90 days	1.11 (0.92–1.34)	0.281

Note: Group (1: switchers, 0: non switchers)**.** HRs not reported for certain time intervals due to low event counts or unstable estimates. **Abbreviations:** HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; GI, gastrointestinal; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

7.3.5. Kaplan–Meier survival estimate

Survival probabilities at fixed time points are reported in **Appendix S.7.1.** Kaplan–Meier analyses (**Appendix S.7.2**) consistently showed that patients who switched from VKAs to DOACs had lower event-free survival compared with non-switchers across multiple outcomes, including stroke, TIA, MI, PE, bleeding events, and mortality. Switching was associated with higher risks of both thromboembolic and bleeding outcomes, as well as all-cause and cardiovascular mortality. When stratified by DOAC type, edoxaban generally demonstrated more favorable stroke-related outcomes, while apixaban was associated with a lower risk of bleeding, particularly gastrointestinal bleeding. However, differences between DOACs were inconsistent across outcomes and often modest or non-significant, indicating that while switching status was strongly associated with poorer outcomes, the choice of DOAC had a more limited and outcome-specific impact. Additionally, the relatively low number of events observed for some outcomes, particularly in comparisons between different DOACs, may have limited statistical power and contributed to uncertainty in the estimates**.**

7.4 Discussion

This large nationwide cohort study investigated the effectiveness and safety of switching from VKA to DOAC therapy in Scotland. Switching from VKAs to DOACs was associated with statistically significant higher risks of thromboembolic outcomes compared with continued VKA therapy, including all stroke (HR 1.38, 95% CI 1.17–1.62), ischaemic stroke (HR 1.67, 95% CI 1.38–2.02), TIA (HR 1.67, 95% CI 1.21–2.32), and MI (HR 1.35, 95% CI 1.09–1.66). Both composite thromboembolic endpoints were also significantly elevated among switchers. Conversely, switching was associated with a lower risk of haemorrhagic stroke (HR 0.69, 95% CI 0.49–0.96) and ICH (HR 0.68, 95% CI 0.48–0.98), consistent with the recognized safety benefit of DOACs regarding major intracranial bleeding. Switching from VKAs to DOACs was not associated with a statistically significant increase in GI bleeding risk. Although hazard ratios were consistently higher among switchers, the

magnitude of the association was modest and did not reach statistical significance (HR 1.15, 95% CI 0.98–1.36; p = 0.090).

When examining individual DOACs using apixaban as reference, rivaroxaban was associated with lower all stroke risk but higher GI bleeding risk. Edoxaban showed similar stroke and mortality risks as apixaban but carried higher GI bleeding risk. No significant differences were observed for MI, systemic embolism, or intracranial bleeding between agents.

Time-Dependent Effects

These findings demonstrate time-dependent effects. Using a Cox proportional hazards approach with time-split intervals, no significant increase was observed in the risk of ischaemic stroke, TIA, or all stroke during the initial 90 days following the switch (e.g., for ischaemic stroke, HR 1.55 [95% CI 0.95–2.53], p = 0.077). Similarly, there was no significant increase in MI risk during the early post-switch period, and bleeding outcomes including GI and intracranial bleeding were not significantly elevated. This absence of early risk may reflect several factors: the short-term clinical stability of patients at the time of switching, continuity of anticoagulant therapy with minimal treatment interruption, and the limited time window for cumulative effects of altered anticoagulant exposure to manifest.

However, elevated risks became evident with longer-term follow-up and persisted thereafter. The hazards of ischaemic stroke, TIA, and all stroke increased significantly after 90 days (e.g., HR for ischaemic stroke >90 days: 1.69 [95% CI 1.38–2.07], p < 0.001), suggesting that elevated risk manifests over a longer period rather than acutely. For MI, a statistically significant increase was also observed after 90 days (HR 1.33 [95% CI 1.06–1.68], p = 0.014).

For mortality outcomes, switching was associated with an initial protective effect within the first 90 days. However, after approximately 900 days (around 2.5 years), the risk increased substantially among patients who switched to DOACs, with hazard ratios of approximately 2.0 for both all-cause and cardiovascular mortality (HR 1.98 and HR 1.95, respectively).

The increased GI bleeding risk associated with rivaroxaban and edoxaban relative to apixaban became apparent only after 90 days of follow-up, rather than in the early period (<90 days). These findings differ from Norby et al. (2017), where elevated GI bleeding risk with rivaroxaban was most pronounced within the first 90 days (HR

2.31, 95% CI 1.71–3.11), with lesser but still elevated risk after 90 days (HR 1.33, 95% CI 1.10–1.62; p for interaction = 0.002) (304). However, Norby et al. compared rivaroxaban initiators with prior VKA exposure with warfarin users, whereas this analysis assessed rivaroxaban against apixaban, which may partly explain the different temporal patterns observed.

These findings highlight the need for long-term assessment of bleeding risk after switching anticoagulants and emphasize the importance of ongoing monitoring beyond the immediate post-switching interval, assessing time-varying hazards rather than cumulative effects alone.

Comparison with previous studies

Switching between OACs is relatively common, particularly from VKAs to DOACs, and treatment changes are associated with clinical events. A recent scoping review of eighteen studies comparing patients who switched from VKAs to DOACs with those who continued VKA therapy reported conflicting findings regarding the risks of ischaemic stroke/TIA/ systemic embolism and GI bleeding (266), with individual studies reporting higher, lower, or no difference in risk (266,304–311). However, among studies evaluating major bleeding, ICH, and MI in the overall switching population, several reported no significant difference in risk compared with continued VKA therapy, although definitions of bleeding outcomes varied across studies (266). This heterogeneity may reflect differences in patient selection, duration of follow-up, adjustment for confounding factors, clinical reasons for switching, such as suboptimal VKA control versus patient preference, and the specific DOAC initiated after switching.

Despite this variability, findings of the present study align closely with previous observational studies and meta-analyses. In particular, the meta-analysis by Hellfritzsch et al. (2020), which included eight cohort studies and conducted separate analyses for dabigatran and rivaroxaban, reported three key findings: an increased risk of arterial thromboembolism associated with switching to dabigatran but not rivaroxaban, an increased risk of GI bleeding following switching to either dabigatran or rivaroxaban, and a reduced risk of ICH among dabigatran switchers compared with continued VKA use (308).

The present study found that switching from VKA to DOAC therapy was associated with significantly increased risk of thromboembolic outcomes, including ischaemic

stroke and MI. The magnitude of risk observed for ischaemic stroke in the Scottish cohort (HR 1.67, 95% CI 1.38–2.02) closely aligned with the pooled estimate reported for dabigatran in the Hellfritzsch meta-analysis (RR 1.61, 95% CI 1.19–2.19) (308). Similarly, MI risk estimates were comparable between studies (previous studies: RR 1.29, 95% CI 1.10–1.52; present study: HR 1.35, 95% CI 1.09–1.66). Consistent with prior evidence, a significant reduction in ICH risk was also observed following switching, supporting the established intracranial safety advantage of DOACs over VKAs (meta-analysis RR 0.45, 95% CI 0.32–0.64 for dabigatran vs. this study HR 0.68, 95% CI 0.48–0.98) (308).

However, important differences were observed with respect to GI bleeding. In the Hellfritzsch meta-analysis, switching from VKA to dabigatran was associated with a significantly increased risk of GI bleeding (pooled RR 1.63, 95% CI 1.36–1.94), and a similar increase was observed for rivaroxaban (RR 1.55, 95% CI 1.32–1.83) (308). In contrast, when all DOACs were analysed together in the Scottish cohort, only a modest and non-significant increase in GI bleeding risk was observed (HR 1.15, 95% CI 0.98–1.36). This is likely reflecting the inclusion of all four DOACs as opposed to dabigatran alone or rivaroxaban alone, thereby diluting drug-specific risks observed in prior studies.

The drug-specific analyses in this study revealed that GI bleeding risk was significantly higher with rivaroxaban (HR 1.91 [1.31–2.80]) and edoxaban (HR 1.55 [1.16–2.06]) when compared with apixaban, supporting the presence of agent-specific rather than class-wide effects. These findings are consistent with Atreja et al. (2025), who found that apixaban was associated with significantly lower rates of stroke or systemic embolism and major bleeding compared with both dabigatran and rivaroxaban among patients who switched from warfarin (275). Thus, both this study and previous research highlight clinically relevant differences among DOACs following a switch from warfarin, with apixaban consistently demonstrating a more favourable safety and effectiveness profile compared to rivaroxaban, edoxaban, and dabigatran. This supports the need for individualized DOAC selection based on patient characteristics and risk profiles, especially for those at higher risk of bleeding or thromboembolic events.

Recent evidence from a nationwide Danish case-crossover study found that switching from VKA to DOACs in patients with AF was associated with significantly increased short-term (30-day) risks of ischaemic stroke, TIA, or systemic embolism

(OR 1.74, 95% CI 1.21–2.51), any bleeding (OR 1.42, 95% CI 1.13–1.79), GI bleeding (OR 1.72, 95% CI 1.24–2.40), and death (OR 1.81, 95% CI 1.56–2.09) (312), with no evidence of increased MI or intracranial bleeding. In contrast, this study found no significant increases during the early post-switch period, with risks becoming evident only with longer-term follow-up. These differences may likely reflect methodological distinctions between the study designs. The Danish study employed a case-crossover approach, including only patients who experienced an outcome and evaluating switching as a transient exposure during narrowly defined 30-day hazard windows. This design is particularly sensitive to detecting acute risk elevations and may capture clinical instability or treatment transitions occurring immediately prior to an event. In contrast, the present study used a time-to-event cohort design including all eligible patients, regardless of outcome status, and estimated hazard ratios over extended follow-up. Even in analyses restricted to the first 90 days, the exposure window in the present study was broader than the peri-switch period assessed in the case-crossover analysis. Consequently, the present study provides complementary evidence on cumulative and longer-term risks following switching, rather than isolated acute effects.

Contrasting findings have been reported by Bellin et al. (2019)., who found that patients who switched from VKA to DOAC had no significant difference in cardiovascular events or bleeding while still on VKA but experienced a significantly lower risk of both outcomes after switching compared to those who remained on VKA (HR ≈ 0.5, p-values 0.0255 and 0.0419) (313). However, the statistical significance was modest, the switched group was small (n = 239), outcomes were reported as composites, and the population included both new and prevalent users, which may limit the generalizability of the findings. The discrepancy with our results may reflect differences in study design, population characteristics, follow-up duration, and outcome definitions (313).

Study context and Generalizability

The present study differs from earlier research in both the study period and patient selection. Previous meta-analyses predominantly included studies conducted between 2011-2016, shortly after DOAC approval, with most focusing on dabigatran or rivaroxaban and having shorter follow-up periods. This study covered a more recent time period (2018–2021), during which all four DOACs were in routine use in Scotland, and spanned the COVID-19 pandemic, during which there was a

substantial increase in switching from VKA to DOACs, which transformed switching practices from selective clinical decision-making to broader healthcare delivery considerations (244). As a result, the switching group is likely to be more representative of the broader population of VKA-treated patients in routine clinical care, and the findings may therefore be more generalisable to current practice than earlier studies, which largely reflect more selectively switched populations.

Methodologically, this study focused on incident rather than recurrent events by excluding patients with prior outcomes, reducing bias from individuals at higher baseline risk. Many earlier studies did not distinguish whether outcomes occurred before or after switching (266,310). Furthermore, the Cox regression approach applied in this study reports adjusted hazard ratios rather than risk ratios, providing more detailed understanding of time-varying risks.

AF was highly prevalent across the cohort, including both patients who switched from VKAs to DOACs and those who continued VKA therapy, consistent with it being the primary indication for oral anticoagulation. However, observed proportions may underestimate the true prevalence of AF in this population, as AF diagnoses recorded exclusively in primary care were not captured in the available data. Previous studies have shown that a substantial proportion of patients with AF are diagnosed and managed solely in primary care settings (314,315). Consequently, the true proportion of patients with AF in this cohort is likely to have been higher than recorded.

Individual Risk Assessment and Patient Selection

It is also important to individualize risk assessment when considering a switch to DOACs, as specific populations may experience different outcomes. The FRAIL-AF trial showed that frail patients aged ≥75 years who were switched from warfarin to a DOAC had a significantly higher risk of bleeding complications, with a 69% increase compared with those who remained on warfarin (HR 1.69, 95% CI 1.23–2.32), and no reduction in thromboembolic events (HR 1.26, 95% CI 0.60–2.61) (309). This RCT was stopped early due to futility, indicating that in very elderly or frail patients with stable INR control, routine switching to DOACs may not provide benefit and could increase harm (309).

Evidence from the Netherlands suggests that switching from well-controlled VKA therapy to a DOAC may improve convenience and patient satisfaction, but may also

be associated with an increased risk of adverse effects (316). In addition, a small pilot RCT conducted in the Netherlands in 2019 found no significant differences between switching to a DOAC and continuing well-controlled VKA therapy among patients with AF in terms of stroke, major bleeding, MI, or all-cause mortality at one year of follow-up (317). However, this reflected a highly selected population with stable anticoagulation and was not powered to detect modest or longer-term differences. In contrast, the present study examined routine clinical practice, including patients with varying VKA control and comorbidity. Switching in real-world settings is frequently prompted by clinical instability, treatment dissatisfaction, or emerging risk factors, which may contribute to higher observed event rates.

These findings suggest that switching should primarily be considered for patients who are dissatisfied with VKA therapy, as they stand to benefit most from switching to a DOAC (316). The decision should be made collaboratively between physician and patient, carefully weighing potential benefits in quality of life and convenience against individual risk of adverse outcomes, with patient preference playing a key role in guiding anticoagulant selection. However, in routine clinical practice, and particularly in the context of large-scale service reorganization such as during the COVID-19 pandemic, switching decisions may also be influenced by system-level factors, including efforts to reduce face-to-face monitoring and healthcare utilization. Such factors are not fully captured in administrative data. As a result, the extent to which individual patient preferences and shared decision-making informed switching in this cohort cannot be directly assessed.

Switching as a Risk Factor

Previous studies have also reported that any switch between OACs, whether from VKA to DOAC or vice versa, may be associated with an increased risk of adverse clinical outcomes. For example, Holbrook et al. (2020) found that switchers had a significantly higher risk of stroke and systemic embolism (adjusted RR 2.24, 95% CI 1.46–3.45), major bleeding (RR 1.41, 95% CI 1.04–1.91), and net clinical harm (RR 1.54, 95% CI 1.29–1.85) compared with non-switchers, though the timing of events relative to switching was not specified (310). This is consistent with clinical concerns that the peri-switching period represents a vulnerable phase.

Several mechanisms may explain this association. For example, switching may occur in response to clinical instability, suboptimal anticoagulation control, or prior adverse events in a subset of patients, which could indicate a higher underlying

baseline risk among switchers (310). Second, the peri-switching period may involve transient anticoagulation instability due to incomplete overlap, dosing errors, or variability in anticoagulant effect. Finally, switching may temporarily affect adherence as patients adjust to new regimens. It remains challenging to disentangle whether adverse outcomes are driven by the switch itself or the underlying clinical context in which switching occurs (310).

Recent evidence from a population-based cohort study in Catalonia found that among patients who initiated DOAC therapy, switching between different DOACs during follow-up was associated with an increased risk of all strokes, cerebral haemorrhage, and GI haemorrhage (318). The study notes that the reasons underlying treatment switches may contribute to these elevated risks, and highlight that maintaining adherence to DOAC therapy and avoiding switches may help reduce the risk of stroke and cerebral haemorrhage (318).

Potential Role of DOAC Dosing

Inappropriate DOAC dosing in clinical practice may also contribute to the observed excess thromboembolic risk following switching. Real-world evidence suggests that approximately one in five patients receive off-label DOAC doses (319,320), with underdosing being most common (20%) (321). Off-label underdosing has been consistently associated with increased risks of stroke, systemic embolism, and all-cause mortality compared with per-label dosing (322–324), while paradoxically, overdosing has also been linked to increased thromboembolic events in addition to bleeding (324). Furthermore, a large Swedish cohort study comparing DOACs with warfarin in routine care, subgroup and exploratory analyses demonstrated similar effectiveness and safety outcomes in high-risk patients aged 80 years and above. The advantages of DOAC treatment appeared most pronounced with standard dosing in patients under 80 years of age, and with dose reduction in older patients (325). Elderly patients with multiple comorbidities, who are likely overrepresented in switching groups, are at particularly high risk of inappropriate dosing (319). UK evidence indicates that edoxaban has the highest rate of per-label dosing (84.7%), followed by apixaban (82.2%). In contrast, dabigatran and rivaroxaban were associated with higher rates of inappropriate dosing, with underdosing observed in 16.8% of dabigatran users and overdosing in 9.6% of rivaroxaban users (320). Variation in dosing accuracy across DOACs may partially explain differential

outcomes observed in this study, particularly among patients switched during periods of reduced clinical monitoring, such as the COVID-19 pandemic.

Although inappropriate DOAC dosing represents a plausible mechanism linking switching to adverse outcomes, dosing appropriateness could not be reliably assessed in the present study. While prescription dose was available, classification according to product labelling was not feasible because key determinants required for dose assessment, most notably body weight, which was unavailable, and renal function, which was only available for a subset of patients and not consistently measured at the time of switching, could not be fully ascertained for the entire cohort. In addition, treatment indication could not be reliably determined for all patients.

Role of adherence

Adherence to anticoagulant therapy is a well-recognized determinant of clinical outcomes in patients with AF (326). While DOACs are often assumed to improve adherence due to their fixed dosing and lack of regular INR monitoring, recent research has shown that non-adherence remains common (327). In UK primary care, one-year adherence to OAC was 65.9% overall, with lower adherence among VKA users (51.2%) compared with DOAC users: dabigatran (66.5%), rivaroxaban (63.1%), and apixaban (64.7%) (327). Although adherence was consistently better with DOACs than VKAs, non-adherence and discontinuation remained common and increased over time. Long-term Swedish cohort evidence further highlights the clinical importance of adherence and persistence. Among AF patients initiating DOAC treatment, persistence declined gradually over time, though adherence among persistent users remained high. Both non-persistence and poor adherence were independently associated with increased stroke risk (328).

In the cohort included in this study, many patients had been stable and well-controlled on VKA for years before switching. Changes in medication routines, reduced healthcare contact (particularly during the COVID-19 pandemic), or insufficient education about DOACs may have affected post-switch adherence. Although a study from England conducted during the COVID-19 pandemic showed that telephone follow-up could maintain good persistence after switching (271), whether such improvements translate to Scottish healthcare or other routine settings remains unclear. Additionally, patients' adherence beliefs are shaped by multiple factors, including their interaction with clinicians (271). Prior research shows that

switching from warfarin to a DOAC can trigger early changes in treatment beliefs and quality of life, shifting towards patterns predictive of improved adherence. Whether such improvements are sustained when switching occurs remotely, and what long-term adherence rates are, remains uncertain (271).

Switching patients with pre-existing adherence challenges to anticoagulant regimens requiring less monitoring may not address underlying adherence issues and may reduce opportunities to identify ongoing non-adherence. UK evidence suggests that among patients who switch from VKA to DOAC therapy, a substantial proportion subsequently demonstrate suboptimal adherence during the first treatment year, (23–39%), often linked to modifiable health beliefs at the time of switching (329).

Importantly, this does not imply that switching itself causes non-adherence, but rather that adherence difficulties may persist or emerge in the absence of regular monitoring. Poor adherence or DOAC interruptions, regardless of the specific agent used, are associated with increased risks of stroke and bleeding (330), while good adherence is associated with reduced risks of stroke and intracranial bleeding (318,326). Accordingly, the findings of the present study should be interpreted in the context of the well-established influence of adherence on anticoagulation outcomes.

Clinical Decision-Making for Switching

For patients already established on warfarin, criteria guiding the decision to switch to a DOAC are not always clearly defined. Several professional societies recommend considering switching when time in therapeutic range (TTR) falls below specific thresholds (70% per ESC, 65% per American College of Chest Physicians, 58% per American College of Cardiology), but the extent these recommendations are followed in practice remains unclear (307).

In clinical practice, many patients are switched to DOACs for different reasons, such as patient preference, ease of use, presence of comorbidities, or to reduce the need for frequent INR monitoring, particularly during situations like the COVID-19 pandemic. Consequently, switching decisions are often influenced by a combination of clinical, practical, and patient-centered factors, rather than suboptimal TTR alone. One study analyzed outcomes in patients with NVAF who switched from warfarin to a DOAC, comparing their rates of major bleeding and ischaemic stroke before and after switching, stratifying by TTR thresholds based on guideline recommendations (307). The results suggested that major bleeding rates were not reduced, and

sometimes increased, after switching to a DOAC, with no significant difference in ischaemic stroke rates before versus after switching across all TTR subgroups, and that commonly cited TTR thresholds may not effectively identify patients who might benefit from switching (307). Thus, patients with poor anticoagulation control on warfarin due to adherence issues may continue to face similar challenges after switching to a DOAC.

Strengths and limitations of this study

This study has several important strengths. It is a national-level cohort study using real-world data that reflects current clinical practice. Patients with prior outcome events were excluded from each outcome-specific analysis to reduce bias, and propensity score matching was applied to improve balance between treatment groups. Furthermore, comprehensive adjustment for a wide range of comorbidities and risk factors was performed, along with detailed time-varying analyses, which revealed clinically important differences in both early and late post-switch outcomes.

Nevertheless, this study has several limitations that should be acknowledged. Owing to its observational design, the analysis provides real-world evidence but cannot establish causality. Residual confounding may also persist despite extensive adjustment for measured patient characteristics. In particular, patients who switch from VKAs to DOACs may represent a clinically distinct group, for example those with unstable anticoagulation control, prior complications, or increased clinical complexity, introducing confounding by indication that may not be fully captured in the adjustment model.

In addition, the study did not employ a within-person before–after design to compare outcomes before and after switching anticoagulant therapy; therefore, unmeasured time-invariant patient characteristics may not have been fully controlled, and residual confounding cannot be excluded. However, the matched comparator design more effectively addresses confounding by indication, accounts for changes in patients' risk profiles over time, and controls for secular trends, including the substantial healthcare disruptions during the COVID-19 period.

Uncertainty in the definition and timing of treatment exposure may also introduce bias. In particular, the assignment of index dates and the handling of treatment switching may result in differences in follow-up time between groups, potentially leading to exposure misclassification or time-related biases. Although matching was

performed on VKA start date and duration of use to improve temporal alignment, differences in how follow-up time accrued between switchers and non-switchers cannot be entirely excluded.

The higher complication rates observed among patients who switched to DOACs should therefore be interpreted with caution. Although transient risks during the early post-switch period, such as dosing changes or treatment interruptions, may be expected, time-varying analyses did not demonstrate a higher risk within the first 90 days after switching. However, the relatively low number of events during this period may have limited the ability to detect short-term differences. Overall, the findings suggest that the observed differences are more likely to reflect underlying clinical characteristics or risk profiles that prompted switching, rather than a direct effect of DOAC therapy itself.

Furthermore, the primary analysis pooled all DOACs versus VKA. While this approach highlighted overall class effects, it may have diluted drug-specific risks. Analyses of individual DOAC agents may also be subject to limited statistical power and channelling bias, whereby specific agents are preferentially prescribed to patients with particular clinical characteristics.

Sensitivity analyses applying alternative switching definitions were not conducted for this outcome; although alternative switching definitions were explored in earlier chapters for different outcomes and showed consistent results, the impact of alternative gap definitions on the findings of the present analysis cannot be fully excluded; Any resulting exposure misclassification would most likely be non-differential and therefore unlikely to substantially alter the direction of the observed associations.

NSAID and antiplatelet use were assessed only at baseline using prescriptions in the six months prior to the index date; changes in use during follow-up were not captured, which may have resulted in some exposure misclassification.

7.5 Conclusion

This nationwide cohort study demonstrates that patients who switched from VKAs to DOACs experienced higher rates of ischaemic and thromboembolic events, including stroke, MI, and mortality, although with a clear reduction in ICH and haemorrhagic stroke. Importantly, these excess thromboembolic risks were not

confined to the early post-switch period but became more apparent during longer follow-up, particularly beyond 90 days and up to one year.

Outcomes differed across individual DOACs. Compared with apixaban, rivaroxaban was associated with lower thromboembolic risk but higher GIB risk, while edoxaban showed similar stroke and mortality risks but increased GIB. Overall, apixaban demonstrated the most favorable balance between effectiveness and safety, driven by lower GIB risk without an increase in thromboembolic events.

Overall, these findings suggest that patients who are stable on warfarin may not derive additional stroke-prevention benefit from switching to a DOAC, and that the choice of DOAC plays an important role in determining long-term outcomes. Decisions to switch should therefore be individualized, taking into account patient-specific factors including age, frailty, comorbidities, quality of anticoagulation control, and patient preference. Balancing thromboembolic protection against bleeding risk, while prioritizing patient-specific factors, preferences, and the well-recognized safety advantage of reduced intracranial bleeding with DOACs. Careful patient selection, shared decision-making, comprehensive patient education and close follow-up remain essential to optimize outcomes after any change in anticoagulation therapy.

8 Chapter 8: Influence of renal impairment on oral anticoagulant prescribing patterns among incident OAC users in Scotland

8.1 Introduction

Patients with CKD are at increased risk of developing both AF and VTE (235,331). The prevalence of AF increases with worsening renal function, with end-stage renal disease patients exhibiting prevalence rates of 13-23% (332). Comparable prevalence has been observed in non-dialysis CKD populations (332), compared with approximately 1–8% (depending on age) in the general population without renal disease (333–335). Additionally, data derived from registries, meta-analyses, and observational studies suggest that between 30% and 60% of individuals with AF have mild to moderate renal insufficiency, corresponding to an estimated glomerular filtration rate (eGFR) of 30–89 mL/min (336). Consequently, DOAC utilisation in patients with CKD is substantial and continues to increase (332).

The involvement of renal clearance in DOAC metabolism varies considerably among agents (**Table 8.1**). Dabigatran exhibits the highest degree of renal elimination, while apixaban and rivaroxaban are less dependent on renal clearance. In contrast, warfarin undergoes hepatic metabolism with minimal renal elimination, making its pharmacokinetics largely independent of renal function. Although elimination half-lives are broadly comparable across DOACs under normal renal function (**Table 8.1**), declining kidney function leads to prolongation of half-life and increased drug exposure, particularly for agents with higher renal clearance. These pharmacokinetic differences result in increased DOAC exposure in patients with renal impairment, necessitating appropriate dose adjustments according to renal function (336,337).

Table 8.1: Renal elimination and elimination half-life of DOACs and warfarin under normal renal function (49,175,336).

Drug	Renal elimination (%)	Elimination half-life (hours)	Dosing by renal impairment
Dabigatran	~85%	12–17	110 mg twice daily
Edoxaban	~50%	8–11	30 mg once daily
Rivaroxaban	~33%	11–13 (elderly); 5–9 (healthy)	15 mg once daily
Apixaban	~27%	~12	2.5 mg twice daily
Warfarin	<1%	~20-60	Dose adjusted to INR (no renal dose adjustment)

Note: Doses shown reflect recommended dose adjustments for patients with creatinine clearance ≥15 mL/min, based on approved product characteristics and guideline recommendations. DOACs are generally not licensed for use in patients with creatinine clearance <15 mL/min or those undergoing dialysis, and dabigatran is contraindicated in creatinine clearance <30 mL/min. Warfarin undergoes hepatic metabolism and is dosed according to INR, independent of renal function.

Robust evidence supports the safety and efficacy of DOACs compared to warfarin in patients with mild to moderate renal impairment, with DOACs significantly reducing stroke and systemic embolism risk by 22% and major bleeding risk by 17% in all patients with CKD (171,338), consistent with outcomes observed in patients without CKD in major DOAC trials (85–88). ESC and NICE guidelines recommend DOAC use in patients with mild to moderate renal impairment (creatinine clearance ≥30 mL/min), with appropriate dosage adjustments based on indication, as summarised in **Table 8.1** (5,339).

Given the exclusion of patients with severe CKD, typically defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², from major RCTs, evidence to guide anticoagulation in this population remains limited and recommendations are more complex. Both ESC and NICE guidelines recommend cautious use of DOACs at reduced doses in patients with advanced CKD, contraindicate dabigatran, and provide limited or restricted recommendations for DOAC use in individuals with creatinine clearance ≤15 mL/min or those receiving dialysis (5,339).

Patients with end-stage renal disease (ESRD) and AF face heightened stroke risk due to vascular comorbidities, alongside an increased bleeding risk related to uraemic platelet dysfunction (340). Anticoagulants therapy may increase bleeding risk up to tenfold in ESRD patients compared to those without CKD (340). Nevertheless, a recent metanalysis suggests that DOACs may offer superior safety and efficacy profiles compared to warfarin in patients with advanced CKD, with apixaban increasingly favoured as the preferred option due to its lower dependence on renal clearance (173).

