Trends in prescription of oral anticoagulants in elderly individuals with atrial fibrillation in UK primary care

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Abstract

Background: An increase in oral anticoagulant (OAC) prescriptions in elderly population with non-valvular atrial fibrillation (NVAF) has been documented in western countries since the 2000s. However, no information is available on recent trends in direct oral anticoagulant (DOAC) prescriptions among elderly patients, or about adherence and risk factors of treatment termination in such patients.

Objectives: The primary objective of this manuscript-based thesis was to describe trends in OAC prescriptions to elderly patients with atrial fibrillation in UK primary care between 2011 and 2021.

Methods: Using the Clinical Practice Research Datalink, we defined a cohort of patients aged 80 years and above, registered with a general practitioner and diagnosed with atrial fibrillation between January 1, 2011 and December 31, 2021. Using Poisson regression, we estimated the annual rates of patients newly prescribed vitamin K antagonists (VKAs) or DOACs. We used the Kaplan-Meier method to estimate the median time from NVAF diagnosis to OAC initiation and the median duration of persistence with DOACs or VKAs until first treatment interruption. We also estimated annual period prevalence stratified by age, sex, individual OACs, and UK nation (England, Scotland, Wales, and Northern Ireland). Finally, we reported baseline characteristics of patients newly prescribed an OAC in three calendar time periods (2011-2014 / 2015-2018 / 2019-2021) and the baseline characteristics by individual OAC for the last period (2019-2021).

Results: The cohort included 138,303 patients with mean age of 86 years, of whom 56.7% were female. Crude incidence rate of OAC initiation grew from 1,097.4 (95% CI 1,064.4-1,131.4) in 2011 to 4,799.7 (95% CI 4,702.8-4,898.7) per 1,000 person-years in 2021. The proportion of patients who were anticoagulated increased from 41% in 2011 to 75% in 2021, with notable growth from 9% in 2011 to 52% in 2021 in the age group 95 years and above. The rate ratio of initiating OAC in 2021 compared to 2011 was 4.58 (95% CI 4.27-4.97). The prevalence of OAC prescription grew from 50% in 2011 to 84% in 2021, remaining lower than average for females and patients aged 90 and above. Older patients had lower probability to initiate any OAC treatment and higher probability to be prescribed DOACs rather than VKAs.

Conclusion: During the last decade, anticoagulation in the elderly UK population increased substantially. Further research is needed to offer potential explanations for the trends observed.

Résumé

Contexte: Une augmentation des prescriptions d'anticoagulants oraux (ACO) chez les patients âgés atteints de fibrillation auriculaire non-valvulaire (FANV) a été documentée dans les pays occidentaux depuis les années 2000. Cependant, aucune information n'est disponible sur les tendances récentes de prescription des anticoagulants oraux directs (AOD) dans la population la plus âgée, ainsi que sur l'adhésion et les facteurs de risque d'arrêt du traitement.

Objectifs: L'objectif principal de cette thèse avec manuscrit était de décrire les tendances de prescriptions d'ACO aux patients âgés atteints de FANV par les généralistes au Royaume-Uni entre 2011 et 2021.

Méthodes: À l'aide de la base de données « Clinical Practice Research Datalink », nous avons défini une cohorte de patients âgés de 80 ans et plus, atteints de FANV entre le 1er Janvier 2011 et le 31 Décembre 2021. A l'aide d'une régression de Poisson, nous avons estimé les taux annuels de patients nouvellement prescrits des antagonistes de la vitamine K (AVK) ou des AOD. Nous avons utilisé la méthode de Kaplan-Meier pour estimer le temps médian entre le diagnostic de FANV et l'initiation d'ACO et la durée médiane entre l'initiation d'AOD ou d'AVK et la première interruption du traitement. Nous avons estimé la prévalence annuelle stratifiée selon l'âge, le sexe, les ACO individuels et la nation. Enfin, nous avons rapporté les caractéristiques des patients nouvellement prescrits des ACO sur trois périodes calendaires (2011-2014 / 2015-2018 / 2019-2021) et, séparément, les caractéristiques par ACO individuel pour la dernière année civile (2021).

Résultats: La cohorte comprenait 138,303 patients d'âge moyen de 86 ans, dont 56,7 % étaient des femmes. L'incidence brute d'initiation d'ACO est passée de 1097,4 (IC 95% 1064,4-1131,4) en 2011 à 4799,7 (IC 95% 4702,8-4898,7) en 2021. La proportion de patients ayant initié un ACO dans l'année suivant le diagnostic de FANV est passée de 41% en 2011 à 75% en 2021, avec une croissance exceptionnelle de 9 % en 2011 à 52 % en 2021 dans le groupe d'âge de 95 ans et plus. Le ratio de taux d'initiation d'ACO en 2021 par rapport à 2011 a atteint 4,58 (IC 95% 4,27-4,97). La prévalence de la prescription d'ACO est passée de 50 % en 2011 à 84 % en 2021, restant plus faible chez les femmes et les patients les plus âgés. Les patients plus âgés avaient une probabilité

plus faible de commencer un traitement par ACO et une probabilité plus élevée de se voir prescrire un AOD plutôt que des AVK.

Conclusion: Au cours de la dernière décennie, l'anticoagulation chez les personnes âgées a considérablement augmenté. Des recherches supplémentaires sont nécessaires pour offrir des explications potentielles aux tendances observées.

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Preface

Dr. Christel Renoux conceived the thesis topic. Ekaterina Pazukhina, Dr. Erica Moodie and Dr. Christel Renoux contributed to the design of the study. Ekaterina Pazukhina and Dr. Christel Renoux wrote the study protocol. Ekaterina Pazukhina drafted all the sections of this thesis and manuscript. Ekaterina Pazukhina, Dr. Christel Renoux and Sarah Beradid contributed to the statistical analyses. All authors critically revised the manuscript for important intellectual content. Dr. Christel Renoux acquired the data and supervised the study.

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List of Abbreviations

AF – atrial fibrillation

CHA_2DS_2-VASc – score for risk of stroke assessment among patients with AF

CI – confidence interval

DAPT – dual antiplatelet therapy

DOACs – direct oral anticoagulants

DVT – deep vein thrombosis

ECG – electrocardiography

HAS-BLED – score for assessment of risk of bleeding among patients with AF

INR – international normalized ratio

IRR – incidence rate ratio

NHS – National Health Service

NVAF – non-valvular AF

OACs – oral anticoagulants

OR – odds ratio

ORBIT – score for assessment of risk of bleeding among patients with AF

PE – pulmonary embolism

RR – risk ratio

TIA – transient ischemic attack

VKA – vitamin K antagonists

VTE – venous thromboembolism

Chapter 1: Introduction

Atrial fibrillation (AF) is a persistent condition, characterised by irregular heartbeat. It typically develops in the elderly population. One in three Europeans or White Americans and one in five Black Americans aged 55 years will develop AF in their lifetime (1, 2). Age-adjusted prevalence and incidence of AF approximately quadrupled during the last 50 years in the USA (2), due to increase in life expectancy and better diagnosis of asymptomatic AF.

AF is among the major causes of stroke, heart failure, sudden death, and cardiovascular disease (3), with stroke accounting for about 7.0% of deaths in patients with AF (2). AF is a frequent reason for hospital admission, responsible for up to 593.1 per 100,000 hospital admissions among patients aged 65-84 years, and 1159.5 per 100,000 hospital admissions among individuals ≥85 years (2).

Treatment of AF requires a multidisciplinary approach from clinicians and active involvement and cooperation of patients with AF (1). Undertreatment of AF remains a widely recognized problem, because AF patients without stroke prevention therapy have a two-fold higher risk of recurrent stroke and 2.4 times higher risk of recurrent severe stroke, which affects both life expectancy and quality of life (2).

Direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists for most patients with nonvalvular atrial fibrillation (NVAF) for the prevention of stroke, including elderly patients. However, oral anticoagulants (OACs) are often under-prescribed to the elderly in clinical practice. A better understanding of the prescribing trends since the approval of DOACs for stroke prevention in NVAF in 2011 and obstacles to DOACs prescription in this population could help improve the management of these patients. This thesis will provide a description of temporal trends in prescriptions of OACs in elderly patients in UK primary care between 2011 and 2021. Exploration of annual incident rates of OAC prescriptions, identification of the predictors of OAC initiation and persistence, and an overview of the changes in baseline characteristics of elderly patients newly prescribed OACs over time will provide insight as to how OAC prescribing have evolved in UK primary care practices in the last decade.

Chapter 2: Literature review

The following chapter has 3 sections. The first section provides definition and classification of AF, describes trends in incidence, prevalence, mortality and risk of stroke among patients with AF, discusses key pathophysiological mechanisms and risk factors leading to the development of atrial

fibrillation, and covers key approaches to management of atrial fibrillation. The second section discusses anticoagulants as a mean to prevent strokes in patients with AF, covers their indications and contraindications, and highlights the official guidelines for stroke prevention in patients with AF. The third section summarizes current evidence about trends in anticoagulation for stroke prevention among elderly patients with atrial fibrillation, highlights patterns in characteristics of patients who are prescribed anticoagulants, and discusses reasons for underprescription of oral anticoagulants in elderly patients with NVAF.

1. Atrial fibrillation

1.1. Definition and classification

AF is a common cardiac arrhythmia that increases in prevalence with advancing age (4). It is characterised by rapid (usually faster than 300 bpm), irregular and uncoordinated atrial impulse generation, usually manifesting on electrocardiography (ECG) with indistinct P-waves and an irregularly irregular ventricular response (5). Based on symptom manifestation, AF can be classified as asymptomatic, when no symptoms attributable to AF are registered, or clinical AF (6). AF is diagnosed by surface ECG with the minimum duration of an ECG tracing at least 30 seconds, or entire 12-lead ECG.

From a clinical perspective, AF can be classified as paroxysmal AF (recurrent AF with at least two registered episodes that terminates spontaneously within 7 days or less); persistent AF (lasting more than seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion to restore normal sinus rhythm); permanent AF (when a strategy to pursue a rhythm control is declined, or where cardioversion has either failed or not been attempted); preexcited AF (caused by a preexcitation syndrome such a Wolff-Parkinson-White syndrome). AF typically begins with the paroxysmal form and ends with the permanent form (7).

Based on risk factors, AF can be classified as ‘wear-and-tear’, congenital, or genetic (8). Wear-and-tear AF is caused by environmental factors such as ageing, dietary, lifestyle risk factors, certain diseases (hypertension, diabetes mellitus, obesity, coronary artery diseases, chronic kidney disease, inflammation). Congenital AF develops in individuals with current congenital heart disease, or having previously embryogenesis defects or as a consequence of surgical treatment Genetic AF is caused by genetic predisposition to AF (8).

Based on clinical presentation, AF can be classified as AF secondary to structural heart disease; focal AF; polygenic AF; post-operative AF; AF in patients with mitral stenosis or

prosthetic heart valves; AF in athletes; monogenic AF (1). AF secondary to structural heart disease is defined in patients with left ventricular systolic or diastolic dysfunction, long-standing hypertension with left ventricular hypertrophy, or other structural diseases. Focal AF presents in patients with repetitive atrial runs and frequent short episodes of paroxysmal AF. Polygenic AF is defined in carriers of gene variants which are associated with early onset AF. Post-operative AF develops in patients without prior AF who had surgery, in particular cardiac surgery. AF in patients with mitral stenosis or prosthetic heart valves is defined among patients with prior mitral stenosis who had mitral valve surgery. Monogenic AF presents in patients with inherited cardiomyopathies, including channelopathies.

1.2. Epidemiology

1.2.1. Incidence of AF

The incidence of AF increased gradually in the last 30 years (2, 3, 9). In the UK, between 1998 and 2017, the incidence of AF, standardized by sex and age, increased by 30%, growing from 2,47 new cases per 1,000 person-years to 3,22 per 1,000 person-years among population aged 16 years and older (9). In some subgroups, however, the incidence of AF remained relatively stable: for example, in the USA in a sample of individuals covered by Medicare, the incidence of AF, standardized by sex and age, was 27.3 cases per 1,000 person-years in 1993 and 28.3 cases per 1,000 person-years in 2007, growing only by 0.2% annually (2). Overall, the number of patients with incident AF is projected to reach 16.08 million among males and 16.85 million among females in 2030-2034 worldwide (3). In the USA, the incidence of AF is projected to reach 2.6 million cases in 2030 (2).

The crude incidence of AF ranges from 0.21 to 0.41 cases per 1,000 person-years worldwide (7). The incidence of AF varies in different ethnicities. Black, Hispanic, and Asian individuals in the USA have been shown to have significantly lower incidence of AF compared with White population, with hazard ratio (HR) of 0.84 (95% CI 0.82-0.85) for Blacks, 0.78 (95% CI 0.77-0.79) for Hispanics and 0.78 (95% CI 0.77-0.79) for Asians, respectively (2). In the UK, the incidence rates of AF vary from 8.1 (95% CI 8.1-8.2) in White individuals to 5.4 (95% CI 4.6-6.3) in Asians and 4.6 (95% CI 4.0-5.3) in Black individuals (2). The incidence of AF has been shown to be higher in deprived socioeconomic groups, with the incidence rate ratio (IRR) 1.20 (95% CI 1.15-1.24) for the most deprived patients compared to the wealthiest patients, irrespective of age and sex (9).

The incidence of AF increases dramatically with age (7, 10). At 50 years, the incidence of AF is estimated to be around 0.5-2 cases per 1,000 person-years, increasing to 3-9 cases per 1,000 person-years at 65 years, and reaching 10-39 cases per 1,000 person-years at 80 years (10). However, the estimates of the incidence of AF by age varies in different studies (10). For example, in 1993-2005 in Scotland, the incidence of AF is estimated at 4.7 cases per 1,000 person-years among patients above 65 years, 3.2 cases per 1,000 person-years in the age group 65–74 years, and 6.2 cases per 1,000 person-years in the age group 75–84 years (7). In Germany, the corresponding incidence was 4.1 cases per 1,000 person-years in individuals aged 65 years or older, 10.8 cases per 1,000 person-years in the age group 65-74 years, and 16.8 cases per 1,000 person-years in the age group 75-84 years (7). In the USA, the incidence of AF was estimated at 28.3 cases per 1,000 person-years in the age group 65 years and above, 15.5 cases per 1,000 person-years in the age group 65-74 years, and 33.5 cases per 1,000 person-years in the age group 75-84 years (7). The high geographical variation in the estimates of the incidence of AF may be due to country-specific public health policies, different diagnostic approaches, as well as due to regional variation in health of local populations (7).

The incidence of AF is lower among females than among males (3, 9, 11). Crude incidence of AF is 0.608 per 1,000 person-years among females and 0.612 per 1,000 person-years among males (3). After the age of 65 years, the overall number of new cases among females becomes larger than among males (3). In England in 1998-2017, the age standardized incidence of AF was higher for males, with IRR 1.49 (95% CI 1.46−1.52) in males compared to females (9). In the age group 75-79 years, the incidence of AF reached 234.3 per 1,000 males and 219.2 per 1,000 (11).

1.2.2. Prevalence of AF

The prevalence of AF is estimated to be 1% to 2% of the general population (10). It increased nearly twice in 15 years, from 41 per 1,000 in 1993 to 85 per 1,000 in 2007. The increased prevalence of AF is partly explained by higher detection of asymptomatic AF, as well as by the improvement in survival of patients with AF, in particular by better stroke prevention and better treatment of comorbidities (hypertension, coronary artery disease, heart failure) (7, 10) (2). For example, in the USA among Medicare patients aged 65 years and above, the prevalence of AF increased by about 5% per year, from 41.1 per 1,000 beneficiaries in 1993 to 85.5 per 1,000 beneficiaries in 2007, while the incidence of AF remained stable (2). Permanent AF is the most

frequent form of diagnosed AF, occurring in 40-50% of patients, followed by the paroxysmal and persistent forms (20-30% each) (7).

The worldwide number of people with AF rose from 19.1 million in 1990 to 37.6 million in 2017 (3). In Europe, the number of individuals with AF aged 55 years and older is projected to reach 17.9 million in 2060, whereas in the USA the number of adults with AF is expected to reach 12.1 million in 2030 (2).

AF prevalence grows substantially with age (2, 3, 10, 12). The prevalence of AF increases from 0.5% - 1% at 50 years, to 1% - 4% at 65 years and to 6% - 15% at 80 years (10), reaching its peak value between 90 and 94 years (3). The prevalence of AF increases non-linearly between the age of 65-74 and 75-84 years: from 3.4% to 8.6% among Chinese individuals, from 4.9% to 10.6% among non-Hispanic Blacks, from 7.3% to 9.4% among Hispanics, and from 13.4% to 19.6% among non-Hispanic Whites (12). Black Americans, Asians and Hispanics have significantly lower prevalence of AF compared to White Americans, with odds ratio (OR) of having prevalent AF of 0.49 (95% CI 0.47–0.52) for Blacks, 0.68 (95% CI 0.64–0.72) for Asians and 0.58 (95% CI 0.55–0.61) for Hispanics, compared to Whites, respectively (2).

The prevalence of AF among males is slightly higher than among females, reaching 7.8 per 1,000 person-years for males and 7.5 per 1,000 person-years for females respectively (3). However, after the age of 75 years, the prevalence among females becomes higher than among males (3).

The prevalence of AF varies across different regions and has changed over time. In 1990 the countries with the highest prevalence of AF after adjustment for age and sex were New Zealand (13.3 per 1,000), Sweden (13.1 per 1,000), and Australia (12.9 per 1,000), whereas in 2010 the three countries with the highest prevalence of AF were the USA (13.3 per 1,000), Sweden (12.7 per 1,000), and Canada (12.5 per 1,000) (3). The most rapid growth in the prevalence of AF from 1990 to 2010 was detected in the USA (1.3 times), Ecuador (1.3 times), and Austria (1.2 times) (3).

The prevalence of AF can be highly underestimated. Up to two thirds of the population with AF (both diagnosed and undiagnosed) can have transient or paroxysmal AF, which cannot be detected on ECG (10). In addition, silent AF ranges between 5% and 35% of the general population with AF. Accounting for these factors could potentially triple the prevalence of AF (10). Better

detection of AF by active screening globally could shift the estimated global prevalence of AF up to 3% (7).

1.2.3. Mortality among patients with AF

It is projected that between 2030 and 2034 the annual number of AF-related deaths will reach 2.5 million, with 1.01 million deaths among males and 1.49 million deaths among females (3). The standardized deaths rate increased from 0.43 per 1,000 in 1990 to 0.44 per 1,000 in 2019 (3). The three-year mortality rate decreased from 45% in 1993 to 42% in 2005 (10).

Death among patients with AF is not usually caused by AF itself, but by other comorbidities and complications, since AF has multiple causal relationships and shared risk factors with some serious comorbidities (heart failure, myocardial infarction, chronic kidney disease, venous thromboembolism, stroke, cancer) (13). Ischemic heart disease, stroke, acute myocardial infarction, and dementia are among the most common causes of death in patients with AF (11). The number of deaths directly related to AF increased from 0.12 million in 1990 to 0.32 million in 2019 worldwide, growing by 169.2% (3).

