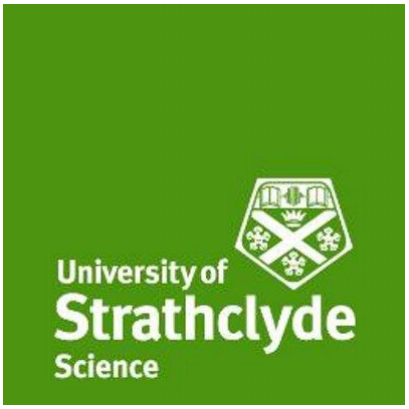

Use of direct oral anticoagulants in Scotland

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A thesis presented in fulfilment of the requirements for the degree of Doctor of Philosophy

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List of Publications and Presentations

Publications

- Mueller T, Alvarez-Madrazo S, Robertson C & Bennie M. 2017. Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: Applying a coherent framework to drug utilisation studies. *Pharmacoepidemiology & Drug Safety*. Published online first: 2017 July 28. https://doi.org/10.1002/pds.4272

Presentations

- Poster presentation – Annual conference of the Royal Statistical Society: *Applying a coherent framework to drug utilisation studies: The use of direct oral anticoagulants in patients with atrial fibrillation in Scotland* (Glasgow, UK, 2017)
- Oral presentation – Pre-conference PhD symposium, Informatics for Health conference: *Applying a coherent framework to drug utilisation studies: The use of direct oral anticoagulants in patients with atrial fibrillation in Scotland* (Manchester, UK , 2017)
- Poster presentation – 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management: *The use of new oral anticoagulants in patients with atrial fibrillation in Scotland – A population based drug utilisation study* (Dublin, Ireland, 2016)
- Oral presentation – 1st Farr International Conference: *Oral anticoagulants in Scotland – utilisation, clinical effectiveness, and safety* (St Andrews, UK, 2015)
- Oral presentation – 1st Farr Institute PhD symposium: *Oral anticoagulants in Scotland – utilisation, clinical effectiveness, and safety* (Manchester, UK, 2015)

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Glossary

ACE	Angiotensin converting enzyme
ADR	Adverse drug reaction
AF	Atrial fibrillation
ANOVA	Analysis of variance
AT-II	Angiotensin-II
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CER	Comparative effectiveness research
CHI	Community Health Index
CI	Confidence interval
CMA	Continuous measure of medication acquisition
CMG	Continuous measure of medication gaps
CMOS	Continuous, multiple interval measure of oversupply
CPRD	Clinical Practice Research Datalink
CR	Compliance Rate
CSA	Continuous, single interval measure of medication availability
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBR	Days between fills adherence rate
DCVP	Data capture validation pricing
DDD	Defined Daily Dosage
DOAC	Direct oral anticoagulant
DUR	Drug utilisation research
DVT	Deep vein thrombosis
EMA	European Medicines Agency
ESPACOMP	European Society for Patient Adherence, Compliance, and Persistence
FDA	US Food and Drug Administration
GP	General practitioner
HR	Hazard ratio
HTA	Health Technology Assessment
ICD-10	International Classification of Disease, 10th edition
INN	International Non-proprietary Name
INR	International Normalised Ratio
ISD	Information Services Division
IQR	Inter-quartile range
LMWH	Low molecular weight heparin
MAS	Minor Ailment Service
MHRA	Medicines and Healthcare products Regulatory Agency
mMPR	Modified Medication Possession Ratio
MPR	Medication Possession Ratio
MRA	Medication Refill Adherence
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NRS	National Records of Scotland
NSAID	Non-steroidal anti-inflammatory drug
NSS	National Services Scotland
OAC	Oral anticoagulant
OPCS-4	Office of Population Censuses and Surveys procedural codes, 4th revision
OTC	Over-the-counter
PAC	Privacy Advisory Committee
PBPP	Public Benefit and Privacy Panel
PDC	Proportion of days covered
PE	Pulmonary embolism
PIS	Prescribing Information System
PT	Prothrombin time
RCR	Refill Compliance Rate
RCT	Randomised clinical trial
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicines Consortium
SMR	Scottish Morbidity Records
SRS	Spontaneous Reporting System
TIA	Transient ischaemic attack
VKA	Vitamin K antagonist
VPN	Virtual private network
VTE	Venous thromboembolism
WHO	World Health Organisation

Abstract

Introduction: Patients with atrial fibrillation (AF), a common arrhythmic disorder, are treated long-term with oral anticoagulants in order to prevent strokes. As warfarin treatment is associated with several problems, the direct oral anticoagulants (DOAC) dabigatran, rivaroxaban, apixaban and edoxaban have been introduced. However, real-world information regarding the utilisation of DOACs as well as their clinical effectiveness and safety is still scarce. Hence, the aim of this project was to increase the evidence from clinical practice regarding the use of DOACs in patients with AF in Scotland.

Methods: This study has been designed as a retrospective cohort study (study period 2009 – 2015), using routinely collected administrative data. Three databases – the Prescribing Information System (PIS); Scottish Morbidity records (SMR); and National Records of Scotland (NRS) – covering prescriptions dispensed in primary care, hospital episodes and death records, respectively, have been linked using Community Health Index (CHI) numbers, a unique patient identifier in Scotland. Based on this data, three analyses have been conducted: a description of DOAC prescribing over time; an evaluation of patients' adherence to DOAC treatment; and an analysis of the comparative clinical effectiveness and safety of DOACs.

Results: In Scotland, the number of patients being treated with DOACs has steadily been increasing, and in 2015, the number of incident DOAC patients exceeded those of warfarin. During the study period, 14,811 AF patients with a mean age of 74.1 years [SD 11.3] initiated DOAC treatment. Adherence to treatment was good overall, with a median Medication Refill Adherence (MRA) of 102.3% [IQR 90.1% – 112.5%]; discontinuation rates were however variable, ranging from 24.9% (apixaban) to 63.3% (dabigatran). Persistence rates 12 months after treatment initiation were 61.8%, 78.6%, and 83.6% among patients initiating treatment with dabigatran, rivaroxaban, and apixaban, respectively. All DOACs were similarly effective in preventing strokes and systemic embolisms – nevertheless, the overall bleeding risk was higher with rivaroxaban as compared to apixaban [HR 1.52, 95% CI 1.21 – 1.91].

Conclusion: DOACs have swiftly been accepted into clinical practice, and adherence to treatment is generally good. As all DOACs are similarly effective, decisions for or against a specific drug should be made based on a wider risk assessment, with a focus on bleeding risks.

Summary

Introduction: Atrial fibrillation (AF) is a common arrhythmic disorder especially among the elderly, and a major independent risk factor for stroke. In order to prevent strokes in patients with AF, oral anticoagulants (OACs) are used long-term; warfarin has been a mainstay of treatment in clinical practice for this purpose for decades, and its utilisation and effects have been widely studied. As warfarin treatment is associated with a range of difficulties, direct oral anticoagulants (DOACs) – dabigatran, apixaban, rivaroxaban, and edoxaban – have been developed as apparently viable alternatives, hoping that their introduction would lead to more eligible AF patients being treated with oral anticoagulants; that patients would be more adherent to DOAC treatment than to warfarin; and that, hence, disease outcomes would eventually improve.

DOACs have proven efficacy and safety in clinical trials, and marketing access has subsequently been granted in several countries, including the UK; as a result, DOACs have been integrated into a range of clinical guidelines. Nevertheless, the usefulness of guidelines remains limited when it comes to differentiating between the various drug options available – not least because no clinical trials have been conducted directly comparing the individual DOACs to each other. In addition, information from clinical practice, useful for supporting clinical decision making, is still scarce. The aim of this project was therefore to increase the evidence from clinical practice regarding the use of DOACs in patients with AF in Scotland. More precisely, the objectives were: to *describe the prescribing practice* of traditional and new oral anticoagulants over time; to *evaluate the quality of drug use* by determining utilisation patterns; and to *analyse the clinical effectiveness and safety* associated with different DOACs.

Methods: This observational study has been designed as a retrospective cohort study, using routinely collected administrative data; the study period spanned from January 2009 to December 2015. Patients who received at least one prescription for any DOAC during the study period were identified from the Prescribing Information System (PIS), a database capturing all prescriptions dispensed in primary care in Scotland; patients with a diagnosis of AF were identified from the Scottish Morbidity Records Inpatient dataset (SMR01), covering discharge records from all Scottish hospitals. A subsequent record linkage based on a unique patient identifier, the

Community Health Index (CHI) number, provided a range of demographic as well as medical information for each cohort participant by combining PIS and SMR01 with the Scottish Morbidity Records Outpatient attendance dataset (SMR00), containing data with regards to outpatient clinic attendances, and National Records of Scotland (NRS), comprising death records. The available information was used to conduct three separate analyses: a description of DOAC prescribing in Scotland over time with regards to prevalence and incidence, geography, and socio-demographic aspects; an evaluation of AF patients' adherence to treatment, comprising measures of adherence, discontinuation, and persistence; and a comparative analysis of the clinical effectiveness and safety of DOACs in patients with AF, with a focus on the main clinical endpoints stroke and systemic embolism; death; and major bleeds.

Results: During the study period, a total of 166,167 patients received at least one prescription for any oral anticoagulant, and OAC incidence rates increased considerably over time – from 242.2 patients per 100,000 population in 2010, to 383.3 patients per 100,000 population in 2015. Particularly the number of patients initiating treatment with DOACs has steadily been rising, and in 2015, 56.5% of all incident OAC patients started treatment with a DOAC. Overall, 64.1% of all new DOAC patients initiated treatment with rivaroxaban, 30.4% with apixaban, and 5.5% with dabigatran; however, there was considerable variation in the usage of individual drugs over time, with dabigatran use decreasing substantially between 2011 and 2015, and apixaban use continuously increasing since 2013. In addition, regional variation was observed: in 2015, between 26.1% and 78.1% of all new OAC patients received a DOAC as drug of first choice, depending on Health Board; the most commonly prescribed drug was either rivaroxaban, or apixaban – both drugs have been used to initiate oral anticoagulation in the majority of patients in 50% of Health Boards.

Of all patients initiating DOAC treatment during the study period, 14,811 had a diagnosis of AF, confirmed in secondary care, and were included in subsequent analyses. 45.6% of AF patients starting DOAC treatment were female, and 37.6% were previously treated with warfarin; the mean age at time of first recorded prescription was 74.1 years [SD 11.3]. Patients had a range of comorbidities, and were treated with a large number of concomitant medications: 87.2% of patients were subject to polypharmacy (taking five or more drugs concomitantly), and the median number of different drugs prescribed to patients prior to DOAC initiation was 10 [IQR

6 – 13]. The study population differed substantially from patients enrolled in the pivotal trials; while stroke risks were noticeably lower (mean CHA_2DS_2-VASc score 2.93 [SD 1.71]) among the study population than among trial participants, bleeding risks were potentially considerably higher – with a mean HAS-BLED score of 2.05 [SD 1.17].

Adherence to DOAC treatment was good overall, with patients generally having enough medication to cover treatment periods, and remained stable over time. The median Medication Refill Adherence (MRA) was 102.3% [IQR 90.1% – 112.5%], and 81.9% of all DOAC patients had an MRA > 80%; adherence differed however between individual DOACs, with median MRAs ranging from 90.3% [IQR 41.4 – 103.3] among dabigatran patients to 103.3% [IQR 91.2 – 115.1] among patients initiating treatment with apixaban. Discontinuation rates ranged from 24.9% (apixaban) to 63.3% (dabigatran), although treatment interruptions were often temporary – resulting in relatively high persistence rates 12 months after treatment initiation of 61.8%, 78.6%, and 83.6% among patients initiating treatment with dabigatran, rivaroxaban, and apixaban, respectively.

There were no statistically significant differences observed in the risks of stroke (ischaemic stroke, haemorrhagic stroke, or all stroke), systemic embolism, or death due to cardiovascular reasons between the different DOACs. In contrast, the risk of myocardial infarction was higher among apixaban patients in comparison to patients being treated with either dabigatran [HR 2.28, 95% CI 1.00 – 5.21] or rivaroxaban [HR 1.71, 95% CI 1.05 – 2.77], and all-cause mortality was higher among rivaroxaban patients in contrast to both apixaban [HR 1.22, 95% CI 1.01 – 1.47] and dabigatran [HR 1.53, 95% CI 1.15 – 2.03] patients. Rivaroxaban patients had a higher risk of other major bleeds than patients receiving apixaban [HR 1.50, 95% CI 1.10 – 2.03] or dabigatran [HR 1.56, 95% CI 1.00 – 2.45]; in addition, the risk of gastro-intestinal bleeds was higher among rivaroxaban patients than among patients being treated with apixaban [HR 1.48, 95% CI 1.01 – 2.16], and the overall bleeding risk was also higher among patients initiating treatment with rivaroxaban than among patients using apixaban [HR 1.52, 95% CI 1.21 – 1.91].

Conclusion: The number of patients being treated with OACs in Scotland is increasing, at least partly due to an increase in the use of DOACs; and DOACs seem to be an accepted treatment option among patients judging from the acceptable levels

of adherence – perhaps with the exception of dabigatran, which showed comparatively higher rates of discontinuation. Hence, it is not inconceivable that DOACs might eventually all but replace warfarin in the long-term treatment of patients with AF. As all DOACs are similarly effective in preventing strokes but seem to diverge slightly in terms of secondary outcomes such as myocardial infarction, all-cause mortality, and bleeding profile, decisions for or against a specific drug should be made based on a wider risk assessment, taking into account not only comorbidities but also concomitant medication – with a particular focus on bleeding risk.

Although several studies analysing the utilisation of DOACs in a population of patients with AF have been published thus far, study specifics – including study focus (e.g. DOACs in general or individual drugs; adherence, discontinuation, or persistence, and/or various combinations thereof), study designs, sample sizes, follow-up periods, and analytical methods – differed considerably, impeding the direct comparison of findings. To decrease the inconsistencies in drug utilisation methodology impacting the comparability of results across studies, the use of a coherent framework – using a combination of discontinuation, persistence and adherence – and the standardisation of measurements is strongly advocated.

Chapter 1 – General Introduction

This prefatory chapter provides the general background for the thesis by first giving a brief overview of pharmaceuticals with a focus on the drug life cycle, including clinical trials and post-marketing surveillance processes; and second introducing pharmacoepidemiology and “big data” research. It also provides definitions of terms and concepts used not only throughout this work, but also in the wider field of pharmacoepidemiology.

1.1 Pharmaceuticals

Drugs in the form of medicinal plants and herbs have been used for centuries, and medicinal products nowadays represent one of the pillars of modern medicine. Pharmaceuticals are widely used in clinical practice globally: in 2013, spending for medicines across the 35 member states of the Organisation for Economic Co-operation and Development (OECD, 2017) accounted for approximately 20% of all health spending, amounting to US$800 billion (OECD, 2015) – and is predicted to reach US$1.4 trillion globally in 2020 (Aitken & Kleinrock, 2015).

Nevertheless, medication as a means of preventing and/or treating diseases has gained its current status only after major scientific discoveries led to the introduction of chemotherapy – the treatment with chemical compounds, obtained through biochemical processes – during the late 19th century. Some of the most widely used drugs today are fairly recent innovations; metformin for instance was introduced as an anti-diabetic drug in 1957 (Bailey & Day, 2004); beta-blockers were discovered during the mid-1960s (Quirke, 2012); and the first statin was approved only in 1987 (Stossel, 2008).

Based on future demographics and observable trends in the prevalence of non-communicable diseases, especially cardiovascular diseases and cancer (Prince et al., 2015), drug use is likely to increase further as many of these conditions are indicative for long-term drug treatment. In addition, new drugs are approved for use every year, in many cases allowing treatment for previously un- or undertreated diseases or improving treatment outcomes – resulting in an increasing prevalence of chronic diseases as mortality due to these conditions decreases.

1.1.1 Definitions

A range of specified nomenclature is being used with respect to pharmaceuticals, particularly with regards to safety and effectiveness. Table 1.1 gives an overview of the most important terms and concepts.

Table 1.1: Important concepts and terms relating to pharmaceutical products (WHO Collaborating Centre for International Drug Monitoring, 2017a)

Concept	Definition
Efficacy	The extent to which a drug provokes the intended effect (under lab conditions or in a selected group of patients) – does it do what it should?
Effectiveness	The probability of a drug provoking the intended effect in patients – how well does it do what it should?
Benefit	positive therapeutic effect of a drug
Harm	potential negative effect of a drug
Risk	the probability of a drug causing harm
Adverse drug event	an event associated with, but not necessarily causally linked to the use of a drug
Adverse drug reaction (ADR)	harmful, unintended response to a drug at a normal dose
Unexpected adverse reaction	not in line with drug characteristics or available drug information
Serious adverse reaction	any reaction regardless of dose that requires prolonged hospitalisation, is life threating, or leads to significant disability or death
Side effect	unintended effect due to the pharmacological properties of a drug, at normal dose

1.1.2 Drug life cycle

The development and marketing of drugs has become increasingly sophisticated, not least due to the tightening of legislation and regulation intended to ensure patient safety; the process of intensified testing of drugs prior to approval is widely attributed to the development of congenital malformations ascribed to thalidomide use during pregnancy in the 1960s (Kim & Scialli, 2011).

Following drug discovery, non-clinical tests – i.e. animal testing, usually with rodents and rabbits – are the first steps in the process, intended to provide initial information about the physiological effects and toxicities of a new substance. Results from non-clinical tests are the basis for further testing in humans; if these clinical trials prove efficacy and safety of a drug, it is subject to approval procedures before gaining market access. After approval, further post-marketing surveillance is aimed at gaining additional information about adverse events as well as long-term effects.

1.1.2.1 Clinical trials

Clinical trials can be differentiated into three distinct phases. Phase I clinical trials are small-scale studies performed over a few months, and are mainly used to transpose pre-clinical trial results from animals onto humans. Drugs are tested in a limited number of healthy volunteers (with the exception of anti-cancer drugs, which are tested in cancer patients) in order to obtain knowledge about their effects in the human body including acute side effects; to establish dosing schemes; and to evaluate appropriate methods of administration. Subsequent phase II trials usually test a drug in a few hundred volunteers affected by the targeted disease; these studies are used to further determine the efficacy and safety of a drug, but are also the basis for the following, large-scale phase III studies – randomised clinical trials (RCTs) including a large number of affected patients who are monitored for up to several years. Phase III trials are conducted so as to prove a drug's benefit for a particular group of patients as well as to provide detailed data regarding a drug's safety; results obtained from these trials are used as evidence when applying for market approval.

RCTs are now mandatory requirements for approval and market access of every drug, and are heavily regulated (Chow & Liu, 2014). Thus, several restrictions with regards to study design and participants apply; it is, for example, not always possible to test a new drug against placebo when an alternative drug is already available, because ethical guidelines demand new treatment options to be tested against the current standard of care. Many trials also exclude certain groups of patients based on ethical objections – for example children or pregnant women (Brody, 2012, Chow & Liu, 2014). Most clinical trials today are non-inferiority trials, designed to ascertain that a new drug is not worse than already approved medicines rather than to determine superiority over existing therapeutic options (Källén, 2011); nevertheless, the determination of superiority of new drugs over already approved alternatives is sometimes attempted, depending on study design and data analysis methods. RCTs are usually designed so as to provide evidence for safety and efficacy of a drug for a specific indication and a clearly defined patient group; despite tight regulations and specified prerequisites regarding study design and population, worries have been expressed about the generalisability of study results – as discussed further in section 1.1.3.

1.1.2.2 Market access

After phase I to phase III clinical trials have been successfully conducted and safety and efficacy of a drug have been established, pharmaceutical companies can apply for market approval – a prerequisite for every drug to become available for use in patients. Decisions about market authorisation of new drugs are usually made by governmental agencies specifically implemented for this purpose; major examples are the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (EMA, 2017c, FDA, 2017). In contrast to decisions made by the FDA, which are accepted in the United States only, EMA approvals are recognised by all member states of the European Union, thus providing a means to achieve simultaneous market access in several countries (EMA, 2017a). Besides seeking centralised approval through the EMA, companies can also apply to the Medicines and Healthcare products Regulatory Agency (MHRA) if drugs are intended for the British market (MHRA, 2017a); similar agencies with national expertise and jurisdiction can be found in every country in Europe, and in most countries globally. However, as legislation and regulatory approaches differ, specific approval processes may vary considerably.

Following approval by a competent authority, many countries require the completion of additional steps in order to make drugs available to patients as part of regular health care provisions – usually, but not always, including some sort of health technology assessment (HTA) used to evaluate patients' benefits of a drug as well as its clinical and cost-effectiveness. In Britain, after either EMA or MHRA approval, these assessments are conducted by the National Institute for Health and Care Excellence (NICE) covering England and Wales, and the Scottish Medicines Consortium (SMC) in Scotland (NICE, 2017a, SMC, 2017b). Newly approved drugs are included in the British National Formulary (BNF) – a compendium of available drugs in the UK, and as such the British equivalent to an essential medicines list – and the relevant standard treatment guidelines where appropriate; both types of documents are however for guidance purposes only, and prescribers can deviate from recommendations if deemed necessary (Joint Formulary Committee, 2017, SIGN, 2017).

1.1.3 Current controversies

The contemporary process of developing, testing, and marketing pharmaceutical products is not without controversies. Apart from issues related to what drugs are deemed worthy of being developed in the first place, as well as discussions about the fairness of drug pricing, ongoing debates mostly focus on clinical trial methodology – with potentially far-reaching implications mainly on the reliability and generalisability of clinical trial results.

Criticisms of clinical trial methodology cover a wide range of aspects, including, but not limited to, the study design (e.g. open treatment groups), the use of proxies as endpoints, or the statistical methods used to analyse data (e.g. intention-to-treat versus per-protocol) – and, most importantly, the selection of study participants. Inclusion and exclusion criteria applied to select patients for a specific trial are, for the most part, pre-determined by the tested medication and its indications, and are naturally influenced by legal and ethical requirements. Nevertheless, concerns have been voiced that pharmaceutical companies regularly exclude, for example, patients with complex disease histories, or those who use several other drugs concomitantly – with the effect that study cohorts are potentially not a very good representation of the patient population that will eventually be treated with the drugs in question (Kennedy-Martin et al., 2015), which may have implications for treatment outcomes in real life versus study settings.

By relying on clinical trial data as a basis for approval, the current licensing system has therefore limitations: the potential benefit of drug treatment in clinical practice might have been overestimated; and/or the possible harm drugs might do to real patients could have been underestimated. Misconceptions about advantages and disadvantages of individual drugs might further be compounded by an increasing trend towards fast-tracking of approvals (with potentially less rigorous testing and reduced scrutiny of results); in addition, pharmaceutical companies have on occasion been accused of not providing all data necessary to properly evaluate results (Cohen, 2014). Hence, conducting observational, post-marketing studies – i.e. gathering further evidence in clinical practice to improve the knowledge base upon which drugs are used – is needed in order to provide optimal patient care.

1.2 Post-marketing surveillance

Even though licensed drugs have proven their ability to cure a disease or, at the very least, to alleviate symptoms, unwanted treatment outcomes do occur, with considerable consequences for morbidity and mortality. Every year, a substantial share of hospital admissions can be attributed to suboptimal use of medicines – including, but not limited to, inappropriate medications, dosing errors, or drug-drug interactions (Royal Pharmaceutical Society, 2016). Elderly patients, for example, are particularly susceptible to adverse drug reactions (ADRs), not least due to the presence of multi-morbidity (two or more medical conditions) and/or polypharmacy (taking five or more different drugs concomitantly) (Davies & O'Mahony, 2015).

Hence, post-marketing surveillance activities play a vital role in ensuring that newly marketed drugs are safe and effective not only in a controlled trial setting, but also in clinical practice – mainly by gathering information about ADRs and the long-term safety of drugs through pharmacovigilance systems, drug registries, and/or additional post-marketing studies, involving efforts not only by governmental agencies and non-governmental organisations, but also health care systems as well as the pharmaceutical industry.

Pharmacovigilance has been defined by the World Health Organisation (WHO) as "[…] *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*" (WHO, 2017c), and is therefore a rather broad, interdisciplinary field of enquiry. Although most commonly associated with spontaneous reporting systems (SRS) such as the Yellow Card Scheme in the UK (MHRA, 2017b), EudraVigilance on a European level (EMA, 2017b), and VigiBase on a global scale (WHO Collaborating Centre for International Drug Monitoring, 2017b) – industry-independent systems implemented to collect individual patient reports of adverse drug events in order to detect safety signals related to the use of medicines – pharmaceutical companies usually operate their own pharmacovigilance departments, frequently either following-up on patients previously included in clinical trials, or conducting new studies in order to provide further evidence of their drugs` safety. These studies can sometimes be mandated by a relevant authority: for instance when an unmet need in a population might seem to warrant the potentially premature authorisation of a drug through early access routes;

or when clinical trial results were originally deemed sufficient to grant market access but crucial questions about drugs and their effectiveness and/or safety arose after approval. In addition to SRS and industry-sponsored studies, drug registries – occasionally initiated, for example, by governmental agencies or research institutes when problems related to drug use are suspected – are a useful method of trying to detect ADRs and to evaluate the long-term safety of drugs; registries can be designed to answer a variety of questions, and could therefore be regarded as being situated somewhere between fulfilling the tasks inherent to pharmacovigilance systems, and pharmacoepidemiology – overlapping areas of interest that are sometimes difficult to distinguish.