Understanding how these clinical considerations translate into real-world prescribing patterns across different stages of renal impairment is therefore crucial for optimising anticoagulation therapy. Given the rapidly evolving evidence base, expanding availability of OACs, and ongoing updates to clinical guidelines, there is a need to evaluate how anticoagulant uptake has evolved over time among patients with different stages of renal impairment.

8.1.1. Study aims and objectives

This study aimed to investigate renal function and OAC prescribing patterns among incident users in Scotland between 2011 and 2020, using routinely collected laboratory and prescribing data. Renal function was categorised according to the

Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (341,342).

The specific objectives were:

- To examine temporal trends in OAC initiation among incident users with documented kidney function assessments, comparing the choice between VKAs and DOACs, across stages of renal impairment classified by eGFR.
- To describe the prescribing trends of individual DOAC agents among patients with varying levels of renal function.

8.2 Methods

8.2.1. Study design

The study was a retrospective cohort study, including patients who had at least one recorded renal function test (serum creatinine, estimated GFR, or creatinine clearance) between 2010 and 2020, and who initiated OAC therapy (warfarin, dabigatran, rivaroxaban, edoxaban, or apixaban) between January 2011 and December 2020.

DOAC-specific prescribing trends were restricted to the period from 2013 to 2020. Data from the year 2011 and 2012 were excluded from drug-specific analyses because of the small number of initiators for certain DOAC agents. Additionally, dabigatran was excluded from DOAC-specific analyses due to low patient numbers.

Inclusion criteria required patients to be incident OAC users, defined as patients receiving their first OAC prescription during the study period. The year 2010 was included as a lookback period to ensure that patients were free from OAC use prior to 2011, allowing identification of new (incident) users starting from January 2011. Kidney function was assessed using the most recent eGFR measurement prior to treatment initiation, and patients were required to have at least one renal function test recorded within 6 months (180 days) preceding the initial OAC prescription date. Patients were included regardless of the clinical indication for OAC therapy.

A sensitivity analysis was conducted using a shorter window of 60 days to ensure that renal function measurements were recent and reflective of kidney function at the time of OAC initiation, and to assess the robustness of the inclusion criterion requiring a renal function measurement within 6 months prior to OAC initiation.

Study population and cohort selection

After exclusion of observations with invalid or missing renal function results, 142 of 146,457 patients were excluded, resulting in a final analytical cohort of 146,315 patients with valid renal function data. Given the focus on incident users, only patients with at least one renal function test recorded on or before the index OAC prescription date were included in the analysis.

Figure 8.1 illustrates the cohort selection process for incident OAC users with available renal function tests, including application of inclusion and exclusion criteria.

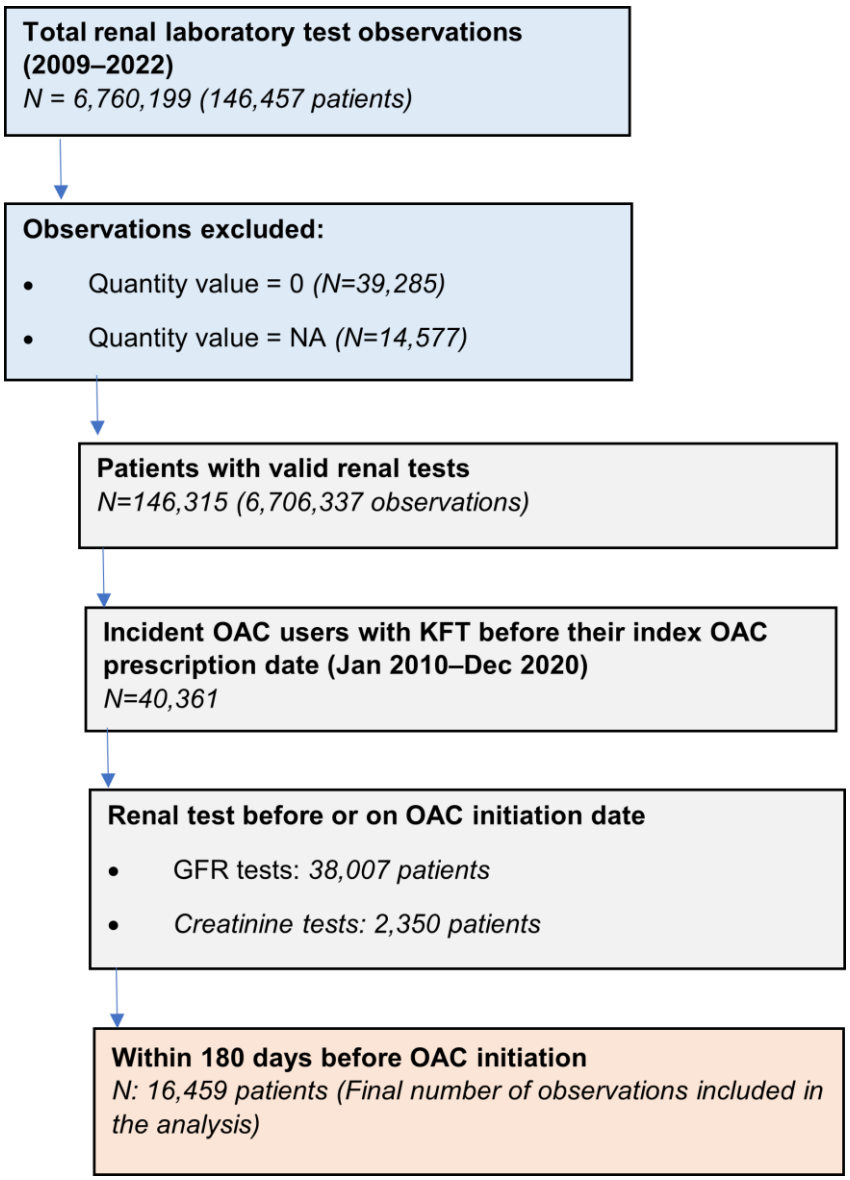

Figure 8.1: Flow diagram of cohort selection for incident OAC users with renal function tests available before initiation (2011–2020)

8.2.2. Data sources and preparation

Five laboratory datasets from the Scottish Care Information (SCI) system were used, covering distinct time periods (2009–2011, 2012–2014, 2015–2016, 2017–2021, and 2020–2022). These datasets were provided as separate extracts by the Safe Haven and were combined for analysis to create a single longitudinal laboratory dataset spanning the full study period. Patient identifiers were standardised by removing prefixes and converting all identifiers into a uniform format to enable linkage across datasets.

Laboratory data were available for patients within NHS Greater Glasgow and Clyde (GGC) health board and therefore represent a regional population rather than the whole of Scotland.

Each dataset originally contained 17 variables (**Appendix S.8.1**), from which a subset relevant to renal function analyses was retained (**Table 8.2**).

Table 8.2: Selected columns included in the analysis

Column Names	Description	
ID	Unique patient identifier	
sample date /time	Date & time when the sample was collected	
report date/ time	Date & time when the test result was reported	
CLINICALCODEVALUELOCAL	Standardized test code	"CREA", "EGFR"
CLINICALCODEDESCRIPTIONLOCAL	Description of the test used in the local lab system	"Creatinine", "Estimated GFR (/1.73m^2)"
QUANTITYVALUE	Measured test result value	
QUANTITYUNIT	Unit of measurement for the test result	"umol/L", "mL/min"
RANGEHIGHVALUE	Upper reference range for the test	
RANGELOWVALUE	Lower reference range for the test	
CLINICALCODEDESCRIPTION	Formal test description	

Abbreviations: CREA = serum creatinine; GFR = glomerular filtration rate; NA = not available. Note: Example laboratory codes and units are shown and do not represent an exhaustive list of all possible laboratory codes or descriptions. The reported reference ranges are the ranges as applied in the health board from where the data originated at the time of data extraction.

Laboratory test selection and data cleaning

Sample dates were extracted from combined sample date/time variable, and both sample and report date/time variables were converted from character to date-time formats. The Quantity value was converted to numeric format.

To ensure relevant laboratory results were included, tests measuring kidney function were selected from each dataset. Specifically, only tests measuring serum

creatinine (CREA), estimated glomerular filtration rate (eGFR), and creatinine clearance (CCL) were retained. These tests were identified using both standardized test codes (CLINICALCODEVALUELOCAL: “EGFR”, “CREA”, “CCL”) and descriptive test names (CLINICALCODEDESCRIPTIONLOCAL: “Creatinine”, “Estimated GFR (/1.73m²)”, “Estimated GFR”, “Creatinine clearance”).

Following the selection of relevant tests, cleaned datasets for all years (2009–2022) were combined into a single dataset. Records were ordered by patient identifier and sample date/time. Observations with invalid or missing values (e.g., QUANTITYVALUE = 0 or NA) were excluded, while valid results for the same patients were retained. Additionally, a review of the dataset showed that for most invalid results (Quantity value= 0), an alternative valid renal function test was recorded on the same or subsequent day.

Kidney function measurements and GFR standardization

Kidney function was assessed using eGFR as the primary measure. Where eGFR was not directly available, values were derived from serum creatinine. A summary of the standardization procedures applied to GFR, and creatinine results is shown in **Figure 8.2.**

Final GFR values were categorized according to CKD staging into four groups: eGFR ≥60 mL/min (normal or mildly impaired kidney function), 30–59 mL/min (moderately impaired), 15–29 mL/min (severely impaired), and <15 mL/min (kidney failure). All stages of renal impairment were included, including patients with ESRD defined as eGFR <15 mL/min. These categories were used in subsequent analyses to evaluate the relationship between renal function and OAC prescribing choice.

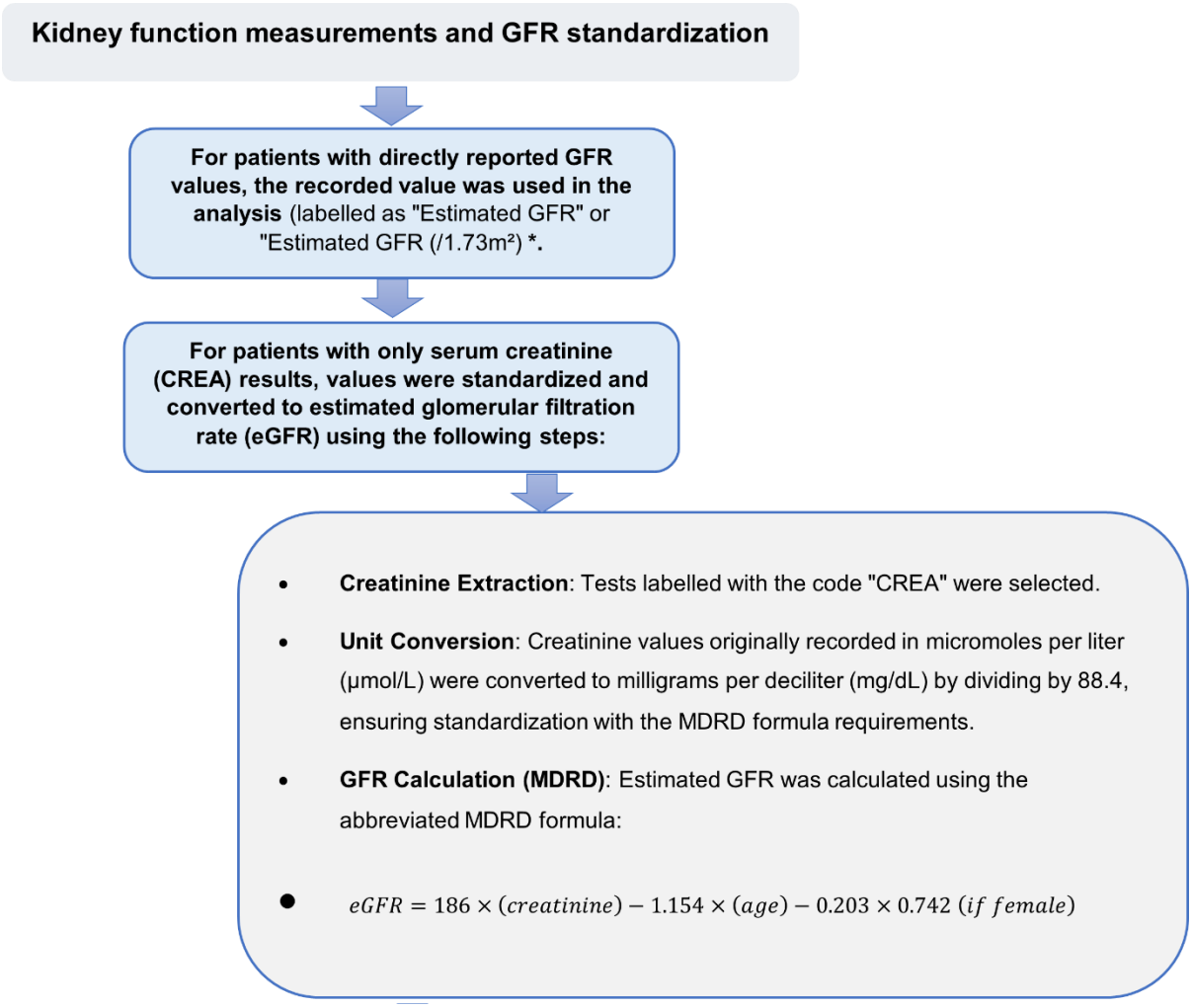

Figure 8.2: Standardization of renal function measurements (flow of data handling for directly reported GFR, and conversion of serum creatinine to estimated GFR).

Note: these values may have been calculated using either the CKD-EPI or MDRD equation, in line with local clinical practices, although the specific formula was not always explicitly reported. For tests labelled "GFR calculated abbreviated MDRD," the eGFR values were known to have been derived using the abbreviated MDRD formula and were used directly.

To identify renal test results within 6 months prior to the first OAC prescription, the following procedures were employed:

Data merging & filtering	The renal function dataset was merged with OAC prescribing records using patient ID (Incident OAC user cohort) .
	Only patients with renal function tests recorded on or prior to their initial OAC prescription date were included.
	The primary analysis used a ≤180-day window between the renal test and OAC initiation; a sensitivity analysis with a ≤60-day window assessed robustness

Duplicate removal & selection of most relevant test	All duplicates were removed.
	For each patient, the latest available renal function test prior to or on the OAC initiation date was selected.
Handling multiple results for the same test on the same day	If the patient had more than one sample collected on this date for creatinine and for GFR, the results of the GFR test was used.
	In cases of multiple results for the same test on the same day, the test result with the latest report date was selected. If the report dates were identical, the test with the latest sample time was retained. This approach ensured that each included patient had a single, most recent, and clinically relevant renal function measurement prior to OAC initiation.

This method ensured the inclusion of one clinically relevant renal function measurement per patient, reflecting the most recent renal status before OAC initiation.

Of the total incident OAC user cohort, the number of patients according to the timing of their most recent renal laboratory test prior to OAC initiation was examined, categorizing them into intervals of within 30, 60, 90, 120, and 180 days (**Table 8.3**).

Based on patient numbers across these intervals, a 180-day window was selected for the primary analysis to maximise cohort inclusion while maintaining clinical relevance of renal function at treatment initiation.

Table 8.3: Number of patients with renal function test within specified time windows prior to first OAC prescription

Days between last renal function test and first OAC prescription	Unique patients
≤ 180 days	16,459
≤ 120 days	13,206
≤ 90 days	11,101
≤ 60 days	8,559
≤ 30 days	5,321

Identification of renal disease using ICD-10 codes

Renal disease diagnoses were identified using ICD-10 codes recorded in secondary care hospital admission data. All hospital admissions occurring prior to a patient's first prescription of an OAC were reviewed. A patient was classified as having renal disease (assigned a value of 1) if at least one admission contained a renal disease diagnosis code from a predefined ICD-10 code list (I12, I13, N00 – N05, N07, N11, N14, N17 – N19, Q61). This approach aimed to maximize the capture of relevant renal disease diagnoses prior to OAC initiation. Patients without any documented renal disease codes across their admissions were classified as not having renal disease (assigned a value of 0).

8.2.3. Baseline characteristics

Baseline characteristics, including age at prescription, sex, renal function stage, and key comorbidities (e.g., CHF, HTN, DM, stroke, vascular disease, and liver disease) as well as CHA_2DS_2-VASc and HAS-BLED scores, were assessed at the time of OAC initiation.

Comorbidities were identified using diagnosis codes recorded in any prior hospital admission available in the dataset before the index OAC prescription date. As comorbidities were included as baseline characteristics rather than as outcomes, all available hospital admission data prior to OAC initiation were used to maximise ascertainment. Antiplatelet and NSAID use was assessed during the 6 months preceding the first OAC prescription.

8.2.4. Statistical analysis

Baseline characteristics were summarised descriptively. Categorical variables were reported as counts and percentages, and continuous variables as means with standard deviations.

The total number of incident OAC initiations was calculated by renal function category to examine prescribing pattern changes over time. For each calendar year from 2011 to 2020, the proportion of patients initiating DOAC or VKA was stratified by renal impairment stage. This was calculated by dividing the number of incident users initiating a specific OAC type by the total number of patients initiating any OAC within the same renal impairment stage, expressed as percentages.

Proportions of incident OAC initiations were also calculated by individual DOAC (approved name) from 2013 to 2020, reflecting the period when multiple DOACs

were available in clinical practice. Specifically, for each calendar year and renal function category, the proportion initiating each DOAC was calculated as the number of patients initiating a given DOAC divided by the total number of patients initiating any DOAC within that renal function category.

Analyses were first performed using the primary 180-day cohort described above and then repeated using the 60-day cohort as a sensitivity analysis. All analyses were descriptive and conducted using R (version 4.5.1).

To evaluate differences in the distribution of incident OAC initiations between DOACs and VKAs across renal function levels, annual cross-tabulations of GFR category and OAC type were performed from 2011 to 2020. Chi-squared or Fisher's exact tests were used to assess whether the distribution of DOAC versus VKA initiation differed across eGFR strata. Pairwise comparisons were conducted between selected eGFR categories (<15 vs ≥60, 15–29 vs ≥60, 30–59 vs ≥60, and 15–29 vs 30–59 mL/min) to identify specific differences in the annual distribution of incident DOAC and VKA initiations. Pearson's chi-squared test was used when expected cell counts were ≥5, and Fisher's exact test when any expected cell count was <5.

8.3 Results

8.3.1. General cohort description/baseline

A total of 16,459 incident OAC users with renal function testing within 180 days prior to treatment initiation were included in the study. Of these, 57.4% (n = 9,443) initiated a DOAC, while 42.6% (n = 7,016) initiated a VKA. The mean age at initiation was slightly higher among DOAC users compared with VKA users, and females accounted for approximately half of the cohort (48%).

Baseline demographic and clinical characteristics of the cohort are summarised in **Table 8.4**, while renal function at OAC initiation, the primary exposure of interest in this chapter, is presented separately in **Table 8.5**.

Comorbidities were common, including HTN, DM, and cardiovascular disease, with broadly similar distributions between DOAC and VKA users. AF was identified in hospital records for just over one-third of patients. AF prevalence was higher among users of certain DOACs, particularly apixaban and edoxaban. A history of prior stroke was reported in 9.9% of patients.

The mean CHA_2DS_2-VASc score was 2.65 across the cohort, with a similar distribution between DOAC and VKA users. Approximately 18.3% of patients had a score ≥2. The mean HAS-BLED score was slightly higher in edoxaban and apixaban users, while lower in dabigatran users. Bleeding history was reported in 15.7% of patients, and 19.1% had a history of DVT or PE. Hip or knee replacement was more frequent in DOAC users compared to those on VKAs.

Table 8.4: Baseline characteristics of incident oral anticoagulant users

				Individual DOAC			
Variable	**Overall**	**DOAC**	**VKA**	**Apixaban**	**Edoxaban**	**Rivaroxaban**	**Warfarin**
N	16459	9443	7016	4533	1256	3470	7001
Female, n (%)	7752 (47.1)	4537 (48.0)	3215 (45.8)	2125 (46.9)	595 (47.4)	1749 (50.4)	3210 (45.9)
Age, mean (SD)	69.51 (14.22)	69.98 (14.37)	68.89 (14.01)	71.09 (13.48)	73.72 (10.96)	67.10 (16.03)	68.90 (14.01)
Clinical comorbidities, n (%)							
CHF	1789 (10.9)	950 (10.1)	839 (12.0)	543 (12.0)	166 (13.2)	230 (6.6)	838 (12.0)
Hypertension	5778 (35.1)	3263 (34.6)	2515 (35.8)	1630 (36.0)	513 (40.8)	1053 (30.3)	2512 (35.9)
Diabetes mellitus	2010 (12.2)	1145 (12.1)	865 (12.3)	599 (13.2)	164 (13.1)	362 (10.4)	862 (12.3)
Prior stroke	1637 (9.9)	963 (10.2)	674 (9.6)	529 (11.7)	144 (11.5)	258 (7.4)	674 (9.6)
Vascular disease	3652 (22.2)	2021 (21.4)	1631 (23.2)	1066 (23.5)	304 (24.2)	613 (17.7)	1629 (23.3)
Liver disease	81 (0.5)	44 (0.5)	37 (0.5)	21 (0.5)	7 (0.6)	14 (0.4)	37 (0.5)
Bleeding history	2577 (15.7)	1515 (16.0)	1062 (15.1)	786 (17.3)	235 (18.7)	460 (13.3)	1061 (15.2)
DVT/PE	3147 (19.1)	1795 (19.0)	1352 (19.3)	819 (18.1)	59 (4.7)	907 (26.1)	1351 (19.3)
Atrial fibrillation	5931 (36.0)	3405 (36.1)	2526 (36.0)	1979 (43.7)	630 (50.2)	714 (20.6)	2524 (36.1)
Valvular AF	1433 (8.7)	677 (7.2)	756 (10.8)	376 (8.3)	132 (10.5)	158 (4.6)	755 (10.8)
Myocardial infarction	1453 (8.8)	826 (8.7)	627 (8.9)	460 (10.1)	128 (10.2)	220 (6.3)	626 (8.9)
Ischemic heart disease	3400 (20.7)	1843 (19.5)	1557 (22.2)	1005 (22.2)	290 (23.1)	515 (14.8)	1554 (22.2)
Risk scores							

CHA_2DS_2-VASc, mean (SD)	2.65 (1.77)	2.65 (1.79)	2.66 (1.76)	2.79 (1.79)	3.01 (1.74)	2.33 (1.76)	2.66 (1.76)
CHA_2DS_2-VASc category, n (%)							
CHA_2DS_2-VASc = 0							
CHA_2DS_2-VASc = 1	1824 (11.1)	1076 (11.4)	748 (10.7)	440 (9.7)	75 (6.0)	536 (15.4)	745 (10.6)
CHA_2DS_2-VASc ≥2	3010 (18.3)	1751 (18.5)	1259 (17.9)	754 (16.6)	178 (14.2)	792 (22.8)	1255 (17.9)
HAS-BLED, mean (SD)	1.81 (1.27)	1.85 (1.32)	1.75 (1.21)	1.98 (1.31)	2.15 (1.32)	1.55 (1.27)	1.75 (1.21)
HAS-BLED category, n (%)							
HAS-BLED 0-1	7406 (45.0)	4205 (44.5)	3201 (45.6)	1797 (39.6)	437 (34.8)	1897 (54.7)	3189 (45.6)
HAS-BLED 2	4485 (27.2)	2487 (26.3)	1998 (28.5)	1254 (27.7)	374 (29.8)	813 (23.4)	1996 (28.5)
HAS-BLED ≥3	4568 (27.8)	2751 (29.1)	1817 (25.9)	1482 (32.7)	445 (35.4)	760 (21.9)	1816 (25.9)
Concomitant procedures and medications, n (%)							
NSAID use	1206 (7.3)	802 (8.5)	404 (5.8)	403 (8.9)	120 (9.6)	265 (7.6)	402 (5.7)
Antiplatelet use	3978 (24.2)	2305 (24.4)	1673 (23.8)	1293 (28.5)	396 (31.5)	553 (15.9)	1673 (23.9)
Hip/knee replacement	1902 (11.6)	1174 (12.4)	728 (10.4)	540 (11.9)	155 (12.3)	461 (13.3)	728 (10.4)

Abbreviations: CHF, congestive heart failure; DVT/PE, deep vein thrombosis or pulmonary embolism; VAF, valvular atrial fibrillation; **HAS-BLED**, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol (risk factors for bleeding); **CHA_2DS_2-VASc**, Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke/TIA (2 points), Vascular disease, Age 65–74, Sex category (female). Note: Only 184 patients-initiated dabigatran during the study period. Owing to the small sample size, dabigatran users were excluded from drug-specific analyses and are not shown in this baseline table. Values are presented as n (%) unless otherwise stated.

Baseline renal function assessment (**Table 8.5**) showed that 13% of the overall cohort had impaired renal function based on ICD-10 diagnosis codes for renal disease. When assessed by laboratory values, 4,502 patients (27.4%) had renal impairment defined as GFR <60 mL/min. The prevalence of renal impairment was similar between DOAC and VKA users (28.3% vs 26.1%, respectively). Most patients (72.6%) had preserved renal function (eGFR ≥60 mL/min), while 23.4% had moderate impairment (eGFR 30–59 mL/min), 2.9% had severe impairment (eGFR 15–29 mL/min), and 1.0% had very severe impairment or kidney failure (eGFR <15 mL/min).

Among individual DOACs, edoxaban users had the highest prevalence of renal impairment, defined as eGFR <60 mL/min, at 29.5% (n=370), followed by apixaban (28.8%, n=1,307), rivaroxaban (27.2%, n=946), and dabigatran (26.1%, n<15). When stratified by renal function category, 24.8% of patients initiating apixaban had an eGFR of 30–59 mL/min, a proportion similar to that observed among edoxaban users (24.8%), rivaroxaban users (23.7%), and warfarin users (22.3%).

In the more severely impaired category (eGFR 15–29 mL/min), the proportions were also comparable, with 3.1% of edoxaban users, 2.9% of apixaban users, and 2.8% of both rivaroxaban and warfarin users falling within this range.
Among those with very severe renal impairment (eGFR <15 mL/min), 1.6% initiated edoxaban, compared with 1.1% for apixaban, 0.7% for rivaroxaban, and 1.0% for warfarin.

Table 8.5: Renal function at oral anticoagulant initiation, stratified by anticoagulant type

Variable	Overall, n (%)	DOAC, n (%)	VKA, n (%)	Apixaban, n (%)	Dabigatran, n (%)	Edoxaban, n (%)	Rivaroxaban, n (%)	Warfarin, n (%)
N	16459	9443	7016	4533	184	1256	3470	7001
Renal disease diagnosis (ICD-10), n (%)	2145 (13)	1452 (15.4)	897 (12.8)	729 (16.1)	18 (9.8)	191 (15.2)	387 (11.2)	836 (11.9)
Renal function category (eGFR, mL/min), n (%)								
>=60	11957 (72.6)	6772 (71.7)	5185 (73.9)	3226 (71.2)	136 (73.9)	886 (70.5)	2524 (72.7)	5175 (73.9)
30-59	3859 (23.4)	2295 (24.3)	1564 (22.3)	1123 (24.8)	38 (20.7)	311 (24.8)	823 (23.7)	1561 (22.3)
15-29	474 (2.9)	277 (2.9)	197 (2.8)	133 (2.9)	<10 (4.3)	39 (3.1)	97 (2.8)	195 (2.8)
<15	169 (1.0)	99 (1.0)	70 (1.0)	51 (1.1)	<5 (1.1)	20 (1.6)	26 (0.7)	70 (1.0)

Note: Values are presented as n (%) unless otherwise stated. Renal function was defined using the most recent eGFR measurement within 180 days prior to oral anticoagulant initiation. eGFR categories were defined according to KDIGO criteria (mL/min/1.73 m²). Renal disease was identified using ICD-10 diagnostic codes recorded prior to OAC initiation. Cell counts <10 are suppressed in accordance with data disclosure guidance. p-values reflect comparisons between DOAC and VKA users, and across individual anticoagulants where s

8.3.2. Incident OAC prescribing by renal function and calendar year

In the primary analysis cohort (patients with an eGFR measurement within 180 days prior to OAC initiation), the most recent eGFR measurement occurred a median of 57 days (IQR 21–108) days prior to OAC initiation. In the sensitivity analysis using a 60-day window, this interval was reduced to a median of 22 days (IQR 8–40) days.

In all renal function categories, there was a consistent trend of increasing DOAC use and decreasing VKA use over the study period, similar to the overall prescribing patterns observed in the full cohort described in Chapter 4.

In the early years (2011–2013), VKAs were the predominant choice across all eGFR groups. For example, among patients with preserved renal function (eGFR ≥60 mL/min), VKA use accounted for 99% of initiations in 2011 and 93% in 2012. This pattern reversed substantially over time, with VKA use declining to 5% by 2020, while DOAC prescriptions increased to 95% in this group as shown in **Figure 8.3**.