Mortality among patients with AF is much higher compared to similar patients without AF (2, 7, 10). The one-year age-adjusted mortality rates in patients with AF ranges between 23% to 27% globally, which is significantly higher than among comparable patients without AF (10). In Sweden in 1995–2008, mortality rates reached 40% during the first 5 years after AF diagnosis, and rose to 60% at 5 to 10 years after AF diagnosis, which is much higher compared to similar population without AF, where the death rates ranged from 20% to 40% (7). In the USA, the global mortality rate was 10.8% in the first 30 days after incident AF, 24.7% in one year after incident AF, and reached 42% in 3 years after incident AF (7). In 2016 in the USA, the age-adjusted mortality rate from AF reached 6.5 per 100,000 individuals (2).

Socioeconomic status is related to mortality among patients with AF (11, 14). The risk of death in most deprived regions was 26% higher compared to the wealthiest region (11). Patients with AF living in neighbourhoods with low socio-economic status had OR of all-cause mortality 1.49 (95% CI 1.13-1.96) compared to patients from neighborhoods with middle socio-economic status (14). The impact of ethnicity is mixed, mediated by comorbidities, which are more prevalent among Blacks and Hispanics, and therefore lead to higher mortality in presence of AF (2).

Mortality increases with age, reaching 84% among males aged 90+ years and 82% among females with AF aged 90+ years (11). In 2019 the deaths rates averaged 0.05 per 1,000 females

and 0.03 per 1,000 males of all ages (3). In individuals above 65 years, the number of deaths among females significantly exceeded the number of deaths among males (3). The adjusted risk of death was significantly higher for females with AF, with risk ratio (RR) 1.12 (95% CI 1.07-1.17) compared to males with AF (2). AF diminished the survival advantage typically observed in females throughout lifetime (2).The relationship between mortality and the type of AF is not clear (7).

1.2.4. Incidence of stroke among patients with AF

AF is associated with an increased risk of stroke (both ischemic and hemorrhagic) (2, 4, 15). Around one fifth of all strokes occur due to AF, reaching almost a quarter among individuals aged 80 years old and above (15). Patients with AF have an age-adjusted risk of stroke five times higher than in overall population, with persistent forms of AF leading to higher stroke risk compared to paroxysmal AF. The relative risk of any stroke in the population with AF is estimated to reach 2.4 (95% CI 2.17 - 2.71), and the absolute risk of stroke associated with AF is 3.6 per 1,000 person-years (95% CI 3.0 - 4.3) (15). Strokes due to AF are associated with poor outcomes: about 70-80% of patients die or become disabled after surviving such strokes (4). Females are at slightly higher lifetime risk of stroke: in the age group 55-75 years 1 in 5 females and 1 in 6 males experience stroke (2). In the USA, lower levels of education and Black ethnicity were factors associated with a higher stroke prevalence (2).

In Sweden the incidence of AF-related ischemic strokes increased in 2001-2010 and declined after 2010, except for the age groups 90–94 years and 95+ years (16). DOAC availability explained most of the risk reduction of stroke among patients 70-79 years old with AF, who were diagnosed in 2015-2017, compared to those who were diagnosed in 2006-2008, however, in the age group 80 years old and above the downward trend in the incidence of strokes was not explained by DOAC utilization (16).

1.3. Pathophysiology

The pathophysiology of AF is complex, heterogeneous and is still being investigated (17). Various pathophysiologic mechanisms contribute to AF unequally in different individuals and at different ages (17). The major pathophysiological mechanisms (18) are atrial fibrosis, abnormal calcium homeostasis, ion-channel dysfunction, autonomic dysfunction, increased oxidative stress, microRNA-mediated dysregulation, and paracrine fat-cell activity.

Two causes of durable disturbances in electrical activity in atria have been identified: re-entry and ectopic activity. Re-entry is stimulated by both the presence of triggers and accumulation of substrate. Triggers originate from one of the following conditions: ectopic beats from muscular sleeves within the pulmonary vein ostia, presence of myocardial sleeves or regional atrial fibrosis in a set of atrial loci (superior vena cava, coronary sinus, left atrial appendage, ligament of Marshall, crista terminalis, left atrial posterior free wall), and other forms of supraventricular arrhythmia (17). Substrate is accumulated due to atrial remodelling, happening either due to changes in ion channel functioning or due to the presence of tissue fibrosis. Ectopic activity happens when atrial tissue, located outside the sinoatrial node, spontaneously depolarizes at rates faster than the sinus rhythm (8). Ectopic activity arises from pulmonary vein activity.

AF episodes lead to accumulation of changes in atria, which, in turn, provoke new AF episodes and further progression of AF (19). For example, structural remodelling provokes abnormal calcium handling, which stimulates new triggers and more ectopic activity, leading to new AF episodes (8). On a molecular level, AF damages DNA, causing electrophysiological and contractile impairment (8), which boost further AF development. Moreover, AF forms bidirectional relationships with some diseases, such as heart failure: AF increases the probability of heart failure through loss of atrial systole, rapid ventricular response, ventricular irregularity, tachycardia-mediated cardiomyopathy, ventricular fibrosis, RAAS (renin-angiotensin-aldosterone system) activation; heart failure provokes further progression of AF through atrial fibrosis, electrical remodelling, stretch and dilatation, oxidative stress, and inflammation (20).

AF is almost always found in patients with many metabolic and systemic comorbidities. Indeed, one third of AF patients have three or more associated comorbidities, whereas patients with no comorbidities constitute one fifth, and patients with cardiac disease only - one quarter of patients (7). This suggests that AF could be a systemic disease or even a cause of some systemic disease, such as an occult cardiomyopathy (17).

1.4. Risk factors

Some behavioral, demographics risk factors, and comorbidities are strongly associated with some pathophysiological mechanisms of developing AF (10). Structural remodelling is associated with older age, hypertension, valve disease, heart failure, prior myocardial infarction, obesity, obstructive sleep apnea, smoking, endurance exercise, diabetes mellitus, thyroid disease; ion currents governing repolarization or remodelling is associated with male sex and thyroid

disease, abnormal calcium handling – with heart failure and prior atrial infarction, conduction slowing or block – with acute atrial ischemia, autonomic changes – with endurance exercise, diabetes mellitus and thyroid disease, pulmonary vein activity – with thyroid disease (10). However, for many risk factors, the relation to pathophysiological mechanisms remains unclear.

Major unmodifiable risk factors of developing AF are age, genetics, sex, and race (10, 12, 21). Age is one of the most significant risk factors, whose contribution increases non-linearly around the age of 75 years (12). Genetics can contribute up to 40% of risk of developing AF among close relatives (12), whereas family history of AF in a first-degree relative doubles the risk of developing AF (10). Higher incidence of AF is observed among males than among females (12), however it is not still clear whether sex is an independent risk factor or an effect modifier for some comorbidities. For example, males have higher risk of coronary disease, whereas females have higher risk of elevated systolic blood pressure and valvular disease (12). Moreover, male sex is shown to be an effect modifier of elevated BMI on the risk of developing AF (21). European ancestry is argued to be a risk factor for developing AF, whereas African ancestry may have a protective effect (12).

Major modifiable risk factors are sedentary lifestyle, smoking, high alcohol consumption, extreme athletic activity, and certain comorbidities. Sedentary lifestyle can affect depolarization through higher systemic inflammation, autonomic dysfunction, elevated sympathetic tone; in addition, sedentary lifestyle often coexists with sleep apnea, hypertension, obesity – risk factors of developing AF (12). Current or past smoking, as well as exposure to second-hand smoke in childhood, is associated with elevated risk of developing AF through multiple paths such as higher systemic catecholamine and myocardial work, lower oxygen carrying capacity, higher risks of coronary vasoconstriction, chronic obstructive pulmonary disease, accelerating atherosclerosis, endothelial function, oxidative stress, inflammation, and thrombosis (12). Smoking is associated with higher occurrence of AF, with an adjusted HR between 1.51 and 2.05, with a dose–response effect (10). Heavy alcohol consumption is associated with an adjusted HR of developing AF between 1.34 and 1.46 (10). Binge drinking has been shown to be a strong predictor of incident AF (8). Excessive physical activity (a cumulative lifetime practice of 1,500 or more hours) is associated with an HR of developing AF of 2.87 compared to people with moderate level of physical activity (10).

Obstructive sleep apnea, diabetes mellitus, hypertension and obesity are the major risk factors for developing AF among comorbidities (12). Patients with obstructive sleep apnea have a four-fold increased risk of developing AF compared to people with normal sleep (12). Hypertension, due to its high prevalence, is the major population-attributable risk factor of developing AF, after age and sex, being attributable to 14% of all cases of incident AF (10). The relative risk of developing AF for individuals with hypertension compared to the population without hypertension is estimated to be 1.5 in males and 1.4 in females (12). Relative risk of developing AF among individuals with diabetes compared to the population without diabetes ranges from 1.4 to 1.6, with severity of diabetes being an effect modifier (10). Glucose intolerance and insulin resistance appear to facilitate the development of AF through accumulation of substrate (12). Obesity increases the risk of developing AF through left atrial enlargement, increased left ventricular mass, and diastolic dysfunction, which decrease conduction velocity (12). For each unit increase in body mass index, the adjusted risk of incident AF increases by 3% to 7% (10). In addition, pericardial fat is argued to be associated with the development of the AF substrate (12).

Some other comorbidities, which contribute to the development of AF, are cardiovascular diseases (heart failure, valvular disease, congenital heart disease, coronary artery disease), subclinical atherosclerosis, disorders of heart rhythm (PR interval prolongation, sick sinus syndrome, Wolff-Parkinson White), inflammation (thyroid disfunction), renal dysfunction, and chronic obstructive pulmonary disease (1).

The major factors of AF-related disability and mortality in the overall population are high systolic blood pressure, high BMI, alcohol use, smoking and diet high in sodium (3). High systolic blood pressure is estimated to contribute 34% to AF-related disability and mortality, high BMI, alcohol use and smoking – up to 20% each, and diet high in sodium contributes about 7.5% (3).

Accumulation of several risk factors or elevation of risk level from optimal to high both increase the lifetime risk of AF. With risk factors at basic levels, the lifetime risk of AF is estimated between 15.4% and 23.4%, whereas with at least one elevated risk factor the lifetime risk of AF grows to 37.8% and higher, with obesity being the most prominent risk factor (22).

1.5. Management of AF

Management of AF includes three major components: eliminating symptoms through rate and rhythm control; detecting and modifying risk factors and comorbidities; and diminishing the risk of stroke.

Rate control can be achieved with medications (beta-blockers, digoxin, diltiazem, verapamil, or combination therapy) or ablation of atrioventricular node and pacemaker implantation (1). Rhythm control can be targeted through pharmacological or electrical cardioversion, AF catheter ablation, concomitant / stand-alone / hybrid surgical and catheter ablation procedures, surgery of AF, or usage of antiarrhythmic drugs (flecainide, propafenone, vernakalant, amiodarone, ibutilide).

Unhealthy lifestyle factors can be modified through weight loss, alcohol and caffeine avoidance, and moderate-intensity exercise. Cardiovascular risk factors are controlled through treating and monitoring hypertension, heart failure, coronary artery disease, diabetes mellitus, and sleep apnoea (1).

The risk of stroke can be decreased with oral anticoagulants: vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), dual antiplatelet therapy (DAPT), as well as with regular assessment of risk factors of stroke and risk of bleeding, left atrial appendage occlusion and exclusion (with devices or surgically) (1). More details about stroke prevention therapy with anticoagulants will be provided in *Chapter 2.2*.

1.6. Stroke prevention among patients with AF

Stroke prevention treatment has remarkably decreased the frequency of strokes in patients with AF. For example, in the USA, the rate of ischemic stroke among patients with AF aged 65 years or above decreased from 48 per 1,000 person-years in 1992 to 17 per 1,000 person-years in 2007, which translated into a decrease in the ischemic stroke rate by 65% in 15 years (3). In Sweden the annual rate of ischemic stroke was 25 per 1,000 person-years among the population treated with OACs and 45 per 1,000 person-years in those who were not treated (7). The HR of ischemic stroke within 3 years from an AF diagnosis came down from 2.39 (95% CI 2.31–2.48) in 2001 to 1.54 (95% CI 1.48–1.61) in 2020, which was largely explained by a substantial increase in the use of DOACs among patients with AF(16).

The following chapter will highlight the major types of anticoagulants – the major stroke prevention therapy – their indications, and the current approaches to anticoagulation.

1.6.1. OAC types

Oral anticoagulants are medications which are used to prevent strokes by affecting blood clotting.

VKAs, is a class of oral anticoagulants, which affect the action of vitamin K, responsible for the activation of clotting factors II, VII, IX, and X. The common VKAs are warfarin, phenindione, acenocoumarol, with warfarin being the most prescribed VKA. The absolute risk reduction of stroke among patients with NVAF prescribed warfarin compared to placebo or no treatment reached 2.7% per year, with relative risk reduction of 67% (95% CI 49-74%) (23). The optimal dose of warfarin is determined through blood international normalized ratio (INR). An INR above 3.0 is associated with increased risk of bleeding, while an INR below 2.0 is associated with increased risk of thromboembolism (24). Changes in diet, alcohol consumption, and liver disease development can all affect INR. Treatment with warfarin must be carefully managed by clinicians through regular monitoring of INR and adjusting the dose of warfarin. In addition, warfarin is reported to interact with multiple commonly used medications (e.g., other anticoagulants, antiplatelet drugs, non-steroidal anti-inflammatory drugs, azole antibiotics, macrolides, quinolones, selective serotonin reuptake inhibitors, omeprazole, lipid-lowering agents, amiodarone, fluorouracil) (25), which can increase the risk of bleeding (26).

Another, newer group of oral anticoagulants, DOACs, reduce the production of direct thrombin and factor Xa inhibitors – the biological catalysts, which accelerate blood clotting (27). DOACs include apixaban, edoxaban, rivaroxaban, and dabigatran. DOACs were shown to provide comparable stroke prevention in patients with AF, with an OR for stroke or systemic embolism of 0.79 (95% CI 0.66-0.94) for apixaban, 0.65 (95% CI 0.52-0.81) for dabigatran, 0.86 (95% CI 0.74-1.01) for edoxaban and 0.88 (95% CI 0.74-1.03) for rivaroxaban compared with warfarin at INR 2.0-3.0 (28). In addition, DOACs do not require constant monitoring and do not have multiple interactions with medications or specific dietary intake. Compared with warfarin at INR 2.0-3.0, they were shown to cause fewer bleedings, with an OR of 0.71 (95% CI 0.61-0.81) for apixaban, 0.80 (95% CI 0.69-0.93) for dabigatran and 0.78 (95% CI 0.69-0.90) for edoxaban (28).

The first DOAC approved for stroke prevention in AF was dabigatran, a direct thrombin inhibitor (approved in the UK in 2012, in the USA and in Canada in 2010) (29-31). The factor Xa inhibitors apixaban, edoxaban, and rivaroxaban were approved in the UK, the USA, and Canada in 2012-2013 (32-34), 2015-2016 (35-37), and 2009-2012 (38-40), respectively. DOACs have been recommended for stroke prevention among NVAF patients in the UK in 2014 (41), in the USA in 2011 (dabigatran only)-2014 (42, 43), in Canada in 2014 (44), with warfarin as an option for those patients for whom DOACs are contraindicated, not tolerated, or not suitable (45). For

example, DOACs are not an option for patients with mechanical heart valves, or with renal or liver dysfunction (46). In contrast, VKAs are preferred for patients with severe renal impairment because of different elimination mechanisms of VKAs and DOACs, and to those with poor adherence due to long offset of anticoagulation effect (47).

1.6.2. OAC indications and contraindications

VKAs and DOACs have similar indications, however, they have several non-overlapping contraindications.

Warfarin is indicated for the prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation, prophylaxis after insertion of prosthetic heart valves, prophylaxis and treatment of venous thrombosis and pulmonary embolism, transient attacks of cerebral ischaemia (48). Warfarin is contraindicated in the following conditions: hypersensitivity to the active substance, haemorrhagic stroke, clinically significant bleeding, within 72 hours of major surgery with risk of severe bleeding, within 48 hours postpartum, pregnancy (first and third trimesters. In addition to these contraindications, warfarin has a large list of precautions against undesirable interactions with food and other medications.

Currently there are two indications for adults, which are common for all DOACs: (1) prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors: prior stroke or transient ischemic attack (TIA), age ≥ 75 years, hypertension, diabetes mellitus, symptomatic heart failure (NYHA Class ≥ II); (2) treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE.

In addition, apixaban and dabigatran are indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Apixaban and dabigatran dosage needs to be reduced for elderly patients. Specific reversal agents to manage severe bleedings are available for dabigatran, apixaban, and rivaroxaban (49).

There are several contraindications for DOACs. Factor Xa inhibitors are contraindicated if a patient has a lesion or condition which is significant risk factor for major bleeding (current or recent gastrointestinal ulceration, presence of malignant neoplasm at high risk of bleeding, recent brain or spinal injury, recent brain, spinal, or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformation, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities) or has concomitant treatment with

anticoagulant agent (unfractionated heparin, low molecular weight heparin, heparin derivatives, oral anticoagulants) (50). In addition, rivaroxaban should not be used during pregnancy or breastfeeding and thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement. Dabigatran is contraindicated for patients receiving concomitant treatment with strong P-gp inhibitors (systemic ketoconazole, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir), for patients with severe renal impairment (CrCL <30 mL/min), or patients with prosthetic heart valves requiring anticoagulant treatment. In addition, all DOACs are not recommended in patients with antiphospholipid syndrome (49).

1.6.3. Guidelines for stroke prevention among patients with AF

The National Health Service (NHS) guideline from 2006 (51) relied on warfarin as the main stroke prevention treatment (in some cases aspirin was recommended if warfarin was not an option) in patients with previous ischemic stroke, TIA or thromboembolic event; age ≥75 with hypertension, diabetes or vascular disease; clinical evidence of valve disease or heart failure, or impaired LV function on echocardiography being the factors associated with high risk of stroke. Current NICE guidelines recommend VKAs for patients with AF only if DOACs are not an option to consider. For patients who take VKAs and have stable anticoagulation effect, treatment should be continued, given the patients are informed about the benefits of DOACs (45).