1.3 Pharmacoepidemiology

Pharmacoepidemiology is a comparatively new, interdisciplinary field of scientific inquiry, best described as the "*study of the use and the effects of drugs in large numbers of people*" (Strom, 2012b, p3). As apparent in its name, it applies epidemiological methods to the field of pharmaceuticals rather than diseases; more specifically, pharmacoepidemiology focuses on content areas of clinical pharmacology – i.e. the beneficial and/or harmful effects drugs might have. Although closely related to pharmacovigilance, aimed at answering similar questions, pharmacoepidemiology has a broader, more research-oriented focus.

1.3.1 Research areas

Pharmacoepidemiological studies can broadly be divided into two categories: first, drug utilisation research, describing how drugs are used in real world settings; and second, comparative effectiveness research, comparing the clinical effectiveness and safety of drugs in clinical practice to results obtained in clinical trials, and/or comparing different drugs used for the same indication to each other.

1.3.1.1 Drug utilisation research (DUR)

Several factors potentially influence the effect drug therapy has on a patient: whether the drug prescribed is appropriate considering the circumstances, for example, or whether it is taken regularly, and accurately – the right dose, at the right time. Quite frequently, treatments do not achieve targeted goals because wrong doses are taken, or treatment is interrupted prematurely; it is estimated that up to 50% of patients do

not take medicines as prescribed, depending on indication (WHO, 2003a). Hence, determinants of treatment outcomes might include – at least indirectly – aspects as diverse as prescribers` adherence to treatment guidelines, or behavioural patterns of patients subject to treatment; aspects which themselves are potentially influenced by a wide range of contextual factors, from socio-demographic characteristics to the perceived image of a prescribed medication in question. Different physicians might prefer different drugs of first choice, for a variety of reasons; and not all drugs work equally well in all patients (Wilkinson, 2005). Paying close attention to how drugs are used is therefore imperative – when and why they are prescribed, by whom, and to whom; and how patients take these drugs, in terms of how, when, and for how long. It is also important to assess when and why patients stop treatment, as this might hint towards previously unknown problems related to the drug in question.

However, all these details are not always known; this is even more true for newly approved drugs. Consequently, in order to gain a better understanding of how medicines are used in society, drug utilisation research has emerged as an interdisciplinary field of study, combining elements of clinical pharmacology, epidemiology, and health systems research (Elseviers et al., 2016). The modern definition of drug utilisation research – "[…] *an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes"* (ibid, p7) – also includes qualitative research, indicating that drug utilisation research nowadays potentially goes beyond traditional limits of pharmacoepidemiology; by offering insights into patterns, determinants, and quality of use, it enables the optimisation of drug treatment and thus facilitates rational use of medicines (WHO, 2003b). Drug utilisation research is therefore an essential part of the post-marketing drug surveillance process.

Drug utilisation studies can broadly be defined as attempts to describe and analyse prescribing trends and use of drugs in a population. First studies, conducted during the 1960s, were intended to assess regional differences in drug utilisation (Scheckler & Bennett, 1970, WHO, 2003b); other early studies focused, for example, on factors influencing prescribing patterns (Stolley & Lasagna, 1969). In order to further facilitate cross-sectional studies, in 1976, the Nordic Council on Medicines published a

medicines classification system, together with a technical unit for comparison of drug quantities – the Anatomical Therapeutic Chemical (ATC) system and the defined daily dose (DDD), respectively: the ATC system categorises drugs according to the organs/physiological systems they affect and their chemical and pharmaceutical characteristics, while DDDs are defined as the average daily maintenance dose, used by an adult patient for its main indication. The ATC/DDD system has since been recommended by the WHO for use in international drug utilisation studies (WHO Collaborating Centre for Drug Statstics Methodology, 2016).

Generally speaking, drug utilisation studies can be either descriptive, or analytical. Descriptive studies are used to quantify drug consumption in a population – not only to compare drug use over time and/or between countries, but also to evaluate the uptake of new drugs, to monitor health care expenditure related to medicines use, or to assess quality of care by examining potential over- or under-prescribing of drugs in certain populations. In addition, studies can be used to estimate crude disease prevalence if indications for prescribing and/or linkages to records containing diagnostic information are available. Many descriptive studies also provide findings that can be utilised further, for example patient numbers used as a denominator in subsequent studies analysing treatment outcomes (Lee & Bergmann, 2012). Analytical studies, in contrast, are aimed at exploring factors underlying prescribing patterns and drug use by patients.

1.3.1.2 Comparative effectiveness research (CER)

Although all new drugs have been subject to at least one clinical trial prior to gaining marketing access – designed so as to prove the safety and efficacy of a drug for a specific indication in a clearly defined patient population – further research is generally mandated in order to provide additional information about a drug's safety and effectiveness in clinical practice – where treatment outcomes could very well differ to those found in RCTs, not least due to differences in patients' characteristics. In addition, further research is frequently needed in order to compare different drugs which are used for the same indication to each other, as many of these comparisons were not subject to any clinical trials.

Studies generating evidence to support clinical decision making by using real-world data are commonly subsumed under the header of "comparative effectiveness

research" (CER). Comparative effectiveness studies are analytical studies aimed at establishing how well drugs work in a clinical context, as opposed to the strictly regulated setting of a randomised clinical trial, and are mostly observational (Strom et al., 2012); nevertheless, as a widely agreed-upon definition is lacking, CER comprises a wide range of diverse studies with regards to aim and objectives, design, and methodology.

Generally speaking, comparative effectiveness studies are mainly conducted in order to provide information about alternative treatment methods; place new treatments into the wider context of clinical practice; foster the use of more effective treatments; and identify patient subgroups most likely to benefit from specific treatments (Strom et al., 2012). Therefore, CER plays an increasingly important role in health technology assessment and health policy; several governmental agencies such as NICE in the UK have integrated CER into their decision making process – to support the development of evidence-based clinical guidelines, standardise the quality of care, and reduce variation in treatment (ibid). In addition, results emerging from comparative effectiveness research can also be used to populate cost-effectiveness models as used in health economics research; cost-effectiveness research is however outwith this project, and is therefore not discussed further in this thesis.

1.3.2 Study designs

As pharmacoepidemiology is a sub discipline of epidemiology, the applied methodology is broadly comparable, particularly in terms of study designs.

The design of a pharmacoepidemiological study is predetermined by its aim and goals, but also depends on the resources available. Hence, these studies are usually observational and most commonly retrospective in nature, although studies can also be experimental or quasi-experimental, depending on circumstances.

Specifics of individual studies may vary, with differences, for example, in participant recruitment and study duration, data collection procedures, and analytical methods applied. Causal inference can, however, only be reached if certain prerequisites are fulfilled, the most important one being the time order of exposure (cause) and outcome (effect): both aspects do not only have to be associated, but the exposure needs to

predate the effect. Therefore, these studies need to be designed differently than studies merely providing a description of the status quo (Wettermark et al., 2016).

1.3.2.1 Ecological studies

Cross-sectional and longitudinal observational studies are examples of ecological studies, i.e. studies using aggregate level data. These studies can be used to examine trends – for example in an exposure and an outcome that are potentially linked – by comparing populations geographically and over time, respectively; while cross-sectional studies use data from different regions or countries at a specific point in time, longitudinal studies analyse data from a single region or country over time. Both study designs do not allow for causal inference as individual level data is lacking, and can therefore only be descriptive; nevertheless, they could be used to provide initial evidence supporting or opposing an existing hypothesis, and may therefore trigger further research – such as a case-control or a cohort study, both of which are analytical studies potentially enabling causal inference (Strom, 2012a).

1.3.2.2 Patient-level studies

Case-control and cohort studies are applied on a patient level, and can be used for analytical purposes – due to the way patients are recruited for these studies, the temporal sequence between exposure and outcome is clearly stated: while study participants in case-control studies are chosen based on the presence or absence of the outcome of interest and exposure is scrutinised retrospectively, cohort study subjects are identified based on the exposure and followed over time until an outcome of interest occurs (Strom, 2012a).

Case-control studies are usually conducted in epidemiology when a disease outcome has potentially been linked to a variety of different exposures; by selecting patients with and without the disease in question, differences in potential risk factors can be analysed simultaneously. They also enable the analysis of rare diseases, as a sufficient number of cases will be included in the study by design. Nevertheless, case-control studies can potentially be subject to selection bias (of the control group), as well as to information bias; exposure data has to be gathered retrospectively – through medical records, questionnaires, or interviews – with potential implications on the validity of this information (Strom, 2012a).

Generally speaking, cohort studies are used to compare disease outcomes in different groups of people with varying exposures to potential risk factors, who are free of the disease in question at the time of study inclusion; they can be used to generate new hypotheses as well as to test existing ones, for instance to confirm a suspected correlation between a specific exposure and a particular disease (Rothman et al., 2008). Cohort studies can, however, also be used to evaluate the association of a variety of potential outcomes to a specific exposure, which makes cohort studies perfectly suited for post-marketing studies of new drugs – where effects of treatment might not yet be completely known. Participants are followed over a period of time, and this can be done either prospectively or retrospectively: in a prospective cohort study, participants are enrolled based on specified criteria (e.g. area of residence, year of birth, profession), and data will be collected over a period of time following enrolment; information is frequently obtained through a combination of surveys, interviews, and medical tests. Study results are, however, frequently only available after several years, depending on the study purpose and the research question. In contrast, retrospective studies make use of data that has already been collected for other purposes after specifying cohort inclusion criteria; this usually includes historic medical records. Retrospective studies enable the presentation of results much quicker, but the data available might not be as suitable to answer specific questions as purposely collected data; nevertheless, cohort studies are less prone to biases than other types of observational studies.

As cohort studies frequently require a lot of time and resources, they have not always been feasible. Due to recent technological developments, the linkage of routinely collected information – conveniently stored in data warehouses and more or less readily available for research purposes – has now emerged as an alternative way of gathering data, thus facilitating large cohort-based studies more easily. This had already had a profound impact on pharmacoepidemiology, with a large percentage of contemporary studies now being conducted using administrative databases (Strom et al., 2013).

1.4 “Big data”

“Big data” is a term that has been used approximately since the 1990s to describe datasets that would have been considered too big to be easily analysable, let alone

stored on a single device; it is however now also associated with a range of techniques such as machine learning, natural language processing, and cloud computing – technologies that have enabled the accessibility and usability of vast datasets for analytical purposes, including research.

Although initially more widely known for its commercial uses, such as the analysis of consumer data, big data is nowadays also frequently used in health research, made possible by the advent of electronic health records – digital records of patients' journeys through the health system. Ideally, these electronic health records come with a unique patient identifier attached: the presence of a unique patient identifier enables reliable linkages of different datasets using deterministic methods (matching records based on the agreement of a specific identifier) instead of less reliable probabilistic methods (matching records based on probabilities that they belong to the same individual, calculated by using, e.g., name, date of birth, or postal codes); and reliable data linkage is seen as an important prerequisite to perform high-quality research and facilitate studies investigating broad topics with a potentially large impact on patient care (Fleming et al., 2012).

While widely praised for its potential among research communities, research utilising big data in general and electronic patient records in particular is however not without critics. The public perception of database research is, for the most part, characterised by misinformation and a lack of understanding – resulting in negative attitudes towards the use of non-consented medical data, especially for commercial purposes (Ipsos MORI, 2016). Nevertheless, when properly informed about the aims of a research project and the safeguards in place to protect patient privacy and confidentiality, patients are generally supportive of using linked administrative data; and this is particularly the case when research has the potential to lead to improvements in health care (ibid). Hence, providing a clear justification for the use of non-consented patient data by highlighting the possible benefits of a research project is the basis for every data linkage project.

Chapter 2 – Clinical use of oral anticoagulants

This chapter is intended to provide the clinical background relevant to the thesis' topic. It briefly summarises the physiological process of blood coagulation, and describes thromboembolic events caused by an imbalance of the blood coagulation process; in addition, it gives an introduction to atrial fibrillation, a major risk factor for the development of strokes – thromboembolic events with potentially debilitating consequences for patients, and considerable impact on health systems. Furthermore, this section provides an overview of anticoagulant treatment as a means to prevent thromboembolic events, including explanations of the drugs available; it also introduces the evidence base for using anticoagulant drugs as well as current clinical guidelines for anticoagulant treatment, with a special focus on oral anticoagulants as used in patients with atrial fibrillation.

2.1. Blood coagulation

The process of blood coagulation involves several proteins and other cofactors so as to prevent excessive bleeding after tissue damage or trauma. Generally speaking, blood vessel injuries trigger a series of subsequent coagulation factor activations (coagulation cascade), resulting in the formation of an insoluble fibrin clot in the presence of activated blood platelets; this fibrin clot eventually seals any vessel damage (Key et al., 2009).

Apart from platelets and other necessary elements such as calcium and vitamin K, eleven coagulation factors are involved in blood coagulation – albeit with differing individual importance (Lip & Shantsila, 2013). These factors are usually identified through roman numerals, with an "a" following the number indicating an activated factor (Giangrande, 2003); however, some are better known by their alternative names, for instance fibrinogen/fibrin (factor I/Ia), prothrombin/thrombin (factor II/IIa), or tissue factor (factor III). Although the coagulation process itself has been described already over a century ago and explored in more detail over the last decades (ibid), some aspects with regards to the relevance of specific factors and their interaction still remain unclear (Antovic & Blombäck, 2013, Key et al., 2009, Morrissey & Smith, 2015).

Depending on the specific pathway – intrinsic due to internal vessel surface damage, or extrinsic after trauma – different factors are responsible for the activation of the

pivotal factor X, which is necessary to transform prothrombin into thrombin. This in turn facilitates the availability of fibrin (Lip & Shantsila, 2013). Figure 2.1 shows a simplified overview of the coagulation cascade; it also indicates where anticoagulant drugs interact with components of this process, as discussed further in section 2.4.

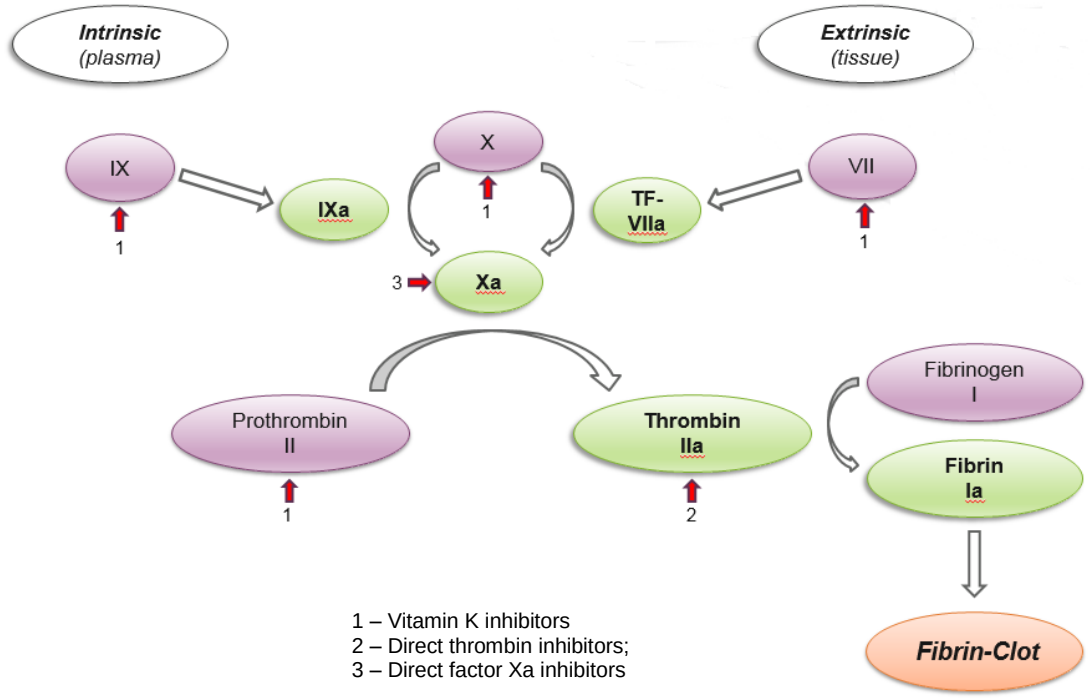


Figure 2.1: Simplified coagulation pathway and targets for oral anticoagulation. Source: adapted from (Lip & Shantsila, 2013)

Under physiological conditions, haemostasis is maintained by the balance of naturally occurring coagulant as well as anticoagulant factors; however, this intricate process is subject to a variety of possible disturbances, potentially leading to either insufficient or excessive coagulation. Insufficient coagulation might result in minor or major haemorrhage, as is for example the case in some haemophilic disorders, while excessive coagulation might give rise to thromboembolic events (Key et al., 2009).

2.2 Thromboembolic events

In contrast to haemostasis, thrombosis occurs in pathophysiological circumstances, originally characterised by the “pathogenic triad” of vessel damage, venous stasis, and hypercoagulability. Essentially, changes in either blood flow or composition

enable the development of intravascular clots; these clots can then potentially occlude a vessel – either locally at the place of origin (thrombus), or at a different location within the body after mobilisation and transportation through the blood system (embolism) (Key et al., 2009).

Thromboembolic events are typically classified as either arterial or venous, depending on a thrombus' point of origin. Thrombi also differ in terms of composition: thrombi originating in veins (venous thrombi) usually have a high fibrin content, while thrombi developing in arteries (arterial thrombi) have a higher amount of platelets (Key et al., 2009, Lip & Shantsila, 2013). This categorisation is, however, most likely an oversimplification as inflammatory processes potentially play a substantial part in the development of all thrombi, and is therefore subject to debate (Jerjes-Sanchez, 2005, Kleinegris et al., 2012, Prandoni, 2009).

2.2.1 Venous thromboembolism (VTE)

The term venous thromboembolism comprises two distinct conditions: deep vein thrombosis (DVT), the development of thrombi throughout the venous system of the lower extremities; and pulmonary embolism (PE), a potentially life-threatening complication of DVT caused by the dislocation of a venous thrombus and the subsequent obstruction of an artery in the lungs (Beckman et al., 2010).

VTE is relatively common, with an estimated incidence of between 100 and 200 cases per 100,000 population in the United States (Beckman et al., 2010, Cushman et al., 2004), and comparable rates in Europe – with estimated incidences for DVT and PE of 148 and 95 per 100,000 population, respectively (Cohen et al., 2007). VTE is usually associated with major surgery and prolonged immobilisation; it is nevertheless also associated with a variety of other conditions: the most important risk factors for its development are advanced age, obesity, pregnancy, cancer, and previous incidences of VTE or stroke (Heit et al., 2016, Perry et al, 2011). Symptoms are often unspecific, but may include pain and swelling for DVT, and dyspnoea and chest pain for PE (Bauersachs, 2012); however, DVTs might not cause any early symptoms (SIGN, 2010, Toth & Cannon, 2010). Although accurate data is lacking, studies indicate that a substantial proportion of cases develop in a hospital setting; nevertheless, approximately 60% to 70% of diagnoses are made in primary care after discharge (Cohen et al., 2007, Spencer et al., 2007). PE is considered as being one

of the most important causes of hospital mortality (Beckman et al., 2010, Lip & Shantsila, 2013, Toth & Cannon, 2010).

2.2.2 Arterial thromboembolism

Arterial thrombi are usually not caused by immobilisation or an imbalance of coagulation factors as is the case for venous thrombi, but can instead be attributed to other underlying conditions such as atherosclerotic diseases or arrhythmias. Risk factors for arterial thromboembolism include behavioural aspects such as alcohol consumption, smoking, and insufficient physical activity, as well as pathophysiological factors such as the presence of co-morbidities like obesity, diabetes, and hypertension (Key et al., 2009).

Arterial emboli can affect several vital organs such as the brain or the heart, and therefore lead to a considerable number of hospital admissions and overall deaths (Key et al., 2009). Strokes for example – changes in blood supply that affect brain function – are to a large percentage categorised as ischaemic, i.e. they are characterised by the reduction of intracranial blood flow due to the obstruction of blood vessels within the brain; estimations range from approximately 60% to more than 80% of all strokes, depending on country (Feigin et al., 2009). Most emboli causing ischaemic strokes originate from atherosclerotic plaques, which developed in large arteries. Emboli can however also originate in the heart (Reddy & Hart, 2014). These cardiac emboli are frequent complications of heart conditions such as atrial fibrillation (AF) and mechanical heart valves: while blood stagnation within the left atrium of the heart is responsible for thrombus formation in AF, the metallic surface of some mechanical heart valves is pro-thrombotic in itself (Key et al., 2009). Atrial fibrillation is discussed in more detail in the next section.

2.2.3 Impact

Cardiovascular diseases (CVD) – encompassing diseases of the blood vessels supplying the heart (coronary heart disease), the brain (cerebrovascular disease), or the extremities (peripheral arterial disease); damage to heart valves and muscles due to bacterial infection (rheumatic heart disease); congenital heart malformations; and venous thromboembolism – are widespread and remain the main cause of death globally; thromboembolic events in particular represent a substantial burden of

disease in developed countries (IHME, 2017, WHO, 2017a). In the UK in 2015 for example, cardiovascular and circulatory diseases came second only to cancer in terms of disability-adjusted life years (DALYs); among the elderly (aged 70 years or older), cardiovascular and circulatory diseases had the highest share of DALYs (see figure 2.2 for details). Although ischaemic heart disease constitute the majority of these (12.7% of all DALY's among patients aged >70 years), ischaemic and haemorrhagic strokes still account for 7.2% of all DALYs in this age group. Though generally in line with UK-wide figures, stroke accounts for a slightly higher share of all DALYs in Scotland, with 8.1% among those aged 70 years or over, and 4.3% overall (ibid). Being one of the most important causes of death and disability in the UK (Murray et al., 2013), production losses associated with stroke amounted to almost £1 billion in 2009, with additional costs of approximately £1.78 billion for health care (Townsend et al., 2012).

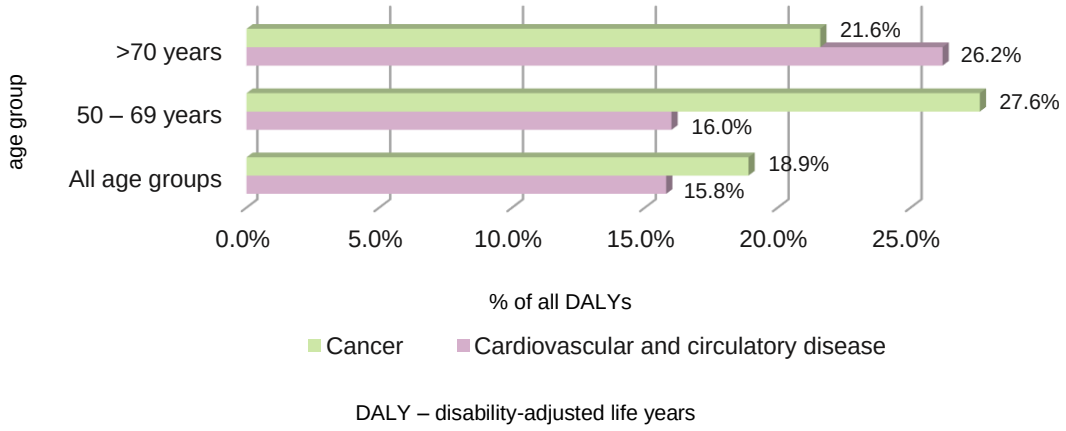


Figure 2.2: Burden of disease in the UK for selected diseases [% of all DALYs]. Data source: Global burden of disease study 2015 (IHME, 2017)

2.3 Atrial fibrillation

2.3.1 Disease overview

Atrial fibrillation is the most frequent arrhythmic disorder, and can be paroxysmal (self-terminating), persistent (not self-terminating, but sinus rhythm can be restored), or permanent (sinus rhythm cannot be restored). Symptoms include palpitations, dyspnoea and chest-pain, but patients can also be asymptomatic. Atrial fibrillation is an important independent risk factor for stroke, increasing the risk up to five-fold (Wolf

et al, 1991); it also negatively impacts a patient's prognosis after having a stroke, resulting in higher risks of disability and death. The presence of AF is frequently associated with a range of other cardiovascular conditions such as coronary heart disease and hypertension, and comorbidities including diabetes, heart failure, chronic pulmonary disease, and obesity are common among AF patients (Steger et al., 2004, Zoni-Berisso et al., 2014).

AF affects approximately 2% of the general population in developed countries; among the elderly, prevalence has been found to be significantly higher, rising to more than 10% in patients aged 80 years or older (Zoni-Berisso et al., 2014). In Scotland, at least 1.8% of the total population and over 6% of people aged over 65 years are affected, according to recent estimates (SIGN, 2014). Prevalence rates are however most likely underestimations, as AF screening is not routinely done, and symptoms are usually unspecific. In addition, prevalence is predicted to rise considerably over the next decades due to ageing populations, increased awareness, and better treatment options (Camm et al., 2012, Schnabel et al., 2015). Consequently, AF and conditions linked to its presence – such as stroke – constitute a considerable and potentially increasing burden on health systems.

Depending on the type of AF and the symptoms, general disease management options include rate control, rhythm control, cardioversion, and catheter ablation. While rate control (using beta-blockers, diltiazem, or verapamil) is aimed at asymptomatic patients as well as those with an underlying cause for the arrhythmia, or where rhythm control has previously failed, antiarrhythmic drug treatment (e.g. with amiodarone or flecainide) is recommended in symptomatic patients with recurrent paroxysmal and persistent AF. As an alternative to oral antiarrhythmic treatment, cardioversion can be used to restore sinus rhythm in patients with recent-onset AF, either electric or pharmacological (intravenous administration of an antiarrhythmic drug); catheter ablation to restore sinus rhythm might be recommended in low-risk patients with paroxysmal AF (Camm et al., 2012). Crucially, treatment with oral anticoagulants to prevent strokes is recommended in AF patients with additional risk factors; the risk assessment is explained in more detail in the following section, while anticoagulant drugs and anticoagulant treatment are discussed further in sections 2.4 and 2.5.