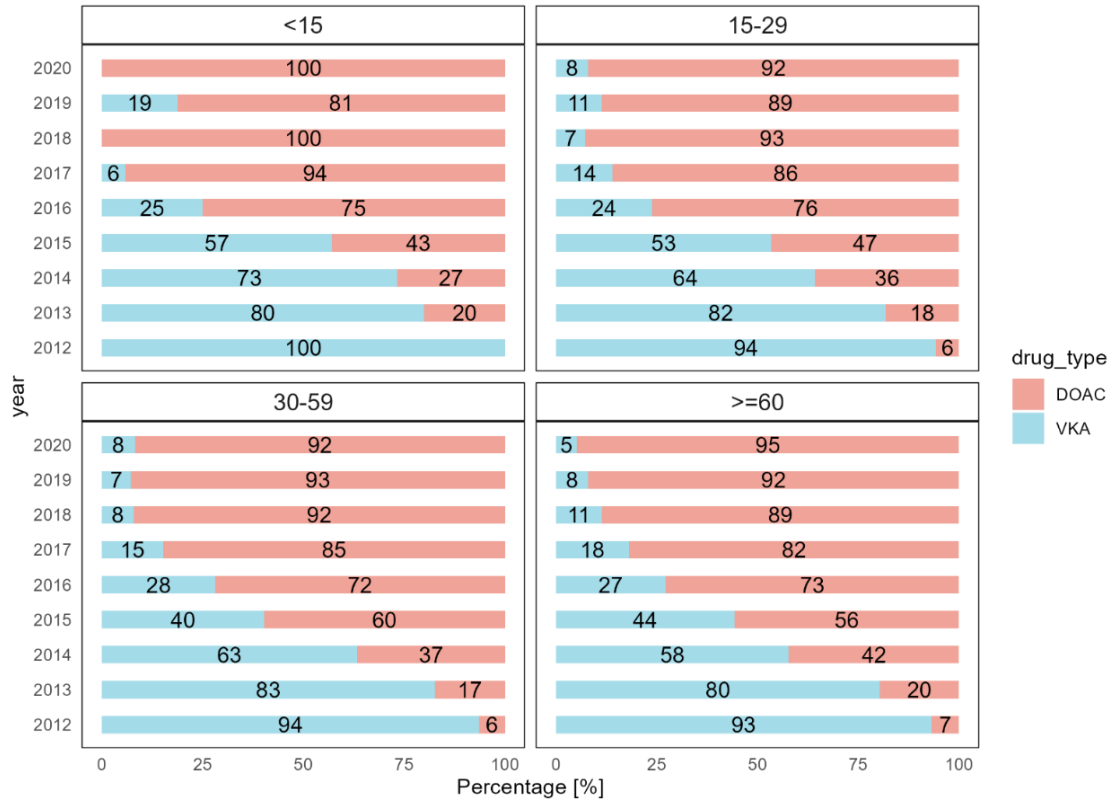

Figure 8.3: Prescribing choice of OAC in incident OAC users stratified by renal impairment stage by calendar year, 180 days maximum between the test date and the first prescription of OAC.

The adoption of DOAC therapy occurred at different rates across renal function categories. Patients with preserved renal function (eGFR ≥60 ml/min) showed the earliest uptake, with DOAC use reaching 56% by 2015. Patients with moderate renal impairment (eGFR 30-59 mL/min) showed initially slower adoption (**Figure 8.3**), increasing from 6% in 2012 to 60% by 2015, ultimately reaching 92% by 2020. Similar patterns were observed in patients with more advanced renal dysfunction, DOAC use among those with eGFR 15–29 mL/min increased from 6% in 2012 to 47% in 2015 and 92% by 2020, while use in the eGFR <15 mL/min group rose from 0% in 2012 to 43% in 2015 and 100% by 2020.

Despite initial differences in adoption rates, DOAC utilisation became comparable across all eGFR categories from 2016 onwards. By 2018, DOAC use exceeded 90% among patients with moderate (eGFR 30–59 mL/min), severe renal impairment (eGFR 15–29 mL/min) and very severe impairment (eGFR <15 mL/min).

By the end of the study period in 2020, DOACs represented over 90% of new anticoagulant prescriptions across all renal function categories. In contrast, warfarin initiation declined substantially, accounting for only 5% of new prescriptions among patients with preserved renal function (eGFR ≥60 mL/min), and 8% among those with moderate (eGFR 30–59 mL/min) and severe renal impairment (eGFR 15–29 mL/min).

When comparing OAC prescribing patterns across all four renal function categories within each study year, no statistically significant overall association was observed between renal function category and OAC type (DOAC vs VKA) in the global tests (all p-values >0.05). Post hoc pairwise comparisons were therefore conducted to explore specific contrasts between renal function categories. These analyses revealed consistent differences between patients with moderate renal impairment (eGFR 30–59 mL/min) and those with preserved renal function (eGFR ≥60 mL/min) across all study years (all p-values <0.0001). Similarly, patients with severe renal impairment (eGFR 15–29 mL/min) differed significantly from those with preserved renal function in 9 of 10 study years ($p < 0.05$), with 2015 being the only exception ($p = 0.65$). In contrast, comparisons between adjacent renal impairment categories (eGFR 15–29 vs 30–59 mL/min) showed no statistically significant differences in any study year (all p-values >0.05).

The nature of these differences evolved over time. During the early adoption period (2012–2015), DOAC use was consistently lower in patients with renal impairment

compared to those with preserved function. However, from 2016 onward, this pattern reversed, with patients in the impaired renal function categories often showing equal or higher rates of DOAC initiation compared to those with eGFR ≥60 ml/min. A sensitivity analysis using a 60-day window between eGFR measurement and OAC initiation produced similar results, supporting the robustness of these findings (**Figure 8.4**).

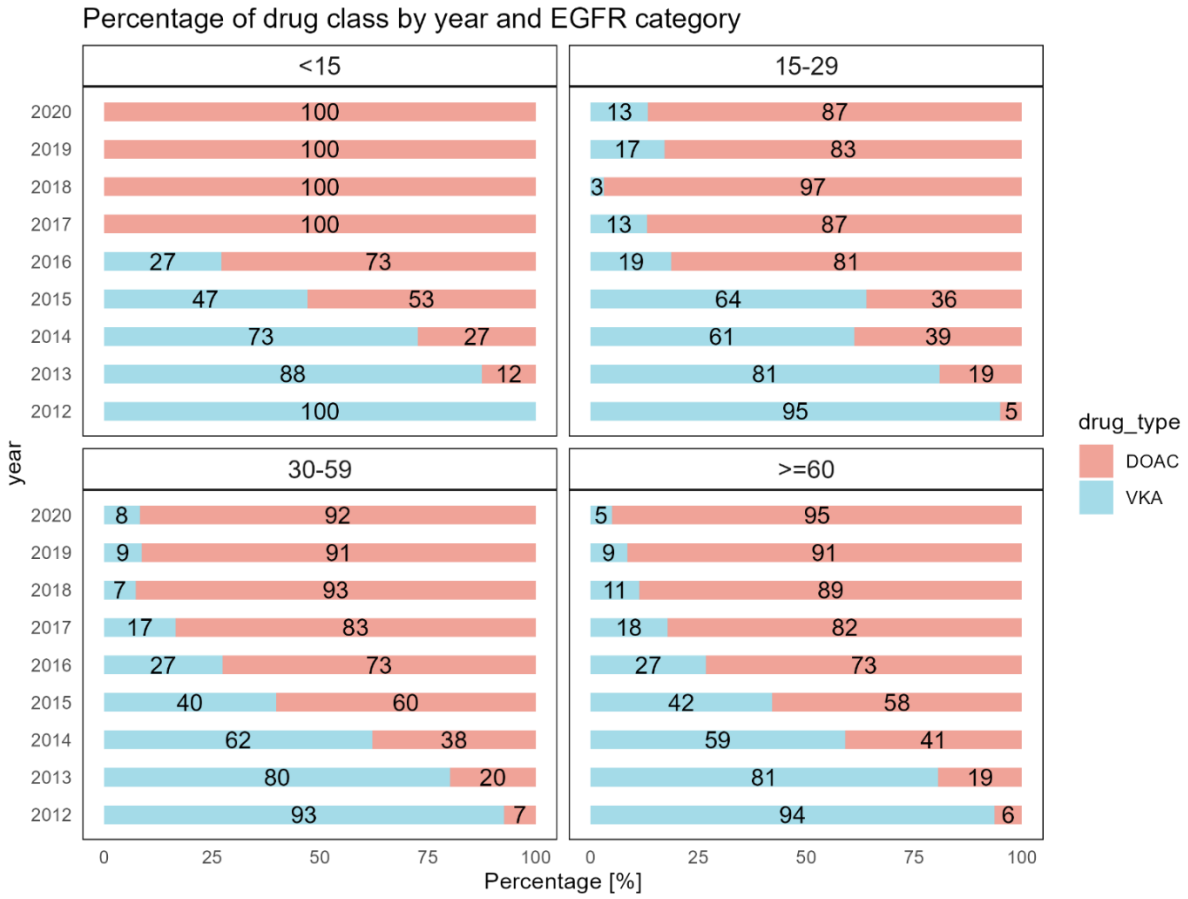

Figure 8.4: Prescribing choice of OAC in incident OAC users stratified by renal impairment stage by calendar year, 60 days maximum between the test date and the first prescription of OAC.

Note: Due to very small numbers of DOAC initiations in 2011, results for that year are not shown

8.3.3. Trends in DOAC type by renal function over time

The results demonstrate the evolution of DOAC prescribing patterns across all renal function categories from 2013 to 2020 (**Figure 8.5**; **Table 8.6**), revealing relatively consistent prescribing preferences across GFR categories with some temporal variations.

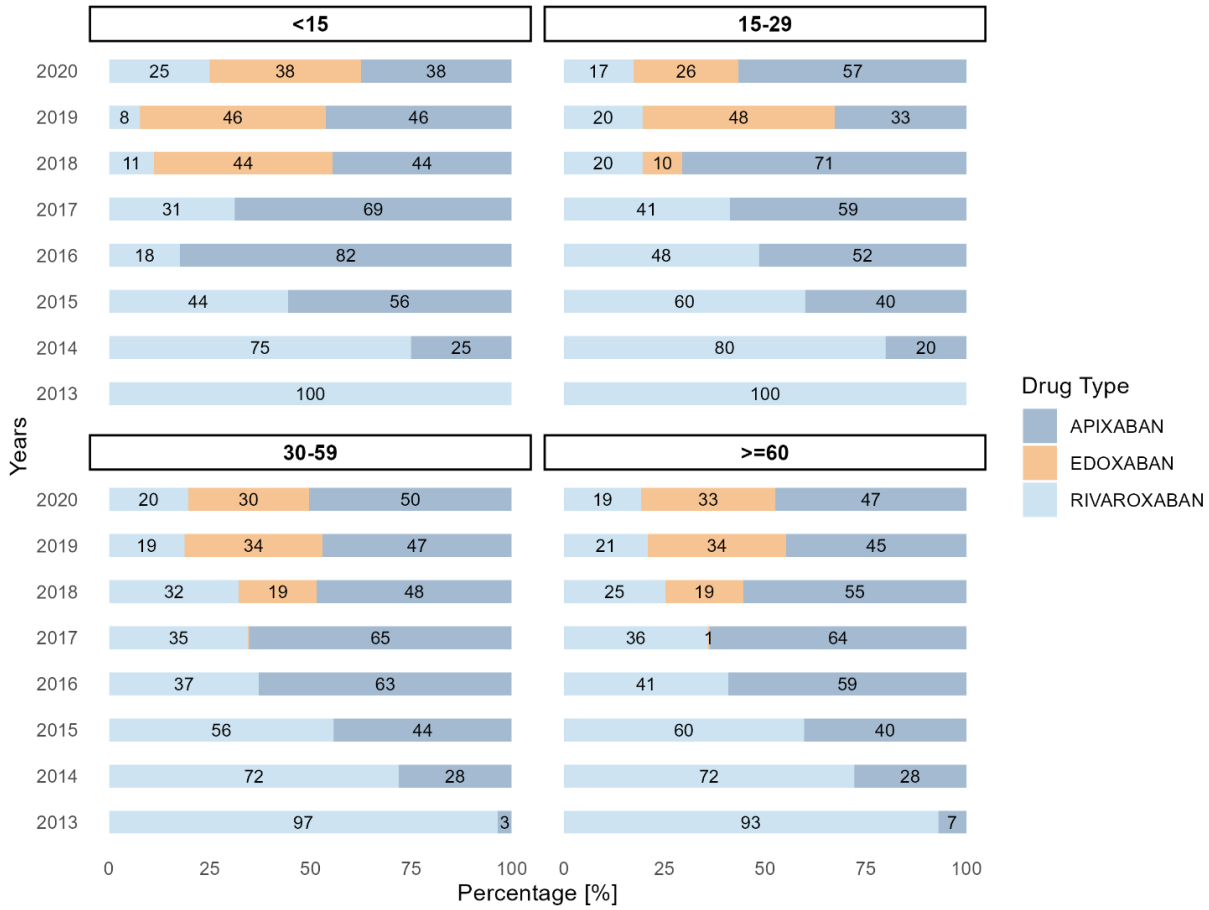

Figure 8.5: Trends in DOAC agent initiation by renal function, using laboratory results within 180 days before first OAC prescription (2013–2020)

Table 8.6: Range of incident DOAC initiations (%) across renal function categories, by year (2013–2020)

Year	Rivaroxaban (%) range	Apixaban (%) range	Edoxaban (%) range	Notes
2013	93–100	0–7	0	Early adoption period
2014	72–80	20–28	0	-
2015	44–60	40–56	0	-
2016	18–48	52–82	0	-
2017	31–41	59–69	0–1	Edoxaban begins to appear (minimal)
2018	11–32	44–71	10–44	wider ranges driven by small <15ml/min group
2019	8–21	33–47	34–48	-
2020	17–25	38–57	26–38	-

Across all GFR categories, a clear shift from rivaroxaban dominance to increased apixaban and edoxaban utilisation is evident. In 2013, rivaroxaban comprised the vast majority of DOAC prescriptions, with minimal apixaban use and no edoxaban prescribing, reflecting the chronological introduction of these agents into clinical practice.

From 2016 onward, apixaban became the most commonly prescribed DOAC across all renal function categories. By 2020, prescribing patterns showed remarkable consistency across most renal function categories, with apixaban and edoxaban becoming the preferred agents regardless of kidney function. Importantly, edoxaban accounted for approximately one-third of DOAC initiations across most renal function categories, indicating substantial uptake alongside apixaban.

Additionally, patients with moderate and severe renal impairment showed a slightly higher preference for apixaban compared with those with normal or mildly impaired renal function, while edoxaban initiation was slightly lower in these groups. Prescribing patterns among patients with eGFR <15 mL/min showed a somewhat different pattern; however, this group had very small patient counts (fewer than 15 annually).

Sensitivity analyses using a 60-day window for renal function assessment produced results consistent with the primary analysis, confirming the robustness of this result (**Figure 8.6**). Statistically significant differences in DOAC choice across GFR categories were observed ($p < 0.001$).

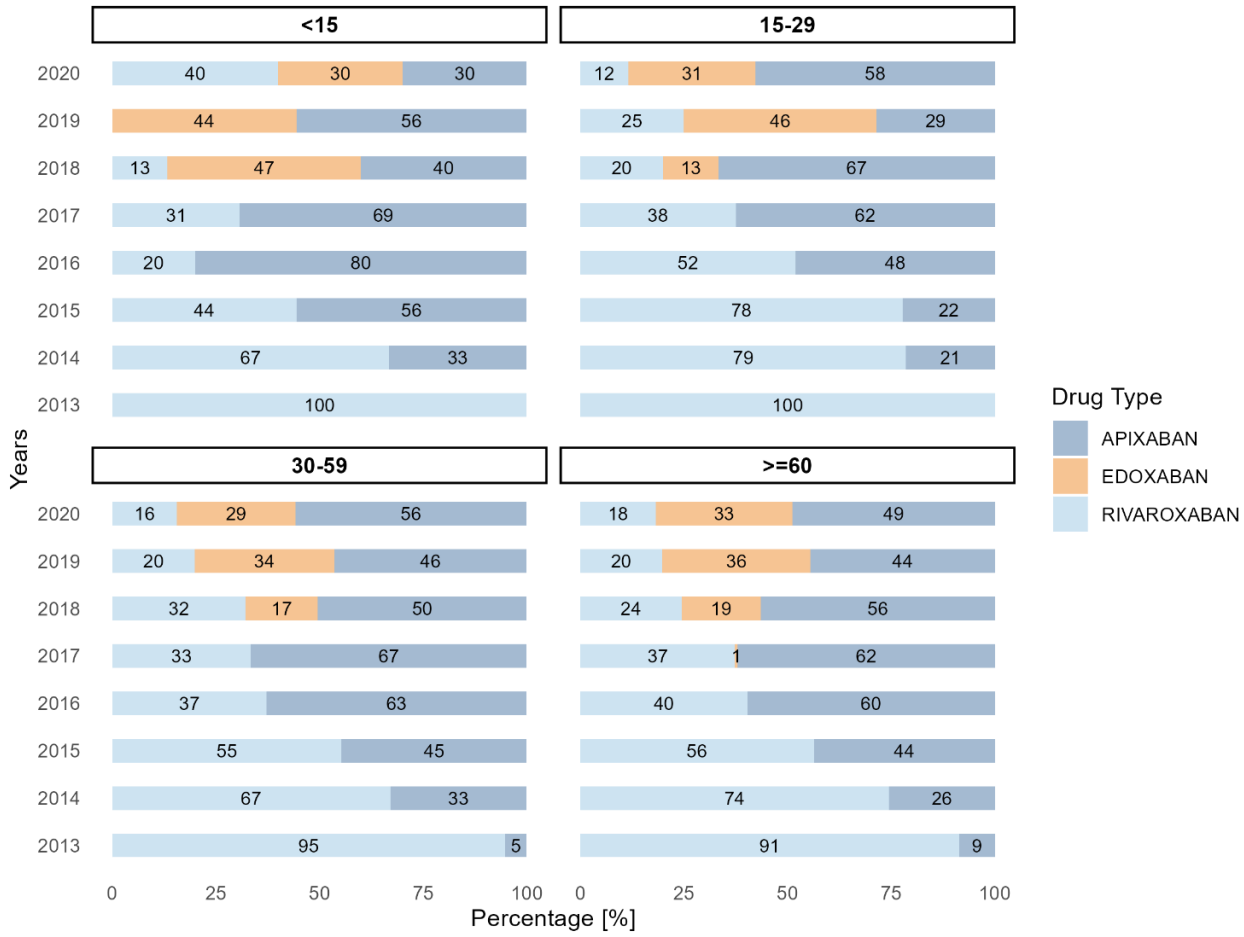

Figure 8.6: Trends in DOAC agent initiation by renal function, using laboratory results within 60 days before first OAC prescription (2013–2020)

8.4 Discussion

There is limited evidence from Scottish primary care settings examining anticoagulant prescribing patterns in relation to CKD presence or severity. This study utilized large-scale primary care data from Scotland (2011–2020) to compare anticoagulant initiation patterns across different stages of renal function, as defined by estimated GFR.

Findings demonstrate a comprehensive shift in anticoagulant prescribing practices which align with the broader prescribing trends observed across Scotland,

characterised by a nationwide transition from VKAs, such as warfarin, to DOACs between 2012 and 2020 (Chapter 4). Importantly, this shift occurred consistently across all eGFR categories throughout the study period, indicating that renal function status did not substantially influence the overall temporal uptake of DOACs. By the later years of the study period, anticoagulant prescribing patterns had become broadly similar across patients with preserved renal function and those with varying degrees of CKD.

The overall similarity in prescribing patterns across renal function categories suggests that, while kidney function remains an important clinical consideration in DOAC selection, the fundamental shift toward DOACs, particularly apixaban and edoxaban, has occurred irrespective of renal status. This likely reflects improved clinical familiarity with DOAC dose-adjustment protocols and growing confidence in their use across the spectrum of renal function, resulting in a healthcare system wide transition in anticoagulation practices.

Comparison with previous studies

These findings are broadly consistent with a large UK real-world cohort study of older adults with AF conducted between 2010 and 2020, which also reported a shift away from warfarin towards DOACs irrespective of CKD status or stage (343). However, when prescribing patterns are examined in patients with more advanced CKD, important differences become apparent.

In the present Scottish cohort, apixaban initiation in 2020 was highest among patients with eGFR 15–29 mL/min, exceeding initiation rates observed in both the 30–59 and ≥60 mL/min groups. This contrasts with findings from the same UK study, which reported the lowest relative use of apixaban among patients with stage 4 CKD (eGFR 15–29 mL/min) and a greater reliance on warfarin in this group, with patients with stage 4 CKD being approximately three times more likely to initiate warfarin compared with those with mild to moderate renal impairment (343).

These observations suggest a distinct prescribing pattern favouring apixaban among patients with advanced renal impairment in Scottish primary care. However, interpretation must be cautious, as the number of patients in the eGFR <15 and 15–29 mL/min categories was relatively small compared with the larger 30–59 and ≥60 mL/min groups. Consequently, further research with larger samples of patients with advanced CKD is needed to confirm these observations.

Moreover, the broader use of apixaban in patients with GFR 15–29 mL/min in this study relates to differences in study populations and indications. While previous studies focused exclusively on patients aged over 65 with AF (343), this analysis included all indications for OAC use, not limited to AF alone. According to the British National Formulary, apixaban dosing recommendations in patients with renal impairment vary by indication. For VTE treatment or prevention, apixaban can be used with caution in patients with creatinine clearance of 15–29 mL/min, whereas for stroke prevention in non-valvular AF, dose reduction to 2.5 mg twice daily is recommended when creatinine clearance is 15–29 mL/min. This indication-specific dosing guidance may explain prescriber confidence in using apixaban across multiple clinical contexts with appropriate dose adjustments in this study.

Additionally, apixaban has been increasingly favoured when a DOAC is prescribed in patients with stage 4 or stage 5 CKD, including those receiving dialysis, based on observational evidence suggesting a more favourable safety and efficacy profile compared with other DOACs and its lower dependence on renal clearance (185).

Temporal changes in prescribing behaviour

Early in the study period (2012–2015), renal function appeared to influence prescribing decisions, with more conservative DOAC use among patients with reduced kidney function. Historically, clinicians favoured warfarin in patients with stage 4 and 5 CKD, partly due to concerns over potential rapid declines in renal function affecting DOAC clearance and the availability of therapeutic drug monitoring with warfarin, providing clinicians with additional reassurance. Additionally, early evidence supporting DOAC use in advanced CKD was largely pharmacokinetic, with apixaban considered a potentially favourable option because of its lower renal clearance rather than robust clinical outcome data (344).

However, observational studies evaluating the use of warfarin in non-valvular AF patients and ESRD, including those undergoing dialysis, present conflicting results (344). Several large retrospective studies and meta-analyses have demonstrated no clear benefit, with some suggesting increased risks of bleeding or stroke, while a small number of studies indicate potential benefit in selected non-dialysis populations. Additionally, use of VKA speeds up vascular calcifications in patients with CKD and especially in those having haemodialysis, contributing to the development of advanced arteriosclerosis (345).

Over time, these disparities diminished. From 2016 onward, patients with renal impairment initiated DOAC therapy at rates comparable to those observed among patients with preserved renal function. By 2019–2020, DOAC initiation rates had become broadly similar across renal function categories: 92% and 95% among patients with eGFR ≥60 ml/min, 93% and 92% among those with eGFR 30–59 ml/min, and 89% and 92% among those with eGFR 15–29 ml/min, respectively.

This temporal evolution indicates evolving clinical confidence in the safety and efficacy of DOACs across all stages of CKD, informed by accumulating observational evidence, pharmacokinetic data, and real-world clinical experience. It also reflects a broader acceptance and integration of emerging evidence into clinical practice.

Individual DOAC selection

Regarding individual DOAC selection, apixaban were observed as the preferred choice across all renal function categories, dominating prescriptions in both patients with preserved function (eGFR ≥60 ml/min) and those with renal impairment (eGFR <60 ml/min). Edoxaban became the second most frequently prescribed DOAC, accounting for approximately 26-33% of all new OAC initiations across all GFR categories. Importantly, edoxaban was prescribed at similar rates even in patients with severe renal impairment (stages 4 and 5).

This preference for DOACs, particularly apixaban and edoxaban, aligns closely with accumulating evidence supporting DOAC use in patients with kidney dysfunction, including those with GFR <30 mL/min. A comprehensive systematic review and meta-analysis examining OACs in AF patients with renal impairment, including advanced CKD with creatinine clearance <30 mL/min, analysed 19 studies encompassing 124,628 patients through April 2021 (173). This analysis included both RCTs and non-randomized observational studies with adjusted effect estimates. Overall, DOAC use was associated with significantly lower risks of stroke or thromboembolism compared with warfarin (HR 0.78, 95% CI 0.73–0.85), as well as lower major bleeding risk (HR 0.76, 95% CI 0.64–0.89), regardless of renal impairment severity. Importantly, these benefits remained consistent in patients with advanced CKD, with reduced risks of stroke or thromboembolism (HR 0.60, 95% CI 0.43–0.85) and major bleeding (HR 0.74, 95% CI 0.59–0.93). In the same network meta-analysis, apixaban and edoxaban ranked highest for efficacy and safety

outcomes, with apixaban demonstrating the greatest probability of reduced major bleeding risk in advanced CKD (173).

Clinical and regulatory implications

Despite clear shifts in prescribing behaviour, findings from this study also highlight important differences between evolving clinical practice and regulatory frameworks. While the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have not licensed any DOAC for use in patients with creatinine clearance <15 mL/min or those undergoing dialysis, the U.S. Food and Drug Administration permit apixaban use in end-stage renal disease, supported by pharmacokinetic studies and observational data. Recent RCT, such as AXADIA-AFNET, provide further evidence supporting the safety and efficacy of apixaban in dialysis patients, suggesting that clinical practice in Scotland is evolving ahead of regulatory frameworks (345).

These observations suggest that anticoagulant prescribing patterns across renal function categories may be influenced by accumulating clinical evidence and practical experience, in addition to formal regulatory guidance. The preference for apixaban in patients with moderate-to-severe renal impairment reflects a real-world translation of pharmacological and observational data into practice, supported by the agent's favourable safety profile and flexible dosing options across different clinical indications.

For policymakers and clinical guideline developers, these trends may warrant consideration in future reviews of licensing restrictions and national guidance, to ensure alignment with emerging evidence and real-world prescribing patterns.

8.4.1. Strength and limitations

A key strength of this study is the inclusion of only incident OAC users, which allows to assess real-world prescribing behaviour at the time of initiation, such as whether DOAC or VKA is chosen based on renal function, without confounding from prior therapy or switching. Furthermore, renal function assessment was restricted to laboratory results obtained within six months prior to OAC initiation, ensuring clinical relevance of kidney function data and minimizing misclassification bias from outdated test results.

This study used the most recent eGFR measurement within 180 days prior to the first OAC prescription to assess kidney function at treatment initiation. Although

laboratory and prescribing data after OAC initiation were available, the analysis was restricted to the initial prescribing decision in patients with renal impairment. Consequently, treatment continuation, switching, dose changes, or changes in renal function following initiation were not assessed. Another limitation of this study is that the unit standardisation of eGFR values could not be verified in all records. While eGFR is typically reported as mL/min in UK clinical practice, inconsistencies in data labelling prevented confirmation of surface area adjustment. This may have introduced minor misclassification in CKD staging, although such errors are unlikely to have meaningfully affected overall trends or comparisons.

As a point of note, specific clinical indications for anticoagulation (e.g., AF vs. VTE) or presence of contraindications that may have influenced anticoagulant choice, could not be determined. Furthermore, although the overall cohort size was large, the number of patients within the eGFR 15–29 ml/min and especially the <15 mL/min categories were relatively low on an annual basis and for individual DOAC types. Although absolute numbers in the eGFR <15 ml/min group were somewhat higher than in the eGFR 15–29 ml/min group, both remained small in comparison to the 30–59 ml/min and ≥60 ml/min groups. This limits the statistical power and generalizability of findings for the most renally impaired patients. As such, these results should be interpreted with caution, and further studies with larger sample sizes in advanced CKD populations are needed to validate these trends and guide evidence-based prescribing.

8.5 Conclusion

DOAC initiation increased across all renal function categories, with consistent adoption patterns observed across all renal stages, particularly from 2016 onwards. By 2020, DOAC prescriptions exceeded 90% of new anticoagulant initiations across all renal function groups, while warfarin accounted for only 5-8% of new prescriptions. Apixaban was the most frequently prescribed DOAC across all renal function strata, followed by edoxaban. Higher relative utilization of apixaban observed in patients with severe renal impairment (eGFR 15-29 mL/min) compared to those with preserved renal function by the end of the study period.