Both NHS guidelines from 2021 and 2014 suggest considering stroke prevention among males with AF if CHA2DS2-VASc score (a score to determine the risk of developing AF, based on age, sex, diabetes mellitus, hypertension, vascular disease, prior congestive heart failure, stroke, transient ischemic attack (TIA) or thromboembolism) equals 1 and offering anticoagulation to patients of both sexes if CHA2DS2-VASc score equals 2 or more. The difference between the two guidelines is that in 2014 the particular type of anticoagulation was not specified, whereas in 2021 the guidelines specify that only DOACs should be considered for stroke prophylaxis among patients newly diagnosed with AF. The method of evaluating bleeding risk changed as well: from HAS-BLED score (based on age, alcohol or drug use, hypertension, renal or liver dysfunction, prior stroke or bleeding, labile INR) in 2014 (46) to ORBIT bleeding risk score (based on age, reduced hemoglobin, bleeding history, kidney dysfunction and treatment with antiplatelet agent) (45) and other risk factors to be considered (uncontrolled hypertension, poor control of INR in patients on VKAs, concurrent medication, including antiplatelets, selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs, harmful alcohol consumption, reversible

causes of anaemia). NHS guidelines from 2021 differ from European guidelines (1) in terms of evaluating risk of bleeding and suggesting OAC treatment. In European guidelines HAS-BLED score is suggested for evaluating the risk of bleeding, and OAC treatment is recommended for CHA2DS2-VASc score 2 or above in men and 3 or above in women, whereas OAC treatment should be considered for CHA2DS2-VASc score of 1 in men or 2 in women (1). In Canada, OAC treatment is recommended if either a person with NVAF is at least 65 years old or has any of the following comorbidities: prior stroke or TIA, hypertension, heart failure, diabetes mellitus; if a patient with NVAF does not satisfy any of the aforementioned conditions, but has either coronary or peripheral arterial disease, they should be prescribed antiplatelet therapy (CHADS-65 algorithm) (52). In the USA, risk assessment of thromboembolic events is suggested to be carried out using any validated clinical risk score, equivalent to CHA2DS2-VASc score (53).

During the COVID-19 pandemic, the NHS recommended healthcare professionals to switch patients with NVAF from warfarin to DOACs in order to minimize the number of regular tests (54). The rate of INR testing was shown to drop by 14% due to transition from VKA to DOACs due to NHS recommendations, with edoxaban and apixaban being the most frequently selected alternatives to warfarin (55).

2. Utilization of OACs in elderly population with AF

The following chapter will provide an overview of OAC prescription trends among patients aged 75 years or above. Firstly, we will review trends in OAC prescription; secondly, we will narrow the scope to trends in prescription of DOACs; third, we will provide the current state of knowledge about trends in prescription patterns of OAC depending on characteristics of patients, such as sex, age, comorbidities, and health related behaviors. Finally, we will discuss the possible reasons of OAC underuse among the elderly.

2.1. Trends in OAC prescriptions to elderly patients with NVAF

The trends for OAC prescription among elderly population 75+ years old with AF has been growing steadily in the last two decades (56-59). In a study of patients with NVAF from Australia (7,258 patients 75+ years old), the incidence of OAC prescription at hospital discharge increased by 12.8% annually in 2009-2016, growing from 25% in 2009 to 45% in 2016. In contrast, the incidence of antiplatelet prescription decreased by 10.7% annually (56), falling from 47% in 2009 to 28% in 2016. In a Spanish cohort of elderly anticoagulated patients (1,584 inpatients 65+ years old), the prevalence of OAC prescriptions in the subgroup of patients aged 75+ increased from

11.2% (of which 64% were for NVAF) in 2008 to 20.9% in 2018 (with 85.1% for NVAF) (57). In a retrospective study in a Danish population with NVAF (43,928 patients aged 75+ years), the incidence of OAC prescriptions among hospitalized patients and outpatients grew steadily from slightly above 40% in 2005 to about 70% in 2015 (58). Similarly, among elderly patients with NVAF aged 80 years and above from China (1,588 patients aged 80-84 years, 1,083 patients aged 85-89 years, 494 patients aged 90+ years), the probability of not being prescribed an OAC decreased every year in 2017-2020, with the OR for not being prescribed an OAC of 0.66 (95% CI 0.52 - 0.83) in 2018, 0.48 (95% CI 0.38-0.6) in 2019, and 0.34 (95% CI 0.27-0.42) in 2020, compared with 2017 (59).

In addition to the remarkable increase in OAC prescriptions among the elderly patients with AF, the probability of an elderly patient being prescribed an OAC substantially increased compared to a younger patient with similar profile of comorbidities (58): the OR of OAC initiation among patients 75 years old and above compared to patients 65 years old and younger was 0.93 (95% CI 0.89 – 0.98) in 2005-2010, and increased to 1.31 (95% CI 1.26-1.36) in 2010-2015. However, a more precise analysis of incidence of OAC initiation by age groups among NVAF patients from the UK CPRD database (72,961 patients aged 75-79, 42,819 patients aged 80-84, 30,614 patients aged 85-89, 19,202 patients aged 90+ years) revealed that older patients had a lower probability of OAC prescription compared to younger individuals, which persisted over time (60). The risk difference of incidence of OAC prescription in patients aged 80-84 years compared with those aged 75-79 years shrank gradually from -0.11 (95% CI -0.12 – -0.10) in 2003-2007 to -0.05 (95% CI -0.07 – -0.04) in 2013-2017. Similarly, the risk difference between patients aged 85-89 years and 75-79 years diminished from -0.25 (95% CI -0.26 – -0.24) in 2003-2007 to -0.18 (95% CI -0.19 – -0.16) in 2013-2017. However, the risk difference between patients aged 95+ years and those aged 75-79 years remained stable: -0.37 (95% CI -0.37 – -0.36) in 2003-2007 and -0.39 (95% CI -0.40 – -0.38) in 2013-2017 (60). Conversely, in China in 2016-2020 the OR of not using an OAC was 1.48 (95% CI 1.25-1.74) among NVAF patients aged 85–89 years relative to patients aged 80-84 years, and 2.66 (95% CI 2.09-3.42) among patients aged 90 years and above relative to those aged 80-84 years (59).

Finally, a substantial sex gap in incident OAC prescriptions among NVAF patients aged 85 years and above was reported: the incidence rate of OAC initiation increased from around 50 per 1,000 person-years in 2003 for both sexes to around 500 per 1,000 person-years for males and

only 400 per 1,000 person-years among females in 2017, whereas for younger patients aged 75-84 years old, no sex difference was found: in 2017, both sexes had a similar incidence rate of OAC initiation of 700 per 1,000 person-years (60).

2.2. Trends in DOAC prescriptions to elderly patients with NVAF

The incidence of DOAC prescriptions among the elderly population increased substantially in the last 15 years (61-64). In the USA, the incidence of DOAC prescriptions to NVAF patients 80 years and older (27,647 patients) grew from less than 5% in 2011 to around 30% in 2019, whereas the incidence of warfarin prescriptions declined from around 30% in 2011 to about 10% in 2019 (61). In Sweden, the incidence of DOAC prescriptions upon hospital discharge increased from 8.7% in 2013 to 70% in 2017 in the age group 75-80 years (1,033 patients), from 5.2% in 2013 to 70% in 2017 in the age group 80-90 (1,464 patients), and from 1.9% in 2013 to 61% in 2017 in the age group 90+ years (446 patients) (62). Conversely, the incidence of warfarin prescription dropped from 78% in 2010 to 27% in 2017 in the age group 75-80 years, from 66% in 2010 to 27% in 2017 in the age group 80-90 years, but remained stable in the age group 90 years and above, at 28% in 2010 and 27% in 2017 (62). In Taiwan, the incidence of DOAC prescriptions to patients with AF aged 85 and older (33,539 patients) increased from 0.4% (2012Q1) to 26.2% among incident AF population aged 85+ years (2015Q4) (63). Another study from the USA (64) showed significant positive temporal trends for incident DOAC prescription to elderly population with AF (6,568 patients) in 2010Q4-2015Q3 for the age group 75–79 years (Pearson correlation coefficient $r=0.86$, $p<0.001$), the age group 80–84 years ($r=0.62$, $p=0.003$), and the age group 85–89 years ($r=0.67$, $p=0.001$).

Age is a weaker determinant of the choice between warfarin and DOACs among older patients with AF (65, 66). In the USA, the OR of DOAC rather than warfarin prescription among patients with AF aged 75 years and above compared to those aged 18-64 years remained at almost the same level in 2010-2012 with an OR 0.44 (95% CI 0.41–0.47) and, in 2013-2014, an OR 0.44 (95% CI 0.41–0.47), but grew up to 0.49 (95% CI 0.46–0.52) in 2015-2017 (66). Similarly, in the UK (65), the choice of DOAC prescription over warfarin among patients with AF or venous thromboembolism in the age groups below 45 years or 75-84 years almost converged over time, with an OR for age group below 45 years relative to age group 75-84 years declining from 2.61 (95% CI 1.79-3.79) in 2009-2012 to 1.02 (95% CI 0.89-1.18) in 2013-2014 and 1.03 (95% CI 0.86-1.23 in 2015). Conversely, in patients aged 85+ years, the probability of initiating DOAC

remained higher than in those 45 years old or younger, with the OR declining from 3.21 (95% CI 2.14-4.81) in 2009-2012 to 1.44 (95% CI 1.24-1.68) in 2013-2014 and 1.42 (95% CI 1.17-1.73) in 2015.

2.3. Trends in DOAC prescriptions to elderly patients with NVAF by molecule

Prescriptions of apixaban, dabigatran, edoxaban, and rivaroxaban to the elderly population have been shown to grow steadily in the last 10 years (63, 66, 67), with the growth in prescriptions varying by magnitude in different countries: rivaroxaban becoming the most preferred DOAC in Taiwan (63) and apixaban in the USA (66). In Taiwan, the incidence of DOAC prescriptions to patients with incident AF aged 85 and older in 2015 reached 6.4% for edoxaban, almost 14.5% for rivaroxaban, and 5.3% for apixaban (63). In US patients with AF aged 75 years and above (66) in 2017, the incidence of apixaban, rivaroxaban, and dabigatran prescribing reached almost 50%, 25% and 3.8% respectively. In another study from the USA (67), the incidence of DOAC prescriptions to individuals with incident AF at least 80 years old increased from 0.8% (dabigatran only) in 2010 to 28.5% (4.3% rivaroxaban, 24.2% apixaban) in 2020.

In the USA (66), the probability of dabigatran prescription rather than apixaban to patients with AF 75 years old and older decreased in 2013-2017, with the OR falling from 0.75 (95% CI 0.65–0.85) in 2013-2014 to 0.69 (95% CI 0.61–0.78) in 2015-2017. Similarly, the probability of being prescribed rivaroxaban rather that apixaban decreased, with the OR decreasing from 0.84 (95% CI 0.76–0.92) in 2013-2014 to 0.64 (95% CI 0.60–0.69) in 2015-2017.

2.4. Patterns in prescriptions of OACs to elderly patients with NVAF

Comorbidities, demographic characteristics, and behavioral risk factors impact the probability of prescribing OAC to elderly patients with AF. However, the impact of the risk factors has changed over time.

The impact of comorbidities and risky behavior on incidence of OAC prescriptions has been shown to change over time among patients with NVAF aged 75+ years old (60). Patients became more likely to be prescribed OAC in 2013-2017 than in 2003-2007 if they had overweight or obesity (compared to normal weight), if they had acute kidney injury or diabetes mellitus. In contrast, patients with heart valve disease, major bleed, intracranial bleed, or dementia were less likely to be prescribed OAC in 2013-2017 than in 2003-2007 (compared to patients without the aforementioned comorbidities) (60). Ex-drinkers and non-drinkers were less likely to be prescribed OAC than ‘current drinkers’, which remained almost the same in 2003-2007 and in 2013-2017.

Current smokers and ex-smokers were slightly more likely to be prescribed an OAC than non-smokers, which did not vary across time as well. Finally, patients with CHA_2DS_2-VASc levels of 6-9 relative to 2-3 had slightly lower chances to be prescribed OAC, and this remained so in 2003-2007 and 2013-2017. Patients with HAS-BLED score of 5-8 were less likely to be prescribed OAC relative to patients with HAS-BLED scores 0-2 in 2003-2007, with the probabilities being almost equal for HAS-BLED scores of 5-8 and 0-2 in 2013-2017 (60).

Patients newly diagnosed AF aged 85 years and older had a higher probability of being prescribed OACs compared to no treatment in 2012-2015 if they had hyperlipidemia (OR 1.21, 95% CI 1.14-1.30) or a CHA_2DS_2-VASc score ≥6 (OR 1.15, 95% CI 1.06-1.25). They had a lower probability of being prescribed OACs compared to no treatment if they had chronic obstructive pulmonary disease (OR 0.82, 95% CI 0.77-0.87), abnormal renal function (OR 0.87, 95% CI 0.81-0.94), anemia (OR 0.70, 95% CI 0.65-0.75), or a history of bleeding (OR 0.86, 95% CI 0.81-0.92). The other factors (age above 90 years, sex, autoimmune disease, cancer, abnormal liver function) were not associated with OAC prescription. Furthermore, hyperlipidemia (OR 1.14, 95% CI 1.02-1.27) and abnormal liver function (OR 1.20, 95% CI 1.07-1.35) were associated with DOAC prescription compared with warfarin. Conversely, a lower odds of DOAC prescription, compared with warfarin was found for patients with abnormal renal function (OR 0.74, 95% CI 0.64-0.84) and anemia (OR 0.81, 95% CI 0.71-0.92) (63).

Females tend to have a lower probability of being prescribed DOACs compared to males. In Scotland, in 2010-2019, females were significantly less likely than males to receive either VKAs (OR 0.68, 95% CI 0.66–0.70) or direct factor Xa inhibitors (OR 0.92, 95% CI 0.90–0.95) (68). The difference was driven primarily by patients with prior bleeding (68). In the USA, in 2008-2015, women had lower incidence of prescriptions of both DOACs and warfarin, with an OR of not being anticoagulated for females compared to males of 1.20 (95% CI 1.18-1.22). A subgroup analysis among anticoagulation-eligible patients with low bleeding risk revealed significant sex differences in the probability of receiving a warfarin prescription (45.7% for men and only 40.4% for women, $p<0.001$) and DOAC prescriptions (14.5% for men and only 13.0% for women, $p<0.001$). In patients with a high risk of bleeding, women had lower probability of being anticoagulated (49.0% women, 53.0% men; $p<0.001$) (53). In Catalonia, in 2011-2020, women eligible for full dose of DOACs were more frequently underdosed than men for all DOAC molecules, except for edoxaban, with apixaban having the highest frequency of underdosing (39%

of women, 27.4% of men; $p < 0.001$) (69). In Canada, in 2008 – 2013, women had 35% higher chances to be prescribed a lower dabigatran dose compared with men (70). However, no studies explored sex differences in DOAC prescription among the elderly population.

2.5. Reasons for underuse of OACs

Physicians sometimes deviate from guidelines, and patients do not always follow clinicians' prescriptions. Patients may not adhere to prescribed OACs because of the fear of bleeding or history of severe recurrent falls, because of their personal beliefs or because of the lack of information (71), unfavorable employment or social environment (72). Physicians tend to give more weight to the risk of bleeding than to the risk of stroke (71), and often report needing more education to use risk scores confidently (73). Early discontinuation of anticoagulation is common, with dyspepsia, abdominal pain, bleeding (74), present sinus rhythm and anemia in the past (75) being the most frequent reasons for discontinuation of DOACs among the elderly population.

Multiple reasons can explain sex differences in DOAC prescriptions. Physicians may perceive women at lower cardiovascular risk in general (53). Women may have different attitude to health risks than man, which has been shown to result in incomplete appreciation of heart diseases among women and lower anticoagulation (53). Another possibility is that women were more likely to receive reduced doses of DOACs because of lower body weight which demanded dose correction (76). Insufficient social support and inadequate access to primary care could lead clinicians to postpone DOAC prescription to elderly women because low time in therapeutic range is associated with both reduced effectiveness and higher risk of adverse effects (68). In addition, pivotal randomized trials of DOACs were not powered to assess sex differences, and females were underrepresented with only 36% of all participants being female (77). There is controversy about the risk of bleeding among female patients with AF treated with DOACs (78). In an Italian study in 2013-2017, elderly females aged 75-84 age had higher gastrointestinal bleeding risk with DOACs compared to elderly males (HR 1.48, 95% CI 1.02-2.16), whereas there was no difference with VKAs (77). However, in Canada in 2012-2017, in a cohort of male and female patients with AF with similar comorbidities, the risk of major hemorrhage patients associated with DOACs (apixaban and rivaroxaban, standard or reduced doses) was similar for males and females (RR, 0.96; 95% CI, 0.81-1.15) (79). Finally, two meta-analyses reported that DOACs were associated with a significantly lower risk of major bleeding in females compared with males.

In addition, there is a substantial knowledge gap about the optimal anticoagulation of elderly patients with AF. Clinical trials of DOACs overrepresent age groups 65-69, 70-74, and 75-79 compared to real-world population structures, whereas age groups 80-84 and 85+ years are underrepresented (80). Only a few studies explored the difference in anticoagulation of elderly males and females. These areas are important knowledge gaps, leaving the elderly population at risk of under prescription due to insufficient scientific evidence, as well as at risk of suboptimal anticoagulation regimes. Moreover, the temporal trends in usage of particular DOAC molecules in the elderly population has been understudied.

Chapter 3: Objectives and hypotheses

The overall objective is to describe patterns and temporal trends of oral anticoagulant prescriptions among elderly patients aged 80 years or older with NVAF in UK primary care between 2011 and 2021.

Primary objectives:

- To estimate the annual rates of patients newly prescribed OACs overall and stratified by age, sex, particular comorbidities, UK nations and individual OAC molecules between 2011 and 2021.
- To estimate the proportion of patients newly prescribed OACs overall and stratified by age, sex, particular comorbidities, UK nations and individual OAC molecules between 2011 and 2021.

Secondary objectives:

- To estimate the annual prevalence of OAC prescription overall and stratified by age, sex, UK nations and OAC molecules between 2011 and 2021.
- To estimate the median time on treatment before switching OAC class/discontinuation.
- To identify the predictors of OAC initiation and persistence.
- To describe changes in baseline characteristics (age, sex, comorbidities, comedications, measures of health utilization) of patients newly prescribed OACs over time.

Chapter 4: Methods (supplemental material)

This chapter provides additional information on data sources and confounders that are not presented in the Methods section in the manuscript (Chapter 5).

1. Data sources

The study used the CPRD, an ongoing primary care database of anonymised medical records from general practitioners (81, 82). As of 2013, the active patients from the CPRD corresponded to approximately 6.9% of UK population, being representative of the UK general population in terms of age, sex and ethnicity. In addition to the data, recorded by GPs during consultations, the CPRD contains data on morbidity and life-style variables and has linkage to secondary care and mortality data, though data from secondary care can be incomplete because GPs record that information manually (81). CPRD has been shown to be have good validity in wide range of medical diagnosis (83). One of the drawbacks of CPRD is that, though the diagnoses are coded using extensive and highly hierarchical system of so called "read codes" with high positive predictive power, in some cases sensitivity may be low, because either patients can fail to present their full history of diseases to GP, or GPs can code diagnoses arbitrarily, sometimes as free text, which leads to non-uniform loss of information (81). In addition, level of social support, over-the-counter medication use, prescriptions in secondary care, prescriptions filled, and adherence to treatments are not captured in the CPRD (81), which limits its usage in pharmacoepidemiology.