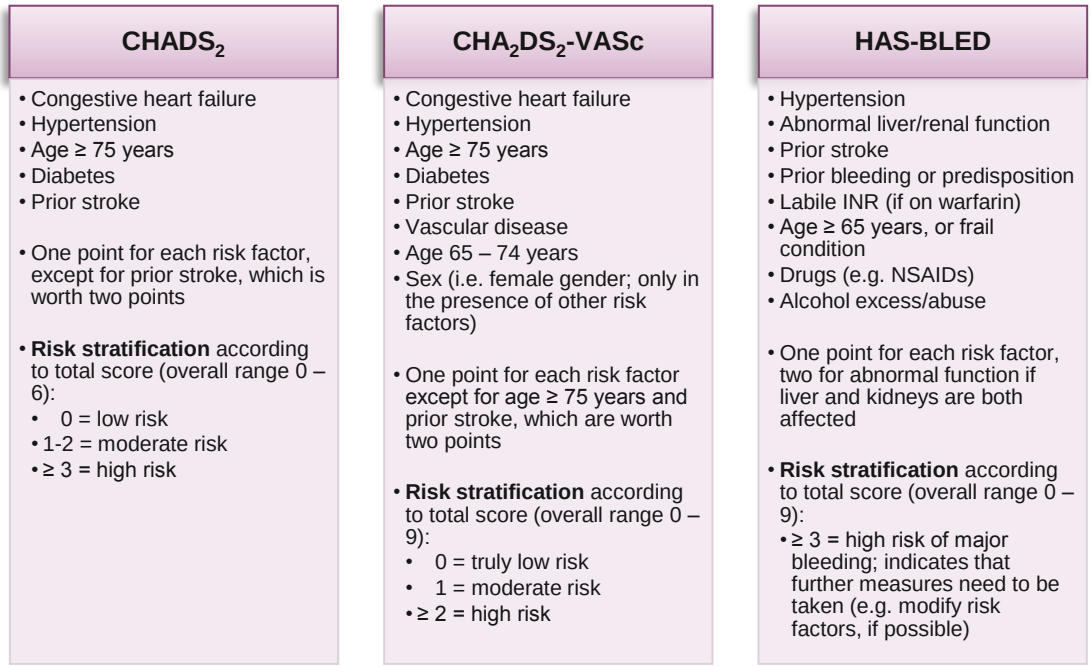
2.3.2 Risk assessment

Even though AF is an independent risk factor for stroke, and oral anticoagulants have proven their efficacy in preventing strokes in patients with AF, treatment with an oral anticoagulant (OAC) might not necessarily be the best option for a patient. OACs can have severe side effects, and individual patients' risk of experiencing a stroke differ depending on additional risk factors; hence, the risks of strokes and bleeding events need to be balanced against each other. For this purpose, several risk assessment scores have been introduced.

The two most commonly used scores to predict the risk of stroke in patients with atrial fibrillation are the $CHADS_2$-score and its derivative, the CHA_2DS_2-VASc-score, developed in 2001 and 2009 respectively. Both scores are utilised in clinical practice to stratify low-, medium-, and high-risk patients in order to determine the necessity for oral anticoagulant treatment, and combine a variety of cardiovascular risk factors (Lip, 2013b). The $CHADS_2$-score mainly focuses on the independent stroke risk factors of congestive heart failure, hypertension, diabetes mellitus, and prior stroke, with a score range of 0 to 6; the validation study found stroke risks among AF patients, stratified by $CHADS_2$-score value, ranging from 1.9 (score 0) to 18.2 (score 6) per 100 patient years (Gage et al., 2001). The CHA_2DS_2-VASc score in addition includes vascular disease and sex, resulting in a score range of 0 to 9, and places greater emphasis on patient age in order to better identify patients with a truly low stroke risk; the validation study estimated stroke rates ranging from 0% for patients with a CHA_2DS_2-VASc score of 0 to 15.2% for patients with a score of 9 during one year (Lip et al., 2010). Stroke risks by risk score according to the validation studies are presented in table 2.1.

The most widely used score to assess bleeding risk is the HAS-BLED score, derived and validated in 2010 (Lip, 2013a, Pisters et al., 2010). It combines a variety of medical conditions known to increase bleeding risk – such as hypertension, abnormal liver and kidney function, and prior strokes and bleeding – with additional information about age, drugs, and alcohol use, with a score range from 0 to 9. The HAS-BLED score has proven effective in predicting major bleeding, including intracranial haemorrhage, and is currently used in combination with the CHA_2DS_2-VASc-score in some clinical guidelines so as to decide about OAC therapy options (Camm et al.,

2012). For details regarding both stroke and bleeding risk assessment scores, see figure 2.3.



INR – international normalised ratio; NSAID – non-steroidal anti-inflammatory drug

Figure 2.3: Stroke and bleeding risk assessment scores in patients with atrial fibrillation. (Gage et al., 2001, Lip et al., 2010, Pisters et al., 2010)

Table 2.1: Stroke risk by $CHADS_2$ and CHA_2DS_2-VASc risk scores (Gage et al., 2001, Lip et al., 2010)

$CHADS_2$		CHA_2DS_2-VASc	
Score	***Stroke rate (per 100 patient years)***	***Score***	***Stroke rate (% per year)***
0	1.9	0	0.0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.2

2.4 Anticoagulants

Anticoagulants are drugs intended to prevent thromboembolic events such as DVT and stroke by interacting with the physiological mechanisms underlying the blood coagulation process – the coagulation cascade, as described in section 2.1. In contrast, low-dose aspirin and other antiplatelet drugs (e.g. clopidogrel, dipyridamole, prasugrel, ticagrelor), which interact with platelet aggregation, are used in conditions largely due to atherosclerosis, for instance to prevent myocardial infarction; these drugs are not discussed any further here.

Anticoagulant drugs are usually divided into oral and parenteral drugs, and further characterised by their mechanism of action – i.e., how they interact with specific components of the coagulation cascade so as to effectively prevent the formation of blood clots. Although a wide range of different factors are involved in the blood coagulation process, not all of them are actively targeted by anticoagulants; instead, most anticoagulant drugs currently in use focus on either factor IIa (thrombin) or factor Xa (either directly or indirectly), with the exception of vitamin-K antagonists (VKAs), which are more unspecific in their range of targets (see also figure 2.1).

2.4.1 Historical development

Anticoagulant drugs have a long history, and the two drugs first marketed for medical purposes – heparin and warfarin – are still used in clinical practice today. However, over the last two decades, new drugs have been developed, and more are most likely yet to come considering the high burden of disease attributable to thromboembolic events (see figure 2.4 for a brief overview).

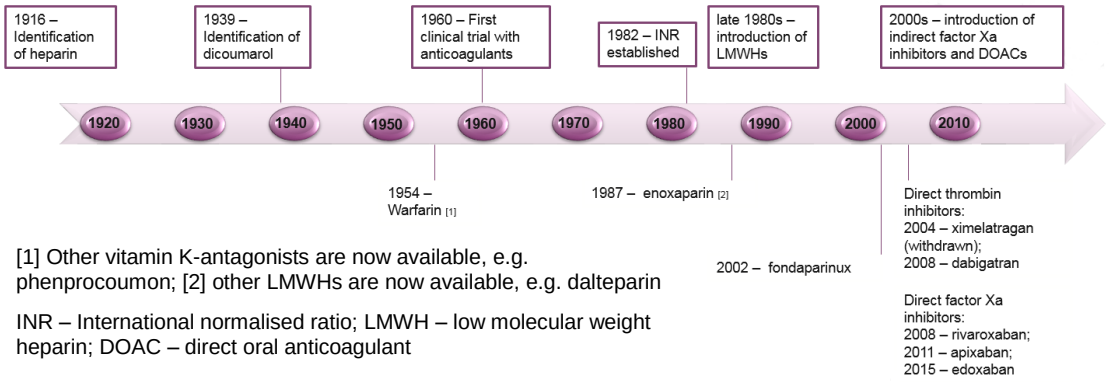


Figure 2.4: Anticoagulant medication timeline. (Duxbury & Poller, 2001, EMA, 2017d, FDA, 2016, Hovanessian, 1999, PMDA, 2015, Wardrop & Keeling, 2008)

Heparin, the first drug to become available, was discovered in 1916 at John Hopkins Medical School in Baltimore, Maryland, and initially commercialised in 1924 despite unsolved problems with observable toxic side effects. After identification of its chemical structure in 1926 and the implementation of a new purification protocol in 1933, an improved form of heparin without previously noted side effects was first used in humans in 1937 after surgery (Wardrop & Keeling, 2008). Since the 1990s, low molecular weight heparins (LMWH) have been developed, having now almost completely replaced un-fractioned heparin due to easier administration and monitoring despite their higher costs (Fareed et al., 2008, Hovanessian, 1999).

Warfarin was introduced in 1948 as an advancement of dicoumarol; dicoumarol itself was originally described in 1939 as the causing agent of the “sweet clover disease” (cattle dying from extensive bleeding after being fed mouldy sweet-clover hay) and first synthesised in 1940 at the University of Wisconsin, Madison (Kresge et al., 2005). Although initially marketed as rat poison, warfarin was soon used for treating human patients due to its advantages over other available drugs – it can be administered orally, and the anticoagulant effect is reversible (Duxbury & Poller, 2001). However, the international normalised ratio (INR), a method to measure and standardise warfarin treatment (further described in the next section), was only implemented in 1982 upon recommendation by the WHO (Poller, 2004).

Since the early 2000s, research and development has focused on anticoagulants directly targeting individual coagulation factors, specifically designed so as to be orally bioavailable. While ximelatragan, an oral direct thrombin inhibitor, has been retracted due to hepatotoxicity (EMA, 2006, Gurewich, 2005), other direct oral anticoagulants (DOACs) including dabigatran etexilate, rivaroxaban, apixaban, and edoxaban have now gained approval for a range of indications in various countries.

2.4.2 Vitamin K antagonists (VKA)

Although warfarin is the best-known vitamin K antagonist (VKA), other coumarin derivatives are available for therapeutic purposes as well, for instance acenocoumarol and phenprocoumon (Scaglione, 2013). The pharmacological properties of these agents differ slightly, especially with regards to elimination half-lives, but they share a common mechanism of action and are used for similar indications (ibid).

Several coagulation factors – namely factors II, VII, IX, and X – depend on the availability of vitamin K, as vitamin K facilitates the crucial γ-carboxylation necessary for the expression of their anticoagulant activity. VKAs such as warfarin indirectly inhibit these vitamin-K dependent factors by inhibiting the enzyme vitamin K epoxide reductase. This leads to a reduced availability of vitamin K which, in turn, results in insufficient carboxylation of anticoagulation factors and, consequently, in a decreased anticoagulation effect (Lip & Shantsila, 2013).

Warfarin is taken orally and has a relatively long half-life of approximately 24 - 58 hours. It is absorbed rapidly with high bioavailability, mainly bound by plasma proteins, and metabolised by the liver. Onset of action can be rapid if loading doses are used, but full therapeutic effect is frequently delayed by up to several days. Anticoagulant activity may be observed for a substantial period of time after discontinuation of administration, usually two to five days (Baker et al., 2004, Scaglione, 2013). Owing to genetic polymorphisms, drug response differs among patients; absorption and bioavailability also vary, based on the high interaction potential of warfarin with other drugs and with certain food ingredients (Lip & Shantsila, 2013). The resulting inter- and intra-individual differences thus require considerable variability in dosing schemes and, in addition, necessitate extensive monitoring due to the narrow therapeutic window of VKAs – overdosing warfarin increases the risk of potentially serious bleeding complications (Nutescu et al., 2011), while too low a dose increases the risk of thromboembolic events (Hylek et al., 2003).

Warfarin therapy is monitored by measuring prothrombin time (PT), the time blood plasma needs to clot after adding thromboplastin (tissue factor) to induce the blood coagulation cascade. As responsiveness to VKAs can differ substantially between thromboplastin preparations originating from different tissues, potentially leading to PT differences across laboratories, commercial thromboplastins are calibrated against an international reference preparation (Kitchener et al., 2013). The prototype calibration was endorsed by the WHO, but can be adapted to local circumstances by means of simplification; results are made comparable by using a common scale, the INR. The validity of values is restricted to INRs between 1.5 and 4.5 (ibid); standard warfarin therapy – as recommended in most cases – has a target INR of 2.0 – 3.0 (Guyatt et al., 2012, Keeling et al., 2011).

Warfarin is widely used in clinical practice globally for a variety of indications, primarily for long-term conditions such as AF due to oral availability (Lip & Shantsila, 2013). Uptake of warfarin treatment has increased over the last three decades for certain conditions (Lip et al., 2014a); among AF patients in the United States for example, warfarin use increased from approximately 12% in 1990 to an estimated 58% in 2001 (Stafford & Radley, 2003). In Scotland, approximately 50% of all AF patients were being treated with this anticoagulant in 2010 (Audit Scotland, 2012). Consequently, warfarin is still one of the most-prescribed drugs, accumulating approximately 275m US$ in global sales in 2013 (Evaluate, 2015) despite its low price.

2.4.3 Direct oral anticoagulants (DOAC)

The direct oral anticoagulants (DOACs) belong to two different categories, dependent on the drug target: direct thrombin inhibitors; and direct factor Xa inhibitors. Both drug groups interact with coagulation factors coming into play during the final steps of the coagulation cascade, therefore blocking both the intrinsic as well as the extrinsic pathway of blood coagulation (Lip & Shantsila, 2013).

Direct thrombin inhibitors prevent the formation of fibrin-clots by inhibiting the enzyme thrombin, which is not only responsible for the transformation of fibrinogen into fibrin, but is also an important activator of platelets (Souza Brito & Tricoci, 2013). Dabigatran is the only oral direct thrombin inhibitor currently available, after ximelagatran has been withdrawn from the market (EMA, 2006).

As dabigatran itself is not orally active, dabigatran etexilate, a non-active pro-drug, is used. Dabigatran etexilate is absorbed rapidly, dependent on an acid environment; formulations therefore contain tartaric acid. Bioavailability after oral administration is however only about 7%. Onset of action can be observed on average within 1.5 hours, and mean half-life is approximately 8 – 10 hours. About 20% is excreted after metabolism via the biliary system, while most dabigatran is eliminated unchanged through the kidneys. The potential for drug-drug interactions is assumed to be low, as is the effect of food ingredients (DeWald, 2014, Scaglione, 2013).

Direct factor Xa inhibitors block the coagulation cascade by selectively and reversibly inhibiting factor Xa. Currently available direct factor Xa inhibitors are rivaroxaban, apixaban, and edoxaban; additional drugs are under development (Lip & Shantsila,

2013, Scaglione, 2013). All three drugs have a rapid onset of action and shorter elimination half-lives than warfarin; nevertheless, bioavailability and excretion pathways differ, as shown in figure 2.5 (Deitelzweig, 2014, Plitt & Giugliano, 2014, Scaglione, 2013). The interaction potential of direct factor Xa inhibitors with drugs inhibiting or inducing liver enzymes has been postulated, albeit not in much detail, while potential interactions with food ingredients are mostly unknown as of now (DeWald, 2014).

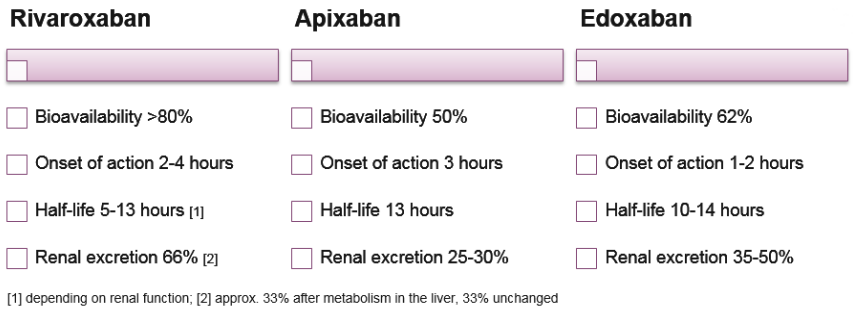


Figure 2.5: Pharmacological profiles of oral direct factor Xa inhibitors. (Deitelzweig, 2014, DeWald, 2014, Heidbuchel et al., 2013, Scaglione, 2013)

DOACs have now been approved for a range of conditions in several countries all across the world. Depending on local treatment guidelines, DOACs might however only be prescribed when patients have contraindications for warfarin use, experience labile INRs, or are unwilling to use VKAs, resulting in potentially substantial regional differences in prescribing practice. Although DOACs are considerably more expensive than warfarin – annual cost of treatment in patients with AF in England has been estimated to be £283 with warfarin, as compared to £767 - £802 with DOACs (NICE, 2014b) – DOACs are in general considered to be cost-effective (Ferreira & Mirco, 2015, Shah et al, 2016); relative costs of oral anticoagulants are however influenced by a range of contextual aspects, and are not discussed any further here.

2.4.4 Parenteral anticoagulants

Parenteral anticoagulants currently in use to prevent thromboembolic events include unfractionated heparin, low-molecular weight heparins (LMWH), fondaparinux, and bivalirudin. Heparin is a naturally occurring substance, extracted from animal intestines; the LMWHs dalteparin, enoxaparin, and tinzaparin are obtained through chemical processing of unfractionated heparin, thereby reducing molecular size. In contrast, fondaparinux and bivalirudin are synthetic molecules, modelled after heparin

fragments and hirudin (a naturally occurring anticoagulant found in leeches), respectively (Garcia et al., 2012, Marmur, 2002).

Heparin, the LMWHs, and fondaparinux are all indirect inhibitors of coagulation factors by amplifying the effect of antithrombin, which deactivates a range of factors including thrombin and factor Xa; the effect on specific coagulation factors differs however between the drugs. While heparin induces effective inhibition of both thrombin and factor Xa, LMWHs are less effective against thrombin due to their smaller molecule size; fondaparinux does not increase thrombin inhibition, and can therefore be categorised as indirect factor Xa inhibitor. In contrast, bivalirudin directly inhibits thrombin. (Garcia et al., 2012).

In the United Kingdom, parenteral anticoagulants are usually utilised in hospital settings; in certain circumstances, they may also be used in outpatients for further preventive measures (NHS Greater Glasgow & Clyde, 2014). This is, however, generally restricted to short-term use due to problems e.g. associated with the route of administration.

2.5 Treatment with anticoagulant drugs

2.5.1 Treatment indications, duration, and choice of drug

Anticoagulation therapy can either be short-term – generally meaning up to three months – or long-term, depending on indication. While short-term treatment is common in secondary care and frequently involves parenteral application of medication, long-term treatment, usually by means of orally administered drug therapy, is mainly maintained in a primary care context. Long-term treatment needs to be more thoroughly adapted to circumstances, as patients are required to be more actively involved once they leave hospital care.

The most common indication for short-term utilisation of anticoagulation is primary prophylaxis of thromboembolic events during and shortly after surgery, and for this indication LMWHs (e.g. enoxaparin) or fondaparinux are currently the standard of care (Gould et al., 2012, NICE, 2017c, SIGN, 2010); DOACs have been approved for use in patients undergoing hip or knee replacement surgery (EMA, 2017d, FDA, 2016). Treatment is usually stopped at discharge, although extended prophylaxis for

up to four weeks following discharge is recommended in high-risk patients, especially those undergoing hip or knee replacement surgery (NICE, 2017c , SIGN, 2010). LMWHs are also frequently used to prevent DVTs during pregnancy and up to six weeks following delivery, albeit with a brief interruption commencing at the start of labour (Bates et al., 2016). Nevertheless, only patients with a medium to high risk of developing a DVT are treated with pharmacological thromboprophylaxis, as other options are available (e.g. anti-embolism stockings); decisions whether to use anticoagulant drugs or not are made based on VTE and bleeding risk assessment (NICE, 2017c, SIGN, 2010).

Patients with VTEs are also initially treated short-term with LMWHs or fondaparinux; however, in order to prevent recurrence, treatment with an oral anticoagulant is continued for three to six months after discharge – usually with warfarin, but DOACs are now recommended for this indication as well (Kearon et al., 2016, , NICE, 2017b, SIGN, 2010). Treatment of acute or recurrent VTE with warfarin might necessitate high-intensity therapy with a target INR of 3.0 – 4.0, especially when a subsequent event occurred while on standard therapeutic level (Lip & Shantsila, 2013).

Long-term anticoagulant treatment is mainly recommended for two major cardiovascular conditions: artificial heart valves, and atrial fibrillation. Both conditions may cause irregular blood flow, thereby facilitating the development of cardiac thrombi and substantially increasing the risk of stroke and other thromboembolic events (Natale & Jalife, 2008, Toth & Cannon, 2010).

Warfarin is the drug of choice for patients with mechanical heart valves, and all patients undergoing heart valve replacement surgery are considered being in need of and eligible for thromboprophylactic medication (Toth & Cannon, 2010). Similar to patients with recurrent VTEs, mechanical heart valve patients may require higher target INRs, dependent on the type and position of the implant (Leiria et al., 2011). Treatment is in general permanent. Dabigatran should not be used for this indication, based on findings from a phase II clinical trial comparing dabigatran to warfarin (Eikelboom et al., 2013); oral direct factor Xa inhibitors have not been approved for this indication either.

In contrast, warfarin as well as all DOACs have been approved for primary and secondary prevention of stroke in AF patients; treatment may be continued life-long,

depending on circumstances. Similar to the prevention of DVT, treatment with anticoagulants in AF patients is dependent on risk-factor assessments using specified scoring tools (Camm et al., 2012, January et al., 2014, NHS Greater Glasgow & Clyde, 2014, NICE, 2014a), designed so as to decide whether initiation of anticoagulation is justified (Lip, 2013a). Optimally, risks for stroke and bleeding are assessed, and an individual patient's score should exceed a certain threshold in order to become eligible for treatment; see also section 2.3 for details.

2.5.2 Issues associated with oral anticoagulant treatment

2.5.2.1 Warfarin

Treatment with warfarin is associated with a variety of challenges, most of which are rooted in the pharmacological properties of VKAs.

Most importantly, VKAs are subject to a wide range of interactions with other drugs as well as several food ingredients, either increasing or decreasing INR levels. Among the large number of drugs which can affect INR levels are frequently prescribed medicines such as antimicrobials, cardiovascular drugs, and analgesics – e.g. ciprofloxacin, amiodarone, or acetylsalicylic acid (Nutescu et al., 2011). Foods and herbs with a proven or assumed effect on INR levels, based on the ability to modify enzyme activity necessary for metabolism of warfarin, include for instance alcohol, cranberry juice, green tea, soy milk, fish oil, garlic, or St. John's Wort, to name just a few (Gage & Milligan, 2005, Holbrook et al., 2005, Nutescu et al., 2011); and as vitamin K can reverse the effect of VKAs, the intake of large amounts of food with high vitamin K content (e.g. broccoli) can cause a decrease in INR levels. As therapeutic success depends on the time spent within therapeutic range (Morgan et al., 2009), the staggering number of possible interactions dictate a strict dietary regime for many patients, and pose significant challenges to patients with comorbidities, especially when concomitant medication is prescribed independently by different doctors and other health care professionals.

Based not only on potential interactions, but also because of observable inter-individual differences in drug response, warfarin use has to be controlled tightly due to its narrow therapeutic window. INR monitoring is, however, a considerable burden for health systems in terms of resource allocation, and also considered a major inconvenience for patients (Cotté et al., 2014): patients need to visit their general

practitioner (GP) or an anticoagulation clinic, a laboratory has to determine the current INR status, and finally a responsible health professional has to contact the patient and adjust the warfarin dosage – a slow and quite inefficient process, especially for patients living in rural areas without close proximity to health care facilities. Although technological advances have led to the development of point-of-care devices, enabling patients to either self-test their INR or even self-manage anticoagulant therapy, only a minority of eligible patients are included in schemes promoting these devices, and results are not always better than with established monitoring activities (Alonso-Coello et al., 2012, Garcia-Alamino et al., 2010, Matchar et al., 2010, Siebenhofer et al., 2014). Despite attempts to improve INR monitoring and to further promote self-monitoring and self-management of warfarin therapy, a substantial percentage of patients are still frequently outside the therapeutic range (Cotté et al., 2014).

Apart from drug-drug and drug-food interactions, labile INRs are also regularly ascribed to non-adherence to treatment (Kaariainen et al., 2013), defined as either unscheduled discontinuation of medication or drug intake different from what was originally prescribed (Ewen et al., 2014). Adherence to warfarin treatment is presumed to be rather low (Skeppholm & Friberg, 2014); reasons for non-adherence are plentiful and may include insufficient acceptance of treatment, a lack of information about the medication, and a variety of socio-demographic factors – although no consistent predictors could be identified thus far (Ewen et al., 2014). Simply forgetting to take medication as required might be another possible explanation, especially among patients with several comorbidities and/or concomitant medication (ibid).