9 Chapter 9: Conclusion and implication of the findings

Over the past decade, DOACs have largely replaced VKAs such as warfarin in the prevention and treatment of thromboembolic disorders, reflecting a major shift in anticoagulation management. Their favourable efficacy, safety, and convenience profiles have been reflected in clinical guideline recommendations and widespread adoption in clinical practice. Nevertheless, despite the consensus on their overall clinical benefit, uncertainty persists regarding the optimal selection among individual DOAC agents, particularly in patients with complex comorbidities, renal impairment, or other risk factors that may influence pharmacokinetics and safety. Furthermore, variations in prescribing patterns across populations and health systems suggest that both clinical and non-clinical factors continue to shape anticoagulant use in real-world settings.

This thesis examined OAC prescribing in Scotland between 2010 and 2020, a decade marked by major change in clinical practice. It brought together a series of complementary studies that collectively explored how prescribing patterns evolved, what factors influenced prescribing choices, how the COVID-19 pandemic affected these patterns, and what clinical outcomes followed when patients switched from VKAs to DOACs. It also examined how renal function shapes anticoagulant choice, given the limited evidence available for patients with impaired kidney function. Together, the findings provide a comprehensive understanding of anticoagulation practice in Scotland and offer insights that can inform safer, more consistent, and evidence-aligned prescribing. The key findings from these studies are summarized below.

9.1 Summary of key findings

Based on the scoping review, the choice of anticoagulant was found to be multifactorial in the published literature, shaped not only by clinical characteristics such as age, renal function, comorbidities and stroke or bleeding risk scores, but also by socioeconomic status, prescriber speciality, and regional variation. Importantly, these associations were not static but evolved over time, reflecting changes in prescriber confidence, accumulated experience, and guideline updates.

The use of OAC in Scotland increased substantially during the study period, likely reflecting both growing recognition of the need for stroke prevention in AF and the broader suitability of treatment options following the introduction of DOACs, which

enabled anticoagulation for patients who were previously considered less suitable for warfarin (224,346,347). The incidence of OAC initiation rose by over 70% between 2011 and 2019, before a modest decline in 2020, likely related to the reduced healthcare activity during the COVID-19 pandemic.

Between 2010 and 2020, DOACs progressively replaced VKAs as the standard of care, in line with accumulating evidence of their safety and convenience and the publication of new clinical guidelines recommending them as first-line therapy (5,6).The introduction of new DOACs, particularly edoxaban after 2015, was accompanied by broadening of therapeutic choices in prescribing, showing how clinicians adapt to new therapeutic options as evidence develops. By 2020, DOACs accounted for more than 90% of all new OAC initiations, with apixaban and edoxaban together making up nearly 80% of all new prescriptions. Although some variation in OAC use by age, sex, and geographic region was evident in the early years of DOAC uptake, these disparities diminished over time. By the end of the decade, prescribing patterns had become broadly consistent across demographic groups and health boards, with apixaban and edoxaban becoming the preferred first- choices among incident OAC users.

The COVID-19 pandemic had a pronounced but complex impact on anticoagulant use. In the early months of 2020, there was a brief surge in prescriptions, likely representing anticipatory prescribing to reduce patient contact for INR monitoring. However, time-series and segmented regression analyses indicated that incident DOAC prescribing declined from April 2020, followed by a gradual recovery beginning in May 2020, with prescribing returning to approximately pre-pandemic levels by November 2020, reflecting the wider disruption to cardiovascular assessment and routine clinical care following the first national lockdown (348). This decline in incident OAC use highlights the indirect effects of the pandemic on the identification and management of patients requiring anticoagulation. At the same time, there was a sharp increase in switching from warfarin to DOACs during the early phase of the pandemic. Supported by national policy and practical considerations, such as the reduced need for regular monitoring, the pandemic effectively accelerated the ongoing shift from VKAs to DOACs in Scotland. These findings highlight how external pressures can accelerate the implementation of practice changes that may otherwise evolve more gradually.

Further analyses examined whether the factors associated with switching from VKAs to DOACs differed before and after the onset of the COVID-19 pandemic. Several factors remained consistent across both periods: female sex, shorter duration of prior VKA therapy, and the presence of non-valvular AF continued to be associated with a higher likelihood of switching, while valvular AF reduced it. However, during the pandemic, switching became more common among older patients and among individuals with higher stroke risk scores, reflecting an increased emphasis on safer, more practical anticoagulation management during periods of healthcare disruption.

Analyses of outcomes after switching from VKAs to DOACs showed a more complex set of findings. Patients who changed therapy had lower rates of ICH and haemorrhagic stroke, supporting their established safety profile of DOACs. However, patients had higher rates of ischaemic stroke, MI, and mortality compared with those who remained on warfarin. These risks were more pronounced during longer follow-up periods, suggesting that patients who are stable on warfarin may not always gain additional protection against thromboembolic events or mortality from switching. Outcomes also differed across individual DOACs. Using apixaban as the reference, rivaroxaban was associated with lower thromboembolic risk but higher gastrointestinal bleeding risk, while apixaban demonstrated a more balanced effectiveness and safety profile. Edoxaban was associated with slightly higher GI bleeding compared with apixaban. These findings reinforce that the decision to switch should be individualized, taking account of each patient's risk factors, treatment history, and preferences.

Renal function was also an important factor of anticoagulant selection. DOAC initiation increased across all levels of kidney function, including among patients with moderate or severe impairment, and by 2020 accounted for more than 90% of incident users regardless of renal status. Apixaban became the most frequently prescribed agent across all renal function categories, reflecting its favourable pharmacological profile and evidence from real-world studies suggesting a lower bleeding risk. This pattern indicates growing clinical confidence in DOAC use among patients with renal impairment. However, as patients with advanced CKD have been under-represented in randomised trials and observational evidence remains limited, further evaluation of DOAC safety and effectiveness in this population is warranted (349).

Taken together, the observed increase in OAC initiation, the rapid replacement of VKAs by DOACs, shifts in switching behaviour during the COVID-19 pandemic, and changes in prescribing by age, risk profile, and renal function demonstrate that anticoagulant prescribing in Scotland has undergone a substantial transformation. While this thesis focuses on the Scottish context, the pattern of increasing DOAC use observed here is broadly consistent with trends reported in many other countries (213), although with variation in the pace and extent of adoption and in the impact of the COVID-19 pandemic on prescribing patterns. The results highlight how prescribing practice can evolve in response to emerging evidence, therapeutic innovation, clinical guidelines, and external pressures.

The findings also demonstrate that real-world prescribing data can provide valuable insight into how evidence is implemented in everyday clinical settings and provide an important contribution to public health. Specifically, this work identifies opportunities to optimize anticoagulation management, including the need for individualized DOAC selection, particularly in patients with renal impairment; recognition that switching stable warfarin users may not always improve outcomes; and understanding of time-dependent risks that can inform can guide monitoring protocols and inform shared decision-making between clinicians and patients. Furthermore, understanding how external pressures such as the COVID-19 pandemic rapidly altered prescribing patterns provides insight into how healthcare systems might better respond to future disruptions while maintaining evidence-based care. These insights can guide clinical decision-making, inform prescribing protocols, and support quality improvement initiatives to ensure safer, more equitable anticoagulation care across Scotland.

9.2 Strengths and limitations

This thesis has several strengths. It is the first comprehensive population-based analysis of OAC prescribing in Scotland covering the full decade from the introduction of DOACs through the COVID-19 pandemic. The use of linked, national-level patient-level healthcare data allowed near-complete capture of prescribing and outcomes across the population, avoiding the biases inherent in small or selective samples. This was facilitated by Scotland's universal access to healthcare, the availability of electronic health records for all residents, and the ability to reliably link these records through a unique patient identifier. Moreover, the validity and accuracy of these datasets are supported by their routine use for healthcare

administration, reimbursement, and national surveillance, as well as by established data quality assurance processes and prior use in epidemiological research (188,189). Combining multiple complementary studies within one thesis enabled both breadth and depth, examining temporal trends, patient-level factors, and clinical outcomes within a coherent analytical framework. The inclusion of renal function data provided an additional layer of clinical relevance that is rarely available in large-scale prescribing analyses. Furthermore, in the patients with prior events were excluded from each respective outcome analysis to reduce bias, and propensity score matching was applied to balance treatment groups. Comprehensive adjustment for a wide range of comorbidities and risk factors was performed, along with detailed time-varying analyses, which revealed clinically important differences in both early and late post-switch outcomes.

However, certain limitations must also be recognised. As with all observational research, causal inference is limited by potential confounding. Although statistical adjustment was applied for known covariates, unmeasured factors, such as adherence, lifestyle, or frailty, may still have influenced the results. Laboratory data were not available for all patients, as renal function measures were only accessible for those registered within NHS Greater Glasgow and Clyde. This limited the ability to assess renal function across the full national cohort.

As no indication for treatment was available, all analyses in this thesis included all patients who received an OAC during the study period irrespective of underlying diagnoses. In addition, the data used in this research were not collected specifically for the purposes of this study but were derived from a limited set of routinely collected administrative records. Thus, in the absence of primary care (GP) data, comorbidities and diagnoses used in the outcome analyses and in examining factors associated with switching were derived from secondary care data. These data were only available for patients who had been admitted to hospital, which may have led to underestimate of some conditions or events managed exclusively in primary care. However, the major clinical outcomes examined, such as stroke, systemic embolism, major bleeding, and other serious complications, almost always require hospital assessment or admission, meaning that the key endpoints evaluated in this thesis are unlikely to have been substantially missed.

Furthermore, as with all routinely collected administrative data, the accuracy of diagnostic coding may vary, introducing the potential for some misclassification of

comorbidities or clinical events. To minimise this risk, the analyses used coding definitions that have been widely applied and reported in the published literature for each condition. While any residual misclassification may have influenced the magnitude of observed associations, potentially underestimating true effect sizes rather than generating spurious findings.

In the switching analyses, selection bias is possible, as patients who changed therapy may have differed systematically from those who remained on warfarin. Although several analytical approaches were used to address confounding, residual differences between groups cannot be excluded, and the findings should therefore be interpreted with caution, although broadly consistent patterns were observed across analyses and with previous studies.

9.3 Implications for clinical practice

The findings of this thesis have direct relevance for clinical decision-making and healthcare policy.

First, they reinforce the dominance of DOACs as the preferred option for most patients requiring oral anticoagulation. However, they also demonstrate that treatment choice should remain individualised. Clinicians should consider factors such as renal function, comorbidity profile, and patient preference when selecting among individual DOACs, rather than viewing them as interchangeable alternatives. There is also a clear need for more refined prescribing guidance that reflects the heterogeneity of patients seen in routine practice, particularly those with severe renal impairment or multiple comorbidities.

Second, the observed increase in thromboembolic events after switching from warfarin to a DOAC highlights the importance of careful patient selection and close follow-up. Patients who are stable and well-controlled on warfarin may not always benefit from switching. For those who do switch, early monitoring and education about adherence are crucial to ensuring safe switching and maintaining therapeutic effectiveness.

Third, the growing use of DOACs in patients with renal impairment reinforces the importance of regular renal function assessment and appropriate dose adjustment. Although current guidelines already recommend baseline and periodic eGFR monitoring, particularly for older adults and those with CKD, these findings highlight the need to ensure consistent implementation in routine practice.

Fourth, the experience of the COVID-19 pandemic showed that healthcare systems can adapt prescribing practices rapidly when supported by clear guidance and flexible infrastructure. The lessons learned, such as streamlining medication reviews, expanding remote monitoring, and prioritising patient-centred approaches, should inform future service design beyond the pandemic context.

Finally, this research demonstrates the value of national data for monitoring drug use and informing policy. Routine analysis of prescribing patterns and outcomes can identify variations, evaluate the impact of guideline changes, and support evidence-based decision-making at the population level.

9.4 Recommendations for conducting drug utilisation research

This thesis also highlights several methodological lessons relevant to future drug utilisation studies.

First, linking national prescribing, hospital, and laboratory datasets allows a comprehensive picture of real-world medication use, enabling the study of both prescribing behaviour and patient outcomes. Continued investment in maintaining and improving such linked data systems is essential to support high-quality pharmacoepidemiologic research.

Second, standardisation of definitions, such as incident versus prevalent use and switching, is vital to ensure comparability across studies and over time. Clear documentation of data sources, and cleaning procedures enhances reproducibility and transparency.

Third, temporal analyses, such as interrupted time-series and segmented regression, are powerful for understanding how external events or policy changes influence prescribing. These methods can be complemented by qualitative approaches exploring clinician perspectives to provide a fuller understanding of prescribing behaviour.

Finally, collaborative research across regions and countries would enable cross-national comparisons and help identify whether observed patterns are due to local factors or reflect broader international trends.

9.5 Future research

Despite providing a range of useful findings with regards to the use of DOACs, several areas warrant further investigation. Comparative effectiveness studies are needed to evaluate safety and effectiveness across individual DOACs, particularly in

high-risk groups such as older adults, those with multimorbidity, extreme body weight, polypharmacy, or high bleeding risk. Robust causal inference methods would help guide more personalised prescribing, with careful attention to dosing, adherence, and persistence.

Furthermore**,** patients with moderate to severe CKD remain underrepresented in clinical trials, yet DOAC use in this population continues to rise. Future research should evaluate optimal dosing strategies, safety and effectiveness across the CKD spectrum, and the impact of renal trajectory and acute kidney injury. Randomised head-to-head comparisons would be valuable, although challenging to conduct; therefore, high-quality observational studies remain essential. Robust approaches (e.g., target-trial emulation, time-updated covariates for renal function, propensity scores/inverse probability weighting, and competing-risk models) would strengthen causal inference. Linkage of prescribing, laboratory, hospitalisation, and mortality data is essential, and subgroup analyses by age, frailty, polypharmacy, and indication (AF vs VTE) would improve clinical relevance.

And finally, future research should focus on developing clear criteria for identifying patients who would benefit most from switching, investigating the role of adherence in post-switch outcomes, and exploring strategies to optimize the switching process to minimize adverse events. In addition, dedicated research should examine “switch-back” from DOACs to warfarin, its drivers, and associated outcomes. Mixed methods approaches, including chart review and clinician and patient interviews, may help identify preventable causes of inappropriate switching, adverse events, or subsequent switch-back to warfarin.

9.6 Conclusion

This thesis demonstrates both the adaptability of clinical practice and the continuing need for balanced, evidence-based decision-making tailored to individual patients. By examining national prescribing trends, determinants of drug choice, the effects of switching, and the role of renal function, this research contributes important real-world evidence to guide future practice and policy. While the widespread move toward DOACs has brought clear advantages in safety and convenience, optimal anticoagulation still requires careful patient assessment, shared decision-making, and ongoing monitoring.

Ultimately, the work presented here highlights the importance of using robust, population-based data to understand how medicines are used in everyday practice. It demonstrates how combining evidence from multiple sources can inform safer, more effective, and more equitable use of therapies. In doing so, the thesis not only documents the transformation of anticoagulation practice in Scotland but also provides a model for how drug utilisation research can guide clinical improvement and healthcare policy more broadly.

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Appendices

Appendix S.2.1

Summary of factors examined in included studies

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
AbuDagga et al, 2014	Identify patient, provider, and health plan characteristics associated with the use of dabigatran versus warfarin among a large cohort of NVAF patients using real-world data	Dabigatran Vs warfarin	Age, sex	Comorbidities (pre-index HTN, pre-index ischemic stroke, pre-index HF, pre-index AF-related procedures, pre-index TIA), higher risk of bleeding (based on ATRIA score), prior use of medications (warfarin, anti-platelet/NSAID medications, dyspepsia medications, rate/rhythm control medications)	Region, health plans, total patient out-of-pocket pharmacy costs, insurance indicator	prescriber specialty, cardiologist compared to primary care/family/internal medicine physician	aOR, 95%CI
Alwafi H. et al, 2020	Investigate factors associated with	warfarin Vs DOACs	Age, weight (BMI 25–29, BMI≥30)	Comorbidities (history of stroke/TIA, CKD), history of			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	the initiation of OAC in patients with T2DM and AF		frailty, smoking, sex	bleeding, medications (a history of using aspirin, a history of using angiotensin-converting, enzyme inhibitors (ACEs/ARBs), history of using beta blockers (BB), thromboembolic risk score, bleeding risk score, pre-index HF, History of HTN, dyslipidaemia, CHD			
Baaik S.H et al, 2016, USA	Evaluated how patient demographics, clinical characteristics, type of insurance, and out-of-pocket expenses were associated with the initiation of warfarin and 2 DOACs—dabigatran and rivaroxaban	DOACs (dabigatran and rivaroxaban) Vs Warfarin	Sex, Age, and race	Comorbidities (history of MI, stroke/TIA, chronic kidney disease, HF, or HTN), previous use of NSAIDs, Timing following DOAC approval	Patient out-of-pocket cost, Type of Insurance		