In this study, two databases - Aurum and GOLD - were used, with repeated records being deduplicated patients from the GOLD database. Up-to-standard date is not available in the CPRD Aurum; however, several data quality assurance process are in place and issues identified are addressed before data are incorporated in the CPRD Aurum. Therefore, we did not expect any differences in the quality and characteristics of the cohorts from GOLD and Aurum databases.

2. Covariates

Relevant baseline characteristics were pre-selected as covariates based on a review of the literature. The following characteristics were considered for both logistic and Cox regressions, all measured before or at cohort entry: age, sex, ethnicity, calendar year, lifestyle-related factors (BMI, measured in the 5 years before cohort entry; alcohol abuse, smoking status), and the following comorbidities, measured at any time before cohort entry: hypertension, diabetes,

coronary heart disease, heart failure, stroke, transient ischemic attack, systemic embolism, peripheral arterial disease, history of bleeding (intracranial, gastrointestinal, other), anemia, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, dementia and cognitive impairment, obstructive sleep apnoea, cancer (other than non-melanoma skin cancer), history of falls, head trauma, depression, as well as the Charlson comorbidity index.

In addition, the utilization of the following medications in the year before cohort entry was considered: antiplatelet drugs, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, loop diuretics, other diuretics, beta blockers, antiarrhythmics, antidiabetic drugs, lipid lowering drugs, nonsteroidal anti-inflammatory drugs, opioids, antidepressants, antipsychotics, anxiolytics, barbiturates and other hypnotics, antiepileptic drugs, corticosteroids, proton pump inhibitors and H2 receptor antagonists.

Finally, health utilization was measured as the number of physician visits in the year before cohort entry. Missing information for BMI and smoking was classified in a separate category. The $CHADS_2$ and CHA_2DS_2-VASc scores were used to estimate the risk of ischemic stroke in AF, and the HAS-BLED score was used to estimate the risk of bleeding in AF.

Chapter 5: Prescribing Trends of Oral Anticoagulants to Elderly Patients with Atrial Fibrillation in Primary Care in the United Kingdom, 2011- 2021

This chapter presents a manuscript on the trends of oral anticoagulation among elderly patients with atrial fibrillation in UK primary care from 2011 to 2021. The manuscript is intended for submission. The figures and tables in the manuscript and supplementary materials are included in Chapter 7.

Prescribing Trends of Oral Anticoagulants to Elderly Patients with Atrial Fibrillation in Primary Care in the United Kingdom, 2011- 2021

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Keywords: oral anticoagulants, atrial fibrillation, trends, CPRD, UK

ABSTRACT

Background: An increase in OAC (oral anticoagulation) prescriptions in elderly population with atrial fibrillation has been documented in western countries since the 2000s. However, no information is available on recent trends in DOAC (direct oral anticoagulation) prescriptions among elderly patients, or about their adherence and risk factors of treatment termination in such patients.

Objectives: To describe trends in OAC prescriptions to elderly patients with atrial fibrillation in UK primary care between 2011 and 2021.

Methods: Using the Clinical Practice Research Datalink, we defined a cohort of patients aged 80 years and above, registered with a general practitioner and diagnosed with atrial fibrillation between January 1, 2011 and December 31, 2021. Using Poisson regression, we estimated the annual rates of patients newly prescribed VKAs (vitamin K antagonist) or DOACs. We used the Kaplan-Meier method to estimate the median time from NVAF (non-valvular atrial fibrillation) diagnosis to OAC initiation and the median duration of persistence with DOACs or VKAs until first treatment interruption. We also estimated annual period prevalence stratified by age, sex, individual OACs, and UK nation (England, Wales, Scotland, Northern Ireland). Finally, we reported baseline characteristics of patients newly prescribed an OAC in three calendar time periods (2011-2014 / 2015-2018 / 2019-2021) and the baseline characteristics by individual OAC for the last calendar year (2021).

Results: The cohort included 138,303 patients with mean age of 86 years, of whom 56.7% were female. Crude incidence rate of OAC initiation grew from 1,097.4 (95% CI 1,064.4-1,131.4) in 2011 to 4,799.7 (95% CI 4,702.8-4,898.7) per 1,000 person-years in 2021. The proportion of patients who were anticoagulated increased from 41% in 2011 to 75% in 2021, with notable growth from 9% in 2011 to 51% in 2021 in the age group 95 years and above. The rate ratio of initiating OAC in 2021 compared to 2011 was 4.58 (95% CI 4.27-4.97). The prevalence of OAC prescription grew from 50% in 2011 to 84% in 2021, remaining lower than average for females and patients from higher age groups. Older patients had lower probability to initiate any OAC treatment and higher probability to be indicated DOAC rather than warfarin.

Conclusion: During the last decade, anticoagulation among elderly population increased substantially. Further research is needed to offer potential explanations for the trends observed.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, increasing with age and affecting 15% of male and 10% of female patients aged 75-84 (1). Oral anticoagulation is essential in the management of AF to prevent stroke occurrence, including silent strokes, and microembolisms (2). Vitamin K antagonists such as warfarin require active monitoring, and their effectiveness depends heavily on diet and genetics (3). Direct oral anticoagulants (DOACs), an alternative to warfarin, were shown to be at least as effective in preventing ischemic stroke or systemic embolism, with a lower risk of major bleeding (4), and are now recommend over warfarin for stroke prevention in patients with nonvalvular AF (NVAF).

According to recent trends, DOACs have largely replaced warfarin in patients with AF, exceeding 70% in prescriptions among individuals aged 65 years or older (5). Among DOACs, the most frequently prescribed drugs are apixaban and rivaroxaban (6). Despite their benefits, DOACs remain under prescribed to elderly individuals with NVAF with elevated risk of stroke (7). Multiple studies explored trends in anticoagulation in elderly patients with AF. The proportion of patients with incident NVAF aged 75 and older at elevated risk of stroke but who did not receive OAC prescriptions decreased in 2010-2020 (8-11). However, advanced age remains associated with a lower probability of being prescribed OACs, compared to younger ages (11-18). DOAC molecules (apixaban, rivaroxaban, dabigatran, edoxaban) are equally recommended in patients with NVAF (19), but apixaban remains the most prescribed DOAC among patients with NVAF aged 75 and older (16).

A few studies have examined the risk factors for OAC under prescription. In one study, predictors for OAC under prescription in patients with incident NVAF aged 85 years or older were chronic obstructive pulmonary disease, abnormal renal function, anaemia and history of bleeding (13). Moreover, patients with hyperlipidemia and abnormal liver function were more likely to be prescribed DOACs over warfarin, whereas those with abnormal renal function and anaemia were more likely to be prescribed warfarin (13). In addition, for elderly patients with NVAF, the association between OAC under prescription and some risk factors such as overweight or obesity, diabetes mellitus, acute kidney injury became weaker between 2003-2007 and 2013-2017; conversely, heart valve disease, major bleed, intracranial bleed, dementia became more strongly associated with OAC under prescription between 2003-2007 and 2013-2017 (12). Furthermore, only a few studies examined the difference in anticoagulation between elderly males and females,

suggesting that elderly women face persistent risk of under prescription and under dosing of OAC compared to males with the same risk of bleeding (20-23). Finally, though some studies explored adherence to OACs, none provided information on elderly patients with NVAF. Thus, several knowledge gaps remain regarding recent prescribing trends of OAC and predictors of initiation and adherence in elderly patients with NVAF.

METHODS

Data source

We used the Clinical Practice Research Datalink (CPRD), a UK primary care electronic medical records database of over 60 million patients from more than 2000 practices (24-25). The CPRD has been shown to be representative of the UK general population in terms of age, sex, and ethnicity. The CRPD records information on demographics, lifestyle (e.g. smoking and alcohol consumption), prescriptions, medical diagnoses, and referrals. Drug prescriptions are recorded automatically at the time of issue by the general practitioner (24). The CPRD has been shown to have good validity in wide range of medical diagnosis (26).

Study cohort

The cohort included all patients aged 80 years or more newly diagnosed with AF between January 1, 2011, and December 31, 2021 with cohort entry defined as the date of AF diagnosis. We excluded patients with less than one year of registration with the practice before AF diagnosis, patients with a prior AF diagnosis, and those with an OAC prescription in the year before AF diagnosis. We also excluded patients with a history of valvular surgery (valvular AF), rheumatic valvular disease, oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities at any time before cohort entry. In addition, we excluded patients with hyperthyroidism in the 3 months before cohort entry or a diagnosis of venous thromboembolism or hip surgery in the 30 days prior to and including cohort entry date. Patients were followed from the date of AF diagnosis until end of registration with the general practice, practice last collection date, death, or the end of the study period (December 31, 2021), whichever occurred first.

Exposure definition

All outpatient prescriptions for DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) and VKAs (warfarin, phenindione, acenocoumarol) during follow-up were identified. Patients with at least one DOAC or VKA prescription during one year after first AF diagnosis were considered exposed.

Statistical analysis

Incidence rate of patients newly prescribed OACs

Crude and age and sex standardized annual incidence rates with 95% confidence intervals (CIs) of patients newly prescribed OACs in the year after their first AF diagnosis were estimated based on a Poisson distribution, where the numerator was the number of patients with a first-ever prescription for an OAC and the denominator was the total person-years of follow-up for all cohort members up to the first prescription within that year. We stratified rates by age, sex, individual OACs (VKAs, apixaban, dabigatran, edoxaban, rivaroxaban), UK nation (England, Northern Island, Scotland, and Wales) and presence of frailty, prior stroke/TIA, dementia, chronic kidney disease, CHA_2DS_2-VASc score (higher risk vs lower risk), and HAS-BLED score (3 vs >3).

Rate ratios are estimated to compare the annual rate of OAC initiation to 2011, as well as to the preceding year using a log-linear regression model, adjusted for age and sex. We also estimated the annual excess rate of OAC prescriptions with calendar year as a continuous predictor variable in the log-linear model. All models included an overdispersion parameter to account for extra-Poisson variation. For each calendar year, we also calculated the proportion of patients with a prescription for an OAC within 1 year after the AF diagnosis, as well as the relative proportion of prescriptions attributable to each OAC.

Baseline characteristics of patients newly prescribed OACs

The baseline characteristics of patients newly prescribed an OAC were described in three calendar time periods: 2011-2014, 2015-2018, 2019-2021. The baseline characteristics by individual OAC were presented for the last period (2019-2021).
We considered the following characteristics, all measured before or at cohort entry: age, sex, ethnicity, calendar year, and lifestyle-related factors (BMI (measured in the 5 years before cohort entry), alcohol abuse, smoking status), and the following comorbidities, measured at any time before cohort entry: hypertension, diabetes, coronary heart disease, heart failure, stroke, transient ischemic attack, systemic embolism, peripheral arterial disease, history of bleeding (intracranial, gastrointestinal, other), anemia, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, dementia and cognitive impairment, obstructive sleep apnoea, cancer (other than non-melanoma skin cancer), history of falls, head trauma, depression, and Charlson comorbidity index. We also measured the following medications in the year before cohort entry: antiplatelet drugs, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel

blockers, thiazide diuretics, loop diuretics, other diuretics, beta blockers, antiarrhythmics, antidiabetic drugs, lipid lowering drugs, nonsteroidal anti-inflammatory drugs, opioids, antidepressants, antipsychotics, anxiolytics, barbiturates and other hypnotics, antiepileptic drugs, corticosteroids, proton pump inhibitors and H2 receptor antagonists. We measured health utilization as the number of physician visits in the year before cohort entry. Missing information for BMI and smoking was classified in a separate category. We also calculated the $CHADS_2$ and CHA_2DS_2-VASc scores used to estimate the risk of ischemic stroke in AF, and the HAS-BLED score used to estimate the risk of bleeding in AF.

Multivariate logistic regression models were fitted to identify predictors of OAC initiation and DOACs vs VKAs initiation.

OAC treatment persistence and trajectory

We used the Kaplan-Meier method to estimate the median time from NVAF diagnosis to OAC initiation and the median duration of persistence with DOACs or VKAs until first treatment interruption, modified for competing risks to account for deaths occurring during follow-up, and censoring at the date of major bleeding. Patients were considered exposed for the intended duration of the prescription, plus a grace period of 30 days to account for residual treatment effects and/or prescription refill time in the event of nonoverlapping prescriptions. Switching within an OAC class (e.g., from one DOAC to another DOAC) was not considered discontinuation. In a sensitivity analysis, we increased the grace period to 60 days to assess the impact on the estimated duration of use until first discontinuation. We also described the patterns of switching between individual OACs. A Cox proportional hazards model was used to identify predictors of treatment discontinuation.

Annual prevalence of patients prescribed OACs

The period prevalence of OAC prescription was estimated for each calendar year as the number of patients with an OAC prescription divided by the number of patients in the cohort in a particular year. We also estimated annual period prevalence stratified by age, sex, individual OACs, and UK nation. For this analysis, the cohort included all patients with a diagnostic of NVAF any time before or at cohort entry, with follow-up starting on the patient's 80^{th} birthday, 1 January 2011, one year after the patient's registration date with the practice, or one year after the date on which the practice started contributing valid data to the CPRD ('up to standard date'), whichever occurred later.

All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). The study protocol (23_003487 was approved by the independent scientific advisory committee of the CPRD, and the research ethics committee of the Jewish General Hospital (Montreal, Canada).

RESULTS

The cohort included 138,393 patients with 40,487 person-years of follow-up, of whom 92,622 (66.9%) initiated an OAC during the first year after AF diagnosis. Females accounted for 56.7% of all patients. Patients from age group 80-85 years composed 43.7% of all patients, whereas age groups 85-90 years, 90-95 years, and 95+ years accounted for 33.9%, 17.3%, and 5.1%, respectively.

Incidence rate of patients newly prescribed OACs

Crude annual incidence rates of patients newly prescribed OACs in the year after AF diagnosis increased from 1,097.4 per 1,000 person-years in 2011 to 4,799.7 per 1,000 person-years of follow up in 2021 (**Figure 1**). Similarly, age and sex adjusted annual incidence rates increased from 1,097.4 per 1,000 person-years in 2011 to 4,939.8 per 1,000 person-years in 2021 (**Figure 1**).

The most remarkable growth in age stratified rates was in patients aged 95 years and above, where annual rates of patients newly prescribed OACs increased almost 10-fold, from 206.8 per 1,000 person-years in 2011 to 2,138.4 per 1,000 person-years in 2021 (**Figure 2**). Sex stratified rates almost converged in 2021, though in 2011-2020 females had slightly lower annual rate of OAC initiation than males (**Figure 3**). Most of the growth of OAC initiation is attributable to the high growing rates of apixaban initiation, which increased from 19.5 per 1,000 person-year in 2013 to 3,132.0 per 1,000 person-years in 2021, whereas the rate of VKA declined steadily from 1,091.0 per 1,000 person-years in 2011 to 80.6 per 1,000 person-years in 2021 (**Figure 4**). Annual rates of OAC initiation for patients with frailty grew gradually from almost zero level in 2011 to 4,659.6 per 1,000 person-years in 2021 (**Figure 5**). Patients with prior stroke had slightly higher rates of OAC initiation in 2011-2014 compared to patients without prior stroke, and slightly lower rates after 2015, reaching 4,891.7 per 1,000 person-years among patients without prior stroke and 4,511.1 per 1,000 person-years among patients with prior stroke in 2021 (**Figure 6**). Patients with

dementia had much lower annual rates of OAC initiation (2,551.7 per 1,000 person-year in 2021) compared to patients without dementia (5,163.9 per 1,000 person-years in 2021) (**Figure 7**). Patients without chronic kidney disease had slightly higher annual rates of OAC initiation in 2012-2021 than patients without chronic kidney disease, reaching 4,935.3 and 4,581.1 per 1,000 person-years in 2021 respectively (**Figure 8**). Annual rate of OAC initiation among patients with a high risk of stroke grew from 1,115.7 to 4,866.3 per 1,000 person-years in 2011-2021, whereas among patients with low risk of stroke annual rate of OAC initiation grew from 880.7 to 3,987.6 per 1,000 person-years in 2011-2021 (**Figure 9**). Annual rate of OAC initiation, stratified by risk of bleeding, grew substantially both for high-risk group (from 1,134.7 to 4,751.7 per 1,000 person-years in 2011-2021) and low risk group (from 1,054.5 to 4,877.9 per 1,000 person-years in 2011-2021) (**Figure 10**). Finally, substantial difference in incidence rates of OAC initiation was observed between UK nations: in 2021 annual rates of OAC initiation were the lowest in Scotland (3,254.6 per 1,000 person-years), almost the same in England and Wales (4,984.0 and 4,858.2 per 1,000 person-years respectively) and the highest in Northern Ireland (6,562.4 per 1,000 person-years) (**Figure 11**).

Incidence rate ratio of OAC initiation in 2021, adjusted for age and sex, was 4.58 (95% CI 4.27-4.91) compared to 2011, and 1.28 (95% CI 1.21-1.35), compared to 2020 (**Table 1**). The annual excess rate was equal to 1.188 (**Table 2**). The percentage of patients who initiated an OAC during the first year after NVAF diagnosis increased from 41% in 2011 to 75% in 2021, with the percentage in patients aged 95 years and above growing from 9% in 2011 to 52% in 2021 (**Figure 12**).

The relative proportion of patients prescribed VKAs decreased from 99.5% in 2011 to 1.7% in 2021. The relative proportion of patients prescribed apixaban, edoxaban, rivaroxaban and dabigatran reached 65.3%, 20.1%, 12.6% and 0.4% respectively in 2021 (**Figure 13**).

Changes in patients' baseline characteristics in 2011-2021

Although patients shared lots of similarities in their characteristics in 2011-2021, there were several remarkable differences. The relative proportions of patients aged 90-95 and 95+ years grew from 11.1% and 1.4% in 2011-2014 to 15.9% and 4.0% in 2019-2021. Several comorbidities became more prevalent in 2019-2021, such as diabetes reaching 30%, dementia – 8%, history of bleeding – 37%, and history of falls – 35%. Patients in 2019-2021 used fewer antiplatelet drugs

(56%), but more lipid lowering drugs (67%), nonsteroidal anti-inflammatory drugs (73%), opioids (71%), antidepressants (41%), antiepileptic drugs (17%), proton pump inhibitors (69%). A lower proportion of patients smoked in 2019-2021 (52.7%) than in 2011-2014 (58.4%) (**Table 3**).

In 2019-2021 patients aged 90+ initiated apixaban more frequently than other OACs. Hypertension, diabetes, heart failure, anemia and chronic kidney disease were slightly more common among patients on warfarin compared to the patients on DOACs. In addition, the proportion of patients prescribed loop diuretics was slightly higher for patients on warfarin (**Table 3**).

OAC treatment persistence and trajectory

Half of patients initiated OACs during the first 35 days after AF diagnosis. The median treatment persistence was 631 days (using a grace period 30 days) and 1503 days (using a grace period 60 days (**Table 4**).