Hence, warfarin therapy needs to be planned meticulously in all phases, from careful initiation of treatment so as to detect an optimal dosage to potentially far-reaching changes in life-style. In addition, the slow onset of action and the prolonged time of clinical effectiveness well after discontinuation of medication require the arrangement of transient therapeutic options prior to scheduled surgery, and potentially pose risks in emergency situations (Lip & Shantsila, 2013, Perry et al, 2011). Prescribing warfarin has therefore not always been considered as being in the best interest of the patient; this has resulted in a reluctance to initiate warfarin treatment particularly in very elderly patients (Bungard et al., 2000).

Misguided perceptions of risks and merits of anticoagulants, based on incomplete or outdated information, is considered one of the main reasons for the low uptake of VKA treatment among eligible patients (Lip & Shantsila, 2013); especially the importance of falls among elderly patients might commonly be overrated (Donzé et al., 2012). The reluctance of doctors to prescribe warfarin also coincides with a lack of communication with their patients about available treatment options (Bungard et al., 2000, Dantas et al., 2004, Devereaux et al., 2001). Hence, calls for alternatives to replace warfarin as the drug of choice for long-term treatment in patients with atrial fibrillation have been made for some time. The demand for new medicines with a more favourable pharmacological profile, easy administration, no major drug and food interactions, and without the necessity for tight monitoring eventually led to the development of the new, direct oral anticoagulants (Deitelzweig, 2014).

2.5.2.2 Direct oral anticoagulants

Although potentially less problematic than warfarin, treatment with direct oral anticoagulants is also associated with several challenges.

The main issue related to the use of DOACs is the overall lack of data, in particular the scarcity of real-world data pertaining to the utilisation of DOACs in clinical practice, and with respect to their long-term effectiveness and safety.

No sufficient information has for instance been published to date in order to determine the possible extent of problems linked to co-morbidities or concomitant medication. Considering pharmacological features such as high levels of renal excretion (especially dabigatran) or liver metabolism (e.g. apixaban), individual drugs might be unsuitable for specific patients, including those with severe kidney and/or liver disease. Possible drug-drug interactions have been postulated, which may pose challenges similar to treatment with warfarin – albeit to a considerably lower degree (Dempfle, 2014, Kimachi et al., 2014, Savelieva, 2014); some proven or suspected interactions have however been included in recommendations for DOAC usage and dosing (Heidbuchel et al., 2013). Reports with respect to adverse events are still inconclusive, especially regarding bleeding incidences linked to DOAC usage in comparison to VKAs (Abraham et al., 2017, Bruins Slot & Berge, 2013, Miller et al., 2012, Salazar et al., 2014, Thorne et al., 2014,), and the possibility of an increased risk for myocardial infarction (Larsen et al., 2014, Stolk et al., 2017). And long-term

safety data, potentially indicating the occurrence of previously unknown adverse effects, are naturally scarce considering the limited time DOACs have been available.

The non-availability of specific antidotes for direct factor Xa inhibitors has been considered as being particularly challenging, as this necessitates the usage of non-specific reversal therapies in emergency situations involving patients being treated with rivaroxaban, apixaban, or edoxaban – even though efficacy and safety of these methods have not been established in connection with DOACs (Kaatz & Crowther, 2013, Peacock et al., 2016, Siegal & Cuker, 2014). Antidotes are currently under development (Siegal et al., 2015), and the availability of target-specific antidotes for all DOACs might eventually improve clinical outcomes of bleeding events related to treatment, but also alleviate problems linked to trauma and unplanned surgery (Peacock et al., 2016).

Additionally, tools to specifically monitor the effect of DOAC therapy with sufficient precision and validity are so far not widely available. Although the assessment of anticoagulation status is not routinely recommended, it may be desirable or necessary in certain circumstances; this is however currently not easily possible, as common tests routinely used in warfarin monitoring are unreliable or not applicable, and available drug-specific assays are either impractical, potentially inaccurate, or rely on commercially available but not approved calibration methods (Adcock & Gosselin, 2015, Peacock et al., 2016).

The issue of adherence to treatment also deserves further attention. Non-compliance may lead to problems similar to those observable in warfarin regimes, including insufficient protection against strokes and major bleeding events – but in contrast to warfarin therapy, no routine monitoring is done, and insufficient or excessive anticoagulation might not be detected in time. Although DOACs have a much larger therapeutic window than warfarin, the rapid onset of action and the comparably short half-life of DOACs (as listed in figure 2.5) might give rise to previously unidentified, unwanted treatment outcomes (Deitelzweig, 2014). Data about adherence rates among AF patients in clinical practice have only recently been made available, and are limited in scope thus far; short-term adherence to DOAC treatment seems to be higher than for warfarin, but data is still insufficient to make predictions regarding long-term usage (see chapter 7 for a more in-depth discussion of adherence to treatment).

Finally, the lack of clinical trials directly comparing the different drugs currently complicates the uptake and understanding of DOAC use. Direct comparisons between the agents have not taken place presumably based on issues connected to intellectual property rights, trial costs, and feasibility; ethical issues naturally limit any testing against placebo. Decisions for a specific medication regime might therefore not necessarily be made based on robust clinical evidence, but potentially take into account prescribers' and patients' preferences instead.

2.6 Evidence base for use of oral anticoagulants in patients with atrial fibrillation

Even though oral anticoagulants are used in clinical practice for a range of conditions, the purpose of this section is to present evidence mainly related to the prevention of stroke in patients with atrial fibrillation. As atrial fibrillation is the main indication for oral anticoagulation, and currently the only indication where DOACs are used long-term, this patient population is the focus of both the drug utilisation and the clinical effectiveness studies as represented in this thesis, further described in chapters 7 and 8 respectively.

2.6.1 Clinical trials

Randomised controlled trials with anticoagulants had not been performed until 1960, when treatment with anticoagulants was first compared to no treatment in patients with PE (Wardrop & Keeling, 2008). All currently available anticoagulants have since been subject to several RCTs; nevertheless, conducted trials differ in scope, design, and methods, mainly due to differences in context.

Warfarin has been tested extensively against placebo as well as other existing therapeutic options (Andras et al., 2012, Laupacis et al., 1994, Taylor et al., 2001, van Walraven et al., 2002). Most major RCTs testing warfarin against placebo or antiplatelet drugs for primary or secondary prevention of stroke in AF patients have already taken place during the 1980s and 1990s, including the Copenhagen AFASAK study (Petersen et al., 1989), the Veterans Affairs SPINAF study (Ezekowitz et al., 1992) and the European Atrial Fibrillation Trial (Koudstaal et al., 1993). These studies, along with a variety of additional trials, provided sufficient evidence that warfarin is safe and efficacious for stroke prevention and more effective than antiplatelet drugs

for this indication, thus being the basis for contemporary clinical guidelines. In addition, they provided evidence for an increased risk of bleeding under anticoagulant therapy, therefore mandating risk assessments prior to warfarin initiation and adequate therapeutic monitoring.

Approval of market access for DOACs for stroke prevention in patients with atrial fibrillation relied mainly on four large multicentre studies: RE-LY (Connolly et al., 2009), ROCKET-AF (Patel et al., 2011), ARISTOTLE (Granger et al., 2011), and ENGAGE AF-TIMI 48 (Giugliano et al., 2013). These trials investigated the efficacy and safety of dabigatran, rivaroxaban, apixaban, and edoxaban for this indication by comparison with warfarin, respectively. All trials were designed as non-inferiority trials, and provided evidence that DOACs reduce the risk of strokes to at least the same degree as warfarin, with similar risks of major bleedings (see figure 2.6 for details).

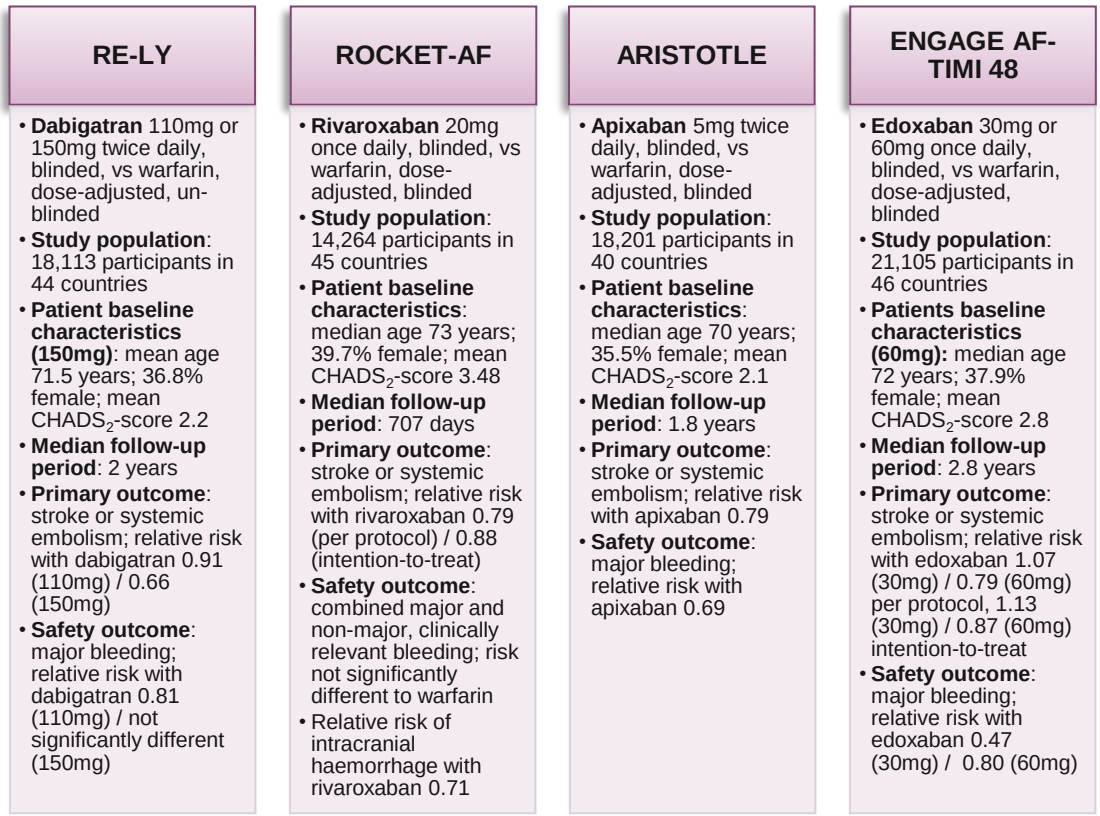


Figure 2.6: Comparison of randomised clinical trials – prevention of stroke in patients with atrial fibrillation (Connolly et al., 2009, Giugliano et al., 2013, Granger et al., 2011, Patel et al., 2011)

Although these four trials were similar, several important differences have to be pointed out, hampering the direct comparison of their findings and asking for caution in interpreting results. Most importantly, study populations were different, based on inclusion and exclusion criteria: while the RE-LY and ARISTOTLE trials enrolled mostly AF patients with a moderate stroke risk, participants included in both the ROCKET-AF and ENGAGE AF-TIMI 48 studies had a much higher average $CHADS_2$-score. In addition, patients with active liver disease were excluded in the RE-LY trial, but not in the other studies, and thresholds for excluding patients with renal insufficiency differed as well. Crucial differences can also be found in outcome definitions: in the ROCKET-AF trial, for example, major and non-major haemorrhages have been combined, whereas the other studies only accounted for major bleedings as a primary safety point; secondary safety outcomes have been specifically defined only in the ARISTOTLE and ENGAGE AF-TIMI 48 trials. Definitions for and criteria of primary efficacy outcomes (stroke, systemic embolism, and/or composites thereof) also diverged (Connolly et al., 2009, Giugliano et al., 2013, Granger et al., 2011, Patel et al., 2011).

Furthermore, several other issues with trial management and the reported findings have been pointed out, including the usage of faulty equipment to measure INR levels in ROCKET-AF (Cohen, 2016); the non-disclosure of potentially vital data regarding drug monitoring and bleeding events from RE-LY (Moore et al., 2014); and aspects of the analytical methods applied in all four RCTs (Chan et al., 2014, Cohen, 2016). Hence, indirect comparisons of DOACs based on trial results are potentially prone to errors due to existing uncertainties and insufficient data.

More recently, RCTs have also been conducted involving agents to be used as antidotes to DOACs. Idarucizumab has been approved for the reversal of dabigatran etexilate in 2015 based on the RE-VERSE AD trial (Pollack et al., 2015); andexanet alfa has provided preliminary evidence of being able to reverse the anticoagulant effect of direct factor Xa inhibitors in the ANNEXA-A and ANNEXA-R studies, and is now subject to a phase III trial (Siegal et al., 2015)

2.6.2 Meta-analyses and observational studies

Clinical trials assessing oral anticoagulants for patients with a diagnosis of AF have been reviewed numerous times, including systematic reviews conducted under the

auspices of the Cochrane collaboration. Findings of these meta-analyses indicate that, in general, oral anticoagulants decrease the risk of stroke while increasing the risk of major bleeding; odds ratios/relative risks differ however depending on the drug in question and patients' characteristics.

Reviews were generally supportive of the routine use of warfarin (Saxena & Koudstaal, 2004a, Saxena & Koudstaal, 2004b) as well as the direct oral anticoagulants (Bruins Slot & Berge, 2013, Hicks et al., 2016, Salazar et al., 2014), although evidence has been perceived to be less conclusive for DOACs; reviews frequently pointed out knowledge gaps and the need for further research, especially with regards to the treatment of patients in clinical practice (Aguilar & Hart, 2005, Aguilar et al., 2007, Bruins Slot & Berge, 2013, Salazar et al., 2014). Additionally, the lack of specific antidotes for DOACs and missing long-term safety data have been highlighted (Bruins Slot & Berge, 2013); these issues have however since been partially addressed as a first reversal agent (for dabigatran) has been approved for use, and others are in development.

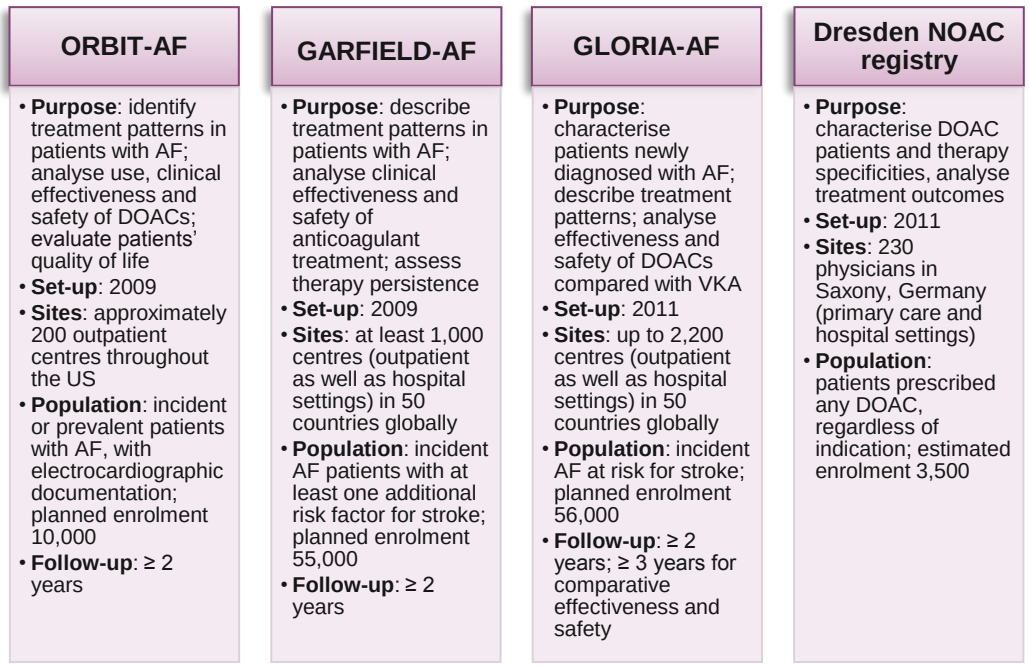
Indirect comparisons of DOACs conducted thus far, based on the systematic reviews and meta-analyses of clinical trials, broadly concluded that all DOACs are similarly safe and efficacious for the indication of stroke prevention in patients with AF (Rasmussen et al., 2012, Schneeweiss et al., 2012). Nevertheless, potential differences between individual drugs have been pointed out: while dabigatran seems to slightly increase the risk of bleeds – most prominently gastro-intestinal bleeding – compared to factor Xa inhibitors in general, and apixaban in particular, studies also suggested dabigatran and apixaban to be more efficacious in preventing strokes than rivaroxaban (Cope et al., 2015, Mitchell et al., 2013, Sharma et al., 2015). As no direct comparisons of DOACs have been performed, results need to be interpreted with caution though, as the RCTs were not designed to be used for a comparison between individual DOACs; trial protocols for instance differed, with potential implications on the validity and accuracy of findings (Cope et al., 2015, Mitchell et al., 2013).

Observational studies, evaluating the safety and effectiveness of DOACs in clinical practice, are now also becoming available, although the number of published studies based on real-world data is still limited to date. Major large-scale studies published so far have been conducted in the US and in Denmark; all used warfarin as a comparator.

Two studies from the US used commercial claims data to analyse treatment outcomes in patients with AF: one focusing on dabigatran, analysing records from October 2010 – December 2012 and including 64,935 patients (Lauffenburger et al., 2015); and another with a focus on apixaban, utilising data from January 2013 – September 2015, comprising 76,940 patients (Li et al., 2017). The Danish studies have all been conducted on a national level, using electronic patient records. The first Danish study covered the period from August 2011 – December 2012, and compared outcomes in 14,267 AF patients treated with dabigatran (either standard or reduced dose) or warfarin (Larsen et al., 2013); the second, using records from August 2011 – November 2015, compared treatment outcomes in a total of 61,678 AF patients using standard dose apixaban, dabigatran, rivaroxaban, or warfarin (Larsen et al., 2016); and a third used data from August 2011 – February 2016 to compare treatment outcomes in 55,644 patients using either warfarin or reduced doses of apixaban, dabigatran, or rivaroxaban (Nielsen et al., 2017). So far, findings are broadly in line with results published based on trial data: all DOACs are apparently similarly safe and effective, and perform no worse than warfarin – however, minor differences between individual DOACs have been observed (Larsen et al., 2016, Nielsen et al., 2017). Further research using administrative and/or claims databases is currently being conducted (for example Holbrook et al., 2016).

In addition, several registry studies are on-going so as to address the issue of lacking long-term safety and effectiveness data, including the Global Registry on Long-term Oral Antithrombotic Treatment in patients with Atrial Fibrillation (GLORIA-AF), the Global Anticoagulant Registry in the FIELD (GARFIELD-AF), the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), and the Dresden NOAC registry, amongst others (Beyer-Westendorf et al., 2014, Huisman et al., 2014, Kakkar et al., 2012, Piccini et al., 2011). Important aspects of these major, ongoing registries are summarised in figure 2.7.

Previously published findings from observational studies, in comparison to results emerging from this study, are discussed in more detail in subsequent chapters 6 (patients' baseline characteristics), 7 (DOAC utilisation), and 8 (clinical effectiveness and safety).



AF – atrial fibrillation; DOAC – direct oral anticoagulant; VKA – vitamin K antagonist

Figure 2.7: Overview of ongoing, prospective registries with a focus on direct oral anticoagulants (Beyer-Westendorf et al., 2014, Huisman et al., 2014, Kakkar et al., 2012, Piccini et al., 2011)

2.7 Guidelines for the use of oral anticoagulants to prevent strokes in patients with atrial fibrillation

Based on data gathered in clinical trials, DOACs are considered beneficial in terms of clinical outcomes and are deemed safe to use, and have therefore gained approval for the indication of long-term stroke prevention in patients with atrial fibrillation in several countries – for instance throughout the European Union and in the United States (EMA, 2017d, FDA, 2016). Consequently, recent updates of many clinical guidelines for stroke prevention in AF patients now include one or more DOACs in addition to warfarin.

The European Society of Cardiology for example recommends anticoagulant treatment in patients with non-valvular atrial fibrillation and at least one risk factor for stroke (CHA_2DS_2-VASc score ≥ 1); the decision between warfarin and a DOAC is made dependent on patient's characteristics and preferences. DOACs are in general favoured over warfarin due to their convenience, but neither one is specifically

recommended in any given situation considering the scarcity of information available (Camm et al., 2012). Nevertheless, for patients with valvular forms of atrial fibrillation, VKAs are the drugs of choice. Antiplatelet therapy is not recommended, and should in any case only be considered when patients either refuse anticoagulation, or contraindications other than an elevated risk of bleeding exist (ibid).

In the UK, guidelines issued by NICE recommend uptake of anticoagulation for patients with a CHA_2DS_2-VASc score of ≥ 2 with any OAC, depending on patients' clinical features and preferences. Aspirin monotherapy should not be used for stroke prevention in AF patients (NICE, 2014a). By contrast, the Scottish Intercollegiate Guidelines Network (SIGN) guideline for stroke prevention in patients with AF recommends treatment at a CHA_2DS_2-VASc scores of ≥ 1 for men or ≥ 2 for women with either warfarin or a DOAC; although warfarin is favoured over DOACs due to limited experience and the lack of specific antidotes, DOACs are considered to be valid alternatives (SIGN, 2014). The use of rivaroxaban is however restricted to patients with poor INR control and/or allergy to or intolerable side-effects from warfarin (SMC, 2017a). Hence, status of INR control as well as patients' preferences should be taken into consideration when deciding about a specific anticoagulant drug. Similar to European guidelines, antiplatelet therapy should only be initiated when OACs have been declined by the patient (SIGN, 2014).

For use in the US, a guideline jointly prepared by the American Heart Association and the American College of Cardiology recommends anticoagulation therapy in AF patients with a CHA_2DS_2-VASc score of ≥ 2, and treatment options include warfarin as well as DOACs. The choice of drug depends on an individual patient's values and preferences; in patients with labile INR, DOACs are preferred. In contrast to British guidelines, aspirin may be considered for a CHA_2DS_2-VASc score of 1, as an alternative to no treatment (January et al., 2014).

Despite minor differences, guidelines are comparable between the UK and the US; OAC treatment is recommended for all patients with at least one clinically relevant risk factor for stroke (i.e. a CHA_2DS_2-VASc score of ≥ 2) in both countries, and DOACs are included as alternative to warfarin in all reviewed documents. However, even though guidelines highlight the current lack of relevant information and the weak evidence base for recommending one drug over another, physicians may usually

choose any one drug depending on patients' preferences; patient factors such as comorbidities are rarely directly included in therapeutic decisions (only the US guideline differentiates treatment options for patients based on renal function), and monitoring of DOAC treatment is not routinely required. Hence, due to their limited granularity regarding patient phenotypes, the usefulness of these guidelines may be limited; more evidence to underpin the recommendations made – up-to-date and based on clinical practice – is certainly desirable in order to make better informed treatment decisions and to increase the benefit of treatment for a patient, while reducing potential harm.

Table 2.2 gives a summary of the aforementioned guidelines. Guidelines prepared in other countries within the EU are presumably similar to British guidelines as the statement issued by the European Society of Cardiology most likely acts as a template throughout the region.

Table 2.2: Summary of treatment guidelines for the prevention of stroke in patients with atrial fibrillation

Region	Patient group	Recommendation	Warfarin	DOAC	Comments
EU (European Society of Cardiology) *(Camm et al., 2012)*	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristic and preferences
	CHA_2DS_2-VASc ≥ 1 (male)	Oral anticoagulant should be considered	✓	✓	First choice: DOACs
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	Antiplatelet therapy should be considered when patients refuse OAC therapy or cannot tolerate anticoagulants for reasons other than bleeding
UK (NICE) *(NICE, 2014a)*	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristics and preferences
	CHA_2DS_2-VASc ≥ 1 (male)	Oral anticoagulant should be considered	✓	✓	First choice: none
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	Consider DOACs for patients with labile INRs
Scotland (SIGN) *(SIGN, 2014)*	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristics and preferences
	CHA_2DS_2-VASc ≥ 1 (male) or ≥ 2 (female)	Oral anticoagulant should be considered	✓	✓	First choice: warfarin Antiplatelet therapy should be considered when patients refuse OAC therapy
US (AHA & American College of Cardiology) *(January et al., 2014)*	CHA_2DS_2-VASc = 0	No antithrombotic therapy			Choice of drug based on patient characteristics and preferences
	CHA_2DS_2-VASc = 1	No treatment, OAC, or aspirin may be considered	✓	✓	First choice: none
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	For patients with kidney disease, reduce dosed DOACs can be considered; in end-stage kidney disease, warfarin is the drug of choice
	- Patients with moderate to severe CKD		✓	✓	
	- Patients with end-stage CKD or on haemodialysis		✓		DOACs recommended for patients with labile INRs

AHA – American Heart Association; CKD – chronic kidney disease; DOAC – direct oral anticoagulant; INR – International Normalised Ratio; NICE – National Institute for Health and Care Excellence; OAC – oral anticoagulant; SIGN – Scottish Intercollegiate Guidelines Network

Chapter 3 – Thesis overview

3.1 Thesis rationale

Direct oral anticoagulants have been introduced as an apparently viable alternative therapeutic option to prevent thromboembolic events in patients with atrial fibrillation. They have proven efficacy and safety in clinical trials, and market access has subsequently been granted in several countries, including the UK; as a result, DOACs have been integrated into clinical guidelines such as those issued by the European Society of Cardiology and the Scottish Intercollegiate Guidelines Network (SIGN), among many others – although guidelines remain limited when it comes to differentiating between the various drug options available.