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	among patients newly diagnosed with atrial fibrillation						
Bang O.Y et al, 2022	Explore the clinical factors associated with the type of antithrombotic (antiplatelet agents, warfarin, and DOACs) in clinical practice, chosen for NVAF patients both before and after the introduction of DOACs.	warfarin Vs DOACS	Sex, Age	CHA2DS2-VASc, HASBLED scores, CCI, prior use of medications (Antiarrhythmic drug, NSAIDs, PPI, H2 receptor antagonist, statin, digoxin use), comorbidities (stroke, MI, PAD, bleeding, HTN, DM, CHF, COPD, renal disease)			aOR, 95%CI
Beier L et al, 2022	evaluate predictors of treatment prescription of the last phase of GLORIA-AF registry program (phase III) as well as compare results with those from	DOACs Vs VKA		AF cardioversion, CHA2DS2-VASc score, type of AF (Persistent compared to permanent), HAS-BLED risk score, impaired kidney function	Area of living (Latin America, Europe), medical treatment reimbursed by self-pay/ no coverage, not self-pay), Type of site (specialist office,	physician speciality (GP/PCP/GERIATRICIAN, Internist, cardiologist, Neurologist)	RR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	phase II (November 2011 and December 2014).				community hospital, university hospital)		
Bezabhe, W.M et al, 2021	to investigate patient demographics and clinical characteristics associated with OAC initiation and choice in patients with newly diagnosed AF in Australian primary care	warfarin Vs DOACS Apixaban Vs rivaroxaban OR dabigatran Vs rivaroxaban	Age, sex	comorbidity conditions (CHD, anxiety, dementia, GFR, ORBIT and CHA2DS2-VASc score, HF)	Area of living/ State in Australia TAS (Tasmania), New South Wales NSW and ACT Australian Capital Territory, Victoria (VIC). Queensland (QLD) Western Australia (WA), South Australia (SA) and Northern Territory (NT), socio-economic indexes for areas (SEIFA)		aOR, 95%CI
Bielecka B et al, 2021	to identify predictors of using DOACs in patients treated with	DOACs Vs VKA	Age	Previous thromboembolic event, non-permanent AF, eGFR, LA diameter,			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	anticoagulant therapy			Antiplatelet drug/ drugs, thromboembolic risk, Bleeding risk score, CHF, DM, vascular disease			
Boivin-Proulx, L.-A et al, 2022	to determine whether the publication of the 2016 Canadian Cardiovascular Society AF guidelines were associated with a shift in practice patterns in the management of atrial fibrillation and flutter (AF) patients undergoing percutaneous coronary intervention (PCI). (Determinants of OAC prescription 1 month	DOACs Vs Warfarin	Age, sex	chronic renal failure (eGFR≤ 30 mL/min), previous stroke CHADS2 score >/= 3 vs < 3, DOAC use within the 2 weeks prior to cohort entry, warfarin uses 2 weeks prior to cohort entry, prior exposure to low-dose ASA within the 2 weeks prior to cohort entry, baseline p2Y12 inhibitor use 2 weeks prior to cohort entry History of bleeding, Bleeding risk score, Liver disease, vascular disease			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	following cohort entry)						
Brais C et al, 2017	to assess clinical predictors associated with the use of DOACs over warfarin among new users of OAC for AF in a hospital-based population.	DOACs Vs Warfarin	Age, weight, or BMI, sex	Creatinine clearance≥ 30mL/min, history of PAD, clopidogrel prescribing at discharge polypharmacy, prior bleeding, previous stroke, CHF, HTN, Liver disease, DM, CHD, history of falling, dementia		Prescriber specialty	aOR, 95%CI
Brown J et al, 2016	to assess the use of OAC in 2013 and compare it with the years 2005–2009 (the 'preDOAC' era) among incident cases of NVAF.	DOACs Vs Warfarin	Age, sex	CCI score, cancer, metastatic cancer, hyperlipidemia, thromboembolic risk score, history of dementia	area of living (urban Vs rural) region		OR 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Campitelli M.A et al, 2021	(1) examine recent time trends and correlates of oral anticoagulant use, including DOAC versus warfarin use, among a population-based cohort of older adults with AF newly admitted to Ontario nursing homes; and (2) examine variation in trends by frailty and CKD.	warfarin Vs DOACS	Age, frailty	Concurrent medication use, NSAIDS, prior hospitalization for hemorrhagic stroke, CKD, Frailty, CHF, HTN, liver disease, DM, vascular disease		Prescriber speciality, specialists visit last year.	aRR, 95%CI
Cheng W. H et al, 2021	To investigate the influence of introducing DOACs on rates of OACs initiation among elderly patients (>=85) with newly diagnosed AF	DOACs Vs Warfarin	Age, Sex	renal dysfunction, Anaemia, Hyperlipidaemia, malignancy, abnormal liver function, history of bleeding, thromboembolic risk score			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Chen Q et al, 2021	To identify characteristics associated with anticoagulant use and to examine heterogeneity in associations for warfarin versus DOAC use, and by anticoagulant indication	DOACS Vs warfarin	Age Race/ Ethnicity, sex BMI (BMI > 40 kg/m2)	Polypharmacy 6-10 and > 10 medications patients had a diagnosis of AF, Thromboembolic risk Bleeding risk score Prior antiplatelet use Prior NSAID use, functional dependency			aPR, 95%CI prevalence ratio
Chopard R et al, 2019	to identify patient- and physician-related factors influencing the decision to prescribe DOACs rather than other anticoagulants	DOACs Vs Non-DOACS		active malignancy impaired renal function			aRR, 95%CI
Desai N.R. et al, 2014	To identify whether the adoption of	DOACS Vs warfarin	Age, Sex region/ area of living	CHADS2 score (per 1-point increase) HAS-BLED score (per 1-point increase), Renal	Income/ Median household income in zip code, Education level		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	the novel anticoagulants in typical practice is consistent with the controlled trials on which there approval was based			function, liver disease, History of bleeding, Prior antiplatelet &NSAID use, CHF, Previous thromboembolic event, HTN, DM, CHD			
Douros A. et al, 2021	to assess factors associated with the initiation of DOACs in NVAF patients with liver disease.	Apixaban Vs rivaroxaban DOACS Vs warfarin	Age > 70, weight (BMI), smoking, frailty, Sex	SSRIs use, Antiplatelet use, Prior ischemic stroke/ TIA. higher CHA2DS2-VASc score ≥3 BMI 25–29 AND > 30 CKD, History of bleeding, malignancy Bleeding risk score, HTN, DM, hyperlipidemia, CHD, vascular disease			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Douros A et al, 2017	to identify predictors of treatment initiation with DOACs relative to VKAs after NVAF diagnosis	DOACs VS VKA	Age ≥ 80 years, Sex	Comorbidities (prior MI, prior venous thromboembolism, congestive heart failure, HTN, vascular disease, blood dyscrasias, chronic kidney disease, liver disease, a CHA2DS2-VASc score ≥ 2, prior bleeding, Prior antiplatelet use Time from NVAF diagnosis to treatment initiation 31–60 days Time from NVAF diagnosis to treatment initiation >365 days Calendar year of NVAF diagnosis, 2012			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
				Calendar year of NVAF diagnosis, 2014 History of falling, history of dementia, cancer			
Efird L.E et al, 2016	to examine predictors of novel oral anticoagulant use in patients with AF	rivaroxaban and dabigatran Vs warfarin	Age, Sex	carrying a diagnosis of heart failure, CHADS2 score, moderate compared with low risk, CHADS2 score, high compared with low risk, Diabetes	the poverty rate in the county of practice site, Rural compared with urban, practice site (cardiology compared with general medicine)		aOR, 95%CI
Ehrlinder H et al, 2020	investigate the influence of clinical factors in the choice of antithrombotic. strategy	DOACs VS warfarin	Age, Weight or BMI, Sex	CHADS2 score ≥5, thromboembolic risk high bleeding risk, HAS-BLED score ≥3 impaired renal function (ref GFR ≥ 60, GFR <15, GFR ≥30 -<45)			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Fohtung, R.B et al, 2017	To examine changes in anticoagulation prescribing practices for older adults with AF since the introduction of DOACs in 2010, with particular attention to the associations between age, sex, race, comorbidities, and socioeconomic status with use of anticoagulation	DOACs VS warfarin	Age, Sex, race, weight, or BMI	creatinine clearance (≥50 vs <50 mL/min), hypertension, stroke or TIA, history of intracranial bleeding, HAS-BLED score ≥3, CHF, time from start of the analysis (per 1-quarter increase, medical service (vs surgical service), DM, CHD, vascular disease, history of dementia, haemoglobin (per 1-g/dL increase)			aOR, 95%CI
García-Sempere, A. et al, 2017	to quantify the influence of the geographical healthcare administrative boundaries (Health Areas) on variations in treatment choice,	DOACs Vs warfarin 20	Age, Sex	DM, renal disease, DVT or, PE, previous stroke, or TIA, hemorrhagic stroke, CHA2DS2-VASc score ≥2, HASBLED Score ≥2, CHF, polypharmacy	Emergency Department visits (≥1) Cardiologist visits (≥1) income		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	identify contextual and individual factors associated with initiation pattern						
Gorczyca, I et al, 2020	determined the predisposing factors associated with the administration of non-vitamin K antagonist oral anticoagulants (DOACs) in elderly patients with AF	DOACs Vs warfarin	Age	non-permanent AF, renal impairment, Thrombocytopenia, CHD, necessity of combining AP therapy with OAC. Prior antiplatelet use, CHF			aOR, 95%CI
Gorczyca I. et al, 2020	to evaluate the frequency of use of apixaban, dabigatran, and rivaroxaban, and attempt to identify factors predisposing.	apixaban Vs dabigatran & rivaroxaban dabigatran Vs apixaban & rivaroxaban	Sex, Age	previous bleeding, GFR<60, heart failure vascular disease, type of AF Non-permanent AF, malignancy, prior antiplatelet use			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	their administration.	rivaroxaban Vs apixaban & dabigatran					
Gregory Y.H. Lip, 2015	Examined regional differences in presentation and treatment of contemporary patients with AF in Europe, as managed by European cardiologists.	DOACS (rivaroxaban or dabigatran)	Region/ area of living				OR, 95%CI
Grymonprez M. et al, 2022	To explore factors associated with the choice of OAC in newly treated AF Patients	DOACS Vs VKA	Age, frailty, Sex	having recently fallen, HTN, HF, lower gastrointestinal tract disorders, using antiplatelets, valvular heart disease, CKD, CAD, PAD, DM, liver disease, prior major or clinically relevant non-major bleeding, using SSRIs, corticosteroids, PPIs, dementia multimorbid (CCI≥4vs. <4), upper		prescriber specialty, time period (July 2016–2019 vs. 2013–June 2016)	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
				gastrointestinal tract disorders, thromboembolic risk score bleeding risk score, DM, dementia			
Guerriero F, 2018	Investigate the use of DOACs and predictors of its initiation, as opposed to warfarin, in elderly patients with AF	DOACs Vs Warfarin	Age, Sex	Receiving Platelet aggregation inhibitor Number of co-prescribed medicines, 5-9 Number of co-prescribed medicines, 10+ Receiving antiplatelet, polypharmacy			aOR, 95%CI
Gurusamy V.K. et al, 2019	to investigate associations between sociodemographic factors and initial treatment with a DOAC (vs. warfarin) in oral anticoagulant	DOACs versus warfarin	Sex, Age	renal function history of bleeding, CHD risk of stroke, CHF, DM AF duration	region or area of living (rural area), Education level, Occupation, income		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	naïve patients with non-valvular atrial fibrillation (NVAF).			dementia, history of falling. the year of first anticoagulant prescription 2011,2012.2013,2014			
Ha AC et al, 2016	to assess how Canadian physicians assess stroke and bleeding risk in adults with NVAF and how they form therapeutic decisions for stroke prevention at a time when warfarin and DOACs are available	warfarin Vs DOACs	Age, History of smoking, Frailty	CAD, Non-paroxysmal AF improved side effect profile (as perceived by the patient) superior efficacy (as perceived by the physician)	lower cost		aOR, 95%CI
Ha HS et al, 2020	examined the antithrombotic agent usage patterns and identified factors related to the	DOACS Vs VKA	Sex, smoking frailty	ESRD, chronic kidney disease (CKD), history of valvular heart disease, History of bleeding			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	use of DOACs or warfarin agents in a modern, prospective, multicentre AF registry		weight/BMI	cancer			
Halvorsen S et al, 2022	to assess baseline characteristics, drug utilisation patterns, and primary healthcare use for OACs following the introduction of DOACs among patients with AF, using Norwegian population-based nationwide registries from 2010–2018	DOACS Vs VKA	Sex, Age	HAS-BLED score CHA2DS2-VASc score prior stroke prior bleeding			aOR, 95%CI
Huiart L et al, 2018	to identify the initial oral anticoagulant therapy used in a	DOACS Vs VKA	Age, Sex	Pt with renal failure 2014		prescriber specialty of first anticoagulant	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	cohort of patients newly diagnosed with NVAF for the prevention of stroke and systemic thromboembolism It also sought to describe changes in the characteristics of patients who initiated treatment during the first 5years of DOAC availability in France.			Pt with renal failure 2011 History of bleeding, 2015 HTN 2015, liver disease, DM, CHD Ischemic heart disease, HF, cancer, dementia, history of ischemic stroke Prior antiplatelet use			
Ilomäki J et al, 2019	to investigate the incidence and prevalence of warfarin and DOAC use, and to determine the predictors of DOAC Vs warfarin initiation in people with AD and the	DOACs Vs warfarin	Sex Age	Those with arrhythmias, pain, end-stage renal disease, arrhythmias, HTN, using antiplatelets having CHF in the general population sample			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	general population			Gastric acid disorder in the general population sample diabetes in the general population sample IHD/angina in the general population sample, hyperlipidaemica			
Jobski K et al, 2018	examine factors influencing whether treatment is initiated with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs)	DOACs Vs VKA	Age, Sex	previous stroke, recent hospital stays. care level, dementia, year of cohort entry 2013 or 2014 compared to 2012. Renal disease, the presence of a prosthetic heart valve Comedication, previous bleeding, liver disease, MI, HF, HTN, DM		prescriber specialty	aOR, 95%CI
Kjerpeseth L J et al, 2018	To investigate risk factors for	DOACs Vs VKA	Age, Sex	previous vascular disease, congestive			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	stroke in patients initiating oral anticoagulants for atrial fibrillation in Norway and their association with receiving DOACs versus warfarin			heart failure, history of ischemic stroke, TIA, or arterial, thromboembolism, DM, Pre-existing HTN thromboembolic risk score, vascular disease			
Komen J et al, 2017	to investigate the influence of patient characteristics such as age and stroke and bleeding risks on decisions for antithrombotic treatment in patients with AF.	DOACs Vs VKA	Age	renal disease, vascular disease, risk of stroke risk of bleeding (Atria score 5-10), Liver disease, VTE, using NSAIDs, dementia.			aOR, 95%CI
Koziel M et al, 2021	Assessed temporal changes in antithrombotic prescription patterns. within specific	DOACS Vs warfarin	Weight or BMI, Region	enrolment year/ year 4 compared to year 1 HAS-BLED score	medical treatment reimbursed by Self-pay/no overage	type of site (university hospital, GP/primary care, specialist office, community hospital, and other)	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	geographical regions, starting from initial DOAC approval. Also analysed changes in types of OAC prescribed in relation to CHA2DS2-VASc and HAS-BLED risk scores during each year of enrolment			categorization of AF (lower probability of symptomatic AF compared with asymptomatic AF), CHA2DS2-VASc score, type of AF (lower probability of persistent or permanent AF compared with paroxysmal AF) BMI, chronic gastrointestinal disease, cancer	compared to Not self-pay		
Lauffenburger JC et al, 2015	assess these factors associations with selection between dabigatran and rivaroxaban, and explore the extent of the variation in	DOACS Vs warfarin DOACs Vs DOACs		Ischemic stroke risk, CHA2DS2-VASc, risk of bleeding (ATRIA score) score,			aRR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	anticoagulant selection driven by these factors						
Lee, KK et al, 2023	to evaluate the trends in oral anticoagulation prescribing for women and men admitted to the hospital with nonvalvular AF and compare the factors influencing the prescription of vitamin K antagonists and DOACs.	DOACS Vs VKA	Sex, Age	CCI scores/ pt. with comorbidities history of prior bleeding, CHA2DS2-VASc score	Deprivation index, the Scottish Index of Multiple Deprivation (SIMD)		aOR, 95%CI
Lodzinski P et al, 2020	we evaluated associations between patients' clinical characteristics and drug choice as well as between the type	DOACS Vs warfarin		lone AF, history of ischemic stroke history of PE or history of permanent AF			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	of antithrombotic management			Device therapy (PM/CRT /ICD), First-diagnosed AF			
Lorenzo A et al, 2022	to identify predictors of the use of DOACs for initial and/or long-term therapy of VTE based on patient-related factors, institution-related factors or over time, as such, DOACs vs. those using other anticoagulant drugs and, each DOAC (vs. the other DOACs)	DOACS Vs DOACS DOACs Vs other anticoagulants	Age, Body weight (weight > 120 kg), Sex, fragile patients	Initial or prior VTE presentation as PE recent bleeding renal insufficiency (CrCl levels <30 mL/min) liver cirrhosis platelet count <100,000/μL atrial fibrillation prior VTE Region	European countries America, in the rest of the world, Spain		aOR, 95%CI
Luger S et al, 2014	To characterize, in a multicentric approach, a representative secondary prevention population from	DOACS vs VKA	Age, Sex	Lower serum creatinine, no prior OAT HTN, diabetes, higher premorbid			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	four active stroke centers and identify patient characteristics that independently influence therapeutic decision-making to prescribe DOAC if the patient appears suitable for OAT.			mRS (modified Rankin Scale), higher NIHSS (National Institutes of Health Stroke Scale) at admission, Higher mRS at discharge			
Martinez K A, 2022	to assess variation in anticoagulation prescribing among primary care physicians in a large integrated health system.	DOACs Vs warfarin	Race Sex Age	History of falls, CHA2DS2-VASc or HAS-BLED scores, dementia diagnosis, or insurance type, History of dementia	Patients in the highest median annual income quartile Insurance type	Physician's anticoagulation prescribing tertile (compared to lowest)	aOR, 95%CI
Marzec, L.N et al,2017	patient factors associated with prescription of warfarin, DOACs, and overall OAC use in patients with	DOACs Vs warfarin	Age, Sex Weight or BMI	Diastolic BP (per 10 mm Hg increase), Systolic BP (per 10 mm Hg increase), Dyslipidaemia, HTN,			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	nonvalvular AF at moderate to high risk of thromboembolism. In addition, assesses the extent of practice-level variation in OAC and DOAC use.			previous stroke/TIA, CAD, heart failure, PAD, DM), increased heart rate, CHD			
McDermott A et al, 2022	to assess the independent association between neighbourhood disadvantage and initiation of anticoagulant therapy for patients with incident AF managed in the Veterans Health Administration (VA).	DOACs Vs warfarin			The composite score of ADI is valued from 0 (least disadvantaged) to 100 (Most disadvantaged). stratified the distribution of ADI scores into quintiles, with the least disadvantaged neighborhoods in quintile 1 (ADI 1–29) and the most disadvantaged in		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
					quintile 5 (ADI 79–100)		
McIntyre WF et al, 2018	to identify patient, physician, and temporal factors associated with the stroke-prevention strategy prescribed for North American patients in the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF).	DOACs Vs VKA	Smoking Frailty, sex	HF, DM, History of falling, Use of additional antiplatelet drug HTN, Prior stroke/TIA, Prior bleeding Alcohol ≥8 U/week, Number of concomitant meds > median Hepatic disease, History of falling, Cancer COPD/emphysema, PAD CHD, Pattern of AF (Paroxysmal, Persistent/permanen) study period	Insurance Statutory/federal Commercial insurance coverage Insurance / Self-pay/no coverage/unknown	Clinical care setting (GP/primary care/Outpatient health care /anticoagulant clinic/University hospital) Community Hospital or Specialist office), Prescriber specialty	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Mostaza J.M. et al, 2021	to describe the demographic, functional, and clinical characteristics of patients with NVAF attending internal medicine departments in Spanish hospitals and the potential factors associated with antithrombotic treatment patterns	DOACs Vs VKA	sex	longer time since diagnosis, institutionalization (yes vs. no), stroke/TIA, CCI score, type of NVAF, life expectancy, CHF, ischemic disease, Prior bleeding, abnormal renal function, DM	Education level/ secondary or university or higher studies		aOR, 95%CI
Nathan, A.S et al, 2019	to evaluate recent time trends in the prescription of DOACs among a large, commercially insured population of VTE patients, and we assessed whether race and income were	DOACs Vs VKA	Race/ethnicity Age	Ischemic stroke/transient ischemic attack presence of IVC filter	Household income		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	predictors of the likelihood of receiving DOACs versus VKA.						
Olesen, J.B et al, 2014	To examine changes and temporal trends in OAC use among OAC-naive AF patients and characteristics of AF patients who initiate the DOACs compared with those who initiate warfarin	DOACs Vs warfarin	Age, sex	history of stroke, PAD, history of bleeding, alcohol abuse, heart failure, ischemic heart disease, chronic kidney disease, liver failure, MI, female gender, Calendar years, 1-year increments, HTN, DM, Concomitant pharmacotherapy, NSAID, Antiplatelet Dipyridamole, Beta-blockers, Calcium channel blockers, Loop diuretics, Amiodarone, Renin-angiotensin system inhibitors			aOR, 95%CI
Pandya E.Y. et al, 2017	to document the use of antithrombotic in hospitalized	DOACs Vs warfarin	Age	renal impairment			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	patients with AF; report the proportion of patients prescribed DOACs compared with warfarin; and identify the factors predicting the use of NOACs versus warfarin						
Park S. et al, 2021	to investigate clinicians' prescription behaviours and the factors influencing the choice between DOACs in alignment with the current clinical evidence. To see how patient-related clinical factors, such as age,	dabigatran Vs rivaroxaban Apixaban Vs rivaroxaban Edoxaban Vs rivaroxaban	Sex, Age	prior stroke/TIA Patients with renal disease AF type paroxysmal, CHF, HTN, DM, cancer, antiplatelet use, ATRIA score	Type of medical institution/ Tertiary (R) primary &others insurance type Region/ Capital reference / Metropolitan or others		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	sex, and comorbidities, have been incorporated in the process. of DOAC selection in a real-world setting						
Patel P.A et al, 2015	to characterize the prevalence, patterns, and predictors of DOAC versus warfarin therapy at discharge among AF patients hospitalized with ischemic stroke or TIA.	DOACs (dabigatran & rivaroxaban Vs warfarin)	Age Race /ethnicity Frailty Smoking, Sex	Anticoagulation before admission worsening creatinine, prosthetic heart valve, Impaired ambulation/Ambulatory status (vs ambulate independently), Unable to ambulate (more significant) or ambulate with assistance, discharge antiplatelet therapy. Medical history of coronary disease	Hospital region, NO. of beds, Rural vs. urban Insurance type (Medicare or Medicaid insurance status)		aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
				previous stroke/TIA, Discharge to home (vs other), Prior antiplatelet use, HF, HTN, DM			
Potpara TS et al, 2017	patterns of AF management in routine practice in the Balkan Region the Serbian Atrial Fibrillation Association (SAFA) and the uptake of DOAC use	DOACS Vs warfarin		Malignancy, HF, Valvular heart disease A rhythm control strategy prior OAC, prior antiplatelet use	Healthcare setting (treatment in a hospital-based)	Treatment by a cardiologist	aOR, 95%CI
Rodríguez-Bernal, C.L. et al, 2017	To assess patterns of initiation of VKA and DOAC in naive patients with non-valvular atrial fibrillation and the factors associated with starting treatment with DOAC	DOACs Vs VKA	Age	Previous ischemic stroke or TIA, Intracranial haemorrhage patients with renal, CHD, DM, DVT at least two emergency department visits, CHF	annual income	Health care utilization/ cardiology visit/neurologist visit	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Sanghai S R et al,2021	To assess the relations between OAC prescription and frailty among older patients with AF and evaluate the use of VKA vs. DOAC medications in this population	DOACs Vs VKA 53	pre-frail, non-Frail Frail				aOR, 95%CI
Shurrab M et al, 2019	To assess whether increased frailty of older atrial fibrillation (AF) patients in long-term care (LTC) facilities influenced physicians to prescribe DOACs over warfarin	DOACs Vs warfarin	Age, Sex	A CHESS scores, congestive HF, DM, stroke, HTN, CHADS score, and dementia			aOR, 95%CI
Sur N B et al, 2019	to identify utilization patterns of aspirin, warfarin,	DOACs Vs warfarin	Ethnicity, Sex				aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	and DOACs in hospitalized patients with IS and AF and to explore race-ethnicity and sex disparities in the treatment of AF prescribed at discharge from stroke hospitalization						
Urbaniak A M et al, 2017	Describe NOAC prescription patterns across the VTE surgery, AF, and DVT/PE indications; compare NOAC and warfarin patient characteristics such as age, gender, and cardiovascular (CV) co-medications across the	DOACS Vs Warfarin	Age, Sex	co-prescription of cardiac drug/ digoxin or vasodilators, co-prescription of antithrombotic agents clopidogrel and ticagrelor prescription of cardiac stimulants prior use of antiplatelet Using amiodarone, antihypertensive, diuretics, peripheral			aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	indications; and lastly identify predictors of DOAC prescribing in AF.			vasodilators, agents acting on renin-angiotensin system Comedication with Vaso protectives, b-blocking agents, and calcium channel blockers			
Wheelock K M, 2021	assessed DOAC prescribing practices of clinicians across the US between 2013 and 2018, evaluating both the proportion of clinicians prescribing DOACs relative to warfarin and the volume of their prescriptions across Part D Medicare beneficiaries over time	DOACs Vs Warfarin				clinician specialty, use of a DOAC in 2013, physician graduation year	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
Yong C M, 2017	Evaluated the association of patient insurance type to OAC prescription and type of therapy (warfarin or DOAC) among insured patients with AF at moderate to high risk of stroke (CHA2DS2-VASc ≥2)	DOACS Vs Warfarin			insurance type /private relative to Medicare /Military relative to Medicare /Medicaid relative to Medicare /Other insurance relative to Medicare		aOR, 95%CI
Zhu J, 2018	The associations of patient demographic characteristics (e.g., age, sex) and clinical factors (e.g., ischemic stroke risk, prescribing specialty) with prescription of a DOAC versus	DOACs Vs warfarin DOACS Vs DOACS	Age, Sex, race/ ethnicity	CHA2DS2-VASc, HAS-BLED, CCI score ≥4	education level, Income household net worth, Region of residence (Northeast, Midwest, South, West)	Prescriber specialty, Cardiologist, Primary care physician,	aOR, 95%CI

Author, year	Outcome of interest	Warfarin Vs DOACS **or** DOACS Vs DOACs	Patient-related factors	Clinical related	Socioeconomic	Prescriber related	Reported as
	warfarin, and the choice of DOACs						

OAC, oral anticoagulants; VKA, vitamin K antagonists; DOACs, direct oral anticoagulants; AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; PCI, Percutaneous coronary intervention; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation (Age , Anaemia, Severe renal disease, history of haemorrhage, Hypertension) ;ORBIT, (Older age, reduced haemoglobin, bleeding history, insufficient kidney function, treatment with antiplatelet therapy ;DVT_PE, deep vein thrombosis and pulmonary embolism; VTE_surg, prevention of venous thromboembolic events after a hip or knee surgery; TIA, transient ischemic attack; MI, myocardial infarction; PAD, peripheral arterial disease; T2DM, type2 diabetes; HTN, hypertension; HF, heart failure; COPD, chronic obstructive pulmonary disease ;CHD, coronary heart disease; BMI, body mass index; CKD, chronic kidney disease; NA, not available; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CCI score, Charlson comorbidity index; IVC, inferior vena cava filter; AP, antiplatelet; NSAIDs, nonsteroidal

Appendix S.2.2

Quality assessment of Cohort studies										
Author, year	Were the two groups similar and recruited from the same population?1	Were the exposures measured similarly to assign people to both exposed and unexposed groups?2	Was the exposure measured in a valid and reliable way?3	Were confounding factors identified?4	Were strategies to deal with confounding factors stated?5	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?6	Were the outcomes measured in a valid and reliable way?7	Was appropriate statistical analysis used?11	Total score	Rating
AbuDagga et al, 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7/8	Low risk of bias
Alwafi H. et al, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Bang O.Y et al, 2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7/8	Low risk of bias
Bezabhe, W.M et al, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Boivin-Proulx, L.-A et al, 2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7/8	Low risk of bias
Brown J et al, 2016	Yes	Yes	Yes	Yes	NO	Yes	NO	NO	5/8	Moderate risk of bias
Campitelli M.A et al, 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7/8	Low risk of bias

Cheng W. H et al, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Chopard R et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Desai N.R. et al, 2014	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	6/8	Moderate risk of bias
Douros A. et al, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Douros A et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Fohtung, R.B et al, 2017	Unclear	Yes	Yes	Yes	Yes	No	Unclear	Yes	5/8	Moderate risk of bias
García-Sempere, A. et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Gorczyca, I et al, 2020 /A	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	5/8	Moderate risk of bias
Gorczyca I. et al, 2020/B	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	7/8	Low risk of bias
Guerriero F, 2018	Yes	Yes	Yes	NO	Yes	Yes	Un clear	Yes	6/8	Moderate risk of bias
Grymonprez M. et al, 2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7/8	Low risk of bias
Ha HS et al, 2020	Yes	Yes	Yes	Yes	Yes	NO	Unclear	Yes	6/8	Moderate risk of bias

Halvorsen S et al, 2022	Yes	Yes	Yes	Yes	Yes	NO	yes	Yes	7/8	Low risk of bias
Jobski K et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	7/8	Low risk of bias
Kjerpeseth L J et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Komen J et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Koziel M et al, 2021	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	5/8	Moderate risk of bias
Lauffenburger JC et al, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Lee, KK et al, 2023	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	7/8	Low risk of bias
Lodzinski P et al, 2020	Yes	Yes	Yes	Unclear	Yes	NO	NO	Yes	5/8	Moderate risk of bias
Lorenzo A et al, 2022	Yes	Yes	Yes	Yes	Yes	Unclear	NO	Yes	6/8	Moderate risk of bias
Luger S et al, 2014	Yes	Yes	Yes	Yes	Yes	NO	Unclear	Yes	6/8	Moderate risk of bias
Martinez K A, 2022	Yes	Yes	NO	Yes	Yes	NO	Unclear	Yes	5/8	Moderate risk of bias
Marzec, L.N et al,2017	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	7/8	Low risk of bias

McDermott A et al, 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Nathan, A.S et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Olesen, J.B et al, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Pandya E.Y. et al, 2017	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Yes	5/8	Moderate risk of bias
Patel P.A et al, 2015	Yes	Unclear	Yes	Yes	Yes	NO	Yes	Yes	6/8	Moderate risk of bias
Rodríguez-Bernal, C.L. et al, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Sanghai S R et al,2021	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	7/8	Low risk of bias
Shurrab M et al, 2019	Yes	Unclear	Unclear	Yes	Yes	NO	Yes	Yes	5/8	Moderate risk of bias
Sur N B et al, 2019	Unclear	Yes	Yes	Yes	Yes	NO	Yes	Yes	6/8	Moderate risk of bias
Urbaniak A M et al, 2017	NO	Yes	Yes	Yes	Yes	NO	Yes	Yes	6/8	Moderate risk of bias

Wheelock K M, 2021	Unclear	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	7/8	Low risk of bias
Yong C M, 2017	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	7/8	Low risk of bias
Zhu J, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Baaik S.H et al, 2016, USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Quality assessment of Cross-sectional studies										
Author, year	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?2	Was the exposure measured in a valid and reliable way?3	Were objective, standard criteria used for measurement of the condition?4	Were confounding factors identified?5	Were strategies to deal with confounding factors stated?6	Were the outcomes measured in a valid and reliable way?7	Was appropriate statistical analysis used?8	Total score	Rating
Beier L et al, 2022	Yes	unclear	Yes	Yes	Yes	Yes	unclear	Yes	6/8	Moderate risk of bias
Bielecka B et al, 2021	Yes	NO	Yes	Yes	Yes	Yes	Yes	Yes	7/8	Low risk of bias

Brais C et al, 2017	Yes	Yes	NO	Yes	Yes	Yes	Yes	Yes	7/8	Low risk of bias
Chen Q et al, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Efird L.E et al, 2016	Unclear	Yes	Yes	NO	Yes	Yes	NO	Yes	5/8	Moderate risk of bias
Ehrlinder H et al, 2020	Yes	Yes	Yes	Yes	Yes	NO	NO	NO	5/8	Moderate risk of bias
Gurusamy V.K. et al, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Ha AC et al, 2016	Yes	Yes	Unclear	Yes	Yes	Yes	NO	Yes	6/8	Moderate risk of bias
Huiart L et al, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8	Low risk of bias
Ilomäki J et al, 2019	NO	Yes	NO	NO	Yes	Yes	Yes	Yes	5/8	Moderate risk of bias
McIntyre WF et al, 2018	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	7/8	Low risk of bias
Mostaza J.M. et al, 2021	Yes	Yes	Yes	NO	Yes	Yes	NO	Yes	6/8	Moderate risk of bias
Park S. et al, 2021	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	7/8	Low risk of bias
Gregory Y.H. Lip, 2015	Unclear	Yes	Yes	Yes	YES	NO	NO	NO	4/8	High risk of bias

Potpara TS et al, 2017	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	7/8	Low risk of bias

Appendix S.2.3

Direction of association between key factors and oral anticoagulant choice

Factor	Total No. of Studies	DOAC vs Warfarin	DOACs vs DOAC	DOACs vs warfarin	DOACs Vs DOACs
Demographic factors					
Age	46	44	7	✓8/44 (18%) *Older age groups more likely to be prescribed DOACs over warfarin. ✕22/ 44 (50%) * Older age groups less likely to be prescribed DOACs over warfarin. — 14/44 (32%) * No significant association between age and OAC choice.	✕3/7 (43%) An increase in age is associated with lower dabigatran use. ✓6/7(85.7%) Older age groups were more likely to be prescribed apixaban. — 1/7 (14%) Neither age above 79 nor below 65 influenced edoxaban prescribing — 1/7 (14%) No association between increasing age and rivaroxaban choice.
Sex	42	39	5	✓14/ 39 (35.8%) *A significant positive association between female sex and the prescription of DOACs ✕ 6/39 (15%) *Female sexes were less likely to be initiated on DOACs compared to men. — 20/39 (51%)	✕ 2/5 (40%) Female gender negative with dabigatran ✓2/5 (40%) Female gender positive with apixaban ✓1/5 (20%) Female gender positive with rivaroxaban

				*No significant association between sex and OAC choice.	✓1/5 (20%) Male gender positive with rivaroxaban and ✕ negative with apixaban
Ethnicity	8	8	1	✓4/8 (50%) *White patients had a statistically significant positive association with the use of DOACs compared to other ethnicities. *Asian/Pacific Islanders, and Hispanics, were more likely than whites to be prescribed a DOAC ✕ 4/ 8 (50%) *Black patients are significantly less likely to be prescribed a DOAC compared to white patients and other racial groups. — 1/8 (12.5%) *No association between ethnicity and OAC choice	— 1/1, no association between ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian) and the choice among DOACs
Frailty	4	3	1	✓2/3 (66.6%) *Being frail is significantly associated with higher odds of being initiated on DOAC instead of warfarin when compared to non-frail patients. — 1/3 (33.3%) *No significant association between frailty and OAC choice.	✓1/1 Apixaban was the preferred DOAC among fragile patients
Weight/BMI	10	10	2	✓ 1/10 (10%) * Lower BMI (<18.5 kg/m²) was positively associated with DOAC prescribing.	✕1/2 (50%) body weight >120 kg was an independent negative factor for using edoxaban, and — not a factor for

				✕ 2/10 (20%) *Higher BMI (>40 kg/m² and 25-40 kg/m²) had a lower prevalence of DOAC use. *Body weight (<50 kg or >120 kg) was a negative factor for DOAC use compared to weights of 50-120 kg. — 8/10 (80%) *No significant association between weight or BMI class and OAC choice	prescribing rivaroxaban or apixaban compared to weight 50-120 kg. ✕1/2 (50%) apixaban initiators were less likely to be overweight (BMI > 30) compared to the other DOACs.
Region/area of living	12	12	-	The nature and strength of this association varied depending on the specific region under investigation.	-
Clinical factors					
Kidney-related problems	35	33	5	✓ 6/33 (18%) *Preserved kidney function strong factor in choosing DOAC. ✕ 24/33 (73%) *Renal impairment associated with a reduced likelihood of using DOACs, and instead favoured warfarin. — 2/33 (6%) *Abnormal renal function was not identified as a factor associated with the choice of DOACs compared to VKAs.	✕ 5/5 (100%) a significant positive association between the prescription of apixaban and decreasing renal function

History of bleeding	24	23	2	✓ 6/23 (26%) * History of bleeding was a positive factor for DOAC prescribing. ✕6/23 (26%) *Prior bleeding was a negative factor for the use of DOAC compared to other anticoagulants. — 11/23 (47.8%) * No significant association between various bleeding types and OAC choice.	✕1/2 (50%) rivaroxaban is less frequently prescribed for patients with recent bleeding compared to apixaban and dabigatran. ✕1/2 (50%) rivaroxaban less frequently prescribed for patients with recent bleeding, ✓ apixaban more frequently prescribed for patients with recent bleeding. — 2/2 (100%) no association between recent bleeding and the choice of edoxaban compared to other DOACs
Bleeding risk	22	21	3	✓1/21 (4.7%) *Higher HAS-BLED scores favoured the use of DOACs. ✕ 9 /21 (43%) *pre-index higher risk of bleeding associated with significantly lower odds of DOAC use. — 52% (11/21) HAS-BLED score ≥ 2, compared to < 2, or ORBIT bleeding score did not significantly influence oral anticoagulant choice.	✓ 2/3 (66.6%) apixaban preferred over dabigatran or rivaroxaban as a new prescription in patients with higher HAS-BLED scores
Thromboembolic Risk	26	26	6	✓ 5/26 (19%) * Higher thromboembolic risk significantly favoured DOAC initiation. ✕ 8/26 (30%)	✓ 3/6 (50%) individuals with higher baseline thromboembolic risk (CHADS-VASC score ≥ 3) were more likely to be initiated on apixaban compared to dabigatran or rivaroxaban

				*Increased thromboembolic risk, indicated by higher CHA2DS-VASc scores (≥ 2), (≥ 4), and (≥5), reduced the odds of DOAC use — 12/26 (46%) *No significant association between thromboembolic scores and OAC choice.	— 3/6 (50%) no significant association between CHADS-VASC score 1 and≥ 2 for the choice among DOACs.
Prior Stroke or TIA	26	25	2	✓ 9/25 (36%) *A history of stroke or TIA significantly favoured DOAC use ✕ 10/25 (40%) * A preference for warfarin. — 6/25 (24%) * No significant association.	✓2/2 apixaban is more likely prescribed in patients with a history of prior ischemic stroke or TIA when compared to rivaroxaban
Anti-platelet medication	24	23	1	✓ 7/23 (30.4%) * Using antiplatelets was associated with significantly higher odds of being initiated on DOACs. ✕ 11/23 (47.8%) *Antiplatelet use negatively influenced DOAC prescribing — 5/23 (21.7%) *No significant association between antiplatelet use on OAC choice.	— 1/1 no association found between antiplatelet use and the choice among individual DOACs.

Pre-index heart failure (HF)	29	28	1	✓ 2/28 (7%) *HF significantly favoured DOAC use. ✕ 17/28 (60%) *a negative association between HF and DOAC use, favouring warfarin — 9/28 (32%) *No significant influence of HF on OAC choice	— 1/1 no association between HF and the choice among different DOACs.
Prior use of OAC	5	5	-	✓ 2/5 (40%) * Prior DOAC use within the 2 weeks before cohort entry was a significant factor for DOAC use, and no prior OAT use was a strong independent factor of the decision to initiate a DOAC. ✕ 4/5 (80%) * Prior use of warfarin was a determinant of being less likely to be prescribed DOACs.	-
Liver disease	14	13	2	✓1/13 (7.6%) *DOAC more likely to be prescribed for patients with abnormal liver function. ✕ 6/13 (46%) * Liver disease significantly associated with lower odds of initiating DOACs compared to warfarin. — 6/13 (46%)	— 1/2 No association was observed for the choice of apixaban — 1/2 no association was observed for the choice of rivaroxaban ✓1/2 liver disease increased the probability of receiving rivaroxaban. ✓1/2 in patients with acute VTE, liver cirrhosis was an independent positive factor for edoxaban use.