In 2011-2014 the most common patterns of switching were from warfarin to rivaroxaban (44%), dabigatran (22%) and apixaban (12% of all switches). Among DOACs, the most common type of switching was from dabigatran to rivaroxaban (6%). In 2015-2018 switches from warfarin to DOACs still accounted for more than a half of all switches (32% from warfarin to apixaban, 26% from warfarin to rivaroxaban). The most common switches in DOACs were from rivaroxaban to apixaban (11%) and from apixaban to rivaroxaban (5%). In 2019-2021 the proportion of switches from warfarin to DOACs were 27% from warfarin to apixaban, 12% from warfarin to edoxaban, 9% from warfarin to rivaroxaban). Among patients prescribed DOACs, the most common switch patterns were from rivaroxaban to apixaban (13%), from apixaban to rivaroxaban (8%) and from apixaban to edoxaban (11%) (**Table 5**).

Risk factors of OAC prescription, OAC type indication and treatment persistence

Older age was significantly associated with lower probability of OAC initiation, higher probability of DOAC rather than warfarin initiation, and lower treatment persistence. (**Table 6**).

The following comorbidities were associated with an increased probability of OAC initiation: hypertension, diabetes, coronary heart disease, heart failure, stroke, systemic embolism, peripheral arterial disease. Conversely, history of bleeding, anemia, chronic kidney disease, liver

disease, dementia or cognitive impairment, cancer, history of falls, head trauma and depression were associated with a lower probability of OAC initiation.

Patients with heart failure, systemic embolism, anemia or chronic kidney disease and those taking antiplatelet drugs or loop diuretics were more likely to be prescribed warfarin than DOACs. Patients with dementia or cognitive impairment, history of falls or head trauma or taking lipid lowering drugs, nonsteroidal anti-inflammatory drugs, proton pump inhibitors were more likely to be prescribed DOACs (**Table 6**).

Higher treatment persistence was associated with lipid lowering drugs and antiepileptic drugs therapy, whereas lower treatment persistence was significantly associated with thiazide diuretics, loop diuretics, opioids and corticosteroids (**Table 6**).

Overweight and obesity was associated with OAC initiation and higher treatment persistence than patients with normal weight. Finally, smokers had significantly lower probability to initiate OAC than non-smokers (**Table 6**).

Annual prevalence of patients prescribed OACs

Overall prevalence of OAC treatment grew from 50% in 2011 to 84% in 2021 (**Figure 14**). Prevalence of OAC treatment among males remains steadily higher than among females, growing from 55% in 2011 to 85% in 2021, compared to the growth of prevalence among females from 46% in 2011 to 83% in 2021 (**Figure 15**). Prevalence in age group 95+ years grew 5.3 times in 11 years, from 13% in 2011 to 66% in 2021, followed by age group 90-95 years, with its prevalence growing 2.3 times, from 34% in 2011 to 79% in 2021. The highest prevalence in 2021 is reached in the age group 80-85 years old (89%) (**Figure 16**). The highest prevalence by molecule prescription in 2021 is reached by apixaban (40%), followed by rivaroxaban (18%). Prevalence of warfarin prescriptions declined from 49% in 2011 to 16% in 2021 (**Figure 17**). Among UK nations, the prevalence in Scotland remained consistently lower compared to England, Wales and Northern Ireland, growing from 49% in 2011 to 79% in 2021, whereas the prevalence in England and Northern Ireland increased to 85% and 87% in 2021 respectively (**Figure 18**).

DISCUSSION

This population-based cohort study described the temporal trends in anticoagulation in the elderly population with NVAF in UK primary care practices between 2011 and 2021. In accordance with the global trends of anticoagulation among elderly individuals with AF (8-11), our results showed that incidence rates of elderly patients newly prescribed OACs increased 5-fold between 2011 and 2021. The growth of OAC initiation was driven by apixaban, whereas the rate of VKA initiation declined steadily throughout the study period. By 2021 the relative proportion of prescriptions attributable to apixaban reached 65.3%, whereas warfarin accounted only for 1.7% of all OAC prescriptions.

Although the most remarkable growth in incidence rate of anticoagulation was observed among patients aged 95 years and older, individuals from this age group consistently remained the least treated age group, even after controlling for comorbidities, which leaves them at elevated risk of stroke with potentially poor outcomes (27), even though this risk could potentially be mitigated with proper OAC treatment. Underprescription of OACs to the elderly population may be explained by the tendency of physicians to give more weight in their decisions to the risk of bleeding than to the risk of stroke (28), as well as by a substantial gap in optimal anticoagulation of elderly patients with multiple comorbidities (29), even though both VKAs and DOACs were shown to have comparable efficacy and similar risk of bleeding in this population (30). As a result, the incidence of OAC initiation among patients with NVAF aged 95 years and older in 2021 remained almost 1.5 times lower compared to patients aged 80-85 years. Similarly, the proportion of patients newly prescribed OAC who initiated OAC during the first year after diagnosis, remained consistently the lowest for patients aged 95 years and older throughout the study period, although it grew substantially from 9% in 2011 to 52% in 2021. The relatively low proportion of anticoagulated elderly patients with NVAF during the pre-DOAC era may partly be explained by the complexities associated with warfarin treatment including regular monitoring to keep INR levels in the range of 2.0-3.0, frequent visits to physicians for dose correction, multiple interactions of warfarin with other commonly prescribed medications, and risk of bleeding in case of INR above 3.0 (31)). During the era of DOACs' availability, we showed an increase in the rate of elderly individuals prescribed OACs, with DOACs, and apixaban in particular, being the most prescribed OACs. These trends are similar to what has been reported in younger patients with AF where most patients are prescribed DOACs over VKAs, in accordance with guidelines

recommending DOACs over VKAs for most patients with NVAF given their similar efficacy and safety and ease of use compared with VKAs.

We have shown that elderly NVAF patients with frailty have a slightly lower incidence of OAC initiation, whereas for patients with dementia the incidence of OAC initiation was twice as low than for patients without dementia. Neither frailty nor dementia are listed among contraindications for OAC prescription (32, 33) as well in the relevant UK NICE guidelines (19). Our results show that several comorbidities were associated with a lower probability of OAC initiation. However, the decision to avoid anticoagulating elderly patients with comorbidities, not listed explicitly as contraindications in the guidelines, could be potentially harmful for a large proportion of patients, since multimorbidity is typical for elderly patients with AF (34), with several comorbidities being risk factors for developing AF (35). We also showed that elderly smokers with newly diagnosed NVAF had a lower probability to initiate OACs than non-smokers. Taken together with the fact that smoking is associated with higher occurrence of AF (35, 36), smokers could be a relevant target for public health interventions both in terms of AF prevention and stroke prevention.

In accordance with limited existing evidence suggesting lower anticoagulation of females compared to males with AF (12, 20-23), our study revealed that females had slightly lower incidence of OAC initiation and prevalence of OAC than males, in all years of our study, with the temporal trends showing a tendency towards similar initiation rates. In the regression analysis, after controlling for comorbidities, medical therapy and lifestyle factors, males had a slightly lower chance to initiate OACs compared to females. However, our analysis did not include information on dosage, which could reveal more gender disparities in OAC utilization.

We found disparity among UK nations in both incidence and prevalence of anticoagulation, with Northern Ireland characterized by the highest and Scotland with the lowest rates of OAC initiation and OAC persistence. This finding could be explained by socio-economic disparities between the nations, since AF has been shown to be more prevalent in deprived neighborhoods (37). Ethnic variation across the nations, different real-world practices of detecting and treating AF, as well as different access to NHS resources may also contribute to these differences between UK nations.

The study had several strengths. We presented the most recent update on the trends in anticoagulant prescription for the elderly population with NVAF in UK primary care. Using the

CPRD allowed us to collect a relatively large sample of the elderly population, representative of the overall UK population (138,393 patients with NVAF aged 80+ years), and focus our study on multiple age groups, including nonagenarians. The relatively long follow-up of 11 years allowed us to explore the long-term trends in VKA prescription as well as trends in newer DOAC molecules. Moreover, the CPRD contains unique lifestyle variables, which allowed us to study the impact of smoking and obesity on initiation and persistence of OAC.

Some limitations should be considered. The CPRD contains information about prescriptions issued only by GPs, whereas the prescriptions issued by specialists or during hospitalizations are not available. However, due to the central role of GPs in managing chronic conditions in the UK, the CPRD is expected to contain the majority of OAC prescriptions, minimizing potential exposure misclassification. Moreover, the prescriptions recorded in CPRD are those issued by general practitioners, not those filled or actually taken, which could also lead to exposure misclassification.

In summary, anticoagulant prescription in UK primary care increased steadily between 2011and 2021 among the elderly population with NVAF aged 80 years and above. Over the study period, VKAs were almost fully replaced with DOACs, with almost two thirds of prescriptions in 2021 attributable to apixaban. While these trends are encouraging, several comorbidities, as well as older age, were associated with not initiating OACs. Further studies are needed to offer explanations for the observed deviation from guidelines, which puts a large proportion of patients at risk of stroke.

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Figures and tables

Manuscript

Figure 1. Crude and age and sex standardized annual incidence rates of patients newly prescribed OACs in the year after AF diagnosis