Uptake thus far potentially differs greatly globally depending on health systems, population needs, and available resources, but will presumably increase considerably in most countries in the near future, not least due to demographic developments and the potential prospective availability of additional DOACs, antidotes and monitoring tests. Changing guidelines will most likely have a substantial impact on prescribers' and patients preferences, and consequently on the usage of DOACs; in addition, as treatment with these new drugs is more convenient than with traditional medication, the currently observable reluctance of physicians and patients alike to initiate oral anticoagulant treatment might decrease, potentially impacting overall usage and prescribing patterns. Recent studies have already indicated a substantial shift in prescribing practices, although these findings are thus far limited to a relatively small number of countries where electronic patient records can be analysed on either a regional or a national level, including Australia, Canada, Denmark, Norway, Sweden, and the USA (Alalwan et al., 2017, Baker et al., 2016, Kjerpeseth et al., 2017, Komen et al., 2017, Staerk et al., 2016, Weitz et al., 2015). Overall, knowledge about the current utilisation of DOACs in clinical practice remains scarce; factors influencing actual uptake and usage are largely unknown.

Considering the risks inherent in anticoagulant treatment, additional information is needed in order to provide a sufficient evidence base for adequate treatment decisions for a number of reasons. *First of all*, the effectiveness and safety of DOAC use in real-life patients in contrast to clinical trial participants is unclear. Clinical trials do not perfectly emulate conditions found in clinical practice: real-life patients for example tend to be older and have more comorbidities than patients participating in

clinical trials, with the potential of substantially affecting safety and effectiveness of treatment; and while patients are closely monitored during clinical trials, this is usually not the case in real life – potentially impacting adherence to treatment. *Second*, no direct comparisons between individual DOACs have been performed, and guideline recommendations for one DOAC over another are therefore either absent or vague even though not every DOAC might be suited for every patient, keeping in mind the pharmacological differences between the substances. And *third*, data with regards to long-term treatment outcomes are still scarce (Alamneh et al., 2016, Noseworthy et al., 2017); this information is, however, vital as OAC treatment in patients with AF is potentially life-long.

3.2 Study aims and objectives

The overall aim of this study is to increase the evidence from clinical practice regarding the use of the direct oral anticoagulants dabigatran, rivaroxaban, and apixaban, for the prevention of stroke in patients with AF in Scotland. In order to enable the implementation of adequate and suitable options for anticoagulant treatment and ensure sufficient effectiveness and safety, especially with respect to long-term exposure, the objectives are as follows:

1. To describe the prescribing practice of traditional and new oral anticoagulants over time in Scotland, with regards to
    - Prevalence and incidence;
    - Geography (Health Board, urban/rural location); and
    - Socio-demographic aspects (age, sex, level of deprivation);
2. To evaluate the quality of drug use by determining drug utilisation patterns in AF patients in Scotland, expressed in terms of
    - Adherence;
    - Discontinuation; and
    - Persistence; and
3. To analyse the clinical effectiveness and safety associated with different DOACs in patients with AF in Scotland, including
    - Risk of stroke;
    - Risk of cardiovascular death; and
    - Risk of major bleeding events.

3.3 Study setting

3.3.1 Demographics

The study comprises the entirety of Scotland, defined as a distinct country within the United Kingdom. In 2015, Scotland had an estimated 5.37 million inhabitants, the majority of people were living in urban areas, and the proportion of females was approximately 51.4% (NRS, 2016a). The overall median age was 41 years, but was lower in the big cities of Glasgow, Aberdeen, and Edinburgh, compared to more rural areas; 18% of people were aged 65 years or over (ibid). Similar to most other industrialised countries, the Scottish population is predicted to age significantly over the next decades (NRS, 2016c).

The average life expectancy at birth (born in 2014) was 77.1 years for males and 81.1 years for females. However, there were considerable differences between different regional areas: life expectancy ranged from as low as 73.1 years in Glasgow City for males and 78.7 years in West Dunbartonshire for females, to 80.7/83.9 years in East Dunbartonshire for males and females, respectively. In general, life expectancy for both genders was higher in rural than in large urban areas (NRS, 2016a). The main causes of death were cancer, coronary heart disease, and stroke, together accounting for approximately 47% of all deaths in Scotland in 2015. Although the proportions of deaths due to circulatory diseases have decreased steadily since the 1980s, rates are still considerably higher than in other parts of the UK (NRS, 2016c).

3.3.2 Health System

The Scottish Health System is tax-funded, and services are largely available free at the point of delivery to all inhabitants; prescription fees were abolished in April 2011. Primary as well as secondary health care is provided by the National Health Services (NHS) Scotland, either directly through the Managed Service or through contracting with independent healthcare providers (Steel & Cylus, 2012). In most cases, General Practitioners (GPs) are the first point of contact for health services; while patients can access emergency care through self-referral, access to NHS specialist care requires a referral, usually from a GP (ibid).

NHS Scotland is currently divided into 14 Health Boards, each covering a distinct geographical region as shown in figure 3.1. Health Boards are responsible for

planning and delivering services to their respective populations, with their main functions being strategy development, resource allocation, implementation of local health plans, and performance management. They have wide discretion with respect to their allocated budget, thus local provisions and priorities may differ; however, Health Boards have to ensure "*efficient, effective and accountable governance*" (Steel & Cylus, 2012, p.28), and quality of service delivery is audited regularly (ibid). Health Boards in their current form were introduced in 2001, replacing existing structures including NHS trusts, and have since been amended twice: in 2006, the originally implemented 15th Health Board (Argyll & Clyde) was dissolved, and responsibilities were transferred to the NHS Boards Greater Glasgow & Clyde and Highland; and area boundaries were changed slightly in April 2014 in order to align Health Boards with council boundaries for administrative purposes (ISD Scotland, 2016a, Scottish Government, 2013a). The latter change affected only very few patients though, in contrast to the first change in 2006 (Scottish Government, 2013a). Distinctions are usually made whether 2001, 2006 or 2014 Health Board areas are referred to.

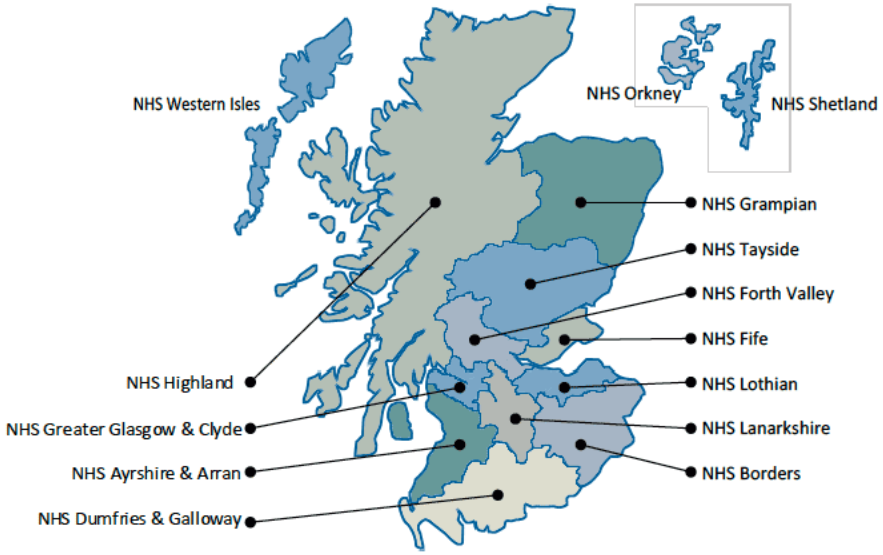


Figure 3.1: NHS Scotland Health Boards as of 2015: Source: (Scottish Government, 2016a)

Population size differs considerably among Health Boards, each covering between approximately 21,700 and 1,150,000 people (Orkney and Greater Glasgow & Clyde, respectively). Patient structures are overall similar, although some rural Health Boards have a higher than average share of elderly populations (NRS, 2016a).

3.4 Study design

This observational study has been designed as a retrospective cohort study, using linked, routinely collected administrative data (see chapter 4); the study period spans from January 2009 to December 2015, based on data availability. Two general study cohorts have been chosen, based on the study aims and objectives.

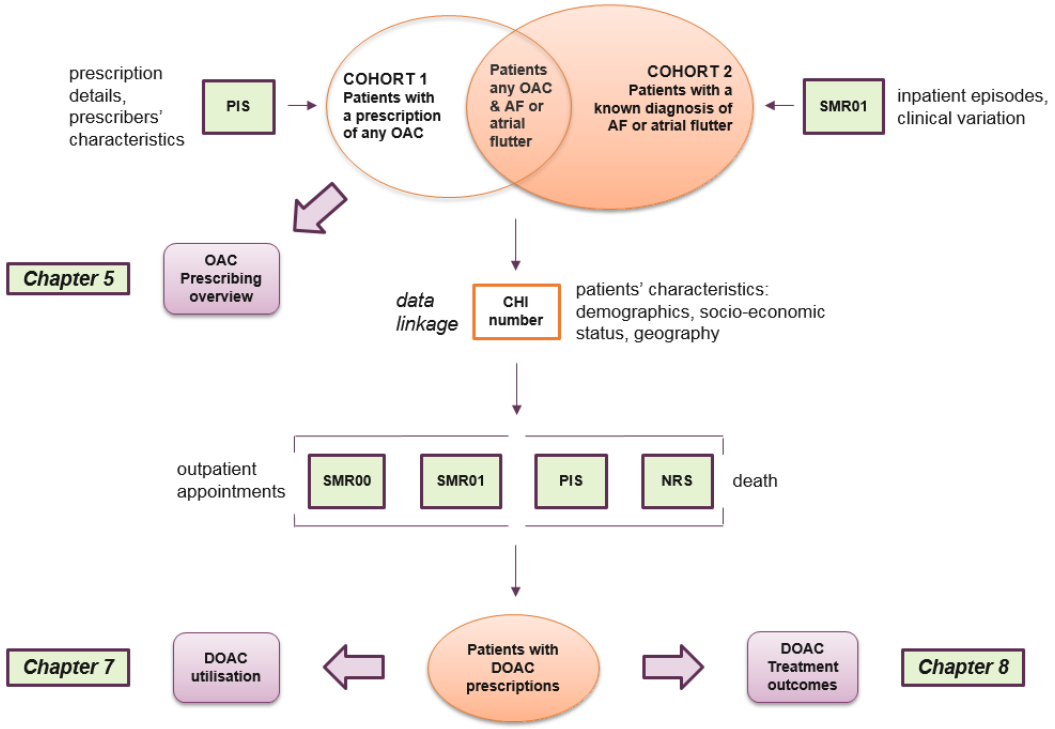
Cohort 1 covers all patients who have received at least one prescription for any oral anticoagulant between January 2009 and December 2015, and have been identified through prescription records by means of the specific drug code (02.08.02.) for oral anticoagulants as used in the BNF prior to edition 70 (Joint Formulary Committee, 2015a). Cohort 1 thus represents patients with a variety of conditions: although atrial fibrillation is the most common indication for long-term treatment with oral anticoagulants, patients with heart valve replacements, pulmonary embolism, and recurrent DVTs are also subject to prolonged treatment. In addition, a range of patients without a long-term indication may be treated with OACs temporarily, for instance following knee or hip replacement surgery (Lip & Shantsila, 2013).

Cohort 2 in contrast captures patients who have been diagnosed with AF while being in hospital between January 1997 and December 2015; or who have been diagnosed at any point prior to December 31st 2015, and have subsequently been admitted to hospital between January 1997 and December 2015 – either due to their condition, or for other reasons – and the presence of AF has been recorded in their hospital discharge record. These patients have been identified through hospital inpatient records by means of the disease specific code for atrial fibrillation (I48) as used within the current WHO framework of identifying diseases (WHO, 2016).

Patients with atrial fibrillation are likely to have been treated with oral anticoagulants, and patients being treated with oral anticoagulants are likely to have been diagnosed with atrial fibrillation – therefore, many patients of interest are bound to appear in both hospital inpatient files and prescription records. However, the cohorts are not identical: AF patients with an inpatient hospital episode who have not been treated with any OAC, or where medication was only administered in hospital but not continued in primary care after discharge, are included in cohort 2 but not cohort 1; and patients who received a prescription for any OAC in primary care for reasons

other than AF, or have been diagnosed with AF but never admitted to hospital, are included in cohort 1 but not cohort 2. Nevertheless, cohorts overlap substantially.

After identification of cohorts, additional information has been gathered for every member of each cohort by retrieving and subsequently linking electronic patient files covering prescription details, inpatient episodes, and outpatient clinical attendances, utilising Community Health Index (CHI) numbers – a unique patient identifier available in electronic patient records in Scotland. An overview of the study design is presented in figure 3.2; data sources are described in detail in section 4.1.



AF – atrial fibrillation; CHI – Community Health Index; DOAC – direct oral anticoagulant; NRS – National Records of Scotland; OAC – oral anticoagulant; PIS – Prescribing Information System; SMR – Scottish Morbidity Records

Figure 3.2: Study design

While chapter 5 gives an overview of OAC prescribing in Scotland regardless of indication and, therefore, includes all patients who are members of cohort 1, the specific study population as used in subsequent analyses (utilisation, chapter 7; and treatment outcomes, chapter 8) comprises patients who are part of both cohorts – i.e. patients with a diagnosis of AF who received at least one prescription for any OAC.

As both these studies focus on direct oral anticoagulants rather than all OCAs available, inclusion of patients has further been refined to those with at least one prescription for any DOAC, as described in chapter 6.

3.5 Thesis outline

Chapter 5 outlines the changes in prescribing of oral anticoagulants in Scotland over time since DOACs have been introduced, improving our knowledge about their uptake and enabling comparisons to prescribing trends in other countries. Chapter 6 gives an overview of the baseline characteristics of patients with AF initiating DOAC treatment in Scotland, in comparison to patients in other countries as well as opposed to those enrolled in the three seminal clinical trials; a detailed description of the patients treated with DOACs in real-life is essential for understanding differences in treatment outcomes which may be observed between different countries, for instance. The two subsequent chapters then detail the utilisation of DOACs and the outcomes of DOAC treatment in the patient cohort introduced in chapter 6, respectively; while chapter 7 gives insights into how patients actually use their medication, chapter 8 presents the risks of thromboembolic events as well as major bleeding in patients taking DOACs.

In addition to providing new insights into the use of DOACs in routine clinical practice, this study also features substantial methodological aspects. On the one hand, the drug utilisation study detailed in chapter 7 is an exemplary case-study of combining a sound theoretical framework with well-defined and documented measurements, intended to encourage standardisation of drug utilisation research by highlighting the importance of analytical methods in pharmacoepidemiology studies; on the other hand, the study outlined in chapter 8 is an approach to using results obtained from a drug utilisation study in order to advance the statistical analysis of drug treatment outcomes.

Chapter 4 – Data sources and data management

Chapter four deals with the technical features of the study by describing the data used, including the data sources and available variables, and discusses aspects of the data management. More detailed descriptions of the methodology applied to individual parts of the analysis – i.e. drug utilisation and treatment outcomes – can be found in chapters 7 and 8, respectively; the selection of the study population used for these analyses is detailed in chapter 6 (patient baseline).

4.1 Data sources

The data available for this study has been extracted from five different data sources: the Community Health Index (CHI); the Prescribing Information System (PIS); Scottish Morbidity Records General/Acute Inpatient and Day Case dataset (SMR01), and Scottish Morbidity Records Outpatient Attendance dataset (SMR00); and National Records of Scotland (NRS).

4.1.1 Community Health Index (CHI)

The Community Health Index (CHI) is a population register, consisting of eight regional databases linked by a search index. Oversight of the CHI system lies with the Chief Medical Office, although data controllers are individual Health Boards (Scottish Government, 2013b). CHI contains demographic information about every person either born in Scotland or registered with a Scottish GP practice; the CHI number, a 10-digit code containing date of birth and an indicator for gender, serves as a unique patient identifier within the health system (ISD Scotland, 2017).

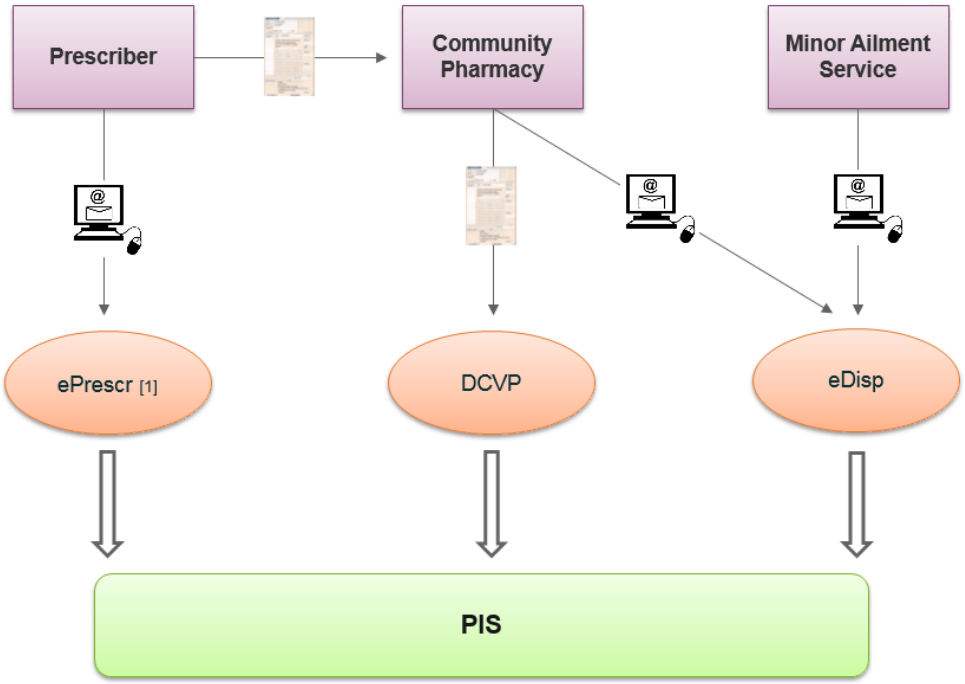
First implemented during the 1970s, CHI has originally been designed to assess immunisation and screening programmes. Its usage is now mandatory in all clinical communications within NHS Scotland, and represents a vital part of the Scottish Government's eHealth strategy (NHS Scotland, 2015, Scottish Government, 2013b). The use of CHI numbers across all parts of the health system enables the tracking of individual patients, and facilitates the linkage of electronic patient records. Although present in the majority of patient records, availability of CHI might still differ depending on the record in question – CHI coverage on drug prescription forms for example varies according to the type of health care professional prescribing (Alvarez-Madrazo et al., 2016).

4.1.2 Prescribing Information System (PIS)

The Scottish Prescribing Information System (PIS) was created in 1993 for payment purposes and combines information about the drugs as well as the prescriber, the dispenser, and the costs, for all prescriptions issued and dispensed in the community in Scotland (ADLS, 2016, ISD Scotland, 2016b).

Prescription information contained in PIS is based on the drug categorisation system used in the British National Formulary (BNF) prior to BNF version 70, released in September 2015; the BNF is currently available in its 74th edition (valid September 2017 – March 2018), and has undergone considerable changes in methodology and structure since 2015 (Joint Formulary Committee, 2015a, Ronning & McTaggart, 2016). Prior to BNF 70, medication was categorised according to disease/affected organ system (chapter), drug class (section), and mechanism of action (subsection). While the 15 original chapters each covered a distinct diagnostic aspect, additional pseudo-chapters served as a catch-all for unclassified drugs and non-drug items, for instance dressings (see also appendix II). Since BNF 70, content within chapters has been restructured, centring on treatment summaries and drug monographs while removing section numbering; drugs are now organised by therapeutic use and drug classification (Joint Formulary Committee, 2015b). The BNF is not based on the ATC system, and therefore does not contain ATC codes.

Data contained in PIS is gathered from three different sources as depicted in figure 4.1, and stored in a data warehouse for further usage. The major source is the Data Capture Validation Pricing system (DCVP), which is the basis for the remuneration of prescription items. DCVP messages are generated by scanning paper prescription forms collected through community pharmacies; the majority of these originate from general practitioners, although a range of other health care professionals, for instance nurses or pharmacists, may also issue prescriptions. In addition to paper prescriptions, GPs use the ePrescribing system to generate an electronic record of each prescription, while community pharmacies have the option to use the eDispensing system to create electronic records of all dispensations. Electronic prescriptions are uploaded onto the secure ePharmacy Message store, readily available for download in community pharmacies via barcodes; eDispensing messages can then be submitted by the pharmacy to support reimbursement claims. (Alvarez-Madrazo et al., 2016).



DCVP – Data capture validation pricing; eDisp – electronic dispensing; ePrescr – electronic prescribing; PIS – Prescribing Information System

[1] General Practitioners only

Figure 4.1: Prescribing Information System: prescribing, dispensing, and reimbursement data

The ePrescribing and eDispensing systems are part of the Scottish eHealth strategy, aimed at introducing an electronic prescribing and medicine administration service to improve medicines safety (NHS Scotland, 2015). eDispensing also covers drugs dispensed through the minor ailment service (MAS) (Alvarez-Madrazo et al., 2016). MAS is a service provided by community pharmacies to deal with minor conditions where no need to consult a medical doctor arises, and commonly includes the dispensing of non-prescription drugs. MAS is, however, only available for patients registered with a GP in Scotland who are exempt from NHS fees (e.g. children, people aged 60 years or over, or on income support) (NHS Scotland, 2016).

Starting in 2004, CHI data has gradually been added to PIS records. Since April 2009, CHI coverage in PIS has been deemed sufficiently accurate and complete to enable patient-level research: as CHI coverage now regularly exceeds 95% (i.e. at least 95% of prescribed items are associated with a valid CHI number), it can reliably be linked with other electronic health records (Alvarez-Madrazo et al., 2016)

PIS data has been used for analytical purposes by the Information Services Division (ISD) of the NHS National Services Scotland (NSS) for many years, chiefly to generate quarterly dispenser remuneration reports. Patient level analyses of specific drugs or indications (e.g. antibiotics, smoking cessation), mainly resulting in scheduled statistical publication, are also being conducted since they were made possible by sufficient CHI completeness. In 2014, first attempts have been made to extract dose instructions from prescription forms and transform free text into structured data, which will increasingly be accessible for analysis (Alvarez-Madrazo et al., 2016); the availability of dose instructions will further enhance the usability of PIS for research, particularly in areas where as precise drug exposure data as possible is required.

4.1.3 Scottish Morbidity Records (SMR)

The Scottish Morbidity Records (SMR) are a series of datasets collecting information about diagnoses and treatment of diseases, gathered through ISD on behalf of the NHS NSS in primary and secondary care (ADLS, 2016). Of the five currently existing datasets, two have been available for this study: the "General / Acute inpatient and day case" dataset (SMR01), and the "Outpatient attendance" dataset (SMR00)[1]. Inpatient data has been collected since 1960, and data is now readily available from 1981 onwards; outpatient data collection started in 1991, with data being routinely available since 1997 (ADLS, 2016, ISD Scotland, 2016b).

SMR00 and SMR01 contain patient level data on appointments in outpatient clinics and inpatient/day care discharge episodes, respectively. Apart from patient identifiers and demographic details, data about patient conditions and/or operations, episode management, and general clinic information are recorded (ISD Scotland, 2016b). Since 1996, International Classification of Disease codes, 10th edition (ICD-10), are used in both datasets to record diagnostic details, while Office of Population Censuses and Surveys procedural codes, 4th revision (OPCS-4), are used to record surgical procedures (ISD Scotland, 2010c). Briefly, the current ICD system has been developed by the WHO based on earlier disease classification systems since 1948, and is now the global standard for reporting on morbidity and mortality; ICD-10 was

[1] The other three datasets are: SMR02 – Maternity Inpatient and Day Case; SMR04 – Mental Health Inpatient and Day Case; SMR06 – Scottish Cancer Registry

endorsed by the World Health Assembly in 1990, and introduced an alphanumerical coding system, classifying conditions based on affected organ or system (e.g. skin, cardiovascular system) and/or disease aetiology (e.g. infections, injuries) (WHO, 2016). In contrast, the OPCS coding system is maintained by the NHS, and its 4th revision was published in 1987; OPCS-4 codes are also alphanumerical, and enable the identification of surgical procedures and interventions (ISD Scotland, 2010d).

SMR datasets are mainly utilised to produce routine statistical publications in order to review and assess health service performance in Scotland. Nevertheless, the data is also available for research, subject to application and anonymisation; this includes record linkages (ISD Scotland, 2016b). As CHI numbers are available in all SMR records, they can easily be linked to each other as well as to other datasets containing CHI numbers, such as PIS and National Records of Scotland (ibid).

4.1.4 National Records of Scotland (NRS)

National Records of Scotland (NRS) is the Scottish government department responsible for the registration of life events such as births, deaths, and marriages; for the archiving and preservation of these information; and for the census. Although record keeping has a long tradition in Scotland – birth and marriage records were first kept in an official register more than four centuries ago – NRS itself was only established in 2011, taking over the roles of the former General Register Office for Scotland and the National Archives of Scotland (NRS, 2016b).

The main data source is the civil registration system, which covers every regular resident of Scotland; additional data, for instance about migration, is collected through the National Health Service Central Register and the Community Health Index. Therefore, NRS records can easily be linked via CHI to other patient records originating from NHS Scotland services (NRS, 2016b).

All existing records are stored in Edinburgh and can potentially be accessed for research purposes, subject to enquiry and anonymisation. NRS itself also conducts statistical analysis of demographic data and regularly publishes scheduled reports and updates, as well as commissioned research findings (NRS, 2016b).