				* Liver disease was not found to be a determinant for prescribing DOACs or warfarin	
Pre-index Hypertension	22	21	1	✓ 5/21 (24%) *Pre-index HTN was significantly linked to an increased likelihood of receiving DOACs ✕ 2/2 (19.5%) *HTN a significantly negative factor for initiating DOACs. — 14/21 (66%) *No significant association between HTN and OAC choice	— 1/1 one study found no association between hypertension and the choice among different DOACs.
Diabetes	25	24	1	✕ 13/24 (54%) *DM significantly associated with a lower DOAC prescribing — 11/24 (45%) *Did not find DM to be significantly associated with OAC choice	— 1/1 no association between DM and the choice of individual DOACs.
Previous Thromboembolic Event	9	8	2	✓2/8 (25%) *Previous thromboembolism was significantly a positive factor for DOAC selection. ✕ 5/8 (62%) *Prior venous thromboembolism such as deep vein thrombosis or pulmonary embolism was negatively associated with DOAC prescribing.	— 1/2 Prior VTE was not a factor for the choice of apixaban. ✓2/2 rivaroxaban was significantly more likely to be used in patients with prior VTE. ✕1/2 prior VTE was an independent negative factor for the use of edoxaban.

				— 1/8 (1.5%) *Thromboembolism was not a significant factor affecting the choice of OAC.	
Coronary Artery Disease (CAD)	19	19	1	✕12/19 (63%) *Ischemic heart disease and previous MI were negative factors for initiating DOACs compared to warfarin. — 9/19 (47%) *No association between coronary heart disease previous myocardial infarction, and the choice between DOACs or warfarin.	— 1/1 no association between the prescription of dabigatran versus rivaroxaban or apixaban versus rivaroxaban in patients with a history of CAD (119).
Vascular Disease	14	14	-	✕ 7/14 (50%) *Vascular disease as a negative factor for DOAC selection and preferred warfarin. — 7/14 (50%) *Peripheral arterial disease and vascular disease were not significant factors for DOAC prescribing.	-
Dementia	12	12	1	✓3/12 (25%) *Found that being diagnosed with dementia was a positive factor of DOAC prescribing. ✕ 2/12 (16%) *Two studies showed that a history of dementia was a significantly negative factor for initiating DOACs.	✓1/1 dabigatran was more commonly prescribed than rivaroxaban, — no significant difference or association observed between the choice of apixaban over rivaroxaban in patients with dementia.

				➖7/12 (58.3%) * Dementia had no association with the choice between DOACs and warfarin.	
Recent Falls/Functional Dependency	8	8	-	✓1/8 (12.5%) *Recent falls were linked to significantly increased odds of being initiated on DOACs compared to VKAs. ✕ 2/8 (25%) *Impaired ambulation, such as being unable to ambulate or ambulate with assistance, was associated with a decreased likelihood of DOAC use versus warfarin. *Patients with a history of falls were less likely to receive a prescription for a DOAC. ➖5/8 (62%) History of falling or functional dependency was not a significant factor for the use of DOACs over warfarin.	-
Cancer	12	12	-	✓3/12(25%) * Malignancy as a positive factor for treatment with DOACs. ✕ 2/12(16%) *Malignancy was associated with non-prescription of DOACs. ➖7/12 (58%)	-

				*Malignancy was not associated with the choice of OAC.	
Type of Atrial Fibrillation (AF)	10	10	1	✓3/10 (30%) *Non-permanent AF was associated with the selection of DOACs over VKAs. ✕ 2/10 (20%) * Non-paroxysmal AF was associated with warfarin use over DOAC use. *Patients with persistent or permanent AF had a significantly lower likelihood of DOAC use compared to those with paroxysmal AF — 5/10 (50%) *Did not find a significant association between AF type and prescribed OAC.	
Year of Anticoagulant Prescription	13	13	1	✓13/13(100%) *Thirteen studies showed a strong association between the year of first anticoagulant prescription (1-year increments from 2011) and DOAC use.	✓1/1 Between different DOACs, the utilization of edoxaban and apixaban increased significantly from 2013-2015 to 2016-2018 and 2019-2021, showing a significantly positive association in later years. ✕ 1/1 Conversely, compared to 2013-2015, the usage of rivaroxaban decreased in 2016-2018 and 2019-2021. Thus, acting as a negative factor for rivaroxaban use.
Charlson Comorbidity Index (CCI) Score	9	9	1	✓4/9 (44%)	✓1/1 In comparison between DOACs, apixaban was generally preferred over dabigatran or rivaroxaban as a new prescription for patients with higher CCI

				*Multimorbidity (CCI ≥ 4 vs. <4) is associated with significantly higher odds of being initiated on DOACs than VKAs. *A higher CHESS score of (≥2) compared to <2 increased the use of DOACs in comparison to warfarin by 2.64 times. ✕ 3/9 (33%) *Higher CCI scores were associated with lower odds of DOAC use. *Burden of comorbidity was associated with less treatment with DOAC and VKA. — 2/9 (22%) *CCI was not a determinant for prescribing DOACs vs warfarin.	scores in both periods 2013-2014 and 2015-2017 (96)
Dyslipidaemia	6	6	-	✓4/6 (66%) *Dyslipidaemia was positively associated with DOAC prescribing. — 2/6 (33%) * No association between hyperlipaemia and the choice of DOAC or warfarin.	-
AF-related Procedures	5	5	-	✓5/5 (100%) A pre-index AF-related procedure was positively associated with DOAC use. Device therapy (pacemaker, CRT, ICD), AF cardioversion, and rhythm control strategies	-

				were all independent positive factors for prescribing DOACs.	
Polypharmacy	4	4	-	✓1/4 (25%) No polypharmacy was a positive factor for DOAC use. ✕ 2/4 (50%) As the number of co-prescribed medicines increased, an increased likelihood of receiving warfarin as opposed to DOACs. — 1/4 (25%) The number of medications (≥6) was not a factor for DOAC prescribing.	-
Socioeconomic factors					
Income Level	7	7	1	✓6/7 (85%) *Significantly higher likelihood of initiating DOACs over VKAs among those with higher incomes. ✕ 1/7(14%) *Significantly a negative association between lower income and the prescription of DOACs.	— 1/1 no association Household net worth and the choice among DOACs
Type of health insurance	7	7	-	The diverse range of health insurance systems/types across different countries led to associations that are specific to each country. Overall, distinctions between having private, military, or public insurance, on the choice of OAC was significant.	-

Education Level	4	4	-	✓2/4 (50%) *a preference for DOACs among individuals with higher education levels (university or advanced degrees) compared to VKA. ✕ 1/4 (25%) * Lower education level ≤ high school compared to college or ≥ bachelor's degree was negative for DOAC use. — 1/4 (25%) *Percent graduated college or high school in zip code were not associated with the choice between warfarin or DOACs.	-
Clinical Care Setting/ institution type	5	5	-	✓4/5 (80%) * In general practice/primary care or specialist office settings were more likely to initiate DOACs than those in university hospital settings. ✕ 2/5 (40%) *Being a hospital-based center was negatively associated with DOAC use, and university hospitals were more likely than community hospitals to prescribe VKAs. — 1/5 (20%) * No significant difference in DOAC vs. warfarin use when comparing cardiology practice sites to general medicine practice sites.	-

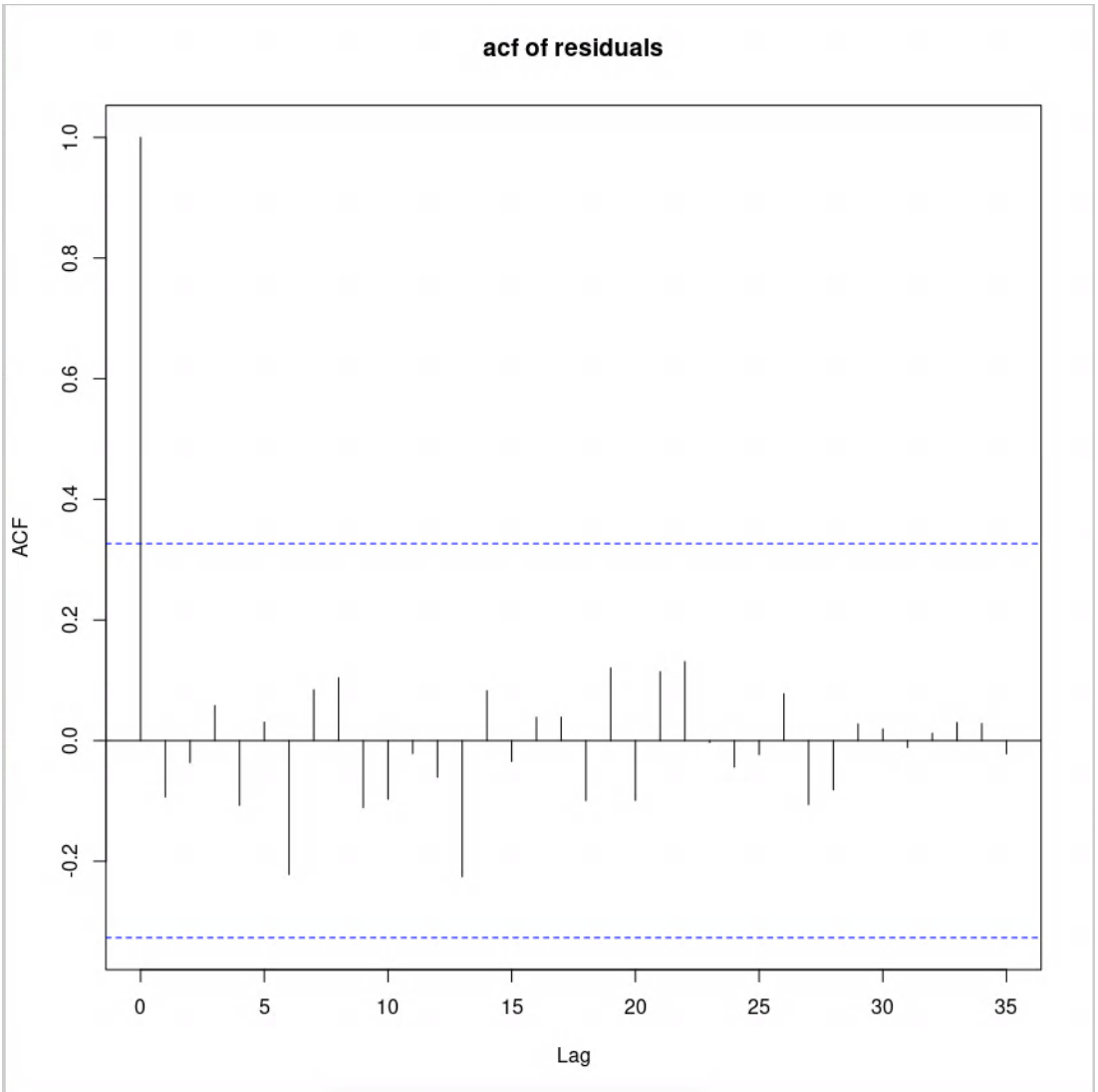
Prescriber related factors					
Prescriber specialty	13	13	1	✓12/13 (92%) *Prescriptions by specialists (e.g., cardiologists, neurologists) were significantly more likely to initiate DOACs rather than VKAs compared to those prescribed by general practitioners, primary care physicians, or family doctors. —3/13 (23%) *Prescriber specialty did not significantly influence the choice between DOACs and VKAs.	1/1 ✓Between 2013 and 2014, primary care physicians were more likely than cardiologists to prescribe rivaroxaban or dabigatran instead of apixaban. However, from 2015 to 2017, this association weakened for rivaroxaban and became statistically insignificant for dabigatran.

OAC, oral anticoagulants; VKA, vitamin K antagonists; DOACs, direct oral anticoagulants; AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation (Age , Anaemia, Severe renal disease, history of haemorrhage, Hypertension) ;ORBIT, (Older age, reduced haemoglobin, bleeding history, insufficient kidney function, treatment with antiplatelet therapy ; TIA, transient ischemic attack; MI, myocardial infarction; PAD, peripheral arterial disease; T2DM, type2 diabetes; HTN, hypertension; HF, heart failure; CHD, coronary heart disease; BMI, body mass index; CKD, chronic kidney disease; CCI score, Charlson comorbidity index; NSAIDs, nonsteroidal anti-inflammatory drugs.CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; ✓positive association, × negative association, — no association

Appendix S.5.1

The autocorrelation function (ACF) of residuals for the incident oral anticoagulant user.

With the exception of lag 0, all autocorrelation coefficients fall within the 95% confidence bounds, indicating no evidence of residual autocorrelation and supporting the adequacy of the model specification.



Appendix S.5.2

Sensitivity analyses for total number of prescriptions using alternative model specifications and treatment of March 2020

	Baseline trend (β1)	Level change after first lockdown (β2)	Time trend after first lockdown (β3)	March 2020 dummy coefficient
One breakpoint (incl. March)	261.4 (-76.4, 599.2)	5721.5 (-3059.6, 14502.5)	-1379.2 (-2298.3, -460.2)	
P-value	0.125	0.195	**0.004**	
One breakpoint (excl. March)	261.4 (-35.5, 558.3)	-605.4 (-9190.9, 7980.2)	-745.1 (-1636.5, 7980.2)	
P-value	0.082	0.886	0.098	
One breakpoint + March dummy	261.4 (-35.5, 558.3)	-605.4 (-1636.5, 146.3)	-745.1 (-1636.5, 146.3)	22186.1 (9006.5, 35365.8)
P-value	0.082	0.886	0.098	**0.0016**

Note: All models use a single breakpoint at March 2020. Models differ in the treatment of March 2020 (included, excluded, or adjusted using a dummy variable).

Appendix S.5.3

Sensitivity analyses for interrupted time series analysis of prevalent OAC users (one breakpoint model)

	Baseline trend (β1)	Level change after 1st lockdown (β2)	Trend change after 1st lockdown (β3)	March 2020 dummy coefficient
One breakpoint (incl. March)	380.35 (197.82, 562.87)	3059.99 (-1685.18, 7805.15)	-803.21 (-1299.85, -306.57)	
P-value	**< 0.001**	0.199	**0.0023**	
One breakpoint (excl. March)	380.34 (217.78, 542.90)	-220.45 (-4921, 4480.08)	-474.42 (-962.47, 13.61)	
P-value	**<0.001**	0.924	0.056	

One breakpoint + March dummy	380.34 (217.78, 542.91)	-220.45 (-4921, 4480.08)	-474.42 (-962.47, 13.61)	11503.43 (4287.62, 18719.22)
P-value	**<0.001**	0.924	0.056	**0.0026**

Note: All models use a single breakpoint in March 2020. Models differ in the treatment of March 2020 (excluded or adjusted using a dummy variable).

Appendix S.5.4

Sensitivity analyses for incident OAC users using one-breakpoint models, excluding March 2020, and including a March 2020 dummy variable.

	Baseline trend (β1)	**Level change after first lockdown (β2)**	**Time trend after first lockdown (β3)**	**March 2020 dummy coefficient**
One breakpoint (excl. March)	0.89 (-4.35, 6.13)	-676.53 (-861.06, -492.01)	73.316 (47.025, 99.61)	
P-value	0.73	**< 0.001**	**< 0.001**	
One breakpoint + March dummy	0.89 (-4.35, 6.13)	-676.53 (-861.06, -492.01)	73.316 (47.025, 99.61)	637.43 (389.66, 885.20)
P-value	0.73	**< 0.001**	**< 0.001**	**< 0.001**

Note: All models use a single breakpoint in March 2020. Models differ in the treatment of March 2020 (excluded or adjusted using a dummy variable).

Appendix S.5.5

Sensitivity analyses of switching from VKA to DOAC using a 90-day gap definition, including alternative one-breakpoint models and treatment of March 2020

Switching Definition	**Baseline trend (β1)**	**Level change after first lockdown (β2)**	**Time trend after first lockdown (β3)**	**March 2020 dummy coefficient**
One breakpoint (incl. March)	0.0022 (-0.0226, 0.0269)	3.238 (2.594, 3.882)	-0.316 (-0.383, -0.249)	
P-value	0.860	**<0.001**	**<0.001**	
One breakpoint (excl. March)	0.0022 (-0.0226, 0.0269)	2.823 (2.173, 3.472)	-0.274 (-0.342,	

			-0.207)	
P-value	0.860	**<0.001**	**<0.001**	
One breakpoint + March dummy	0.0022 (-0.0226, 0.0269)	2.823 (2.173, 3.472)	-0.274 (-0.342, -0.207)	1.456 (0.458, 2.453)
P-value	0.860	**<0.001**	**<0.001**	**0.005**

Note: All models use a single breakpoint in March 2020. Models differ in the treatment of March 2020 (excluded or adjusted using a dummy variable).

Appendix S.7.1

Survival probability estimates for outcomes across time

Time (days)	Treatment group, DOAC type	N at Risk	Cumulative Events	Survival Probability	95% CI (Lower–Upper)
All Stroke					
60	**All**	11781	27	0.997785461	0.997–0.998
180		10476	73	0.993650661	0.992–0.995
365		7776	135	0.987086726	0.984–0.989
1095		488	217	0.963594623	0.957–0.970
60	**Apixaban**	5374	15	0.997298236	0.995–0.998
180		4801	35	0.993341546	0.991–0.995
365		3701	69	0.985563919	0.982–0.989
1095		302	112	0.961262429	0.952–0.970
60	**Edoxaban**	5188	11	0.997961358	0.996–0.999
180		4561	36	0.992863179	0.990–0.995
365		3128	60	0.986870755	0.983–0.990
1095		78	91	0.963755701	0.954–0.973
60	**Rivaroxaban**	1186	<10	0.999174236	0.997–1.000
180		1085	<10	0.998293906	0.995–1.000
365		921	<10	0.994454033	0.990–0.998
1095		105	14	0.977426322	0.964–0.990
Ischaemic stroke					
60	**All**	11818	26	0.997874893	0.997 – 0.998
180		10512	61	0.994744289	0.993 – 0.996

365		7804	116	0.988954523	0.986 – 0.991
1095		489	184	0.969192028	0.963 – 0.975
60	**Apixaban**	5393	15	0.99730825	0.995–0.998
180		4819	30	0.994353141	0.992–0.996
365		3713	61	0.987282456	0.984–0.990
1095		303	91	0.969497408	0.961–0.977
60	**Edoxaban**	5201	11	0.997966635	0.996–0.999
180		4574	30	0.994113594	0.992–0.996
365		3140	50	0.989174232	0.986–0.992
1095		78	80	0.966742506	0.957–0.976
60	**Rivaroxaban**	1190	<10	1	1.000–1.000
180		1089	<10	0.999122037	0.997–1.000
365		924	<10	0.995292728	0.991–0.999
1095		105	13	0.978300655	0.965–0.991
Acute MI					
60	**All**	12020	27	0.997833917	0.997–0.998
180		10675	55	0.995354863	0.994–0.996
365		7944	90	0.991797474	0.990–0.993
1095		503	158	0.969616455	0.962–0.976
60	**Apixaban**	5512	12	0.998	0.997–0.999
180		4897	27	0.995	0.993–0.997
365		3796	45	0.991	0.988–0.994
1095		313	79	0.967	0.956–0.978
60	**Edoxaban**	5772	13	0.998	0.996-0.999
180		4653	24	0.995	0.994-0.997
365		3201	38	0.992	0.990-0.995
1095		78	60	0.976	0.966-0.985
60	**Rivaroxaban**	1189	<10	0.999	0.998-1.000
180		1088	<10	0.997	0.995-1.000
365		914	<10	0.995	0.990-0.999
1095		108	12	0.973	0.959-0.987
TIA					

60	**All**	12669	<10	0.99931633	0.998 – 0.999
180		11239	24	0.998045309	0.997 – 0.998
365		8348	45	0.995993906	0.994 – 0.997
1095		525	69	0.98938767	0.986 – 0.992
60	**Apixaban**	5852	<10	0.999181827	0.998–0.999
180		5200	17	0.996989375	0.995–0.998
365		4021	25	0.995334012	0.993–0.997
1095		323	44	0.986250983	0.981–0.991
60	**Edoxaban**	5521	<10	0.999299196	0.998–0.999
180		4853	<10	0.998705383	0.997–0.999
365		3326	15	0.996855495	0.995–0.998
1095		86	18	0.994671362	0.991–0.997
60	**Rivaroxaban**	1251	<10	1	1.000–1.000
180		1146	<10	1	1.000–1.000
365		964	<10	0.99530979	0.991–0.999
1095		111	<10	0.990080117	0.981–0.998
PE					
60	**All**	11998	<10	1.000	0.999-1.000
180		10651	13	0.999	0.998-0.999
365		7889	24	0.998	0.997-0.999
1095		488	48	0.991	0.988-0.994
60	**Apixaban**	5409	<10	1.000	0.999-1.000
180		4822	<10	0.998	0.997-1.000
365		3721	15	0.997	0.995-0.998
1095		305	24	0.992	0.989-0.996
60	**Edoxaban**	5457	<10	1.000	0.999-1.000
180		4792	<10	0.999	0.999-1.000
365		3286	<10	0.999	0.997-1.000
1095		80	19	0.986	0.978-0.995
60	**Rivaroxaban**	1088	<10	1.000	1.000-1
180		999	<10	1.000	1.000-1

365		846	<10	0.997	0.997-1
1095		98	<10	0.990	0.990-1
Comp1					
60	**All**	11640	27	0.998	0.997-0.999
180		10350	66	0.994	0.993-0.996
365		7678	123	0.988	0.986-0.990
1095		474	202	0.965	0.959-0.972
60	**Apixaban**	5284	16	0.997	0.996-0.999
180		4719	34	0.993	0.991-0.996
365		3640	63	0.87	0.983-0.990
1095		294	99	0.965	0.957-0.974
60	**Edoxaban**	5158	11	0.998	0.997-0.999
180		4535	31	0.994	0.992-0.996
365		31110	54	0.988	0.985-0.991
1095		77	88	0.963	0.953-0.973
60	**Rivaroxaban**	1164	<10	1.000	1.000-1.000
180		1066	<10	0.999	0.997-1.000
365		901	<10	0.994	0.990-0.999
1095		100	15	0.976	0.962-0.990
Comp2					
60	**All**	11,143	32	0.997	0.996 – 0.998
180		9,907	90	0.992	0.990 – 0.993
365		7,334	164	0.984	0.981 – 0.986
1095		457	262	0.955	0.947 – 0.962
60	**Apixaban**	5047	17	0.997	0.995 – 0.998
180		4504	45	0.991	0.988 – 0.994
365		3467	81	0.982	0.978 – 0.986

1095		281	134	0.952	0.942 – 0.962
60	**Edoxaban**	4940	14	0.997	0.996 – 0.999
180		4345	43	0.991	0.988 – 0.994
365		2970	73	0.983	0.979 – 0.987
1095		75	108	0.958	0.948 – 0.968
60	**Rivaroxaban**	1126	<10	0.999	0.997 – 1.000
180		1032	<10	0.998	0.996 – 1.000
365		873	<10	0.990	0.984 – 0.996
1095		98	20	0.966	0.950 – 0.983
Other bleeding					
60	**All**	11,032	48	0.996	0.995 – 0.997
180		9,771	115	0.989	0.988 – 0.991
365		7,242	196	0.980	0.978 – 0.983
1095		444	325	0.943	0.936 – 0.951
60	**Apixaban**	5093	25	0.995	0.993 – 0.997
180		4517	58	0.988	0.986 – 0.991
365		3490	89	0.981	0.977 – 0.985
1095		276	152	0.944	0.933 – 0.955

60	**Edoxaban**	4820	19	0.996	0.995 – 0.998
180		4236	46	0.990	0.988 – 0.993
365		2900	81	0.981	0.977 – 0.985
1095		68	126	0.943	0.929 – 0.957
60	**Rivaroxaban**	1091	<10	0.997	0.993 – 1.000
180		993	<10	0.990	0.984 – 0.996
365		756	26	0.974	0.964 – 0.985
1095		98	47	0.940	0.923 – 0.958
All bleed					
60	**All**	10,023	69	0.993	0.992-0.995
180		8,869	172	0.983	0.980-0.985
365		6,559	290	0.968	0.965-0.972
1095		400	476	0.907	0.897-0.918
60	**Apixaban**	4590	33	0.993	0.991 – 0.995
180		4070	77	0.983	0.979 – 0.987
365		3154	123	0.971	0.966 – 0.976
1095		249	217	0.908	0.893 – 0.924
60	**Edoxaban**	4405	30	0.993	0.991 – 0.996
180		3866	78	0.982	0.978 – 0.986
365		2629	133	0.966	0.960 – 0.972

1095		60	194	0.910	0.891 – 0.928
60	**Rivaroxaban**	1002	<10	0.994	0.990 – 0.999
180		910	17	0.983	0.975 – 0.991
365		756	34	0.963	0.951 – 0.976
1095		89	64	0.908	0.885 – 0.932
Systemic embolism					
60	**All**	13079	<10	1.000	1.000-1.000
180		11601	<10	1.000	0.999– 1.000
365		8630	12	0.999	0.998-1.000
1095		530	26	0.996	0.994 – 0.998
SAH					
60	**All**	13261	<10	1.000	1.000-1
180		11765	<10	1.000	0.999-1
365		8759	<10	1.000	0.999-1
1095		547	<10	0.999	0.999-1
GI bleeding					
60	**All**	11984	32	0.99742404	0.996 – 0.998
180		10609	88	0.992481234	0.990 – 0.994
365		7869	151	0.985860194	0.983 – 0.988
1095		482	235	0.958877166	0.951 – 0.966
60	**Apixaban**	5509	13	0.997731488	0.996–0.999
180		4898	27	0.994994609	0.993–0.996
365		3798	54	0.988944473	0.986–0.991
1095		305	87	0.967332217	0.957–0.976

60	**Edoxaban**	5264	15	0.997254992	0.995–0.998
180		4609	50	0.990270472	0.987–0.993
365		3146	77	0.983480578	0.979–0.987
1095		75	108	0.948680368	0.923–0.974
60	**Rivaroxaban**	1169	<10	0.996649749	0.993–0.999
180		1065	11	0.990367018	0.984–0.996
365		892	20	0.981464576	0.973–0.989
1095		99	38	0.94893897	0.931–0.966
Hem stroke					
60	**All**	13221	<10	0.999926324	0.999 – 1.000
180		11730	15	0.998795019	0.998 – 0.999
365		8736	23	0.998015166	0.997 – 0.998
1095		546	45	0.992524816	0.989 – 0.995
ICH					
60	**All**	13283	<10	1	1-1
180		11784	12	0.999	0.998 – 0.999
365		8778	18	0.998	0.998– 0.999
1095		547	39	0.993	0.990 – 0.996
All-cause mortality					
60	**All**	13508	142	0.989734181	0.988– 0.991
180		12026	663	0.950159841	0.946 – 0.953
365		8969	1332	0.892779699	0.887 – 0.898
1095		561	2364	0.676912744	0.662 – 0.692

60	**Apixaban**	6277	76	0.988187467	0.985–0.990
180		5603	329	0.947026044	0.941–0.952
365		4343	654	0.888189364	0.880–0.896
1095		349	1183	0.675888276	0.656–0.696
60	**Edoxaban**	5870	48	0.992009949	0.989–0.994
180		5172	276	0.951823893	0.946–0.957
365		3569	553	0.895352836	0.887–0.903
1095		89	909	0.65710775	0.625–0.690
60	**Rivaroxaban**	1313	18	0.986582298	0.980–0.992
180		1208	57	0.956494754	0.945–0.967
365		1018	122	0.902188349	0.885–0.918
1095		118	267	0.706640504	0.673–0.741
CVD mortality					
60	**All**	13508	76	0.994495268	0.993 – 0.995
180		12026	369	0.971909625	0.969 – 0.974
365		8969	732	0.939710388	0.935 – 0.943
1095		561	1300	0.808906521	0.796 – 0.821
60	**Apixaban**	6277	45	0.992981526	0.990–0.995
180		5603	180	0.970708845	0.966–0.974
365		4343	351	0.938530913	0.932–0.944
1095		349	640	0.811154548	0.794–0.828
60	**Edoxaban**	5870	22	0.996344942	0.994–0.997
180		5172	157	0.972158625	0.967–0.976
365		3569	308	0.94043417	0.934–0.947

1095		89	508	0.793010382	0.767–0.819
60	**Rivaroxaban**	1313	<10	0.993264128	0.988–0.997
180		1208	32	0.975316989	0.966–0.983
365		1018	71	0.941896469	0.928–0.955
1095		118	149	0.825856617	0.796–0.856

Appendix S.7.2

All figures (A7.3–A7.23) with detailed curve descriptions.

Kaplan–Meier curves by treatment group demonstrated a lower probability of remaining stroke-free over time among patients who switched from VKAs to DOACs compared with those who continued VKA therapy (log-rank p < 0.0001), as shown in **Figure A7.3**. When stratified by DOAC type, Kaplan–Meier analysis of time to all stroke revealed a statistically significant difference in stroke-free survival across DOACs (log-rank p = 0.022). Patients treated with edoxaban exhibited higher stroke-free survival over 36 months compared with those receiving apixaban or rivaroxaban, whose survival curves largely overlapped throughout follow-up. The separation between survival curves emerged early and persisted over the duration of follow-up (**Figure A7.4**).