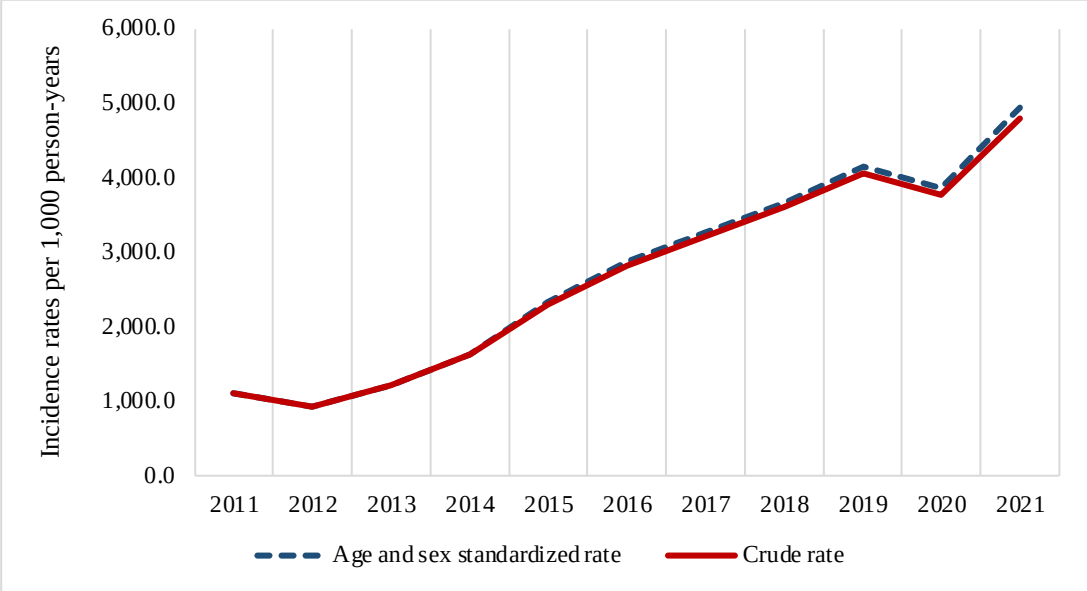


Figure 2. Incidence rate of OAC initiation, stratified by age group

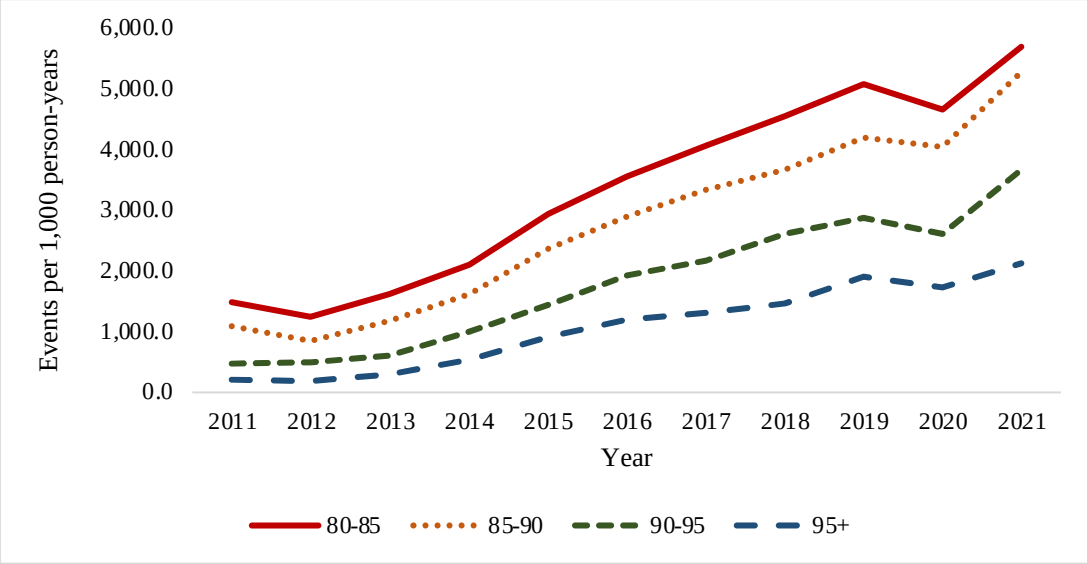


Figure 3. Incidence rate of OAC initiation, stratified by sex

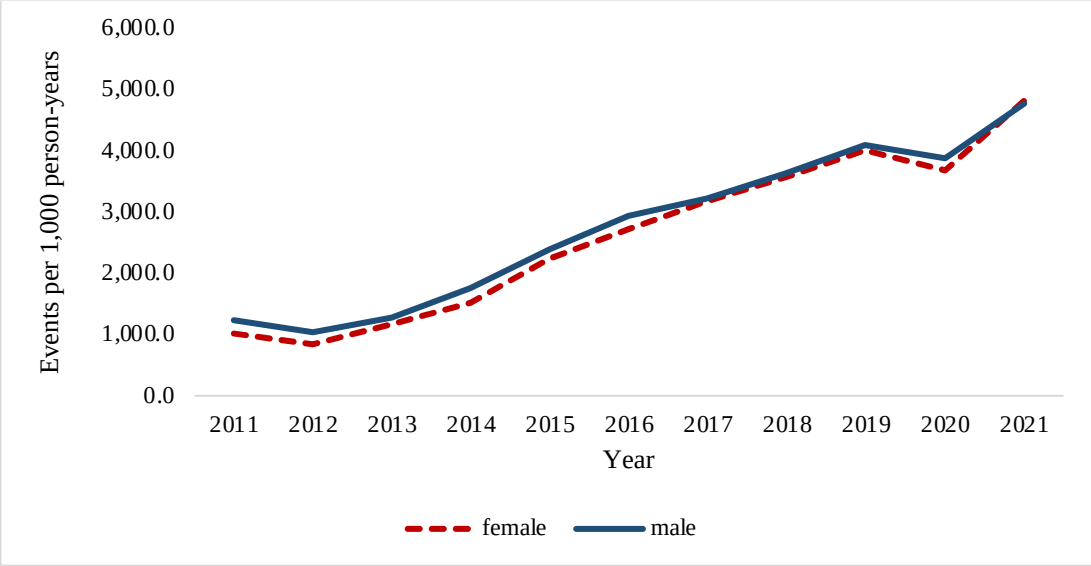


Figure 4. Incidence rate of OAC initiation, stratified by OAC type

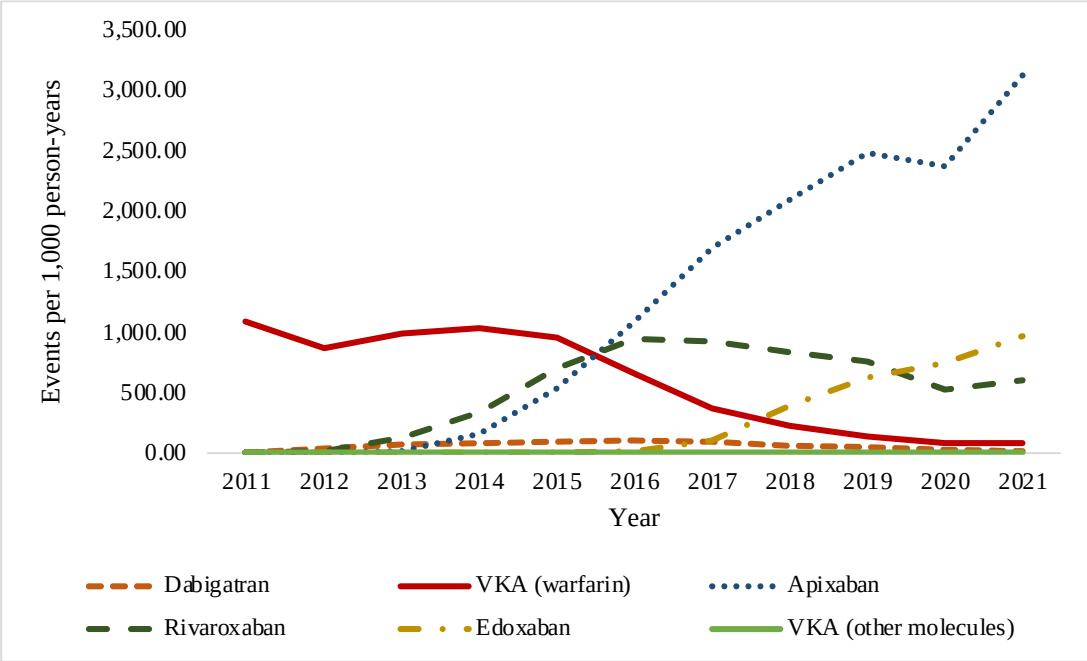


Figure 5. Incidence rate of OAC initiation, stratified by frailty

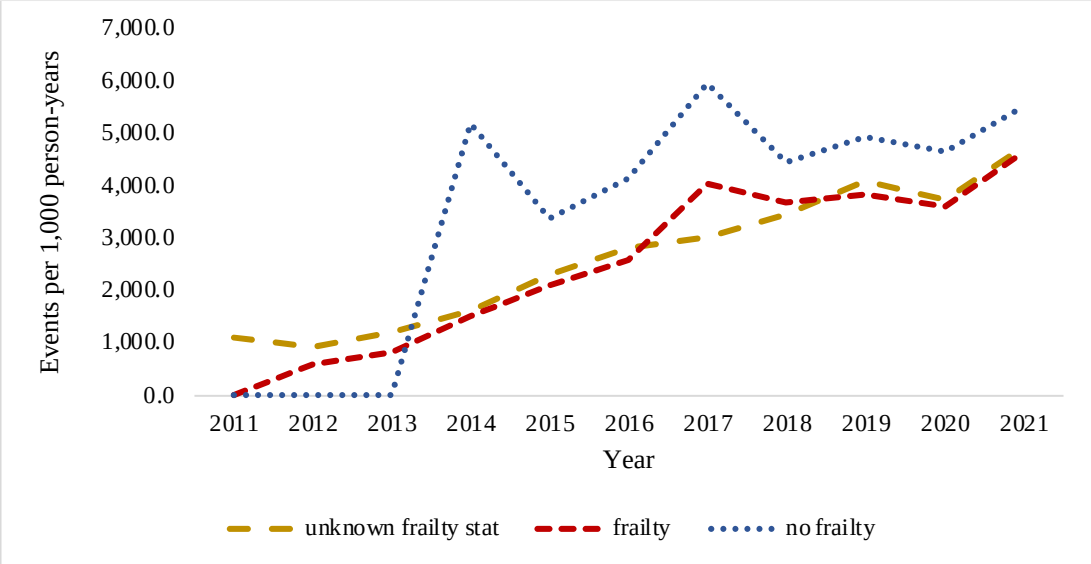


Figure 6. Incidence rate of OAC initiation, stratified by prior stroke / TIA

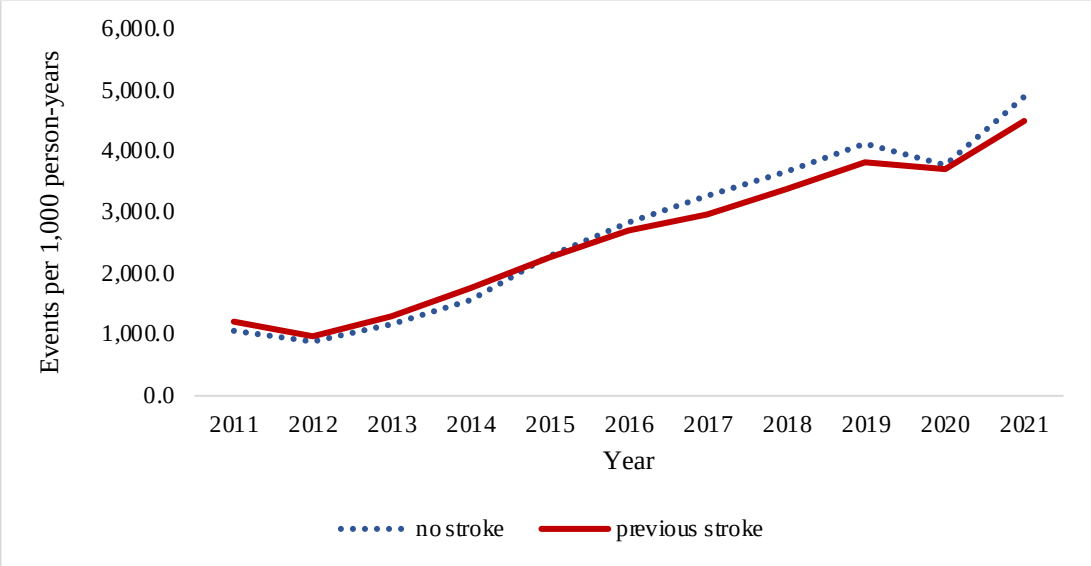


Figure 7. Incidence rate of OAC initiation, stratified by dementia

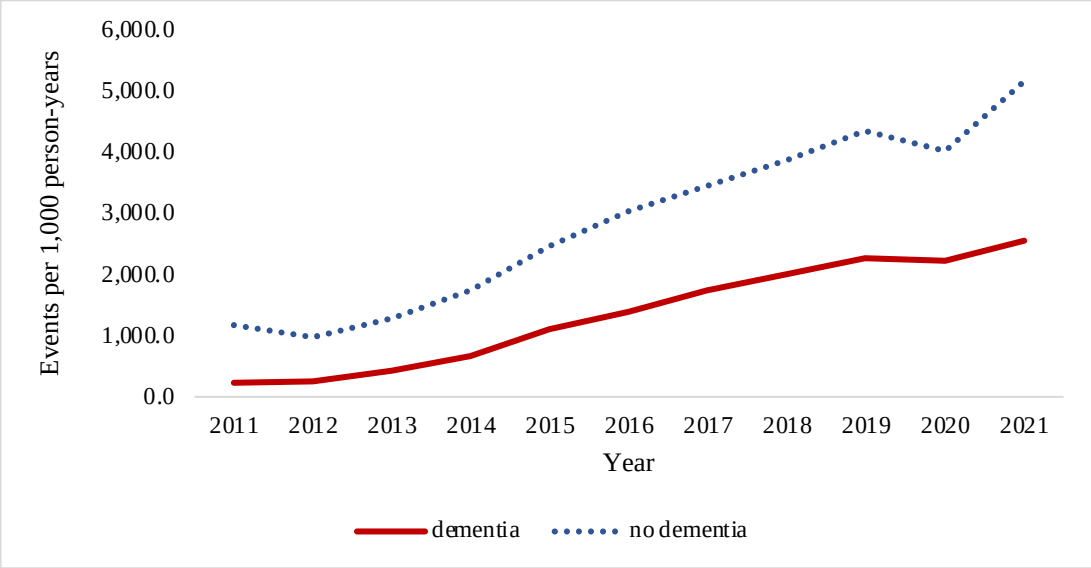


Figure 8. Incidence rate of OAC initiation, stratified by chronic kidney disease

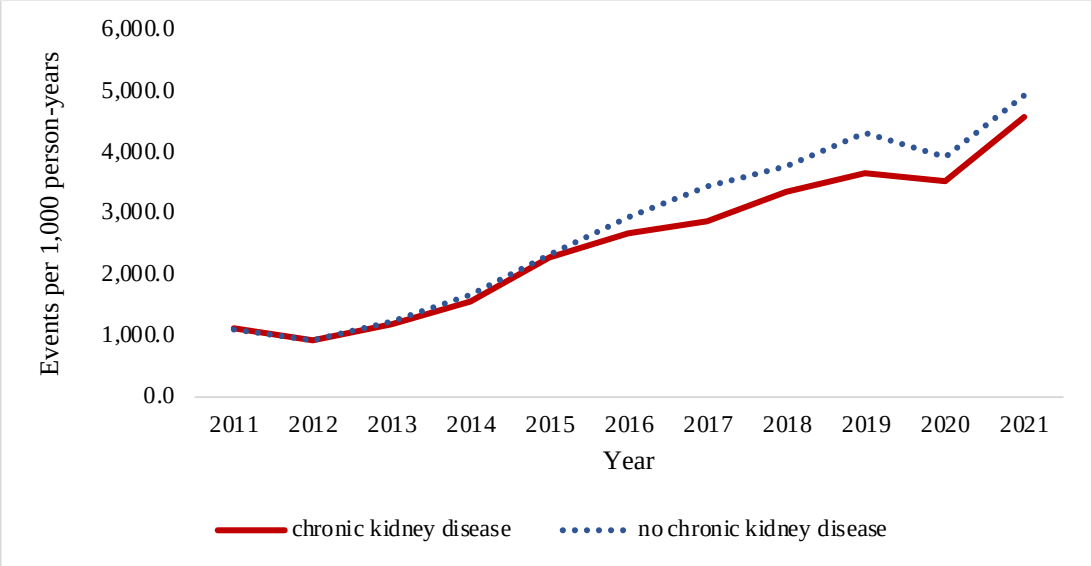


Figure 9. Incidence rate of OAC initiation, stratified by CHA_2DS_2-VASc score

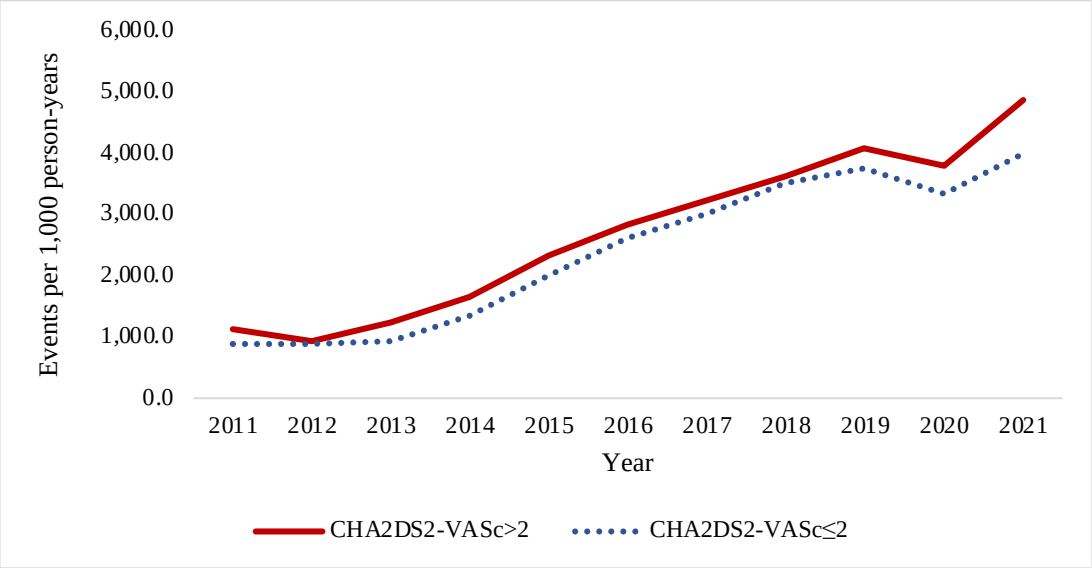


Figure 10. Incidence rate of OAC initiation, stratified by HAS-BLED score

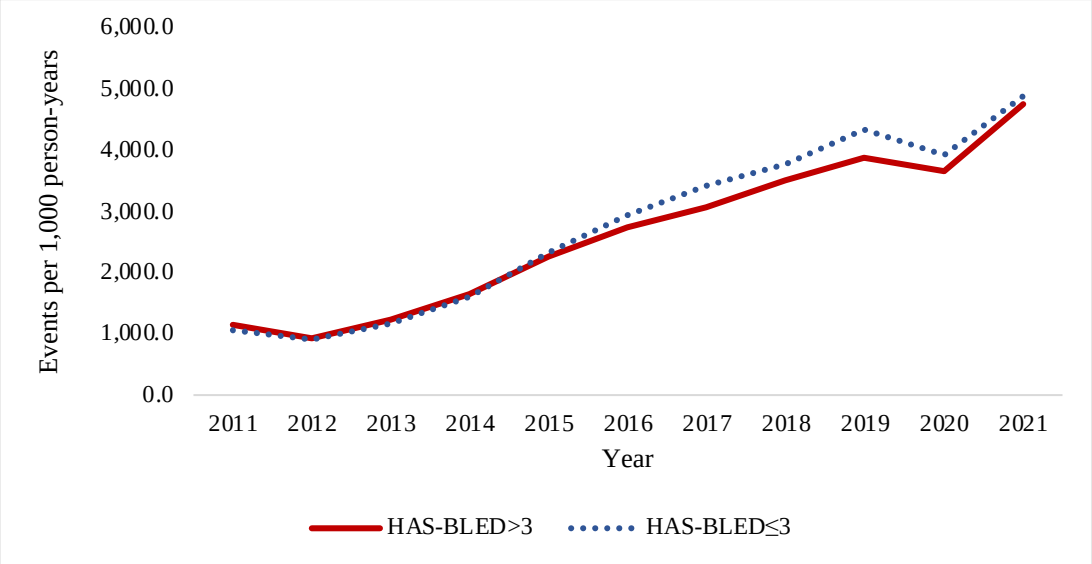


Figure 11. Incidence rate of OAC initiation, stratified by UK nation

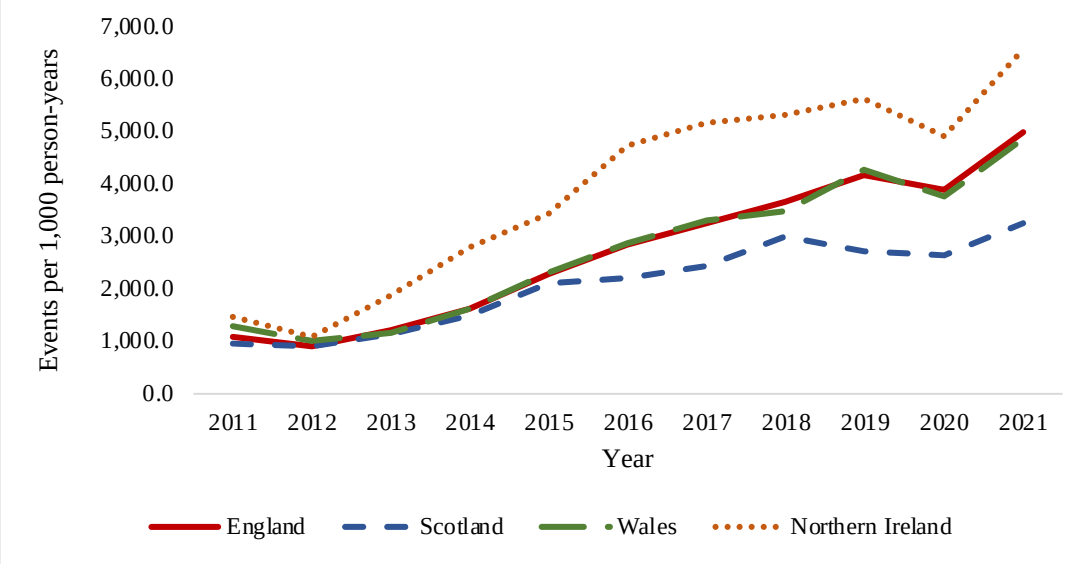


Table 1. Incidence rate ratios of OAC initiation to 2011 and to preceding year, adjusted for age and sex

Year	Crude rate per 1,000 person-years (95% CI)	Adjusted rate per 1,000 person-years (95% CI)	Adjusted rate ratios of the annual rate of OAC initiation to 2011	Adjusted rate ratios of the annual rate of OAC initiation to the preceding year
2011	1097.4 (1064.4-1131.4)	1097.4 (1064.4-1131.4)	Reference	Reference
2012	920 (896.8-943.9)	920.7 (897.4-944.6)	0.84 (0.78-0.9)	0.84 (0.78-0.9)
2013	1207 (1178.7-1236)	1209.4 (1181.1-1238.5)	1.11 (1.03-1.19)	1.33 (1.24-1.42)
2014	1619.7 (1584.2-1656)	1631.1 (1595.4-1667.6)	1.51 (1.4-1.62)	1.36 (1.27-1.44)
2015	2294.8 (2248.6-2341.9)	2330.3 (2283.6-2378)	2.15 (2-2.3)	1.43 (1.35-1.51)
2016	2819.1 (2763.4-2875.9)	2870.3 (2813.9-2927.9)	2.65 (2.47-2.84)	1.23 (1.17-1.3)
2017	3204.8 (3143.1-3267.8)	3267.6 (3204.9-3331.6)	3.02 (2.82-3.24)	1.14 (1.08-1.2)
2018	3603.3 (3535.4-3672.5)	3667.2 (3598.3-3737.4)	3.39 (3.17-3.63)	1.12 (1.07-1.18)
2019	4052 (3976.2-4129.3)	4147 (4069.7-4225.7)	3.84 (3.58-4.11)	1.13 (1.07-1.19)
2020	3760.8 (3680.8-3842.6)	3859.2 (3777.5-3942.6)	3.58 (3.33-3.84)	0.93 (0.88-0.98)
2021	4799.7 (4702.8-4898.7)	4939.8 (4840.5-5041.1)	4.58 (4.27-4.91)	1.28 (1.21-1.35)

Table 2. Annual excess rate of OAC prescriptions

Parameter	Estimate	StdErr	LowerWaldCL	UpperWaldCL	ChiSq	ProbChiSq
Intercept	-340.63	6.05	-352.48	-328.78	3174.45	<.0001
Year	0.1722	0.00	0.17	0.18	3294.41	<.0001
Age	-0.07	0.00	-0.07	-0.06	979.14	<.0001
Sex (female)	0.02	0.02	-0.02	0.05	0.91	0.3388
Scale	2.78	0.00	2.78	2.78	_	_

Figure 12. Percentage of patients who initiated OAC in the year after NVAF diagnosis

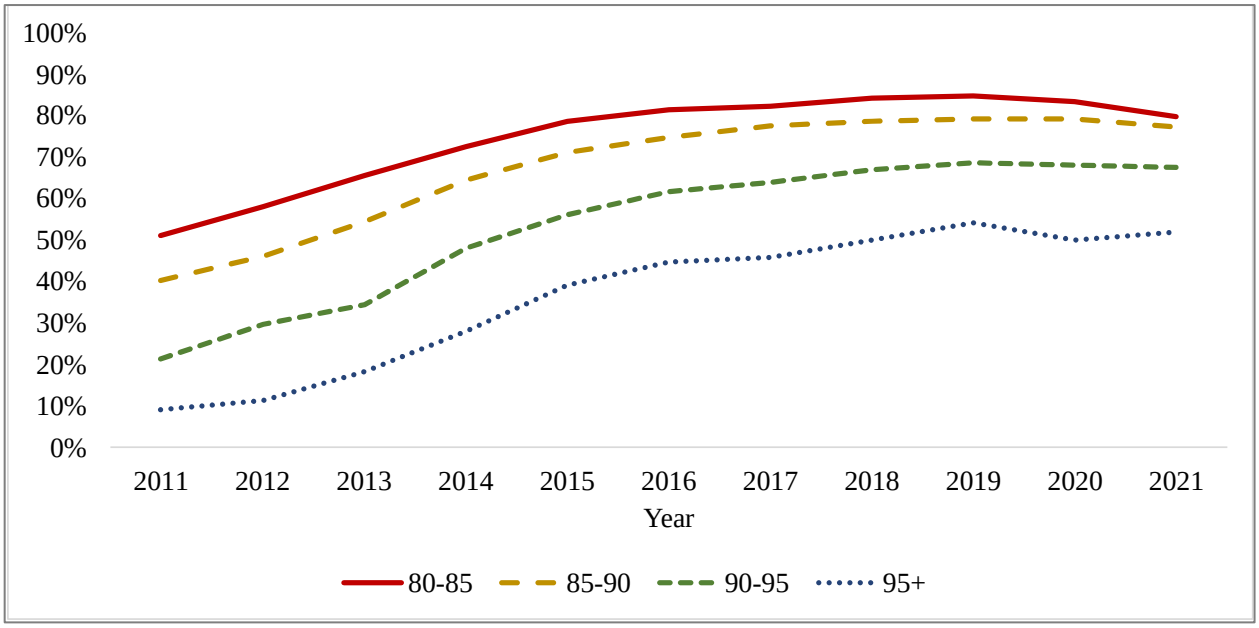


Figure 13. Relative proportion of prescriptions attributable to each OAC

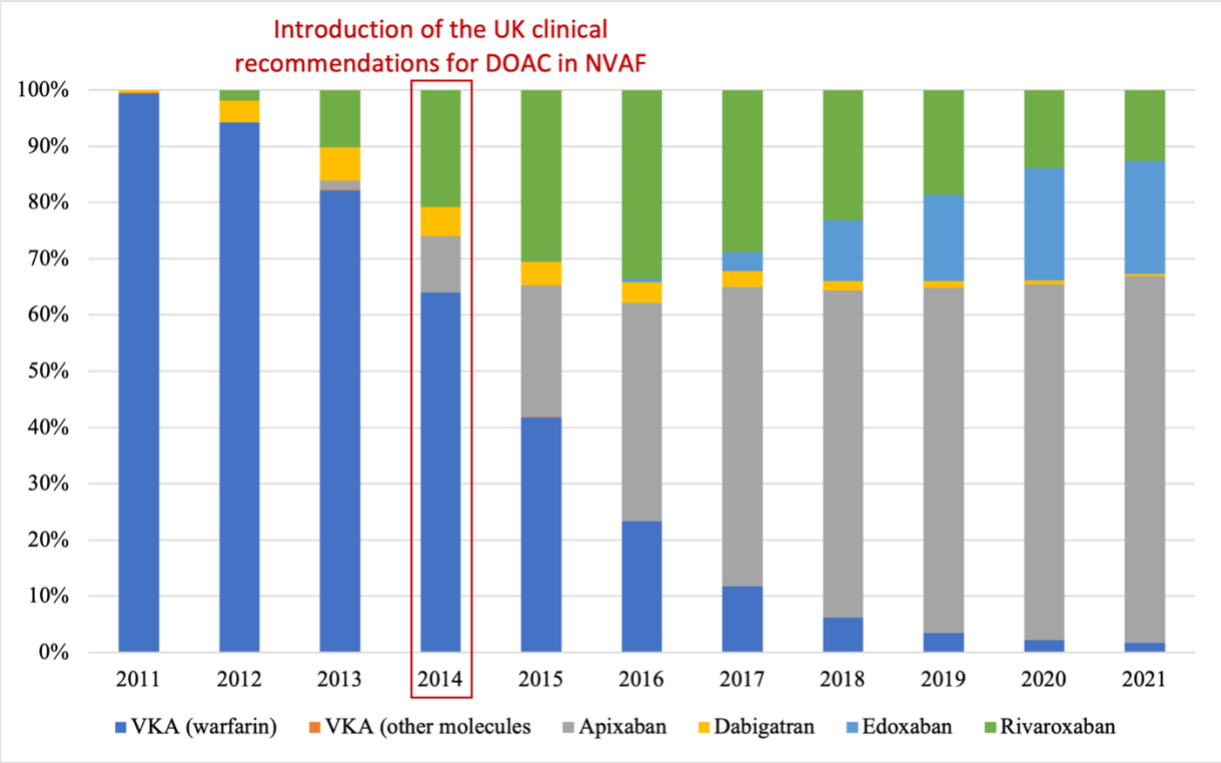


Table 3. Baseline characteristics of patients newly prescribed OACs, in 2011-2014, 2015-2018 and 2019-2021