4.2 Study data overview

A wide range of variables were secured for this study, including socio-demographic data, prescription details, and medical information. An extract from CHI, providing socio-demographic information for all members of cohorts 1 and 2, consisted of 11 variables and 467,509 observations. The complete PIS extract as requested for this study was the largest of the datasets, comprising 59 prescription-related variables and more than 118.6 million observations – capturing all prescriptions issued to patients included in both cohorts between 2009 and 2015, of which approximately 5.7 million were prescriptions for any oral anticoagulant. The SMR00/01 extracts, with 38 and 58 variables respectively, together accounted for an additional 15.3 million observations (covering all recorded inpatient episodes and outpatient appointments for every cohort member between 1997 and 2015), while the NRS extract was the smallest of the datasets with 30 variables, containing details with regards to 223,771 deaths since 1997 – of which 119,274 were recorded during the study period.

However, many of the variables were duplicates, reducing the total number of unique variables considerably. In addition, not all available variables have been used for analysis, either due to data quality issues (mostly the extent of missing values) or usefulness (e.g. similar information expressed in slightly different ways; or information irrelevant to the purpose of this study). The main variables (including data formats and names as used for analysis after data cleaning, as detailed in section 4.3.2) are described in the following section.

4.2.1 Socio-demographic information

Socio-demographic background data originally stemmed from various data sets, mainly CHI, PIS, and NRS. It comprised information about patient date of birth (*pat_dob*), sex (*pat_sex*), and place of residence, as well as the level of deprivation; additional information about ethnicity, marital status, and socio-economic status was available for a subset of patients. While patient age at time of prescription (*pat_age_prescr*) was a numerical variable, derived from date of birth, all other socio-demographic variables were categorical and readily available in the datasets; patient sex was a simple binary variable (male, female).

4.2.1.1 Geographical data

Geographical information comprised two different variables to describe patients' locations: the regional Health Board; and an urban/rural area categorisation, which is based on number of inhabitants and distance to the nearest urban centre.

Health Board of residence for patients (*pat_HB_PIS*) was coded based on current, 2014 area boundaries, using a nine-digit code (see figure 4.2 for details). The codes S08200001 to S08200004 represent patients either living in England, Wales, or Northern Ireland; not having a permanent address; with unknown Health Boards of residence; or living outside the UK.

To identify the urban/rural classification of geographical areas (*pat_ur_PIS*), a single digit code was used, as presented in figure 4.2. This code is based on the 8-fold urban/rural classification scheme as developed and maintained by the Scottish Government (Scottish Government, 2014).

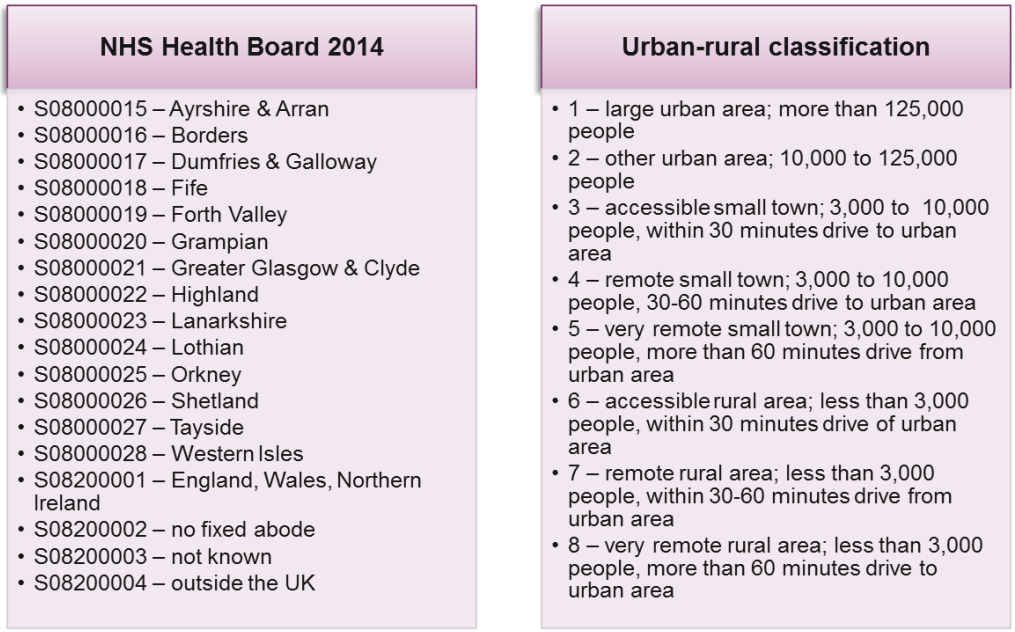


Figure 4.2: NHS Scotland Health Boards and urban-rural classification system, codes and description

4.2.1.2 Deprivation Index

Deprivation, meaning the lack of something considered of necessity in a society, is measured in this context by means of the Scottish Index of Multiple Deprivation (SIMD). SIMD was introduced in 1999 and is a geographical index, mapping out area

differences rather than differences between individuals. SIMD includes indicators across seven domains: income, employment, education, housing, health, crime, and access (Scottish Government, 2017). The index is updated regularly, in order to take into account changes within the social system as well as in population and/or data zone boundaries, with the latest version, SIMD 2016, having been published in August 2016. The ordering of the deprivation categories was reversed in 2009; therefore, different editions of SIMD are not identical (ibid). An overview of the indicators of SIMD as used in this study (SIMD 2012) can be found in appendix II.

Patient deprivation levels, expressed as SIMD scores, are coded in descending order, starting with the highest levels of deprivation – meaning that a coding of 1 characterises the most deprived areas, while a coding of 5 and 10 for quintiles and deciles respectively signifies the least deprived areas. Depending on the variable used, every category therefore represents either 10% (*simd10_PIS*) or 20% (*simd5_PIS*) of the population.

4.2.1.3 Patient ethnicity, marital status, and socio-economic status

Statements about ethnicity, marital status, and occupation/socio-economic group are covered in the census which is conducted every 10 years, the most recent one having taken place in Scotland in 2011 (NRS, 2017c). These variables are included in those vital events datasets which are – at least partially – derived from census information, such as death records; therefore, these information can be found in NRS.

Ethnicity and marital status can also be recorded in SMR datasets (ISD Scotland, 2016b); declarations are however not mandatory, resulting in considerable percentages of missing data – in SMR01 for example, marital status was missing for 8.4% of patients, while information regarding ethnicity was missing for 79.3% of patients. In addition, the reliability of information available is questionable: ethnicity is not consistently defined across services, potentially affecting the way ethnicity is coded (NHS National Services Scotland, 2017); and the currency of marital status and socio-economic group is uncertain as records might not be updated regularly.

Due to these issues with respect to completeness, accuracy, and reliability of data, variables indicating patient ethnicity, marital status, and socio-economic status have not been included in the analyses for this project.

4.2.2 Prescription details

Prescription details can be divided into two sections: information about the prescribed item, including details about the drug itself as well as dates and quantities; and instructions for drug use. All information with regards to individual prescriptions available for this study originated from PIS, and have primarily been sourced via the DCVP system; additional information, relating to dose instructions, have been added to DOAC prescriptions from the ePrescribing system where possible. eDispensing data was not available.

4.2.2.1 Prescribed item

Along with BNF codes and descriptions of the relevant chapter, section, and subsection, PIS contains drug names including the term for the chemical substance and the prescribed name (which can be either a generic name or the brand name), as well as information about prescribed strength/unit, and drug formulation. To simplify the identification of drugs prescribed to patients, only the approved name – which is the generic name of a drug, based on the International Non-proprietary Names (INN) system[2] (WHO, 2017b) – has been used (*item_name*); this was a text variable. Prescribed strength is a combined numeric/text variable, comprising the amount of drug contained in one dose and an accompanying unit such as mg (solid forms) or ml (liquid forms); this variable has been split into its respective parts, and only the quantitative aspect (*item_dose*) retained for further use. Drug formulation was a text variable detailing its physical properties and/or indicating its route of administration (e.g. capsule, tablet, or cream), which has not been used for analyses as all drugs of interest in this study are solid, oral formulations.

Prescription dates (*date_prescr*) in PIS were real dates wherever ePrescribing messages were submitted by the prescriber (95.7% of DOAC prescription dates in this study were real dates), while dispensing dates available for this study were default dates only (defaulted to the payment date, i.e. last day of each month). All dates were recorded in the format *yyyy-mm-dd*. Prescribed and dispensed quantities

[2] A globally recognised system for uniquely identifying pharmaceutical substances, agreed upon by the World Health Assembly in 1950 and in use since 1953.

(*quant_prescr, quant_disp*) were numeric variables, readily available in the dataset; all prescriptions captured in PIS have been dispensed.

4.2.2.2 Dose instructions

Dose instructions available for this study represented free text information as conveyed by the prescriber, captured through ePrescribing messages in PIS. In addition to the original text variable (*dose_instructions*), a variety of information has been extracted by ISD through national language processing (Nangle et al., 2017), and made readily available in the dataset: the number of tablets/capsules to be taken (*amount.min, amount.max*); the frequency of drug intake (*freq.Min, freq.Max*) with accompanying unit (*freq.unit*), such as per day or per week; and flags indicating use as directed or required (*as.dir, as.req*).

As treatment with DOACs follows clearly structured schedules and is in general not subject to day-to-day variation, only the variables indicating the minimum amount of drug to be taken (*amount.min*) and the minimum frequency of drug intake (*freq.Min*) have been used in this study.

4.2.3 Clinical conditions and procedures

Data pertaining to patients' medical conditions were obtained from three sources: SMR01 and SMR00; and NRS. While SMR records contain information about a patient's health conditions known and considered relevant at time of discharge from hospital regardless of disease area, severity, and chronicity, NRS contains data regarding cause of death.

Diagnostic codes, available as character variables, included the main diagnosis, as well as up to five additional diagnoses, in SMR01; and up to four referral reasons in SMR00 (SMR01: *main_con, ocon1, ocon2, ocon3, ocon4, ocon5*; SMR00: *ref_reason1, ref_reason2, ref_reason3, ref_reason4*). In addition, two surgery codes indicated procedures undertaken in hospital (*main_op_a, main_op_b*). NRS provided main (underlying) cause of death as well as up to ten secondary causes (*main_cause_death, ocause_death1* to *ocause_death10*). For every event, accompanying dates – either admission date, date of outpatient appointment, or date of death – were available in the format *yyyy-mm-dd* (SMR01: *adm_date;* SMR00: *clin_date*; NRS: *pat_dod*).

4.3 Data management

4.3.1 Data access

In Scotland, analyses of confidential, patient-level data has been enabled by the implementation of a network of Safe Havens, providing a safe and secure environment and protecting the integrity and confidentiality of all data (NHS Scotland, 2017).

As using the National Safe Haven was an integral part of the study's information governance (see section 4.4 for details), the data used for this study was stored securely on a remote server hosted by NHS National Services Scotland, and data remained under NHS control throughout the study period. Access was granted via a virtual private network (VPN) connection; the data access procedure was password protected, and access was limited to computers with an accredited IP address, which included university-based machines.

The National Safe Haven is a closed system from a user's point of view, meaning that no data can be up- or downloaded. As this restriction includes computer software, the Safe Haven offers a range of software to be used; raw data was therefore provided in the form of .csv (comma delimited values) files – generic spreadsheet files which can be used with a range of commonly used analytical software such as R, SPSS, and Stata. The raw data files were stored in a read-only folder (*Linked_Data*) within the secure environment, and copies of the files placed in an editable research folder (*Research/Tanja*) were required to manipulate data. Research outputs needed to be placed in a separate folder (*Result/Tanja*), and were only released upon request after completion of a review of the results, conducted based on a statistical disclosure protocol (ISD Scotland, 2010a).

All data manipulation and analysis was conducted using the R statistical programming language, version 3.4.0 (R Core Team, 2016); Microsoft Excel (version 2013) was used to collect results and create additional graphs.

4.3.2 Data preparation

Although the quality of data stored in administrative databases such as PIS is in general high, especially when the data is used for statistical and other research on a

regular basis, some preparatory data manipulations were required. Most importantly, a few variables needed to be reformatted into a specific format so as to enable valid analysis, and others required some degree of recoding (mostly pertaining missing values); in addition, several variables have been renamed – for easier usage, but also in order to support a more straightforward combination of individual datasets.

4.3.2.1 Reformatting of variables

Reformatting of variables was necessary due to the raw data being provided as .csv files, which were imported into R for further analysis. As .csv files store information as plain text, they have some inherent limitations with regards to the data they contain; and by default, character variables (also called string variables; variables that contain anything other than numbers, e.g. letters or special characters) are converted into factor variables (also referred to as categorical variables) when imported into R. Hence, reformatting was required mainly for variables that were converted into factor variables but were supposed to be either numeric or character variables; and for numeric variables which should have been factor variables, or dates. Table 4.1 contains the major examples.

Table 4.1: Reformatting of variables

After importing file	After reformatting	Variables
Factor	***Numeric***	Patient ID, drug dose
Factor	***Character***	Drug name, hospital admission reason, cause of death
Numeric	***Factor***	Patient sex, urban/rural classification, level of deprivation
Numeric	***Date***	Patient date of birth, prescription date, hospital admission date, date of death

4.3.2.2 Recoding of variables

Recoding of variables was mainly necessary for missing data, as a range of divergent signifiers have been used across the different data sets – including spaces and special characters. To ensure consistency and facilitate smooth data analysis, all missing values were recoded as "*NA*" ("not available"), the regular indicator for missing data in R – however, where BNF chapter, section, or subsection codes relevant to the study where missing, these were added manually.

In addition, some recoding of variables based on dose instructions (see also section 4.2.2.2) was mandated as data had occasionally been translated incorrectly; these errors were discovered while manually reviewing inconsistencies in dosing schemes (when comparing daily drug exposure calculated based on BNF instructions to daily drug exposure based on dose instructions). In the rare cases (n=3) where dose instructions as issued by the prescriber appeared to be erroneous (an assumption made based on resulting daily drug doses that exceeded the normal dose more than 3-fold), minimum daily amount and frequency were changed to match the standard dosing as recommended in the BNF.

4.3.3 Data quality

4.3.3.1 Data availability

The study period spanned from January 2009 to December 2015, based on data availability and administrative considerations: PIS record linkage using CHI numbers was not reasonably possible prior to 2009 due to insufficient CHI coverage (ISD Scotland, 2016b), and the end of follow-up was determined by the data available when extraction for this study was requested. However, due to the necessity to gather information about patients' prior medical history, the data extraction periods for SMR00 and SMR01 date back to 1997; as of 1997, data coding (e.g. ICD10 codes) and record formatting have been consistent within the individual databases, thus making this the earliest possible date for easy access and linkage of records.

PIS records covering the entire study period were available for every patient with at least one prescription for any OAC issued between January 2009 and December 2015; as well as for all patients with a diagnosis of AF confirmed in hospital any time between January 1997 and December 2015. These records included prescription details for all oral anticoagulants prescribed during this time period, but also cover additional drugs prescribed and dispensed in primary care. SMR00 and SMR01 records covering the time period from January 1997 to December 2015 were available for all patients with a confirmed diagnosis of AF as recorded in hospital discharge records during this time period, as well as for every patient who received at least one prescription for any OAC between January 2009 and December 2015. Death records including date and cause of death were available for every patient who died in Scotland between January 1997 and December 2015 and had a diagnosis of AF made or confirmed in a hospital any time between January 1997 and December 2015,

and/or had received at least one prescription for any OAC between January 2009 and December 2015.

4.3.3.2 Data completeness and accuracy

All residents in Scotland are covered by the NHS, and privately payed for prescriptions – which would not be captured by PIS – are therefore uncommon, indicating that data can be considered to be complete with regards to prescriptions issued for prescription-only drugs in primary care. Due to the original purpose of PIS and the means of data collection, records however do not cover medication dispensed in hospitals, or delivered through alternative distribution channels other than community pharmacies; most over-the-counter (OTC) drugs are also not included, with the exception of items dispensed through MAS (Alvarez-Madrazo et al., 2016). As the main purpose of PIS is to provide a basis for payment to community pharmacies, data contained in the database has been validated and is thus deemed to be of high accuracy (Alvarez-Madrazo et al., 2016). Changes in drug classification and/or coding in the BNF have not been adopted by PIS in order to ensure consistency of data coding over time (Ronning & McTaggart, 2016).

Similar to PIS, data completeness of SMR01 is high, as this dataset has been used to plan hospital finance management since 1989; in contrast, completeness of SMR00 data depends on an outpatient clinic's structure (consultant led vs nurse led) because the dataset was initially designed to cover consultants only (ADLS, 2016). Data quality of all SMR data sets is evaluated on an ongoing basis by the ISD Data Quality Assessment team, ensuring that datasets are accurate and consistent (ISDScotland, 2010d); a recent data quality assurance assessment concluded that SMR01 data is overall accurate and of high quality (ISD Scotland, 2015).

NRS death records are deemed complete and accurate due to implemented data validation procedures (NRS, 2017b).

4.3.3.3 Missing data

While a number of variables across the datasets did not have any values missing (e.g. patient date of birth and sex were available for all members of both cohorts; prescription date, prescribed item name and dispensed quantity were complete for all OAC prescriptions; and dates of hospital admissions/outpatient appointments

were complete for all records available for the study), most variables displayed a varying degree of completeness. The proportions of missing values within the datasets for the main variables are listed in table 4.2.

Table 4.2: Percentages of missing data for main variables

Variable	Name	Source	% data missing	
Patient Health Board of residence	*pat_HB_PIS*	PIS	0.7	[1]
Patient urban rural classification	*pat_ur_PIS*	PIS	0.7	[1]
Patient deprivation	*simd5_PIS*	PIS	0.7	[1]
Item strength (all OAC)	*item_dose*	PIS	0.2	[2]
Dose instructions (all OAC)	*dose_instructions*	PIS	9.8	[2]
Number of tablets / capsules to be taken (all OAC)	*amount.min*	PIS	56.3	[2]
Frequency of drug intake (all OAC)	*freq.Min*	PIS	85.4	[2]
Item strength (DOAC)	*item_dose*	PIS	0	[3]
Dose instructions (DOAC)	*dose_instructions*	PIS	4.2	[3]
Number of tablets / capsules to be taken (DOAC)	*amount.min*	PIS	11.6	[3]
Frequency of drug intake (DOAC)	*freq.Min*	PIS	9.3	[3]
Main condition	*main_con*	SMR1	0	[4]
Other conditions	*ocon1*	SMR1	25.5	[4]
	ocon2	SMR1	44.1	[4]
	ocon3	SMR1	58.2	[4]
	ocon4	SMR1	69.9	[4]
	ocon5	SMR1	79.9	[4]
Referral reasons	*ref_reason1*	SMR0	99.7	[4]
	ref_reason2	SMR0	>99.9	[4]
	ref_reason3	SMR0	>99.9	[4]
	ref_reason4	SMR0	>99.9	[4]

[1] Of all patients with at least one prescription for any OAC; [2] of all OAC prescriptions – includes prescriptions for INR test strips; [3] of all DOAC prescriptions; [4] of all records available for all patients with at least one prescription for any OAC

4.4 Ethical considerations

Adherence to the principals of ethical conduct, as detailed in a range of publications on all levels from university departments to international organisations, is essential in biomedical research, including pharmacoepidemiology. With the adoption of the

Declaration of Helsinki in 1964 (WMA, 2016), the "[…] *health, well-being and rights* […]" (ibid, paragraph 4) of patients participating in research has come into focus, and a clear, well-defined set of prerequisites and requirements for clinical as well as behavioural studies has been introduced since – the most apparent one being the almost universal necessity to acquire informed consent from participants in research projects (Beauchamp & Childress, 2009). Nevertheless, not all studies to be conducted nowadays fit into the research frame envisioned in 1964, resulting in a variety of additional frameworks, codes of conduct, and ethical approval procedures – depending on the topic and subjects of the study, the methodology applied, and the context.

Although this particular project did not necessitate the direct involvement of any participants but instead relied on the usage of existing data, ethical aspects still had to be considered, albeit to a different degree than in studies directly involving patients; while the direct harm potentially done to patients with this study is negligible, adverse effects caused by inadequate data handling are conceivable. Therefore, data safety, patient anonymity, and confidentiality are crucial topics for this type of study – not only enshrined in the university's code of conduct (University of Strathclyde, 2015) but also subject to a range of laws, including the Data Protection Act (UK Government, 1998). In order to avoid any negative consequences potentially arising from this study due to its methodology, mandated precautionary measures based on information governance have been taken; separate formal ethical approval was however not required. The consideration of ethical aspects is now an integrated part of the approval process for this kind of study in Scotland (see also section 4.4.2 for details regarding project approval).

4.4.1 Information governance

Information governance is a framework closely related to research ethics, albeit with a focus on research involving non-consented, confidential patient data. As many studies relying solely on already existing data – and thus not involving direct contact with patients – do not require ethical approval, the principles of information governance have been introduced in Scotland to ensure that research is conducted ethically and in line with current legislation. More specifically, information governance procedures are aimed at guaranteeing that data is obtained legally, stored securely, used scientifically for public benefits, and shared appropriately (ISD Scotland, 2010b).

The Data Protection Act 1998 mandates the involvement of data controllers, tasked with overseeing the lawful use of data; in Scotland, Caldicott Guardians and the Public Benefit and Privacy Panel (PBPP) for Health and Social Care fulfil these functions on a regional and national level, respectively (Pavis & Morris, 2015, Scottish Government, 2016b). Applications for the use of NHS data, addressed to the appropriate data custodian, mandate detailed statements about the purpose, methodology, and scope of the project, including justifications for the information requested and the linkage proposed, as well as declarations about the personnel involved; applications are granted only if proposals show a clear public benefit, every researcher involved in a project provides evidence of successful completion of approved training in information governance, and appropriate measures have been taken to safeguard the data (Pavis & Morris, 2015).

4.4.2 Project approval

Approval for this project has been granted in two separate instances, due to a request to obtain a data update mid-way through the study. The initial application was submitted to the Privacy Advisory Committee (PAC), predecessor to the PBPP (NHS National Services Scotland, 2016), in September 2014 (NSS study number XRB14086); data linkage and release were approved in October 2014, and data – comprising an initial study period from January 2009 to June 2014 – was subsequently made available by April 2015. A PBPP application for a data update was submitted in May 2016 (NSS study number XRB14086 eDRIS-1516-0514), and approved in July 2016; the data update, extending the study period to December 2015, was made fully available by March 2017. PAC and PBPP notifications of approval can be found in appendix I.

Prior to approval, completion of an accredited course in information governance was required; the certificates can be found in appendix I. In order to assure compliance with ethical as well as legal requirements, data was only accessible using the national Safe Haven, as explained previously in section 4.3.1 (ISD Scotland, 2010g).

Chapter 5 – Prescribing of oral anticoagulants in Scotland 2009 – 2015

Chapter 5 is intended to give an overview of how oral anticoagulants were prescribed in Scotland during the study period, and highlights changes in prescribing practice over time. In order to comprehensively tackle study objective 1 as set out in section 3.2 – to describe the prescribing practice of oral and new oral anticoagulants over time in Scotland with regards to prevalence and incidence; geography; and socio-demographic aspects – this descriptive chapter includes all OAC prescribing, regardless of indication.

5.1 Introduction

Oral anticoagulants are used to prevent thromboembolic events such as DVT and stroke, and have been approved for a variety of health conditions – including atrial fibrillation, artificial heart valve replacements, and post-surgery. Warfarin has been used for this purpose for decades; its usage is however complicated by a large number of interactions with other drugs as well as with food ingredients, and the necessity to constantly monitor patients due to its narrow therapeutic window and the bleeding risk associated with INR levels outside the target range. These issues are among the reasons why warfarin has not always been prescribed to patients who might have benefitted from oral anticoagulant treatment; under-treatment might however also be ascribed to misguided perceptions about the risks and benefits of anticoagulation, as well as the generally negative attitude towards warfarin among physicians and patients alike (Bungard et al., 2000, Donzé et al., 2012, Lip & Shantsila, 2013). In addition, patients' adherence to warfarin treatment is relatively low, potentially impairing treatment success (Alamneh et al., 2016, Kaariainen et al., 2013).

The introduction of DOACs since 2008 has widely been anticipated to improve antithrombotic treatment: these drugs have a lower interaction potential than warfarin, a faster onset of action, and a limited time of clinical effect after discontinuation – as these qualities facilitate a much easier treatment scheme and theoretically remove the requirement of monitoring, it was hoped that more patients will be treated, and that treatment outcomes might improve due to better adherence (Alamneh et al., 2016, Sarich et al., 2015). Consequently, DOACs have rather quickly been incorporated into several treatment guidelines (as described in sections 2.5 and 2.7).

Previous studies have shown that DOACs have increasingly started to replace VKAs for preventing thromboembolic events, albeit to varying degrees in different countries (Barnes et al., 2015, Hanemaaijer et al., 2015, Loo et al., 2017, Protty & Hayes, 2017, Weitz et al., 2015). Little information about prescribing patterns of oral anticoagulants in Scotland, including the uptake of DOACs, has however been available thus far; hence, the *purpose* of this study was to describe the prescribing practice of traditional and new oral anticoagulants over time in Scotland.

5.2 Methods

The study period spanned from January 2009 until December 2015, and the study population for this chapter comprised all members of study cohort 1. Cohort 1 – identified within PIS, as described in more detail in section 3.4 – consisted of all patients in Scotland who received at least one prescription for any oral anticoagulant during the study period (either VKAs or DOACs), irrespective of reasons/diagnoses for being treated with an oral anticoagulant.