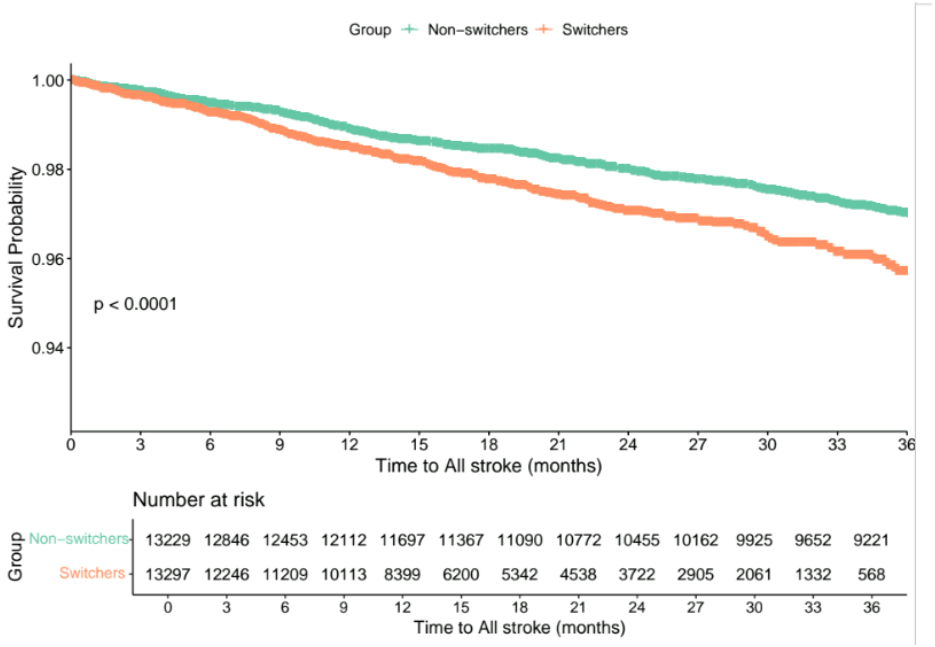


Figure A7.3: Kaplan–Meier survival curves for stroke risk by treatment group over 36 months

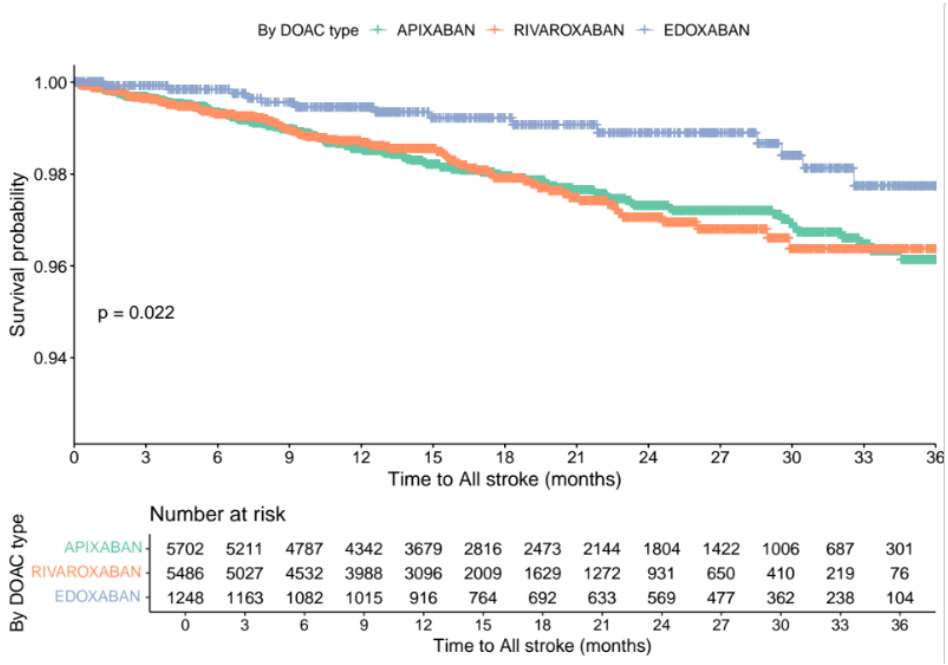


Figure A7.4: Kaplan–Meier survival curves for time to all stroke among patients who switched from VKAs to DOACs, by DOAC type (apixaban, rivaroxaban, and edoxaban) over 36 months.

The Kaplan–Meier survival curve for ischaemic stroke showed lower stroke-free survival probability among switchers compared to non-switchers over the 36-month follow-up period (log-rank $p < 0.0001$). The survival curves began to diverge early, and the separation widened over time, suggesting a sustained difference in risk of ischaemic stroke between the two groups as shown in **Figure A7.5**.

Kaplan–Meier analysis stratified by DOAC type revealed a borderline non-significant difference in ischaemic stroke-free survival over 36 months (log-rank $p = 0.06$). Patients on edoxaban had the highest survival probability throughout the follow-up, followed by apixaban and rivaroxaban. Although the survival curves began diverging gradually after the first year, overlapping confidence intervals and the non-significant p-value indicate that the observed trend should be interpreted with caution (**Figure A7.6**).

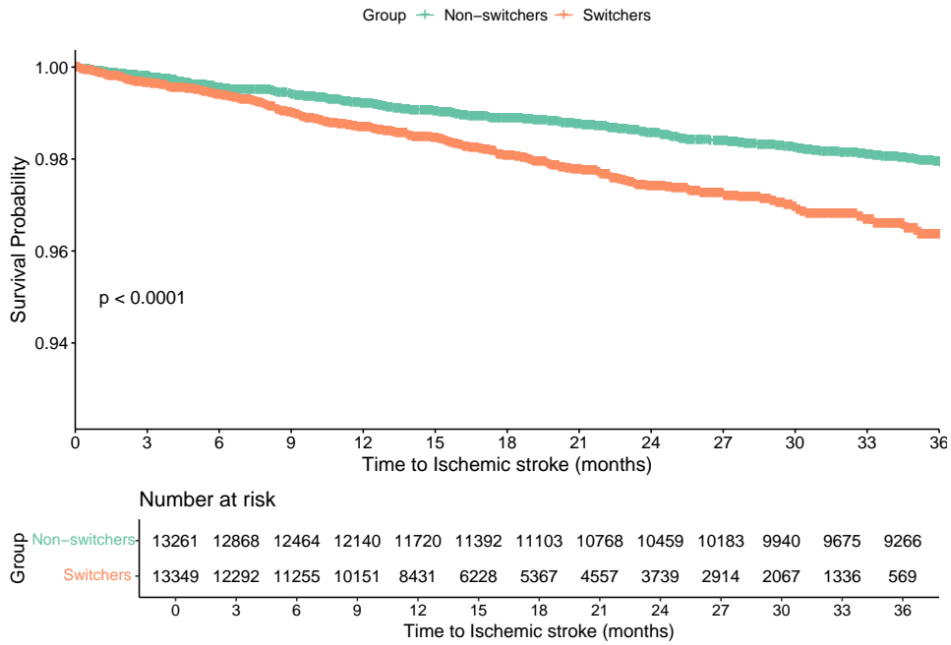


Figure A7.5: Kaplan–Meier survival curves for ischemic stroke risk by treatment group over 36 months

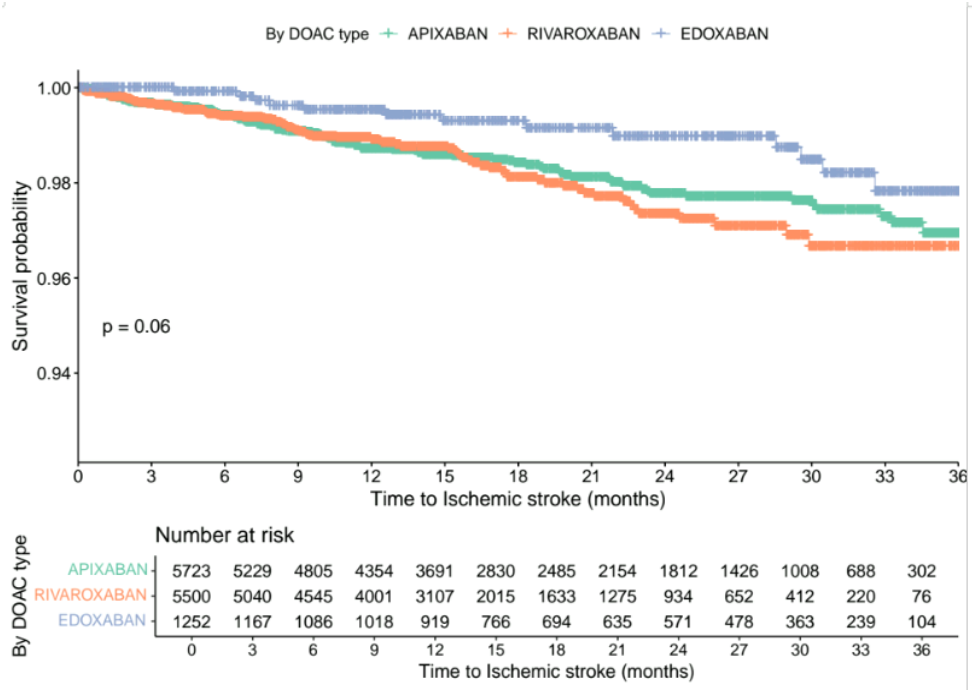


Figure A7.6: Kaplan–Meier survival curves for ischemic stroke risk by DOAC type (apixaban, rivaroxaban, edoxaban) over 36 months

The Kaplan–Meier analysis for time to first TIA showed a significant difference between switchers and non-switchers (log-rank p = 0.0006). Non-switchers consistently demonstrated higher TIA-free survival probability over the 36-month follow-up, indicating a lower cumulative incidence of TIA compared to those who switched to DOAC therapy (**Figure A7.7**).

The Kaplan–Meier survival analysis suggested only minor differences in TIA-free survival probability across DOAC types (log-rank p = 0.043). Over the 36-month follow-up, patients receiving rivaroxaban and edoxaban exhibited slightly higher TIA-free survival compared to those on apixaban, although all groups maintained high survival probabilities overall. The clinical relevance of this difference may be limited due to the small absolute differences observed (**Figure A7.8**).

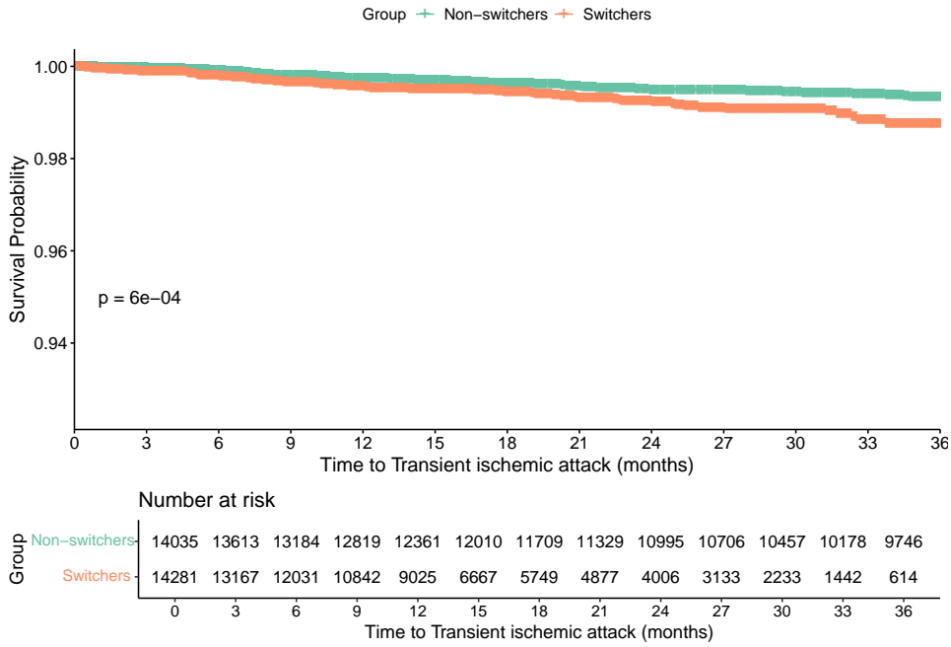


Figure A7.7: Kaplan–Meier survival curves for time to first transient ischemic attack (TIA) comparing switchers and non-switchers

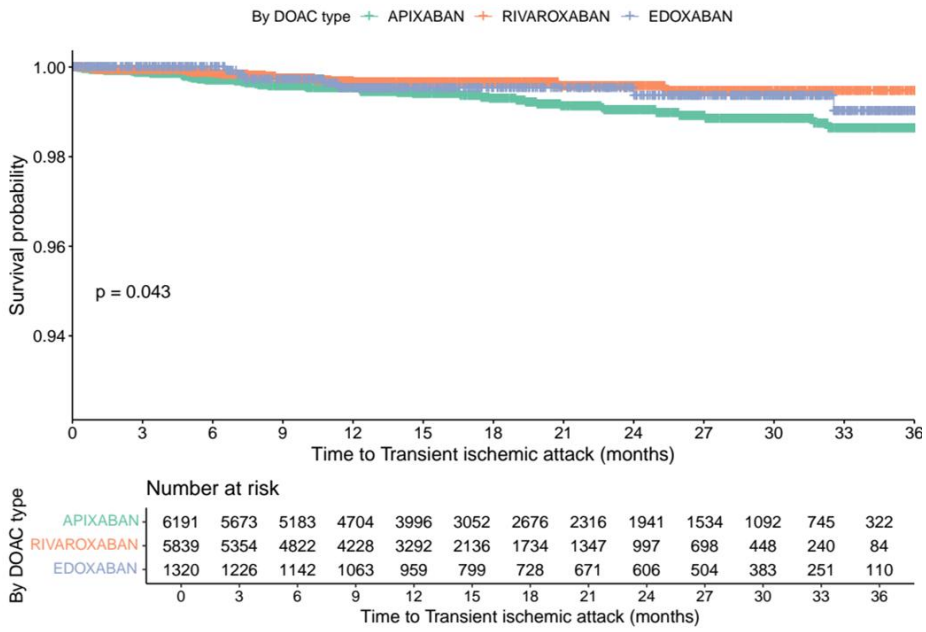


Figure A7.8: Kaplan–Meier survival curves for time to first transient ischemic attack (TIA) by DOAC type (apixaban, rivaroxaban, edoxaban).

In the time-to-event analysis for MI, non-switchers exhibited significantly higher MI-free survival compared to switchers over the 3-year follow-up (log-rank p = 0.0022). As illustrated in the Kaplan–Meier curves, the survival difference between groups widened progressively over time, suggesting an increased risk of MI among those who switched DOACs (**Figure A7.9**). However, Kaplan–Meier survival curves comparing time to MI by DOAC type showed minimal differences between apixaban, rivaroxaban, and edoxaban over 36 months (log-rank p = 0.61; results not shown).

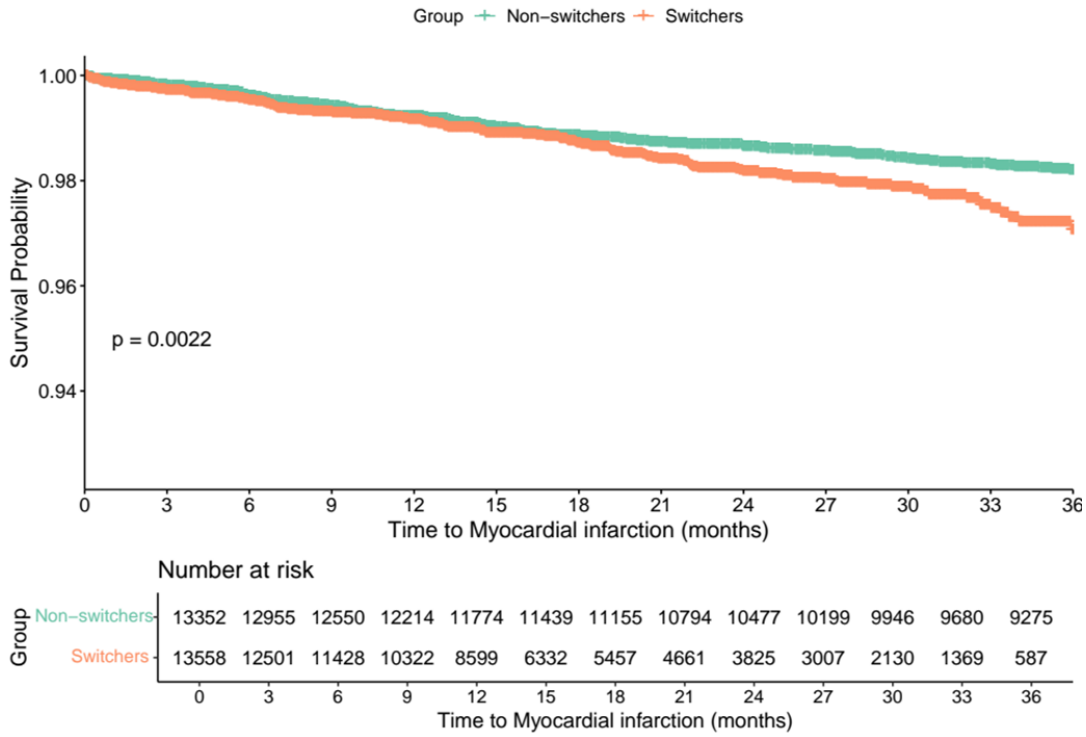


Figure A7.9: Kaplan–Meier survival curves for time to myocardial infarction among switchers and non-switchers over a 36-month period.

The time-to-event analysis showed a statistically significant difference in PE free survival between switchers and non-switchers (log-rank p = 0.044), with switchers exhibiting a slightly lower PE-free survival probability over the 36-month follow-up period (**Figure A7.10**). In contrast, Kaplan–Meier analyses comparing PE-free survival by DOAC type did not demonstrate meaningful differences between apixaban, rivaroxaban, and edoxaban (log-rank p = 0.14; results not shown), despite rivaroxaban showed a slightly higher survival probability.

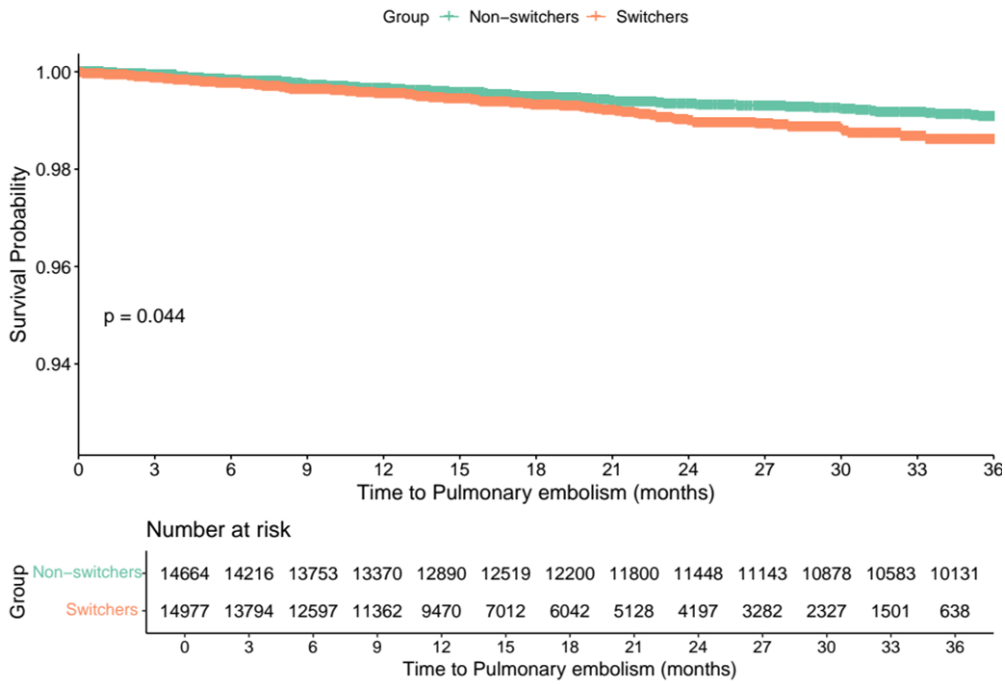


Figure A7.10: Kaplan–Meier survival curves for time to first pulmonary embolism (PE) among switchers and non-switchers.

Composite outcome A occurred more frequently among switchers compared to non-switchers. The Kaplan–Meier curves showed a significantly lower event-free survival in the switcher group (log-rank $p < 0.0001$; **Figure A7.11**). The difference between the groups widened progressively over the 36-month follow-up period. No meaningful difference in the time to Comp 1 was observed among the different DOAC types (apixaban, rivaroxaban, edoxaban) (results not shown).

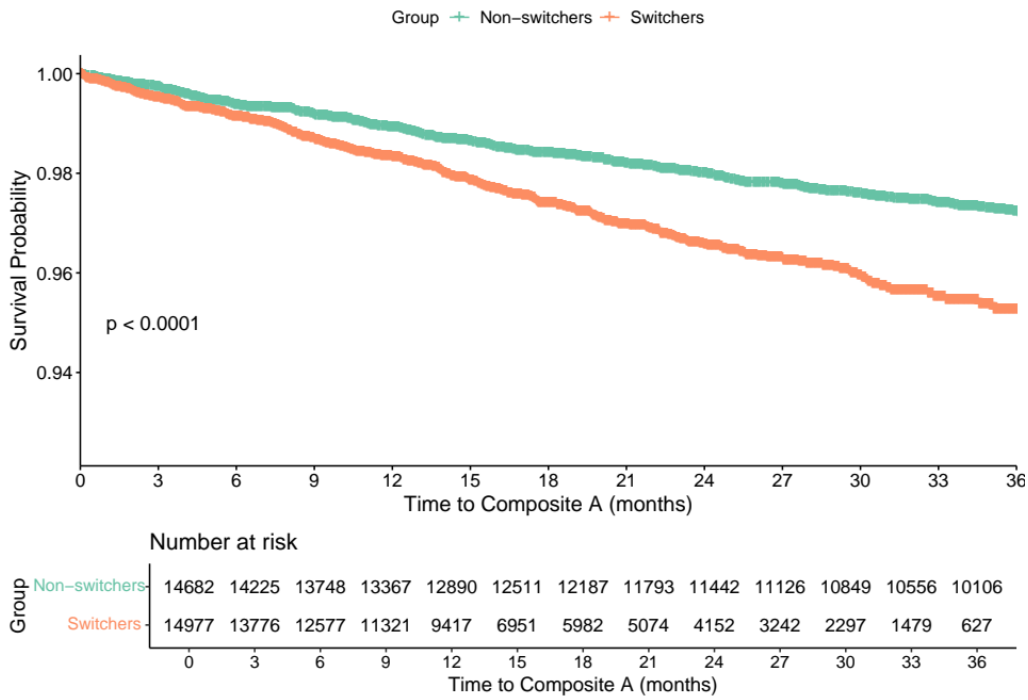


Figure A7.11: Kaplan–Meier curve showing time to composite outcome A in switchers vs. non-switchers.

The cumulative incidence of Comp B was significantly higher among switchers compared to non-switchers over the 36-month follow-up period. The Kaplan–Meier survival estimates demonstrated a clear separation between the two groups (log-rank $p < 0.0001$; **Figure A7.12**). At 36 months, a higher proportion of switchers experienced the outcome relative to non-switchers, indicating a statistically significant association between switching status and risk of Comp B.

The Kaplan–Meier curve in **Figure A7.13** illustrates the time to Comp B across different DOAC types (apixaban, rivaroxaban, edoxaban) over a 36-month follow-up period. Edoxaban was associated with a higher survival probability compared to apixaban and rivaroxaban. The difference between groups was statistically significant ($p = 0.01$), suggesting that the type of DOAC may influence the likelihood of experiencing Comp B.

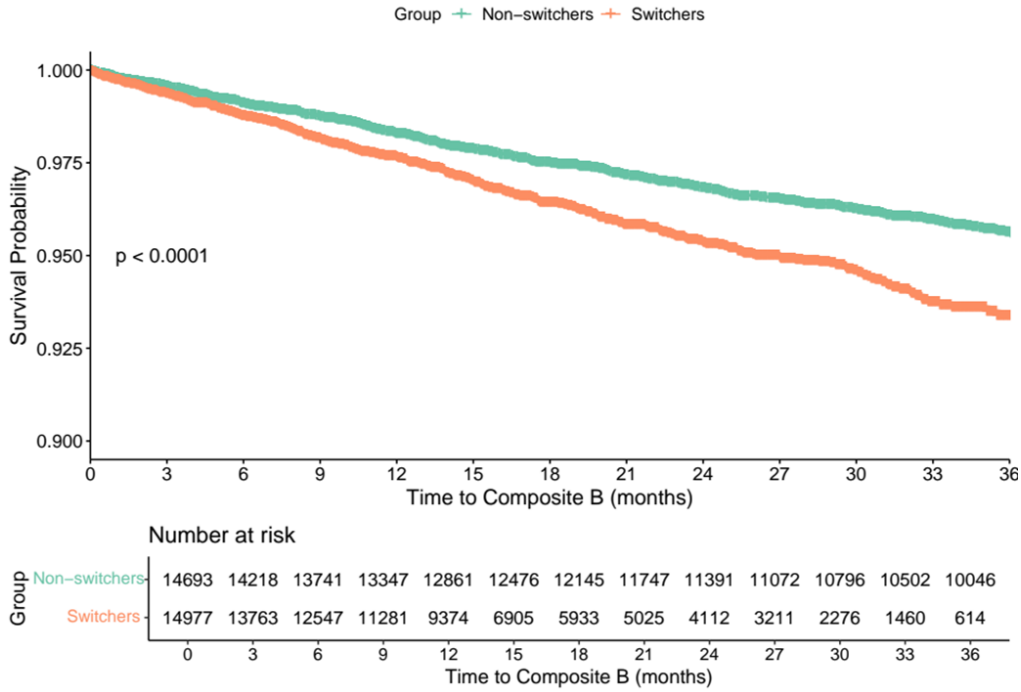


Figure A7.12: Kaplan–Meier curve showing time to composite outcome B in switchers vs. non-switchers.

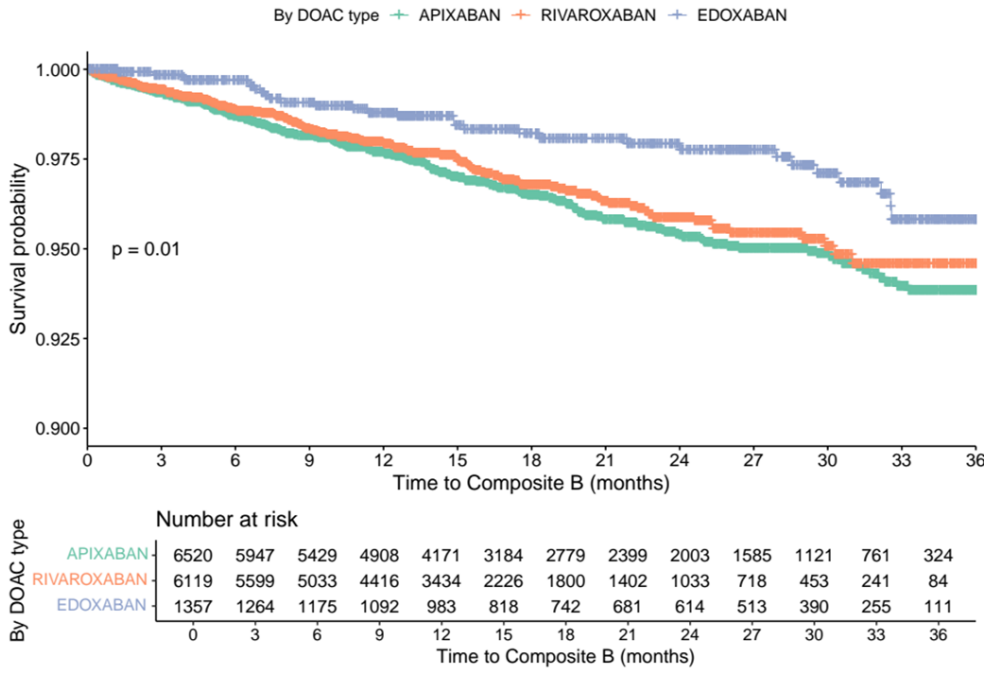


Figure A7.13: Kaplan–Meier curve showing time to composite outcome B by DOAC type.

The Kaplan–Meier curve illustrates the time to other major bleeding events in switchers versus non-switchers over a 36-month period. The survival probability was consistently higher in the non-switcher group compared to the switcher group. The difference between groups was statistically significant (p = 0.036) **Figure A7.14**.