Characteristic	Periods			OAC type (period=2019-2021)				
	2011-2014	2015-2018	2019-2021	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Number of patients	25,517	39,526	27,579	17,468	200	5,042	4,194	673
Patient's age at baseline								
Mean (sd)	84.78 (3.79)	85.45 (4.22)	85.76 (4.34)	85.9 (4.39)	84.78 (3.85)	85.71 (4.3)	85.31 (4.15)	85.49 (4.29)
Median (IQR)	84 (82-87)	85 (82-88)	85 (82-89)	85 (82-89)	84 (82-87)	85 (82-89)	85 (82-88)	85 (82-88)
Age group (%)								
80-85	54%	47.9%	45.4%	44.1%	53%	45.6%	49.8%	47.4%
85-90	33.5%	34.5%	34.8%	34.9%	32%	34.9%	34.1%	35.1%
90-95	11.1%	14.4%	15.9%	16.8%	14%	15.9%	12.7%	13.4%
95+	1.4%	3.3%	4%	4.3%	1%	3.6%	3.4%	4.2%
Sex (%)								
female	55.9%	55.6%	54.5%	56%	50%	52.4%	52%	49.9%
male	44.1%	44.4%	45.5%	44%	50%	47.6%	48%	50.1%
Ethnicity (%)								
White	61.5%	68.2%	73.6%	74.3%	78.5%	69%	76.2%	71.3%
South Asian	0.7%	1.1%	1.5%	1.5%	1%	1%	1.5%	3.6%
Black	0.4%	0.7%	0.9%	0.8%	0.5%	0.8%	1.1%	0.9%
Other	0.2%	0.2%	0.3%	0.4%	0%	0.2%	0.3%	0.3%
Mixed	0.2%	0.2%	0.2%	0.1%	0%	0.2%	0.2%	0.3%
Comorbidities (%)								
Hypertension	73%	74%	73%	74%	70%	72%	73%	79%
Diabetes	22%	26%	30%	30%	19%	27%	30%	36%
Coronary heart disease	7%	9%	9%	9%	14%	8%	9%	10%
Heart failure	14%	14%	16%	17%	17%	15%	14%	23%
COPD	20%	22%	23%	24%	24%	21%	22%	25%
Stroke or transient ischemic attack	23%	22%	23%	23%	30%	23%	19%	21%

Systemic embolism	0%	0%	0%	0%	0%	0%	0%	0%
Peripheral arterial disease	6%	6%	6%	6%	9%	5%	5%	8%
History of bleeding	31%	34%	37%	37%	43%	37%	37%	37%
Anemia	17%	20%	21%	22%	14%	21%	19%	31%
Chronic kidney disease	38%	37%	36%	37%	33%	34%	33%	55%
Liver disease	1%	2%	3%	3%	4%	3%	3%	3%
Dementia and cognitive impairment	3%	7%	8%	8%	4%	8%	7%	7%
Obstructive sleep apnoea	0%	1%	1%	1%	2%	1%	1%	2%
Cancer (other than non-melanoma skin cancer)	19%	22%	23%	23%	19%	24%	23%	25%
History of falls	24%	31%	35%	36%	33%	34%	34%	34%
Head trauma	5%	6%	8%	9%	10%	8%	7%	8%
Depression	16%	18%	19%	20%	20%	19%	18%	21%
Medications (%)								
Antiplatelet drugs	62%	58%	56%	57%	60%	52%	56%	59%
Angiotensin converting enzyme inhibitors	54%	54%	54%	55%	52%	50%	56%	59%
Angiotensin II receptor blockers	23%	25%	26%	26%	29%	23%	26%	32%
Calcium channel blockers	54%	57%	58%	58%	54%	55%	58%	63%
Thiazide diuretics	49%	47%	44%	45%	44%	42%	46%	46%
Loop diuretics	38%	37%	36%	37%	32%	32%	34%	49%
Other diuretics	5%	6%	6%	6%	5%	5%	6%	9%
Beta blockers	51%	50%	48%	49%	47%	45%	47%	52%
Antiarrhythmics	7%	8%	7%	7%	11%	7%	8%	7%
Antidiabetic drugs	12%	14%	15%	16%	10%	13%	15%	21%
Lipid lowering drugs	58%	62%	67%	68%	68%	62%	67%	72%
Nonsteroidal anti-inflammatory drugs	65%	70%	73%	74%	77%	67%	76%	71%
Opioids	65%	69%	71%	72%	78%	66%	72%	74%
Antidepressants	31%	37%	41%	42%	42%	38%	41%	41%

Antipsychotics	23%	25%	27%	27%	26%	25%	26%	24%
Anxiolytics, barbiturates	22%	24%	25%	25%	27%	22%	24%	26%
Other hypnotics	11%	13%	15%	15%	17%	14%	16%	17%
Antiepileptic drugs	9%	14%	17%	18%	22%	17%	16%	21%
Corticosteroids	24%	29%	31%	32%	30%	27%	32%	34%
Proton pump inhibitors	56%	63%	69%	70%	72%	66%	69%	67%
H2 receptor antagonists	18%	20%	21%	21%	26%	19%	21%	23%
BMI								
1 (Underweight)	1.6%	1.9%	2.1%	2.2%	0.5%	2%	1.5%	2.7%
2 (Normal)	26.5%	26.7%	26.1%	26%	25%	27.5%	24.7%	29%
3 (Overweight)	32.7%	31.4%	31.6%	31.8%	31.5%	31%	31.4%	32.1%
4 (Obesity)	21.2%	21.8%	21.8%	21.7%	21.5%	21%	23.3%	21.4%
Smoking								
0 (Nonsmoker)	34.9%	35.6%	35.2%	35.1%	34.5%	35.3%	35.9%	33.1%
1 (Smoker)	58.4%	55.1%	52.7%	52.9%	51.5%	51.6%	52.8%	56.9%
Number of GP consultations (%)								
0-9	16.8%	13.7%	14.1%	14.1%	13%	15.8%	12.7%	10.8%
10-19	34.3%	30.9%	29.4%	29.1%	33%	29.5%	31.2%	24.4%
20-29	24.9%	25.7%	24.8%	24.9%	23.5%	24.1%	25.4%	23.2%
30+	22.3%	27.9%	29.7%	30.1%	28.5%	28%	28.8%	39.5%

Table 4. Median time in days from NVAF diagnosis to OAC initiation in the year after diagnosis and OAC persistence

Measure	Mean (SD), days	Median, days
Time from diagnosis to initiation in the year after diagnosis	134.48 (0.44)	35
Time from initiation to discontinuation (grace period 30 days)	1046.99 (6.31)	631
Time from initiation to discontinuation, (grace period 60 days)	1702.9 (8.28)	1,503

Table 5. Patterns of switching between OACs

Initial OAC \ switch		Switch to:						
		Acenocoumarol	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**	**Warfarin**	**Phenindione**
					2011-2014			
	Acenocoumarol	0%	0%	0%	0%	0%	0%	0%
	Apixaban	0%	0%	1%	0%	1%	1%	0%
	Dabigatran	0%	1%	0%	0%	6%	3%	0%
	Edoxaban	0%	0%	0%	0%	0%	0%	0%
	Rivaroxaban	0%	2%	2%	0%	0%	3%	0%
	Warfarin	3%	12%	22%	0%	44%	0%	1%
					2015-2018			
Switch from:	Acenocoumarol	0%	0%	0%	0%	0%	0%	0%
	Apixaban	0%	0%	1%	2%	5%	2%	0%
	Dabigatran	0%	3%	0%	0%	2%	0%	0%
	Edoxaban	0%	1%	0%	0%	0%	0%	0%
	Rivaroxaban	0%	11%	1%	3%	0%	3%	0%
	Warfarin	0%	32%	3%	4%	26%	0%	0%
					2019-2021			
	Acenocoumarol	0%	0%	0%	0%	0%	0%	0%
	Apixaban	0%	0%	1%	11%	8%	3%	0%
	Dabigatran	0%	2%	0%	1%	0%	0%	0%
	Edoxaban	0%	4%	0%	0%	1%	1%	0%
	Rivaroxaban	0%	13%	0%	5%	0%	1%	0%
	Warfarin	0%	27%	0%	12%	9%	0%	0%

Table 6. Risk factors of OAC initiation, OAC type indication and treatment persistence

Variable	Categories	OAC initiation OR (95% CI)	DOAC vs warfarin initiation OR (95% CI)	Treatment persistence HR (95% CI)
Period	2015-2018 vs 2011-2014	3.11 (3-3.22)***	17.4 (16.56-18.29)***	0.61 (0.59 - 0.62)***
	2019-2021 vs 2011-2014	3.87 (3.72-4.03)***	155.56 (141.31-171.25)***	0.5 (0.49 - 0.52)***
Age group	85-90 vs 80-85	0.77 (0.75-0.8)***	1.15 (1.1-1.22)***	1.05 (1.03 - 1.08)***
	90-95 vs 80-85	0.44 (0.43-0.46)***	1.49 (1.38-1.61)***	1.11 (1.07 - 1.15)***
	95+ vs 80-85	0.23 (0.22-0.25)***	2.01 (1.69-2.38)***	1.21 (1.12 - 1.31)***
Sex	Male vs female	0.8 (0.76-0.85)***	0.98 (0.89-1.07)	1.07 (1.02 - 1.12)**
Ethnicity	South Asian vs White	0.88 (0.78-0.99)*	0.7 (0.58-0.85)***	1.3 (1.19 - 1.42)***
	Black vs White	0.75 (0.65-0.87)***	0.96 (0.75-1.23)	1.33 (1.19 - 1.48)***
	Other vs White	0.95 (0.74-1.21)	0.82 (0.56-1.22)	1.52 (1.29 - 1.81)***
	Mixed vs White	0.84 (0.63-1.13)	1.36 (0.84-2.18)	1.49 (1.23 - 1.81)***
	Not Stated vs White	1.05 (0.98-1.13)	0.93 (0.84-1.03)	1.02 (0.97 - 1.07)
Comorbidities				
Hypertension	Yes vs no	1.21 (1.12-1.3)***	0.89 (0.79-1.01)	1 (0.94 - 1.06)
Diabetes	Yes vs no	1.19 (1.11-1.27)***	0.97 (0.87-1.08)	1.03 (0.98 - 1.09)
Coronary Heart Disease	Yes vs no	1.14 (1.07-1.21)***	1.03 (0.94-1.13)	1.02 (0.98 - 1.07)
Heart Failure	Yes vs no	1.25 (1.17-1.34)***	0.89 (0.79-0.99)*	0.99 (0.94 - 1.04)
COPD	Yes vs no	0.97 (0.93-1.01)	0.96 (0.91-1.03)	1.02 (0.99 - 1.05)
Stroke	Yes vs no	1.56 (1.39-1.75)***	1.17 (0.98-1.4)	0.96 (0.88 - 1.05)
Systemic Embolism	Yes vs no	1.4 (1.09-1.8)**	0.66 (0.45-0.98)*	0.86 (0.7 - 1.06)
Peripheral Arterial Disease	Yes vs no	1.08 (1.01-1.17)*	0.94 (0.83-1.06)	1.06 (1 - 1.12)
History Of Bleeding	Yes vs no	0.93 (0.89-0.97)***	1.03 (0.96-1.1)	1.01 (0.98 - 1.04)
Anemia	Yes vs no	0.76 (0.73-0.79)***	0.91 (0.84-0.97)**	1.05 (1.02 - 1.09)**
Chronic Kidney Disease	Yes vs no	0.92 (0.87-0.96)***	0.82 (0.76-0.89)***	1.06 (1.03 - 1.11)**
Liver Disease	Yes vs no	0.83 (0.75-0.93)***	1.17 (0.98-1.4)	1.06 (0.98 - 1.15)

Dementia / Cognitive Impairment	Yes vs no	0.4 (0.39-0.42)***	1.75 (1.57-1.95)***	0.95 (0.9 - 1)
Obstructive Sleep Apnoea	Yes vs no	1 (0.83-1.2)	0.97 (0.74-1.27)	1.06 (0.93 - 1.21)
Cancer (Other Than Non-Melanoma Skin Cancer)	Yes vs no	0.8 (0.78-0.83)***	0.98 (0.93-1.04)	1.07 (1.04 - 1.1)***
History Of Falls	Yes vs no	0.75 (0.72-0.77)***	1.23 (1.16-1.3)***	1.05 (1.02 - 1.08)***
Head Trauma	Yes vs no	0.89 (0.84-0.94)***	1.12 (1.01-1.24)*	0.96 (0.92 - 1.01)
Depression	Yes vs no	0.93 (0.89-0.97)***	0.98 (0.92-1.05)	0.97 (0.94 - 1.01)
Medical treatment				
Antiplatelet Drugs	Yes vs no	0.99 (0.95-1.02)	0.88 (0.83-0.94)***	1.01 (0.98 - 1.04)
Angiotensin Converting Enzyme Inhibitors	Yes vs no	1.07 (1.03-1.11)***	1.05 (0.99-1.11)	1.01 (0.98 - 1.04)
Angiotensin Ii Receptor Blockers	Yes vs no	1.11 (1.07-1.16)***	0.97 (0.92-1.02)	0.99 (0.97 - 1.02)
Calcium Channel Blockers	Yes vs no	1.09 (1.06-1.13)***	0.99 (0.94-1.05)	0.99 (0.96 - 1.01)
Thiazide Diuretics	Yes vs no	1.01 (0.97-1.05)	0.98 (0.92-1.03)	1.04 (1.01 - 1.06)**
Loop Diuretics	Yes vs no	0.89 (0.86-0.92)***	0.89 (0.84-0.94)***	1.07 (1.04 - 1.1)***
Other Diuretics	Yes vs no	0.9 (0.84-0.96)***	1.07 (0.97-1.19)	1.02 (0.97 - 1.07)
Beta Blockers	Yes vs no	1.07 (1.03-1.1)***	0.97 (0.92-1.03)	0.97 (0.95 - 1)*
Antiarrhythmics	Yes vs no	1.03 (0.97-1.09)	0.97 (0.89-1.05)	1.01 (0.97 - 1.05)
Antidiabetic Drugs	Yes vs no	0.9 (0.85-0.96)***	0.97 (0.88-1.06)	1.02 (0.98 - 1.06)
Lipid Lowering Drugs	Yes vs no	1.15 (1.11-1.2)***	1.09 (1.03-1.15)**	0.93 (0.91 - 0.96)***
Nonsteroidal Anti-Inflammatory Drugs	Yes vs no	1.25 (1.2-1.31)***	1.15 (1.07-1.22)***	0.98 (0.94 - 1.01)
Opioids	Yes vs no	0.99 (0.95-1.03)	1.04 (0.98-1.11)	1.04 (1.01 - 1.07)**
Antidepressants	Yes vs no	0.98 (0.94-1.01)	1.06 (1-1.12)*	1.01 (0.98 - 1.03)
Antipsychotics	Yes vs no	1 (0.96-1.03)	1.01 (0.96-1.07)	0.99 (0.96 - 1.01)
Anxiolytics, Barbiturates	Yes vs no	0.96 (0.93-1)*	1.02 (0.96-1.08)	0.99 (0.96 - 1.02)
Other Hypnotics	Yes vs no	0.99 (0.95-1.04)	1.06 (0.98-1.13)	1.02 (0.99 - 1.06)
Antiepileptic Drugs	Yes vs no	0.95 (0.91-0.99)*	1.03 (0.96-1.1)	0.96 (0.93 - 1)*
Corticosteroids	Yes vs no	0.99 (0.96-1.03)	1.04 (0.99-1.11)	1.03 (1 - 1.06)*
Proton Pump Inhibitors	Yes vs no	1.07 (1.03-1.11)***	1.11 (1.05-1.17)***	0.98 (0.95 - 1)
H2 Receptor Antagonists	Yes vs no	1.01 (0.97-1.04)	0.96 (0.9-1.02)	1.01 (0.98 - 1.04)

Health behaviour				
Number of GP consultations (%)	10-19 vs 0-9	1.07 (1.02-1.13)**	1 (0.93-1.09)	1.03 (0.99 - 1.07)
	20-29 vs 0-9	1.04 (0.98-1.09)	1 (0.92-1.09)	1.06 (1.02 - 1.1)**
	30+ vs 0-9	0.85 (0.8-0.9)***	1 (0.91-1.09)	1.15 (1.1 - 1.19)***
Obesity	Underweight vs normal	0.6 (0.55-0.65)***	1.12 (0.93-1.34)	1.14 (1.04 - 1.25)**
	Overweight vs normal	1.28 (1.24-1.33)***	0.97 (0.92-1.03)	0.94 (0.92 - 0.97)***
	Obesity vs normal	1.38 (1.32-1.44)***	1 (0.94-1.07)	0.93 (0.9 - 0.96)***
	Unknown vs normal	0.95 (0.9-0.99)*	1.11 (1.03-1.2)**	1 (0.97 - 1.04)
Smoking	Smoker vs non-smoker	0.93 (0.9-0.96)***	0.96 (0.91-1.01)	1.02 (0.99 - 1.04)
	Unknown vs non-smoker	1.01 (0.95-1.07)	1 (0.9-1.1)	1.05 (1 - 1.1)*