To further characterise patients being initiated on OACs and to account for geographical differences, a limited set of variables has been used: patient sex and age at time of first prescription, obtained from CHI records; and patients' Health Board of residence, urban/rural classification, and level of deprivation (SIMD), as recorded in PIS. Additional details with regards to the data sources (structure, purpose, information contained) as well as the variables (definitions and coding) can be found in sections 4.1 and 4.2, respectively.

5.2.1 Incidence and prevalence

In order to compare prescribing patterns over time and across regions, incidence and prevalence of OAC use – overall, but also separately for VKAs, DOACs as a group, and individual DOACs – have been calculated. Incidence was defined as the number of patients receiving a first prescription for a drug during a specified period of time; while OAC incidence represents all patients newly initiating any OAC (i.e. previously OAC-naïve patients), DOAC incidence incorporates patients newly initiating DOAC treatment regardless of whether they have previously been treated with VKAs. In contrast, prevalence was defined as the total number of patients receiving a prescription for a drug during a specified time period, and includes new patients as

well as those already on treatment. Consequently, patients could be included in more than one prevalence rate (if they were treated during more than one of the set time periods), as well as in more than one drug category (if they switched from one drug to another) – as opposed to incidence rates, where patients are only counted once (for the first drug they received, in the calendar year this initial prescription has been issued).

Both incidence and prevalence have been calculated by calendar year, and expressed as the number of patients treated per 100,000 population (based on mid-year population estimates):

$$prevalence = \frac{patients\ receiving\ prescription\ /\ calendar\ year}{mid-year\ population\ estimate} \times 100000$$

$$OAC\ incidence = \frac{patients\ iniating\ OAC\ treatment\ /\ calendar\ year}{mid-year\ population\ estimate} \times 100000$$

$$DOAC\ incidence = \frac{patients\ initiating\ DOAC\ treatment/calendar\ year}{mid-year\ population\ estimate} \times 100000$$

As OAC treatment status of patients prior to 2009 was unknown (due to the data available for this study, as described in more detail in chapter 4.3), incidence has only been calculated for the years from 2010 onwards, using the year 2009 as run-in period so as to ensure that patients included in the calculation are indeed new patients.

5.2.2 Mid-year population estimates

Mid-year population estimates for Scotland as a whole, as well as by Health Board, are usually published by NRS in April the following year, based on census information and the civic registration system; estimates for other regional areas including the urban/rural classification system are released a few months later (ISD Scotland, 2010f). An overview of these estimates as used for calculating incidence and prevalence is presented in table 5.1.

Table 5.1: Mid-year population estimates for Scotland 2009 to 2015, by Health Board

	2009	2010	2011	2012	2013	2014	2015
Scotland	**5,231,900**	**5,262,200**	**5,299,900**	**5,313,600**	**5,327,700**	**5,347,600**	**5,373,00**
Health Board							
Ayrshire & Arran	372,430	372,800	373,760	373,220	372,240	371,140	370,590
Borders	113,590	113,690	113,880	113,720	113,880	114,040	114,030
Dumfries & Galloway	151,160	151,100	151,410	150,840	150,280	149,960	149,670
Fife	361,410	362,610	365,300	366,210	366,900	367,250	368,080
Forth Valley	294,190	296,020	298,080	299,090	299,670	300,400	302,650
Grampian	559,210	564,850	569,580	573,400	579,200	584,220	587,820
Greater Glasgow & Clyde	1,122,330	1,127,840	1,135,400	1,137,320	1,137,920	1,142,590	1,149,890
Highland	318,200	319,350	321,660	319,800	320,980	320,730	321,000
Lanarkshire	647,340	649,460	651,620	652,220	652,590	653,300	654,490
Lothian	816,520	825,530	836,610	843,740	849,720	858,120	867,800
Orkney	20,940	21,220	21,420	21,530	21,560	21,580	21,670
Shetland	22,790	23,060	23,240	23,210	23,200	23,220	23,200
Tayside	404,370	407,070	410,250	411,740	412,160	413,800	415,040
Western Isles	27,420	27,600	27,690	27,560	27,400	27,250	27,070
Urban/rural classification [1]							
Large urban area	-	-	1,827,570	1,837,442	1,845,750	1,857,216	1,872,082
Other urban area	-	-	1,873,611	1,875,630	1,877,209	1,879,592	1,884,150
Accessible small town	-	-	500,187	500,618	500,861	501,616	502,269
Remote small town	-	-	118,533	118,233	118,206	118,152	118,427
Very remote small town	-	-	69,104	68,628	68,229	67,585	67,167
Accessible rural area	-	-	596,379	598,881	603,687	609,079	615,214
Remote rural area	-	-	161,790	161,671	161,367	162,043	161,839
Very remote rural area	-	-	152,726	152,497	152,391	152,317	151,852

[1] as there was a change in data zones used to calculate these areas in 2011, population estimates prior to 2011 are not directly comparable to those since 2011; therefore, estimates prior to 2011 have not been used

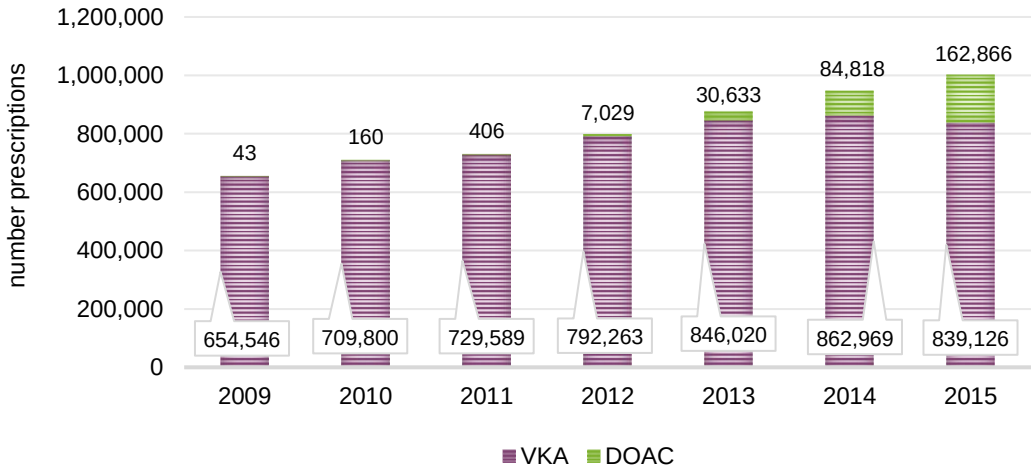
Data source: (ISD Scotland, 2010f, NRS, 2017a)

5.3 Results

During the study period (January 2009 to December 2015), a total of 5,720,268 OAC prescriptions were dispensed (excluding prescriptions for INR test strips), of which 285,955 prescriptions were for a DOAC. The overall study population comprised 166,167 patients: 143,554 patients were treated with a VKA (warfarin, acenocoumarol, or phenindione); 35,339 patients received at least one prescription for any DOAC (apixaban, dabigatran, rivaroxaban); and 12,726 patients were issued prescriptions for both VKAs and DOACs.

5.3.1 Prescriptions dispensed in Scotland over time

The number of OAC prescriptions dispensed annually increased over time, from 654,589 in 2009 to 1,001,992 in 2015; however, the number of VKA prescriptions decreased for the first time between 2014 and 2015 by approximately 3% (from 862,969 to 839,126), while the number of DOAC prescriptions continued to increase – as shown in figure 5.1.



DOAC – direct oral anticoagulant; VKA – vitamin K antagonist

Figure 5.1: Number of OAC prescriptions dispensed in Scotland 2009 – 2015, by calendar year

Even though dabigatran was the first drug to be approved in Scotland, overall prescription numbers were higher for both apixaban and rivaroxaban, with rivaroxaban being the most commonly prescribed DOAC (as depicted in figure 5.2).

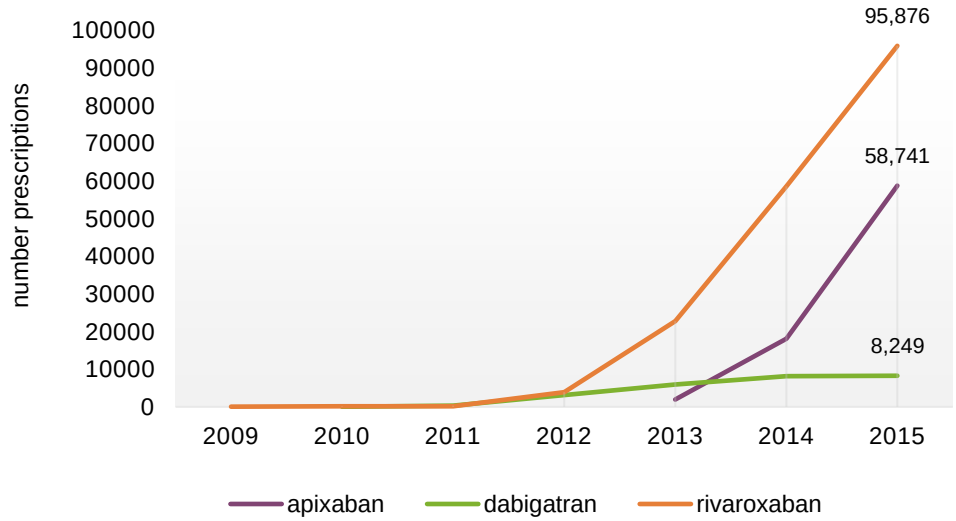


Figure 5.2: Number of DOAC prescriptions dispensed in Scotland 2009 – 2015, by drug and calendar year

In contrast to apixaban, where prescription numbers continued to rise, prescribing for dabigatran and rivaroxaban started to decline slightly during the last quarter of 2015; see also figure 5.3 for details.

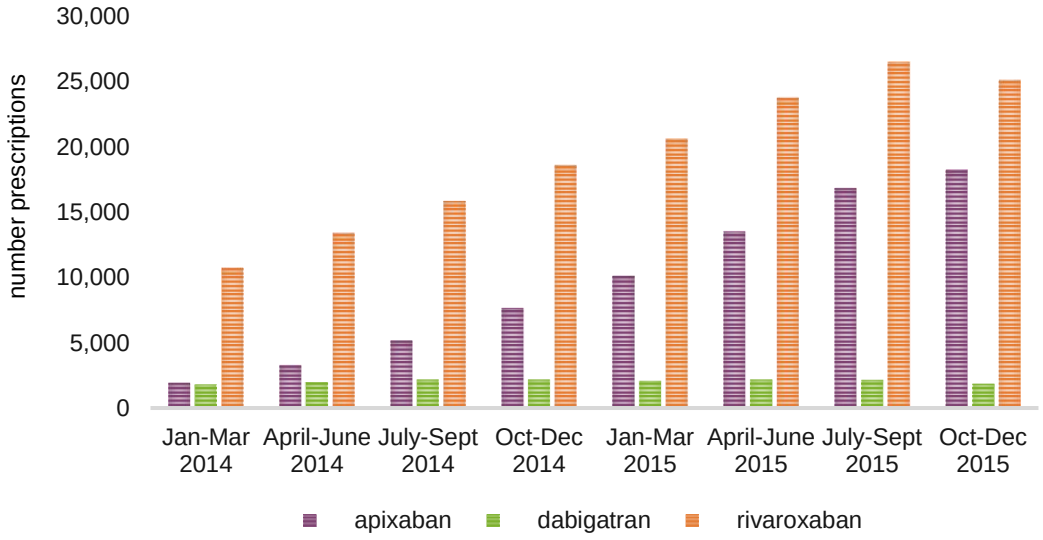


Figure 5.3: Number of DOAC prescriptions dispensed in Scotland in 2014 and 2015, by drug and quarter year

5.3.2 Prevalence and incidence of OAC use in Scotland over time

Prevalence of OAC use overall increased during the study period, from 1309.7 patients per 100,000 population in 2009 to 1904.7 in 2015. While VKA prevalence started to decrease since 2013, DOAC prevalence continued to increase; however, prevalence by individual drug differed considerably. See also table 5.2 for details.

Table 5.2: OAC prevalence in Scotland 2009 – 2015, by calendar year and drug class [number patients treated per 100,000 population]

	2009	2010	2011	2012	2013	2014	2015
OAC, all	1309.7	1340.9	1379.2	1473.1	1592.2	1738.6	1904.7
VKA	1308.9	1338.4	1376.1	1452.9	1501.6	1496.4	1442.1
DOAC	0.8	2.6	40.8	34.7	125.8	300.8	533.8
Apixaban					10.9	71.4	200.5
Dabigatran		0.1	19.6	12.2	19.4	23.3	22.9
Rivaroxaban	0.8	2.5	21.3	23.3	97.6	211.1	319.7

DOAC – direct oral anticoagulant; OAC – oral anticoagulant; VKA – vitamin K antagonist

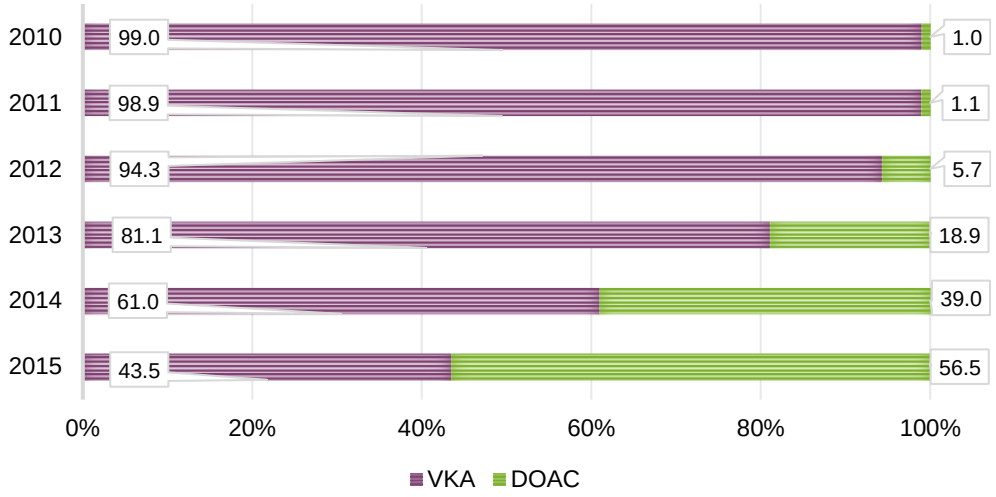
When looking at treatment initiation among all previously OAC-naïve patients, OAC incidence has been increasing steadily throughout the study period – at a rate of approximately 10% per year. Until 2012, this increase was mostly due to an increase in the number of patients initiating treatment with a VKA; since then, the number of patients initiating OAC treatment with a VKA decreased noticeably, whereas the number of patients starting treatment with a DOAC continued to increase. See also table 5.3 for details.

Table 5.3: OAC incidence in Scotland 2010 – 2015, by calendar year and drug class [number patients treated per 100,000 population]

	2010	2011	2012	2013	2014	2015
OAC, all	242.2	251.3	288.3	317.4	350.6	383.3
VKA	239.9	248.5	271.8	257.5	214.0	166.6
DOAC	2.4	2.8	16.6	59.9	136.5	216.7

DOAC – direct oral anticoagulant; OAC – oral anticoagulant; VKA – vitamin K antagonist

While the share of patients initiating oral anticoagulant treatment with a DOAC was very small in 2010 and 2011, this changed considerably over time. In 2015, a DOAC was already the drug of first choice for more than half (56.5%) of all new OAC patients, as highlighted in figure 5.4**.**



DOAC – direct oral anticoagulant; VKA – vitamin K antagonist

Figure 5.4: Share of patients initiating OAC with VKAs or a DOAC 2010 – 2015, by calendar year [%]

DOAC incidence – taking into account all patients being prescribed a DOAC for the first time, regardless of whether they have previously been treated with a VKA – increased from 2.6 per 100,000 population in 2010 to 308.5 in 2015, with considerable differences between individual drugs as detailed in table 5.4. While most of these new DOAC users were OAC-naïve patients, a substantial (although decreasing) share of all patients newly starting DOAC treatment had previously been treated with a VKA (table 5.4).

During the study period, the majority (64.1%) of all patients initiating treatment with a DOAC, irrespective of prior VKA treatment status, received rivaroxaban as drug of first choice; for 30.4% of patients, apixaban was the first drug prescribed, while 5.5% were started on dabigatran. Nevertheless, considerable changes over time have been observed, as shown in figure 5.5.

Table 5.4: DOAC incidence in Scotland 2010 – 2015, by calendar year and drug [number patients treated per 100,000 population]

	2010	2011	2012	2013	2014	2015
New DOAC user, all	2.6	4.0	33.1	101.5	209.5	308.5
Apixaban				10.2	59.0	131.2
Dabigatran	0.1	1.9	10.7	10.9	8.3	4.5
Rivaroxaban	2.5	2.1	22.5	80.4	142.2	172.9
New DOAC user, previously OAC-naïve	2.4	2.8	16.6	59.9	136.5	216.7
Apixaban				4.3	36.0	90.3
Dabigatran		0.8	4.5	5.5	4.6	2.9
Rivaroxaban	2.4	2.0	12.1	50.2	95.9	123.5
New DOAC user, prior VKA treatment	0.2	1.2	16.6	41.6	72.9	91.9
Apixaban				6.0	23.0	40.9
Dabigatran		1.1	6.2	5.4	3.7	1.5
Rivaroxaban	0.1	0.1	10.4	30.2	46.2	49.5

DOAC – direct oral anticoagulant; VKA – vitamin K antagonist

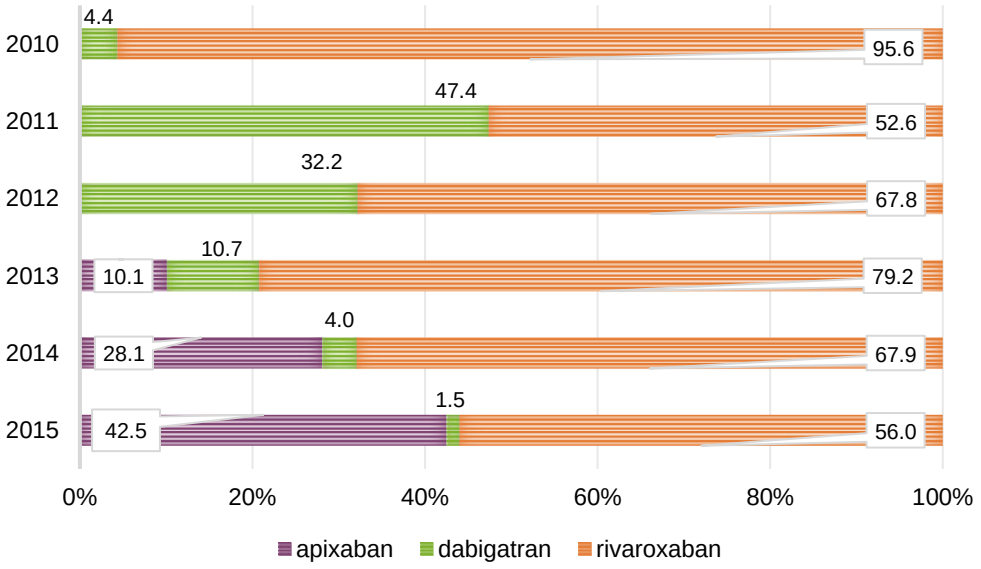


Figure 5.5: Share of patients initiating DOAC treatment with each drug 2010 – 2015, by calendar year [%]

5.3.3 Geographical variation

5.3.3.1 Health Board

There were substantial differences in both overall OAC prevalence as well as DOAC prevalence across Health Boards, as presented in table 5.5.

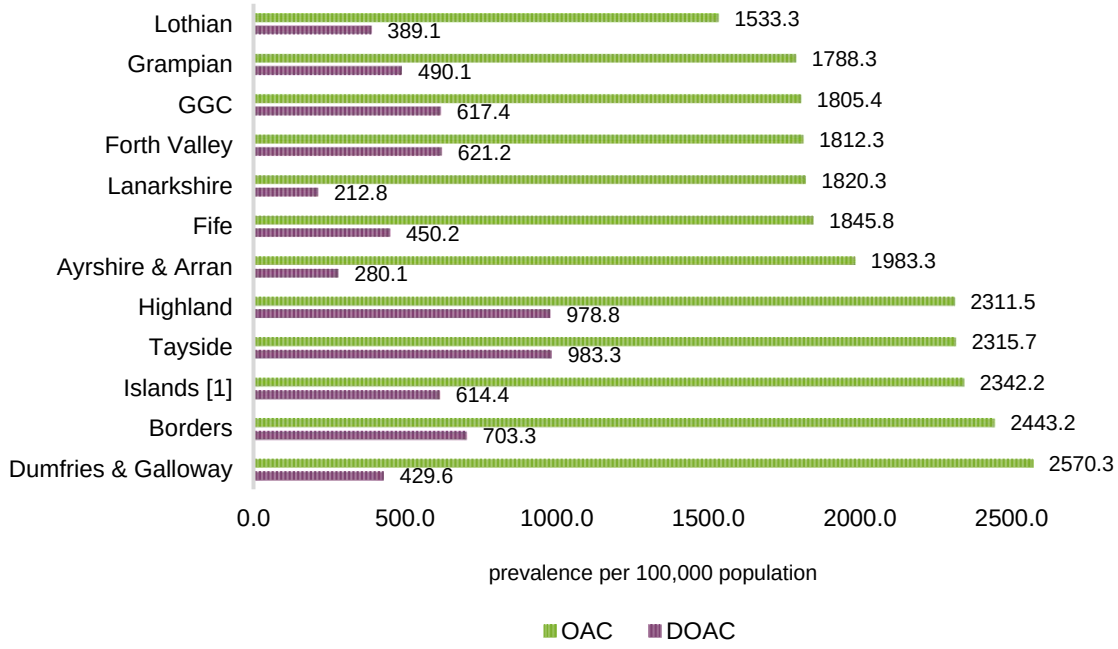
Table 5.5: OAC and DOAC prevalence 2011 – 2015, by Health Board and calendar year [number patients treated per 100,000 population]

	2011	2012	2013	2014	2015
OAC prevalence					
Ayrshire & Arran	1502.3	1609.0	1691.9	1818.7	1983.3
Borders	1750.1	1865.1	1982.8	2198.4	2443.2
Dumfries & Galloway	1904.8	1992.8	2108.7	2307.9	2570.3
Fife	1272.9	1392.1	1527.1	1658.5	1845.8
Forth Valley	1290.9	1398.9	1532.7	1684.8	1812.3
Grampian	1348.0	1463.7	1564.1	1655.0	1788.3
Greater Glasgow & Clyde	1297.0	1360.8	1480.9	1627.5	1805.4
Highland	1567.2	1683.9	1856.2	2082.1	2311.5
Islands [1]	1795.4	1928.1	2059.3	2199.9	2342.2
Lanarkshire	1271.0	1368.9	1494.5	1657.3	1820.3
Lothian	1175.9	1231.7	1309.6	1414.3	1533.3
Tayside	1660.0	1796.8	1967.4	2149.6	2315.7
DOAC prevalence					
Ayrshire & Arran	2.1	7.8	29.0	94.3	280.1
Borders		54.5	188.8	440.2	703.3
Dumfries & Galloway	13.2	27.8	77.9	196.7	429.6
Fife	5.7	47.5	155.4	278.0	450.2
Forth Valley	5.0	35.4	206.2	418.1	621.2
Grampian	3.7	27.0	120.9	264.5	490.1
Greater Glasgow & Clyde	3.7	18.4	95.9	324.4	617.4
Highland	9.0	120.4	296.0	648.2	978.8
Islands [1]		48.4	133.0	308.1	614.4
Lanarkshire	1.5	7.4	25.3	96.0	212.8
Lothian	3.7	12.6	53.0	176.0	389.1
Tayside		116.3	381.2	683.4	983.3

DOAC – direct oral anticoagulant; OAC – oral anticoagulant

[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

In 2015, OAC prevalence was lowest in Lothian (1533.3 patients per 100,000 population) and highest in Dumfries & Galloway (2570.3 patients per 100,000 population); DOAC prevalence ranged from 212.8 (Lanarkshire) to 983.3 patients per 100,000 population (Tayside), as shown in figure 5.6.



DOAC – direct oral anticoagulant; GGC – Greater Glasgow & Clyde; OAC – oral anticoagulant

[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

Figure 5.6: OAC and DOAC prevalence in 2015, by Health Board [number patients treated per 100,000 population]

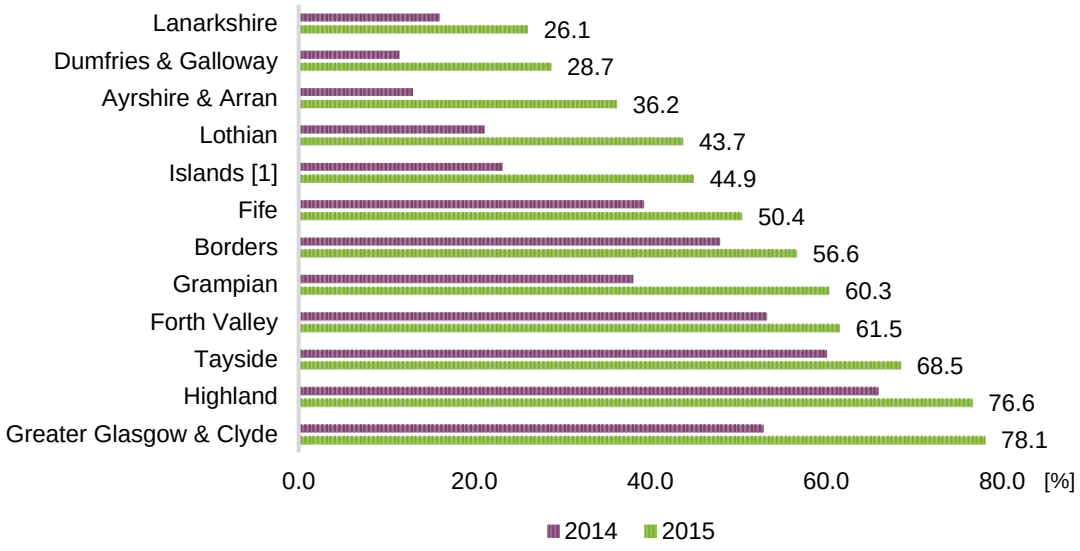
Differences were also sizable with regards to OAC incidence, increasing steadily during the study period and spanning from 297.8 patients per 100,000 population in Lothian up to 525.8 in Dumfries & Galloway in 2015 (see also table 5.6 for details).