The Kaplan–Meier curve shows time to other major bleeding events stratified by DOAC (apixaban, rivaroxaban, and edoxaban) over 36 months. Although minor visual differences in survival probability were observed, the log-rank test indicated no statistically significant difference between groups (p = 0.38). These findings are consistent with the adjusted Cox model, which showed no significant differences in other major bleeding risk across DOAC types (**Figure A7.15**).

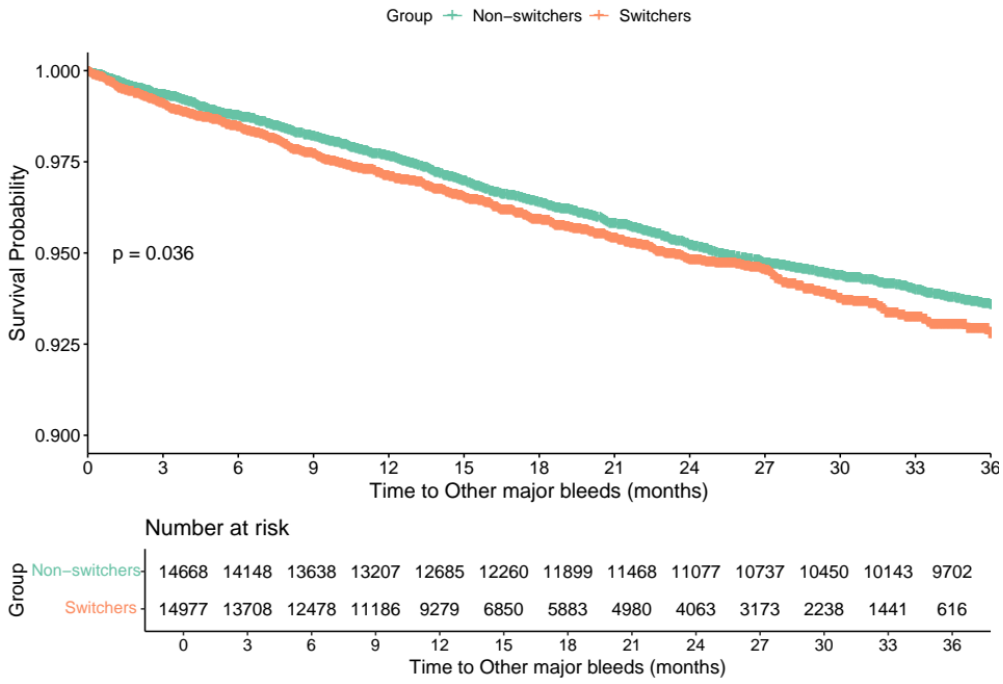


Figure A7.14: Kaplan–Meier survival curves for other major bleeds by treatment group over 36 months

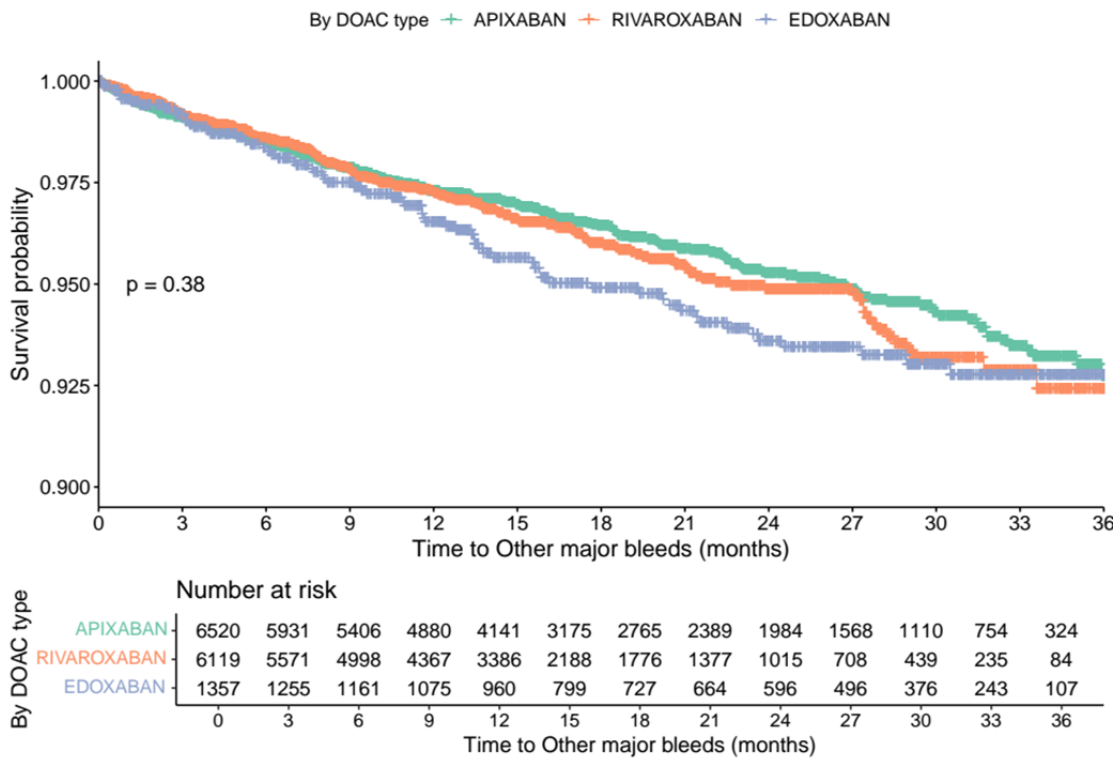


Figure A7.15: Kaplan–Meier curve showing time to other major bleeds by DOAC type.

The Kaplan–Meier curve illustrates time to all bleeding events among switchers and non-switchers over 36 months. Switchers exhibited a significantly higher cumulative incidence of bleeding compared to non-switchers. The difference between the groups was statistically significant (p = 0.0099), indicating a higher bleeding risk associated with switching anticoagulants (**Figure A7.16**).

Kaplan–Meier analysis of time to all bleeding events (composite) stratified by DOAC type over 36 months indicated differences between apixaban, rivaroxaban, and edoxaban (p = 0.014), with apixaban showing a relatively lower cumulative incidence of bleeding compared to the other two agents (**Figure A7.17**).

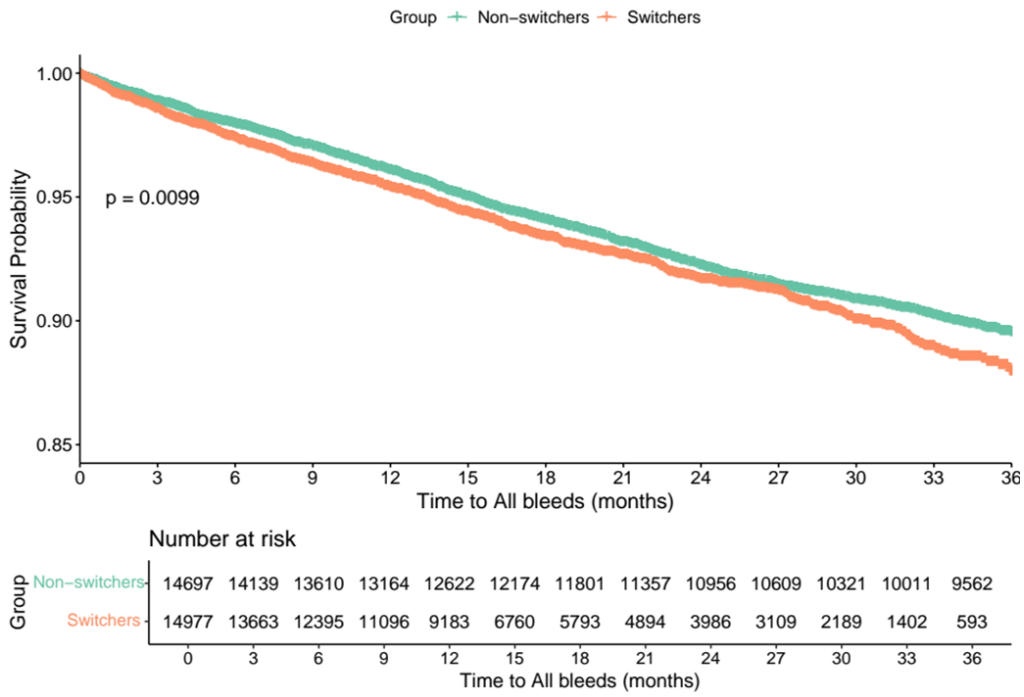


Figure A7.16: Kaplan–Meier survival curves for all bleeds by treatment group over 36 months

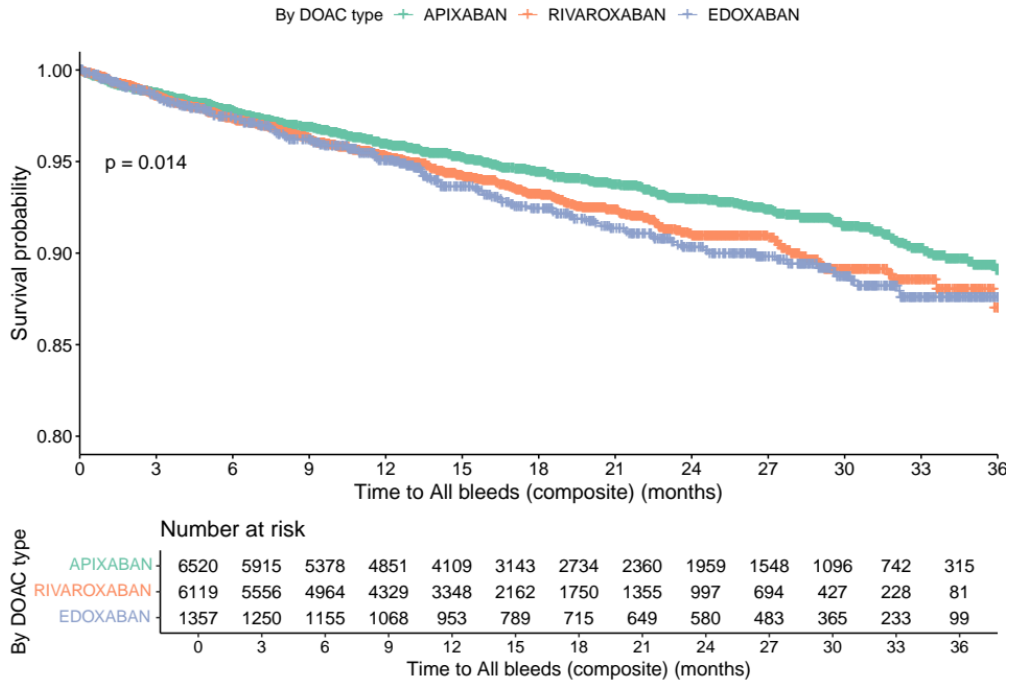


Figure A7.17: Kaplan–Meier curve showing time to all bleeding events (composite) by DOAC type

There was a statistically significant difference in the cumulative incidence of ICH between switchers and non-switchers (p = 0.016), with switchers showing a slightly lower risk over 36 months (**Figure A7.18**). There was no meaningful difference in the risk of intracranial hemorrhage between DOAC types over the 36-month follow-up period (p = 0.11) (results not shown).

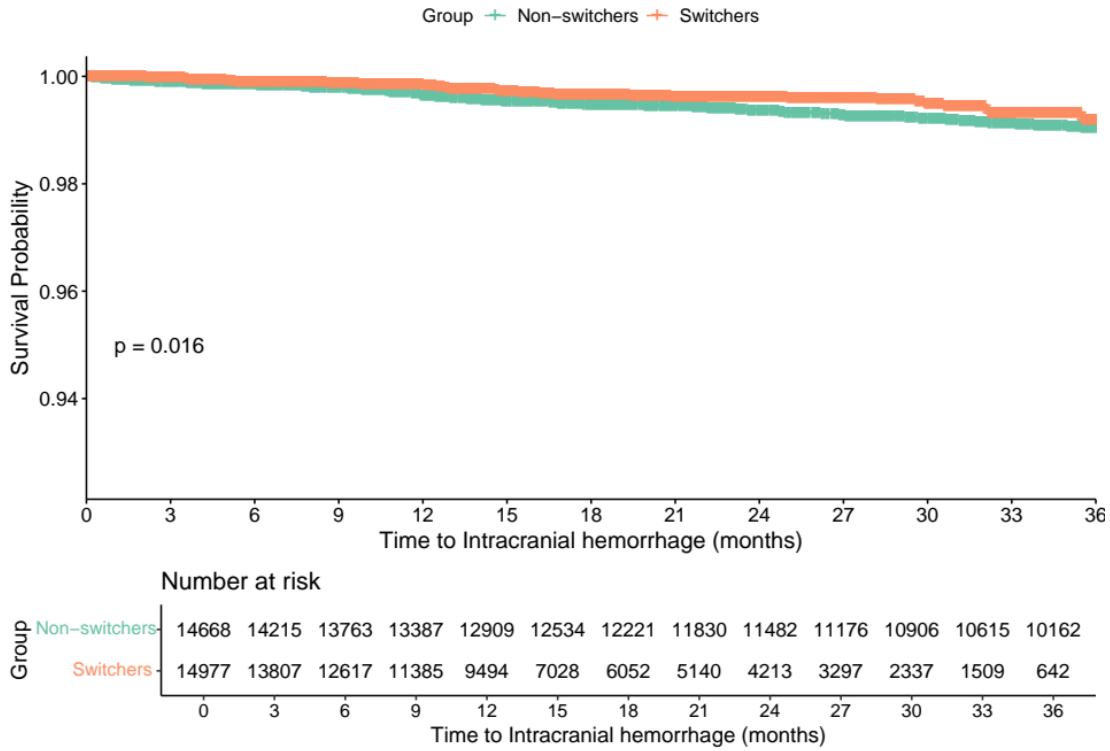


Figure A7.18: Kaplan–Meier curve showing time to intracranial haemorrhage in switchers vs. non-switchers.

Switchers had a significantly higher risk of GI bleeding compared to non-switchers over the 36-month follow-up period (p = 0.027). The survival probability declined more steeply in the switcher group, indicating an increased incidence of events (**Figure A7.19**).

There was a statistically significant difference in the risk of GI bleeding among the three DOACs (p = 0.00073). Apixaban was associated with the lowest cumulative incidence of GI bleeding, followed by rivaroxaban and then edoxaban, which showed the steepest decline in survival probability over time (**Figure A7.20**).

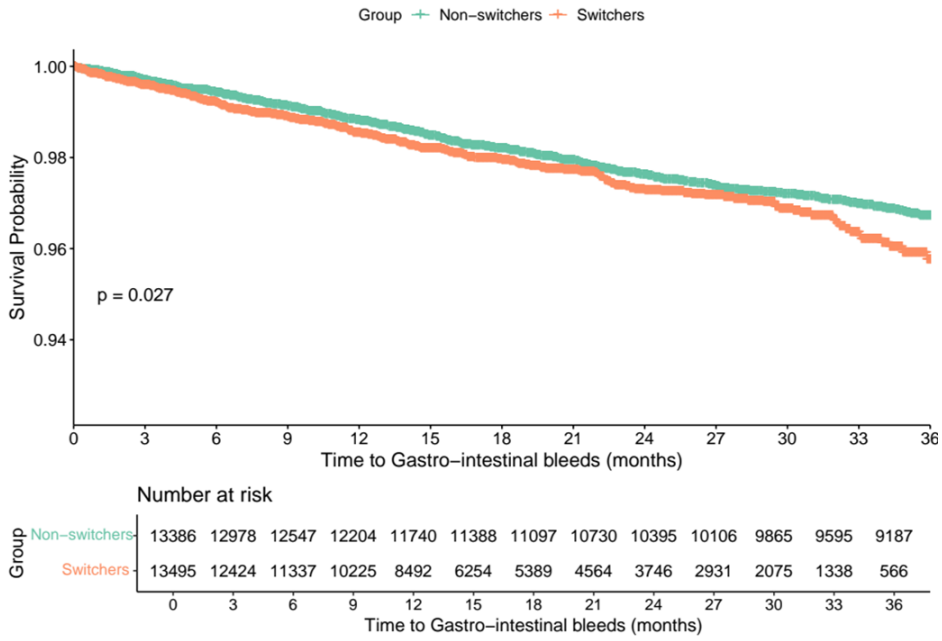


Figure A7.19: Kaplan–Meier curve showing time to gastrointestinal bleeding in switchers vs. non-switchers.

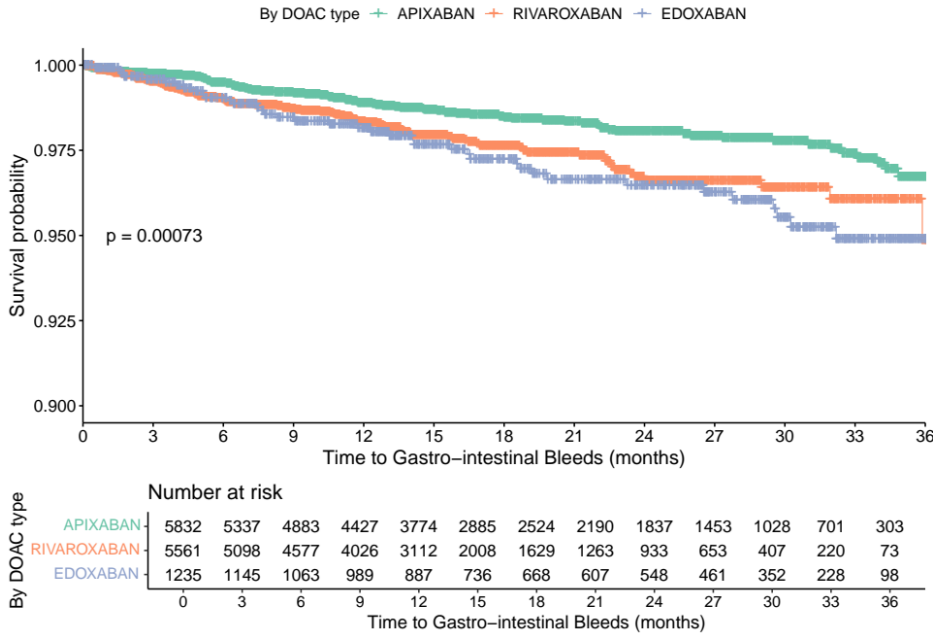


Figure A7.20: Kaplan–Meier curve showing time to gastro-intestinal bleeds by DOAC type

As shown in **Figure A7.21**, switchers had a significantly lower risk of haemorrhagic stroke over the 36-month follow-up compared to non-switchers (p = 0.022). However, the survival probability remained high in both groups. There was no statistically significant difference in the risk of haemorrhagic stroke across the different DOACs (apixaban, rivaroxaban, and edoxaban), as indicated by the log-rank test (p = 0.24) (results not shown).

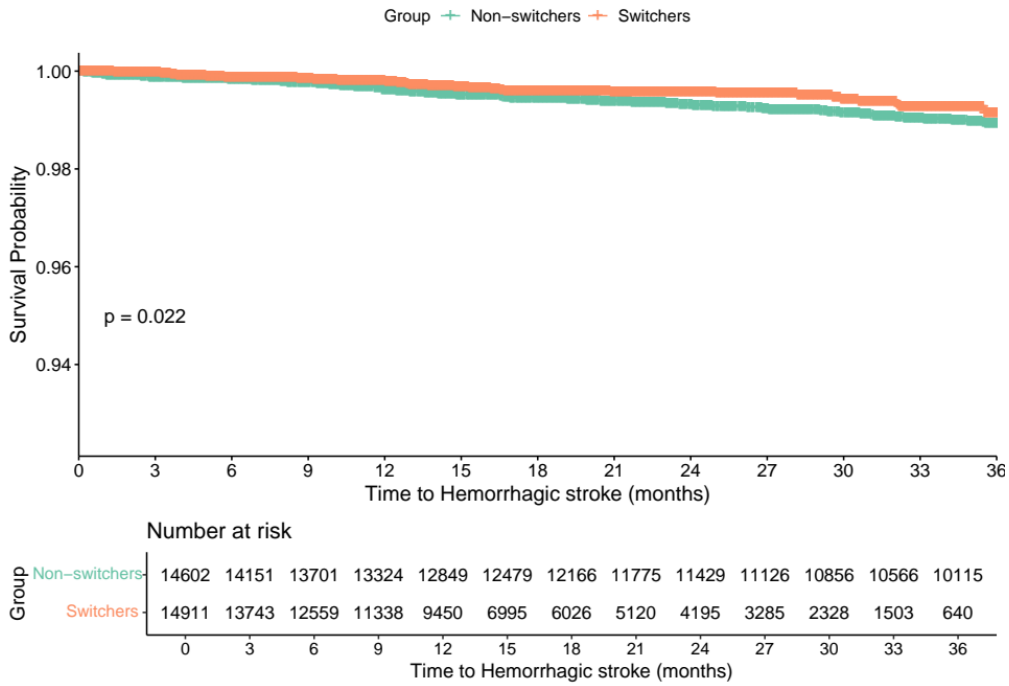


Figure A7.21: Kaplan–Meier curve showing time to hemorrhagic stroke in switchers vs. non-switchers**.**

Switchers exhibited a significantly higher risk of CVD death compared to non-switchers over the 36-month follow-up period (p = 0.00014) (**Figure A7.22**). The survival probability declined more steeply in the switcher group, indicating worse cardiovascular mortality outcomes in this population. There was no statistically significant difference in them risk of CVD death between DOAC types over the 36-month follow-up period (p = 0.43) (results not shown).

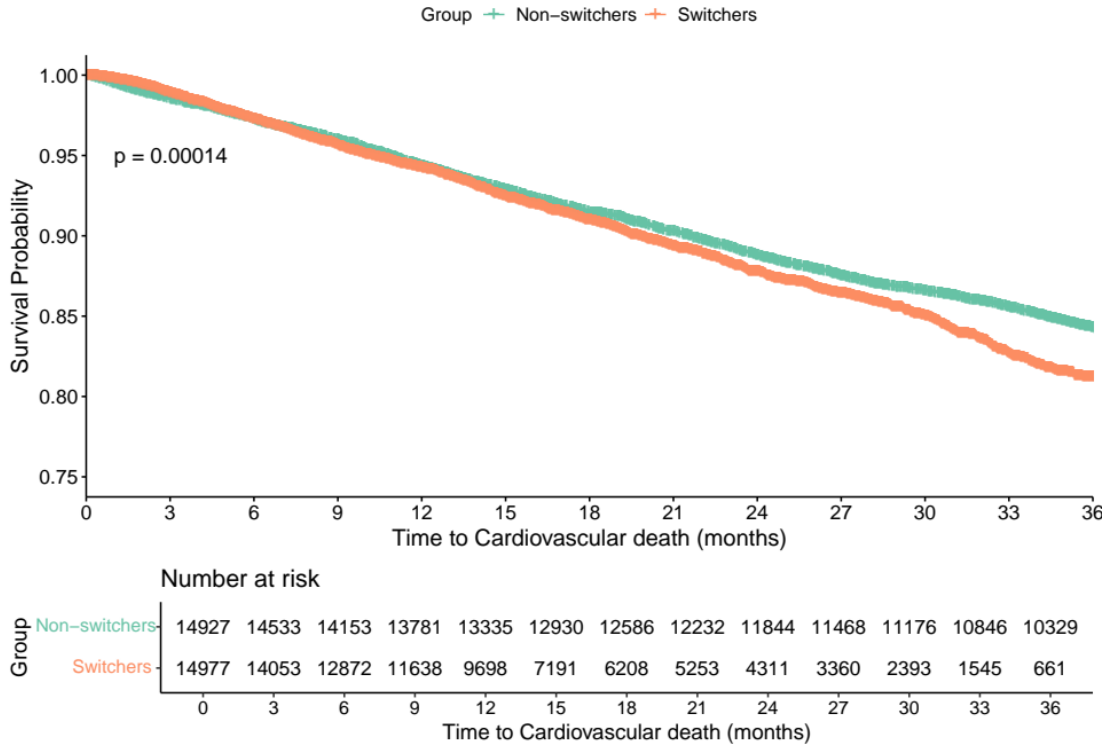


Figure A7.22: Kaplan–Meier curve showing time to cardiovascular death in switchers vs. non-switchers.

Switchers had a significantly higher all-cause mortality compared to non-switchers over the 36-month period ($p < 0.0001$), as shown in **Figure A7.23**. The survival probability declined more steeply for the switcher group, indicating a worse overall survival outcome. In contrast, no statistically significant differences in all-cause mortality were observed between DOAC types over 36 months (log-rank $p = 0.27$; results not shown).

No statistically significant differences were observed in the risk of systemic embolism or SAH between switchers and non-switchers, nor between different DOAC types (results not shown).

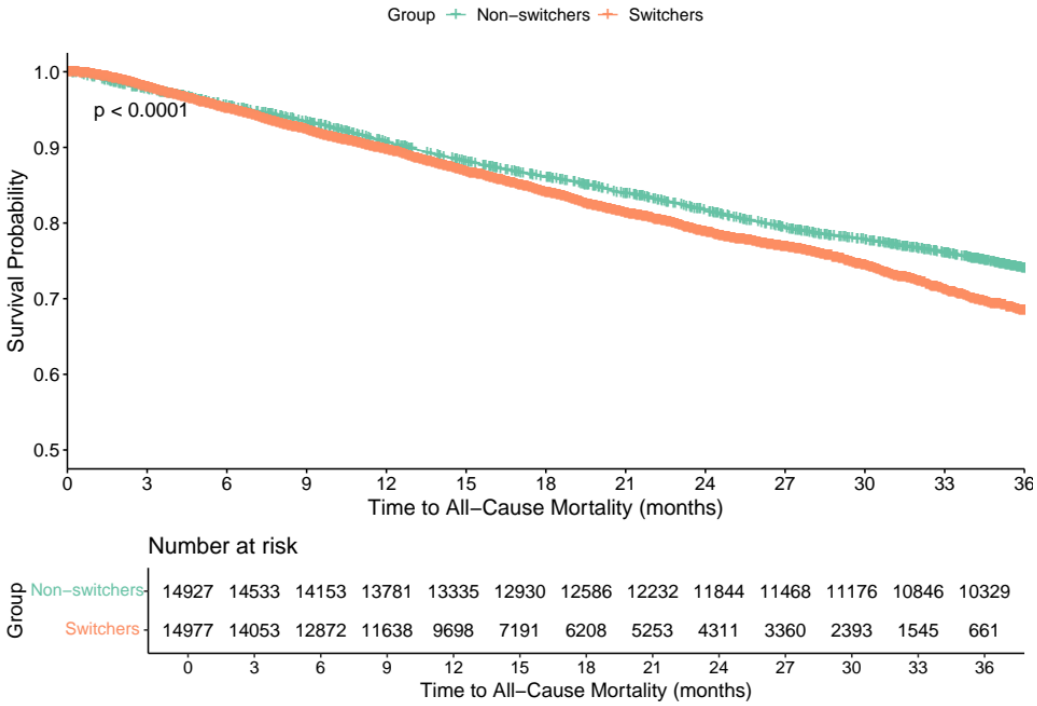


Figure 7.23: Kaplan–Meier curve showing time to all-cause mortality in switchers vs. non-switchers**.**

Appendix S.8.1

Variables in each lab dataset

Column Names	Description	Notes
DISCIPLINE	Biochemistry or haematology	
Sample date/ time	The date and time when the sample was collected	
Report date/ time	The date and time when the test result was reported	
Fasting	-	All NA
SAMPLENAME	Blood, plasma, serum, CSF, fluid, urine	
TISSUETYPE		
CLINICALCODEVALUE		

CLINICALCODEDESCRIPTION	Standardized medical description (formal name)	"Serum creatinine", "GFR calculated abbreviated MDRD"
CLINICALCODEVALUELOCAL	Short test code used in the dataset (abbreviation or code)	"CREA", "EGFR"
CLINICALCODEDESCRIPTIONLOCAL	Local/custom description used in the lab system	"Creatinine", "Estimated GFR (/1.73m^2)"
QUANTITYVALUE	The measured value of the test (result)	
QUANTITYUNIT	The unit of measurement for quantityvalue	"umol/L", "mL/min"
RANGEHIGHVALUE	The upper normal range for this test	
RANGELOWVALUE	The lower normal range for this test	
RANGEUNIT	The unit for the normal range values	
SIMD_2016_DECILE	Socioeconomic decile of the patient (1=most deprived, 10=least deprived)	
SIMD_2016_QUINTILE	Socioeconomic quintile (grouped deciles: 1-2, 3-4, 5-6, etc.)	
ID	Unique identifier for the patient	

Abbreviations: CSF = cerebrospinal fluid; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; SIMD = Scottish Index of Multiple Deprivation; NA = not available.

Note: Values shown in the Notes column are provided as examples and are not an exhaustive list of all possible laboratory codes or descriptions. The reported reference ranges are the ranges as applied in the health Board from where the data originated at the time of data extraction.