Figure 14. Period prevalence of OAC prescriptions

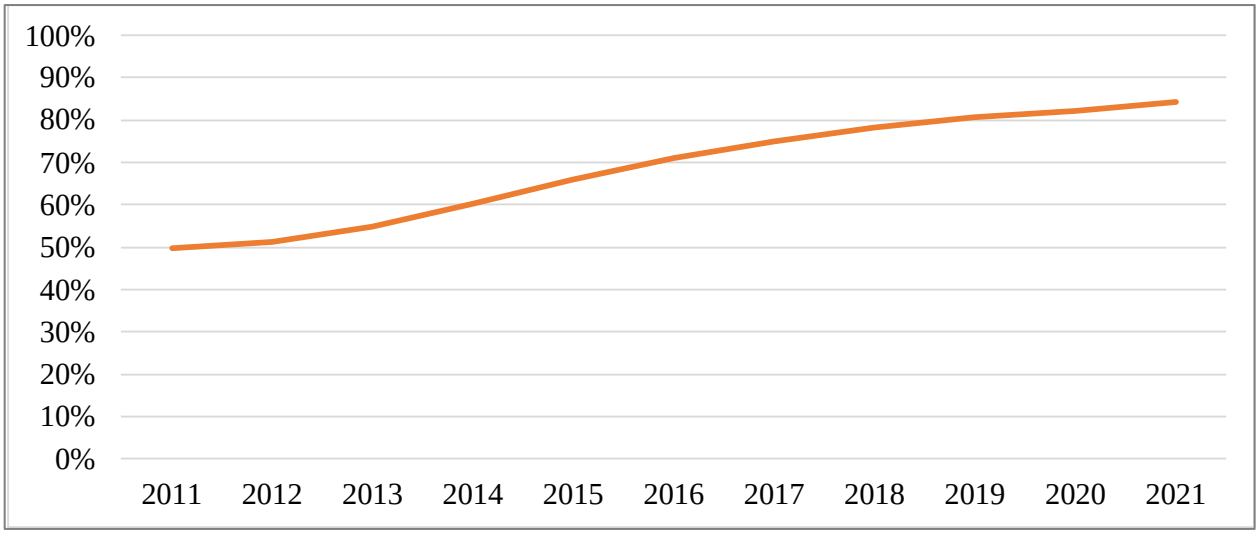


Figure 15. Period prevalence of OAC treatment, stratified by sex

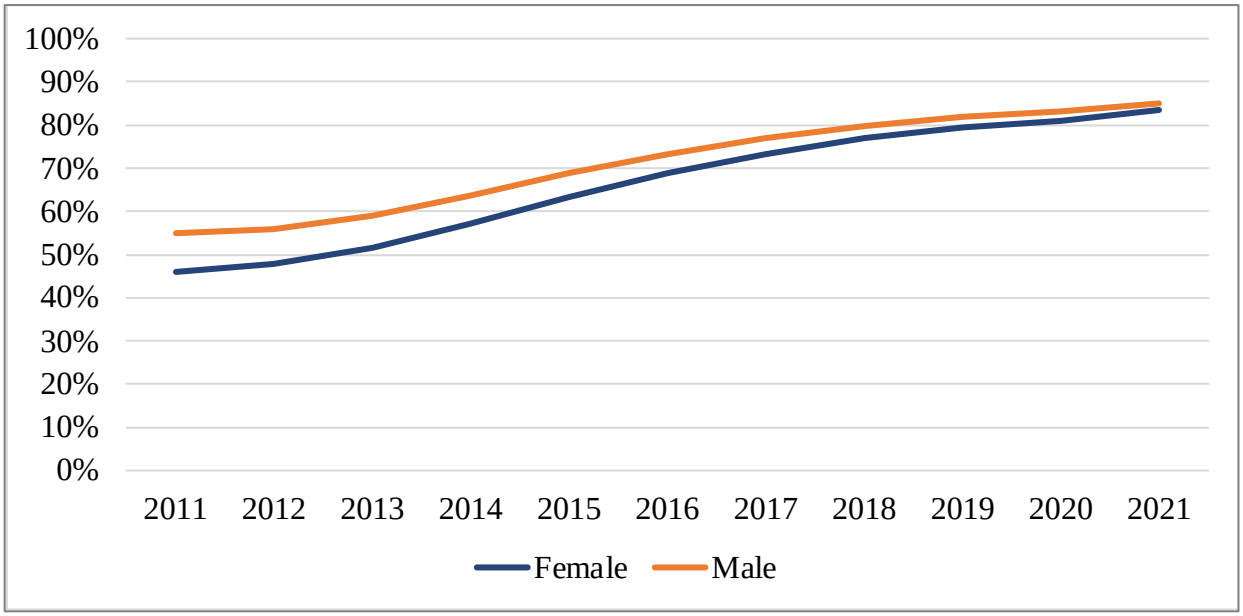


Figure 16. Period prevalence of OAC treatment, stratified by age group

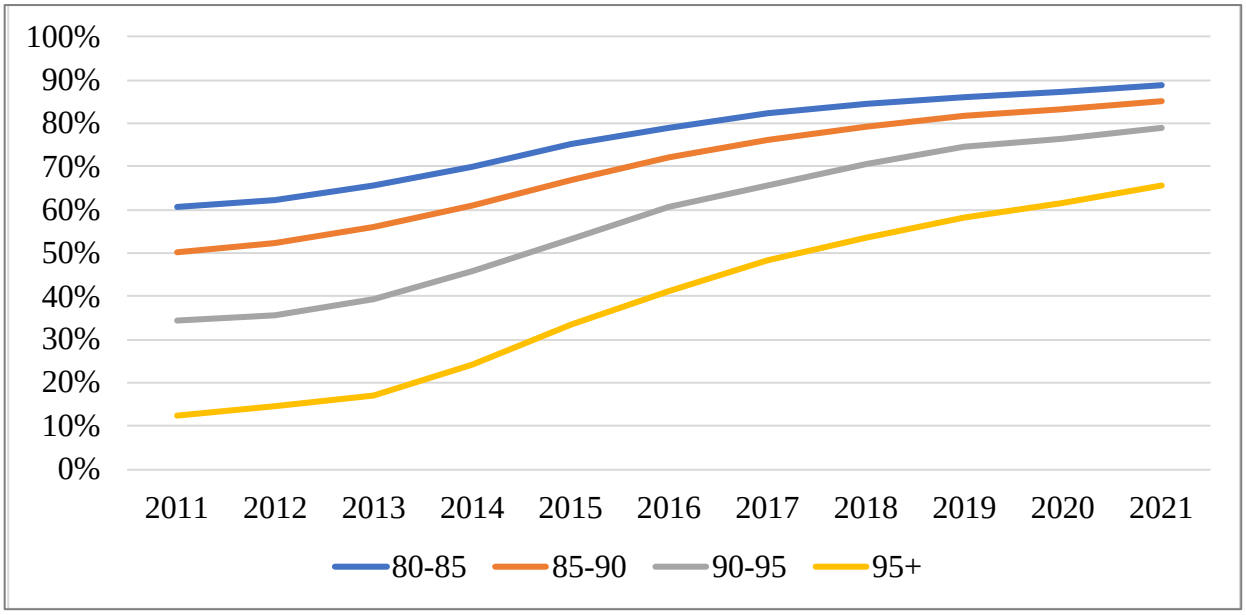


Figure 17. Period prevalence of OAC treatment, stratified by molecule

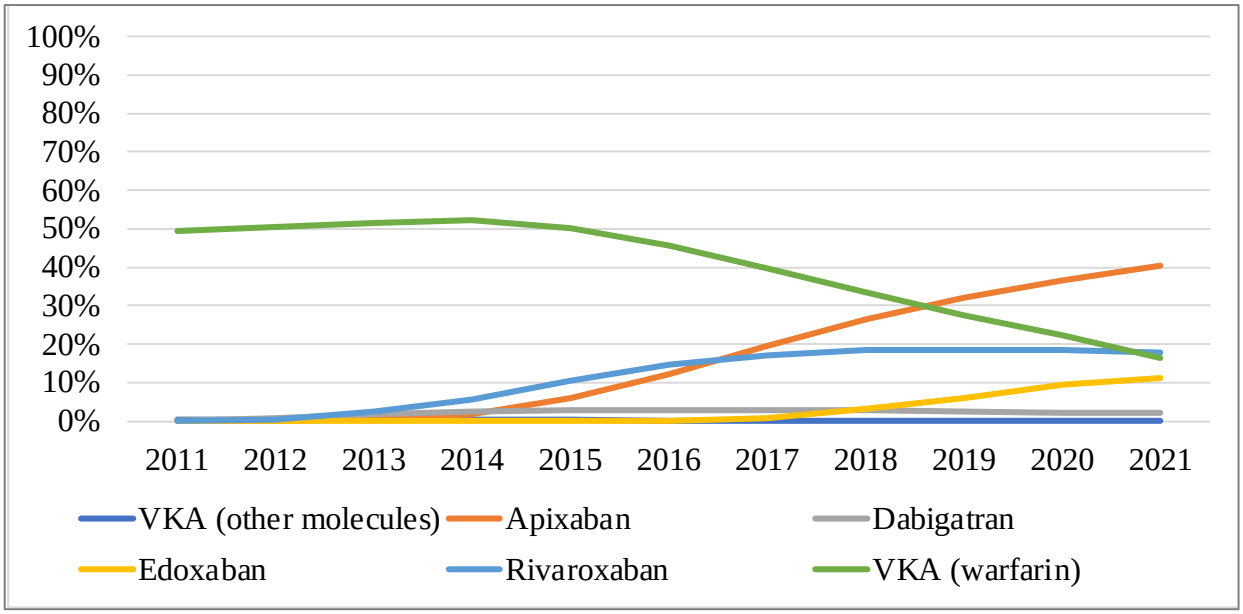
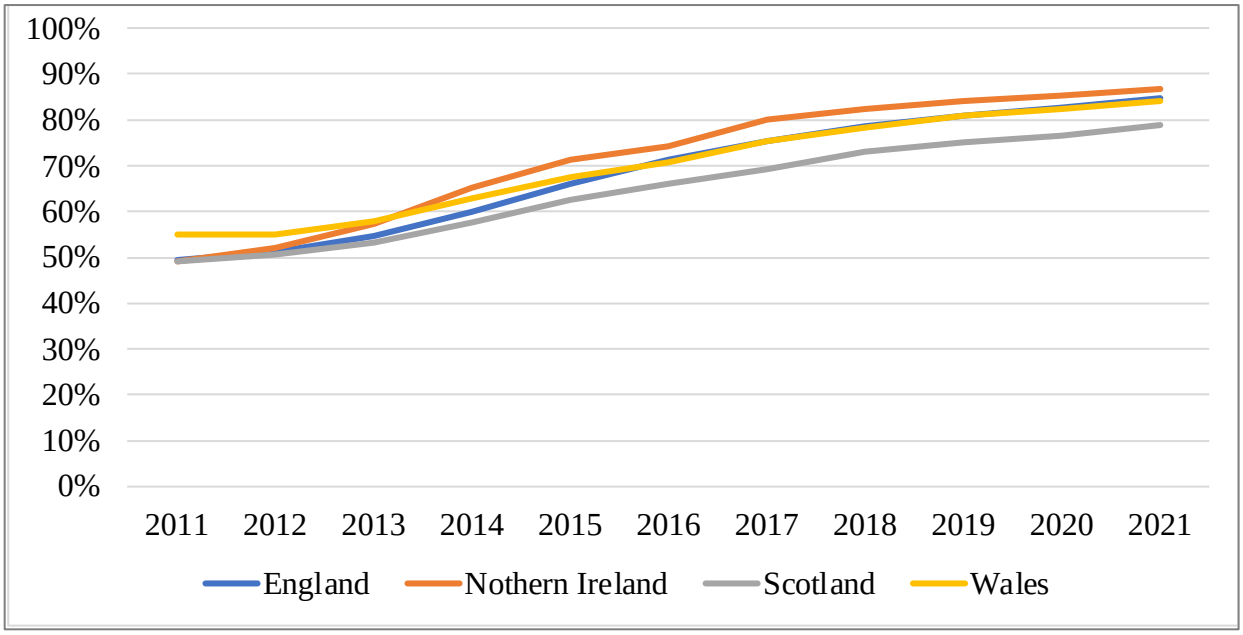


Figure 18. Period prevalence of OAC treatment, stratified by UK nation



Chapter 6: Discussion

1. Summary of objectives and main results

As described in Chapter 2, there is limited evidence about OAC prescription trends and patterns among elderly patients with NVAF. To address this knowledge gap, the primary objectives of this thesis were to to estimate time trends in incidence rate of OAC initiation and proportion of patients newly prescribed OAC, both stratified by age, sex, particular comorbidities, UK nations and individual OAC molecules in the setting of UK primary care. Additionally, the secondary objective of this thesis was to describe temporal trends in the prevalence of OAC prescription, estimate the median time on treatment, describe the predictors of OAC initiation and persistence and describe the changes in baseline characteristics of patients newly prescribed OACs over time.

Crude annual incidence rates of patients 80 years and over newly prescribed OACs in the year after AF diagnosis increased from 1,097.4 per 1,000 person-years in 2011 to 4,799.7 per 1,000 person-years in 2021. In patients aged 95 years and above, the annual rates of patients newly prescribed OACs increased almost 10-fold in 11 years, from 206.8 per 1,000 person-years in 2011 to 2,138.4 per 1,000 person-years in 2021. The rates of apixaban initiation increased from 19.5 per 1,000 person-years in 2013 to 3,132.0 per 1,000 person-years in 2021, whereas the rates of VKA declined from 1,091.0 per 1,000 person-years in 2011 to 80.6 per 1,000 person-years in 2021. Patients with dementia and frailty had lower rates of OAC initiation compared to patients without these comorbidities. Finally, we found large variation in incidence rates of OAC initiation between UK nations, ranging from 3,254.6 per 1,000 person-years in Scotland to 6,562.4 per 1,000 person-years in Northern Ireland in 2021.

The proportion of patients who initiated an OAC during the first year after NVAF diagnosis increased from 41% in 2011 to 75% in 2021, growing from 9% in 2011 to 52% in 2021 for the age group 95+ years. Older patients had a lower probability to initiate OAC, a higher probability to be prescribed DOACs rather than VKAs, and had higher OAC persistence compared to younger patients.

The prevalence of OAC treatment grew from 50% in 2011 to 84% in 2021. Half of patients who initiated OAC treatment continued their treatment at least for 631 days (grace period 30 days) and at least for 1503 days (grace period 60 days). In 2019-2021 the proportion of switches from VKAs

to DOACs fell, whereas in switches between DOACs, the most common patterns were from rivaroxaban to apixaban (13%), apixaban to rivaroxaban (8%) and apixaban to edoxaban (11%).

Our results are in line with a previous study (60), showing that the incidence of OAC prescriptions increased rapidly after the introduction of the UK clinical recommendations for DOAC in patients with NVAF in 2014 (41) due to DOAC prescription growth. Both our findings and the results from (60) show that elderly patients with NVAF remained under prescribed with DOACs, with the proportion of under prescription growing for higher age groups. Our findings show that this tendency remained persistent up to the end of the study period in 2021.

2. Strengths and limitations

In addition to the strengths and limitations noted in the manuscript, this section will discuss further benefits and drawbacks of using a electronic health records database for primary care.

The longitudinal nature of CPRD allowed us to observe changes of trends and patterns of anticoagulation, which reflects the consequences of the introduction of DOACs for stroke prevention in patients with NVAF in addition to VKA, previously used in practice. The richness of CPRD, containing demographic data, lifestyle variables, diagnosis, and prescriptions across long periods of time, sometimes across the lifespan of patients, allowed us to make multiple subgroup analyses. Moreover, the CPRD reflects real-world clinical practice and is particularly useful to identify subgroups of patients who receive insufficient treatment or do not properly adhere to their treatment. Given the representativity of CPRD, our findings can be generalized to the whole UK population.

Nonetheless, several limitations must be considered when using the CPRD. Practices with varying level of data quality and completeness may contribute to the CPRD, meaning that the dataset can be heterogeneous, including variation in coding on practice level or changes in coding standards, missing data, incomplete history of patients' records. However, quality checks are done regularly and only practices deemed up to standard for research are included. Although we studied and reported the patterns of switching and treatment persistence, due to unavailability of text medical records we were limited in interpreting them without information on the reasons for GP's decisions.

One of the limitations of our dataset is the absence of socio-economic characteristics of the patients and their households. As a result, socio-economic status remains an uncontrolled confounder in our study, which could potentially affect the estimates in the regression analysis.

3. Implications of findings and further directions

This thesis contains detailed study of trends in anticoagulation among elderly patients with NVAF in primary care over the study period of 11 years. Our results reflect how anticoagulants are prescribed in primary care setting and how treatment persistent over time. Our findings highlight several aspects of OAC utilization in the elderly population with NVAF, who is at increased risk of stroke and for whom adherence to stroke prevention therapy is crucial.

In the context of an ageing population and the growing number of nonagenarians worldwide, more research on factors determining the GP's decision to prescribe anticoagulants and the choice of OACs is needed. More studies about effectiveness and safety of anticoagulation for elderly patients in the presence of multimorbidity are needed to support GPs in their decisions, for the optimal balance between stroke prevention and the increased risk of bleeding. In the field of public health, studies on effective interventions to improve adherence to stroke prevention therapy among the elderly population could be beneficial, as well as the studies for a better informed and more efficient shared decision making by elderly patients and their GPs.

The results of these future studies, together with the results of this thesis, could provide clinicians and regulators with more evidence about the barriers towards better stroke prevention among elderly and comorbid patients.

Chapter 7: Conclusions

This thesis explored the trends in anticoagulation of patients with NVAF aged 80 years and older in primary care practice. We used the UK CPRD database to assemble a population-based cohort of very elderly patients with new NVAF diagnosis. We showed that the incidence of anticoagulation among elderly patients with NVAF grew rapidly between 2011 and 2021 in all age groups, though patients aged 85 and older were less likely to be prescribed anticoagulants even in the absence of clear contraindications. VKAs were almost fully replaced with DOACs in all age groups as the anticoagulant of choice. Showing systematic deviations of physicians from guidelines, our results might inform public health initiatives to promote anticoagulation among the elderly population with NVAF. Further research is needed to better understand the basis for the decisions of physicians not to prescribe OACs to elderly patients without contraindications.

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