Table 5.6: OAC incidence 2011 – 2015, by Health Board and calendar year [number patients treated per 100,000 population]

	2011	2012	2013	2014	2015
Ayrshire & Arran	264.3	297.4	303.6	341.7	372.9
Borders	310.0	375.5	393.4	463.0	495.5
Dumfries & Galloway	378.4	371.9	401.3	471.5	525.8
Fife	240.6	279.6	305.5	314.0	379.8
Forth Valley	234.2	296.6	321.7	329.6	351.2
Grampian	239.8	309.7	310.1	315.3	356.7
Greater Glasgow & Clyde	227.1	249.7	296.2	339.2	388.9
Highland	284.5	345.2	395.7	463.9	507.8
Islands [1]	380.1	387.3	378.3	365.0	439.3
Lanarkshire	228.2	263.6	295.6	341.7	345.8
Lothian	229.9	242.1	263.6	287.0	297.8
Tayside	288.6	346.8	393.8	426.8	442.4

[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

The share of OAC-naïve patients receiving a DOAC as drug of first choice did not only increase over time, it also differed noticeably across Health Boards – ranging from 26.1% (Lanarkshire) to 78.1% (Greater Glasgow & Clyde) in 2015 (figure 5.7).



[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

Figure 5.7: Share of patients initiating OAC treatment with a DOAC in 2014 compared to 2015, by Health Board and calendar year [%]

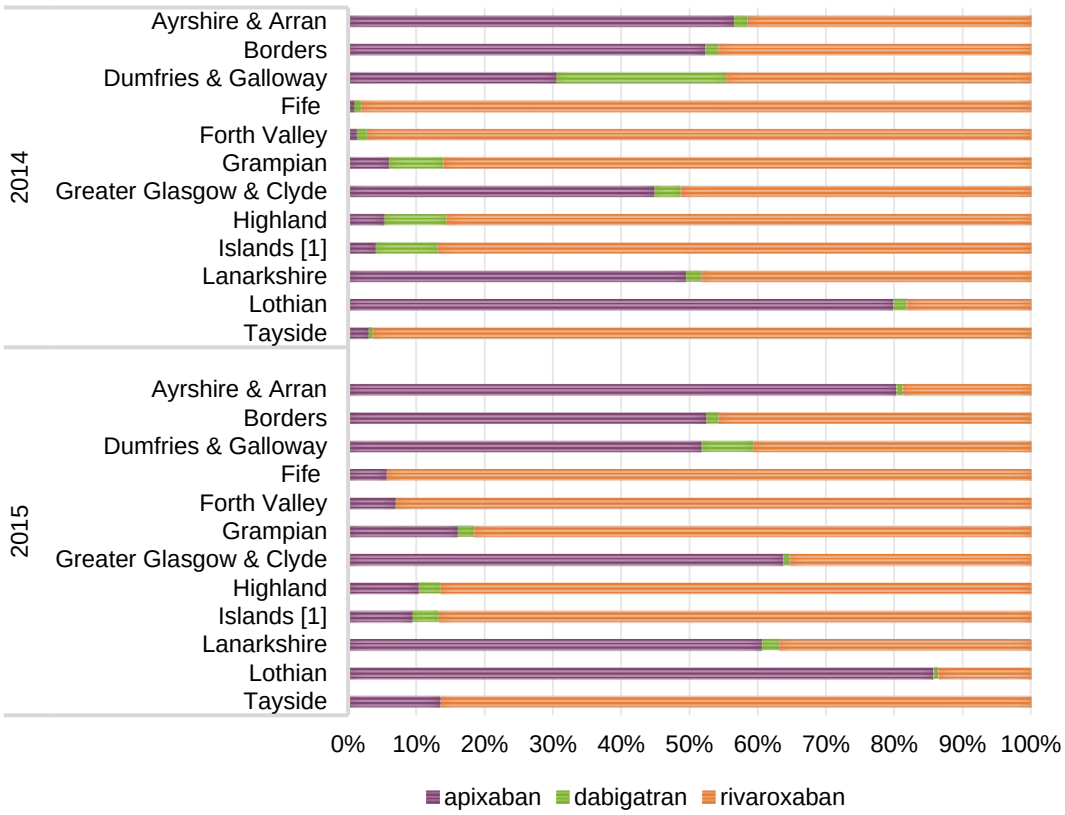
Differences in DOAC incidence were even more pronounced than those in OAC incidence, with a minimum of 135.8 patients per 100,000 population in Lanarkshire and a maximum of 518.1 patients in the Highland Health Board (see table 5.7 for details). These figures contain all patients having started DOAC treatment, regardless of prior VKA treatment status.

Table 5.7: DOAC incidence 2012 – 2015, by Health Board and calendar year [number patients treated per 100,000 population]

	2012	2013	2014	2015
Ayrshire & Arran	6.2	23.9	71.9	202.6
Borders	51.0	148.4	321.8	385.9
Dumfries & Galloway	21.9	55.9	137.4	265.9
Fife	45.6	122.6	175.9	263.5
Forth Valley	33.4	184.9	262.6	311.6
Grampian	25.3	103.8	185.2	305.9
Greater Glasgow & Clyde	17.2	83.4	259.4	372.8
Highland	115.1	210.6	420.6	518.1
Islands [1]	47.0	94.2	201.2	367.0
Lanarkshire	6.9	20.8	77.9	135.8
Lothian	11.5	45.1	133.3	243.3
Tayside	114.9	288.5	394.2	461.9

[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

When starting treatment with any DOAC (regardless of whether patients were OAC-naïve or had previously been treated with a VKA), the drug of first choice differed considerably between Health Boards: in 2015, rivaroxaban was used to initiate treatment in a vast majority of patients (81.5% to 94.3%) in six of the Health Boards, while apixaban was used in a majority of patients (51.8% to 85.7%) in the other six Health Boards. Although a distinction between Health Boards – favouring either rivaroxaban or apixaban – was already becoming apparent in 2014, some changes were observed between 2014 and 2015, as shown in figure 5.8.



[1] Comprises the three island Health Boards: Orkney, Shetland, and Western Isles

Figure 5.8: Share of patients initiating DOAC treatment with each drug in 2014 compared to 2015, by Health Board [%]

While the usage of apixaban increased across all Health Boards between 2014 and 2015 – albeit to very different degrees – the number of patients initiating treatment with dabigatran decreased considerably, except for Lanarkshire (with a minor increase from 2.2% to 2.5% of all patients initiating DOAC treatment); usage of rivaroxaban also decreased in all Health Boards except Highland (minor increase from 85.5% to 86.4% among new DOAC patients), although to a far lesser extent as was the case for dabigatran. These changes in preferences with regards to drug of first choice however resulted in noticeable differences in DOAC initiation patterns between 2014 and 2015 in only two Health Boards: in both Dumfries & Galloway and Greater Glasgow & Clyde, apixaban became the drug used most frequently – at the expense of dabigatran in the former, and rivaroxaban in the latter.

5.3.3.2 Urban/rural classification

Prevalence differed between the diverse areas across Scotland, with very remote rural areas having the highest rates for both OACs in general as well as for DOACs; both OAC and DOAC prevalence increased over time in all areas, regardless of urban/rural classification category. See also table 5.8 for details.

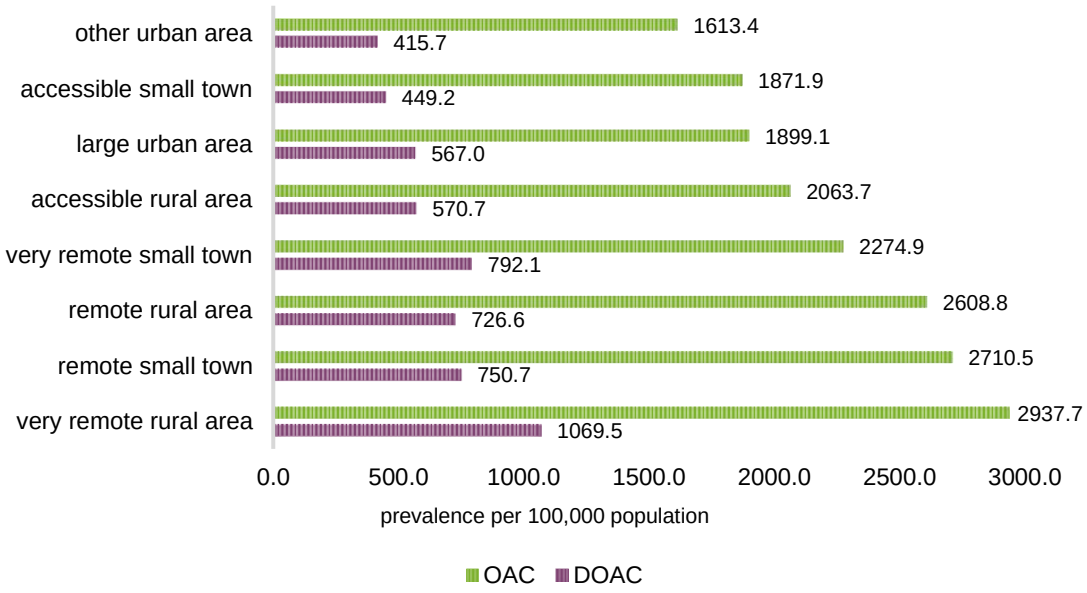
Table 5.8: OAC and DOAC prevalence 2011 – 2015, by urban/rural classification and calendar year [number patients treated per 100,000 population]

	2011	2012	2013	2014	2015
OAC prevalence					
Large urban area	1392.6	1472.3	1592.8	1730.0	1899.1
Other urban area	1172.4	1253.0	1353.9	1479.5	1613.4
Accessible small town	1354.9	1456.2	1555.3	1697.3	1871.9
Remote small town	1996.9	2151.7	2296.8	2516.3	2710.5
Very remote small town	1555.6	1675.7	1837.9	2145.4	2274.9
Accessible rural area	1486.5	1612.3	1743.3	1894.5	2063.7
Remote rural area	1925.3	2027.0	2171.4	2352.5	2608.8
Very remote rural area	1996.4	2171.2	2403.7	2645.8	2937.7
DOAC prevalence					
Large urban area	3.3	24.7	113.0	303.8	567.0
Other urban area	3.6	24.6	101.5	239.0	415.7
Accessible small town	3.4	33.6	104.4	244.2	449.2
Remote small town	-	64.3	196.3	456.2	750.7
Very remote small town	-	61.2	186.1	543.0	792.1
Accessible rural area	6.2	48.8	162.7	333.0	570.7
Remote rural area	9.9	81.0	207.6	415.9	726.6
Very remote rural area	6.5	135.1	303.2	638.8	1069.5

DOAC – direct oral anticoagulant; OAC – oral anticoagulant

In 2015, OAC prevalence ranged from 1613.4 patients per 100,000 population in other urban areas, up to 2937.7 in very remote rural areas; the highest DOAC prevalence rate was found in very remote rural areas with 2937.7 patients per 100,000 population,

whereas DOAC prevalence was lowest (1613.4 patients per 100,000 population) in other urban areas (figure 5.9).



DOAC – direct oral anticoagulant; OAC – oral anticoagulant

Figure 5.9: OAC and DOAC prevalence in 2015, by urban/rural classification [number patients treated per 100,000 population]

Except in very remote small towns, OAC incidence continually increased during the study period, reaching rates between 313.5 patients per 100,000 population in other urban areas and 611.1 patients in very remote rural areas in 2015 (table 5.9).

Table 5.9: OAC incidence 2011 – 2015, by urban/rural classification and calendar year [number patients treated per 100,000 population]

	2011	2012	2013	2014	2015
Large urban area	250.8	284.0	324.5	356.7	398.1
Other urban area	211.4	240.1	266.7	293.9	313.5
Accessible small town	245.9	294.4	285.7	326.3	365.1
Remote small town	340.8	406.8	433.1	478.2	497.4
Very remote small town	299.5	358.5	376.7	513.4	448.1
Accessible rural area	276.3	324.8	352.0	376.8	413.0
Remote rural area	361.6	399.6	418.9	477.0	519.7
Very remote rural area	393.5	453.1	517.7	544.3	611.1

OAC treatment initiation changed noticeably over time, and differed between regions: in 2015, the share of patients initiating treatment with a DOAC rather than with a VKA was highest in very remote small towns (67.8%) and very remote rural areas (65.1%), as depicted in figure 5.10.

Figure 5.10: Share of patients initiating OAC treatment with a DOAC in 2014 compared to 2015, by urban/rural classification and calendar year [%]

Comparable to OAC incidence, DOAC incidence (including all patients newly starting DOAC treatment, regardless of whether they have previously been treated with a VKA) increased considerably over time; overall patterns were also similar, with rates lowest in other urban areas (240.2 patients per 100,000 population) and highest in very remote rural areas (583.5 patients per 100,000 population). See also table 5.10 for details.

The drug used most often to initiate DOAC treatment has been rivaroxaban, across calendar years and regions. However, the percentage of patients receiving apixaban as first drug consistently increased over time; in 2015, the majority of patients (58.1%) in large urban areas were started on apixaban, while rivaroxaban was still the most commonly prescribed drug in all other areas (figure 5.11).

Table 5.10: DOAC incidence 2012 – 2015, by urban/rural classification and calendar year [number patients treated per 100,000 population]

	2012	2013	2014	2015
Large urban area	23.5	96.2	224.2	333.7
Other urban area	23.2	85.2	164.9	240.2
Accessible small town	32.0	79.3	170.4	267.0
Remote small town	63.4	126.1	298.8	408.7
Very remote small town	59.7	126.0	405.4	431.8
Accessible rural area	46.4	125.6	213.9	323.1
Remote rural area	77.3	153.1	266.6	410.9
Very remote rural area	131.8	196.9	406.4	583.5

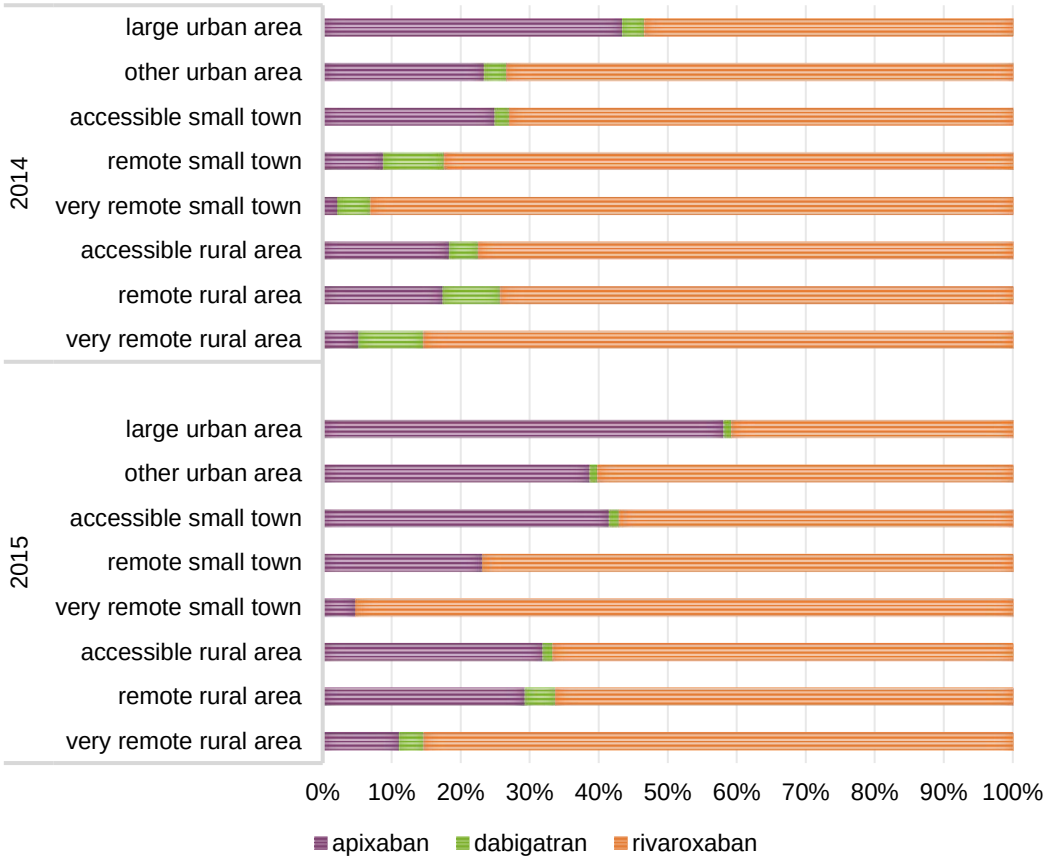


Figure 5.11: Share of patients initiating DOAC treatment with each drug in 2014 compared to 2015, by urban/rural classification [%]

5.3.4 Socio-demographic aspects

5.3.4.1 Patient sex

Differences between patient sexes in regards to both treatment initiation with a DOAC rather than a VKA, and drug of first choice when starting DOAC treatment, were minor. In 2015, 56.8% of all female patients newly initiating OAC treatment received a DOAC; the share among male patients was 56.3%. The distribution of sex among patients newly initiating DOAC treatment between 2011 and 2015 is depicted in figure 5.12.

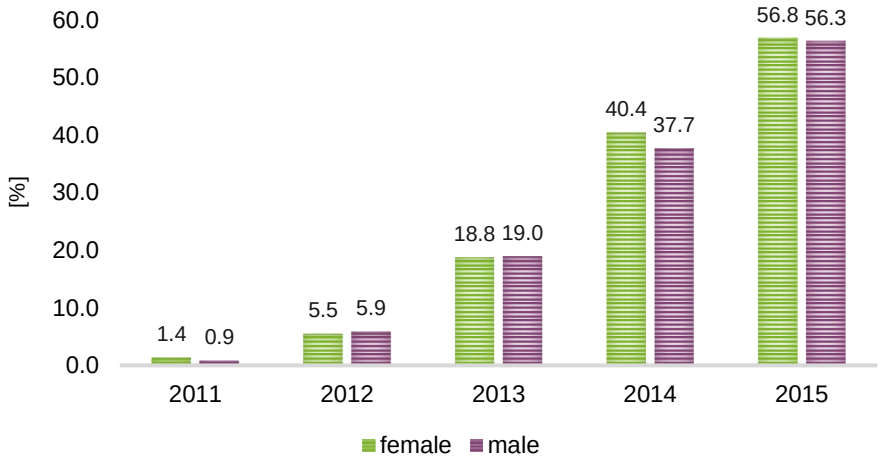


Figure 5.12: Share of patients initiating OAC treatment with a DOAC 2011 - 2015, by patient sex and calendar year [%]

The first drug most frequently prescribed to new DOAC patients was rivaroxaban, across all calendar years and regardless of sex. However, the share of patients initiating treatment with apixaban increased considerably over time, while the use of dabigatran decreased; since 2014, the number of patients receiving apixaban exceeded the number of dabigatran patients. Figure 5.13 displays the changes in drug of first choice when starting DOAC treatment between 2014 and 2015, by sex.

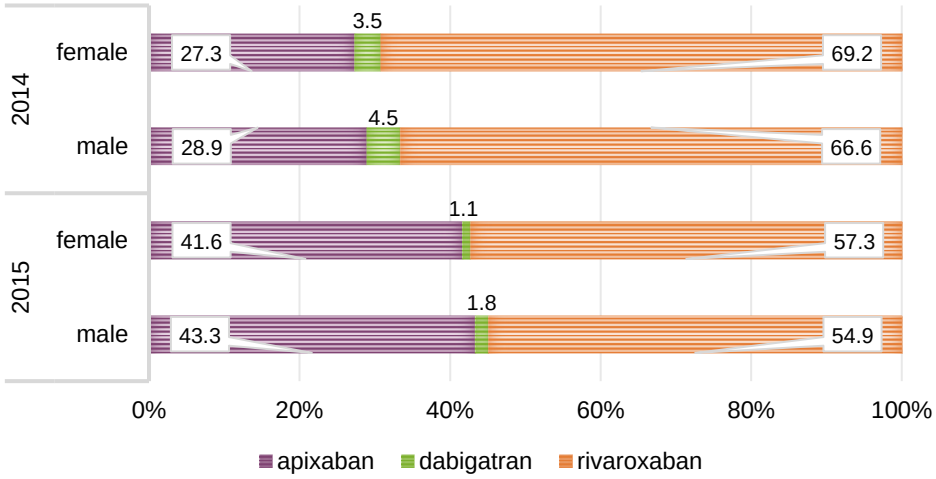


Figure 5.13: Share of patients initiating DOAC treatment with each drug in 2014 compared to 2015, by patient sex [%]

5.3.4.2 Patient age at time of first prescription

The share of patients initiating OAC treatment with a DOAC increased steadily over time for all age groups, and in 2015, the majority of all new patients were prescribed a DOAC. There were, however, differences observed: while 53.1% of patients aged 75 to 84 years at the time of first prescription received a DOAC, the percentage among patients 85 years of age or older was 64.9%; see also figure 5.14.

Figure 5.14: Share of patients initiating OAC treatment with a DOAC 2013 - 2015, by patient age group at time of first prescription and calendar year [%]

Similar to the distribution by sex, the DOAC of first choice was rivaroxaban for the majority of patients newly starting DOAC treatment in all calendar years, irrespective of age group – although treatment initiation with apixaban increased considerably over time. In 2015, slightly more than half of all patients initiating DOAC treatment received rivaroxaban, and slightly less received apixaban; the only exception to this is the youngest age group, where 74.8% of patients were initially treated with rivaroxaban, and 24.1% of patients with apixaban. Dabigatran accounted only for a very small number of new patients in all age groups, as shown in figure 5.15.

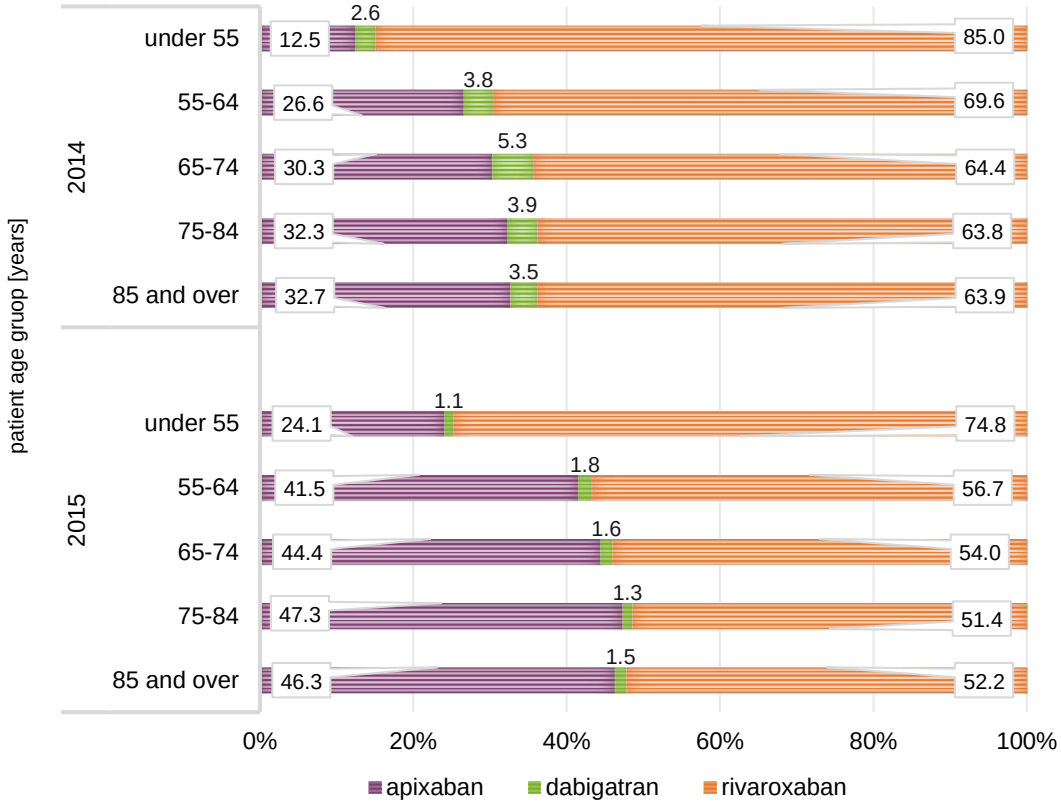


Figure 5.15: Share of patients initiating DOAC treatment with each drug in 2014 compared to 2015, by patient age group at time of first prescription [%]

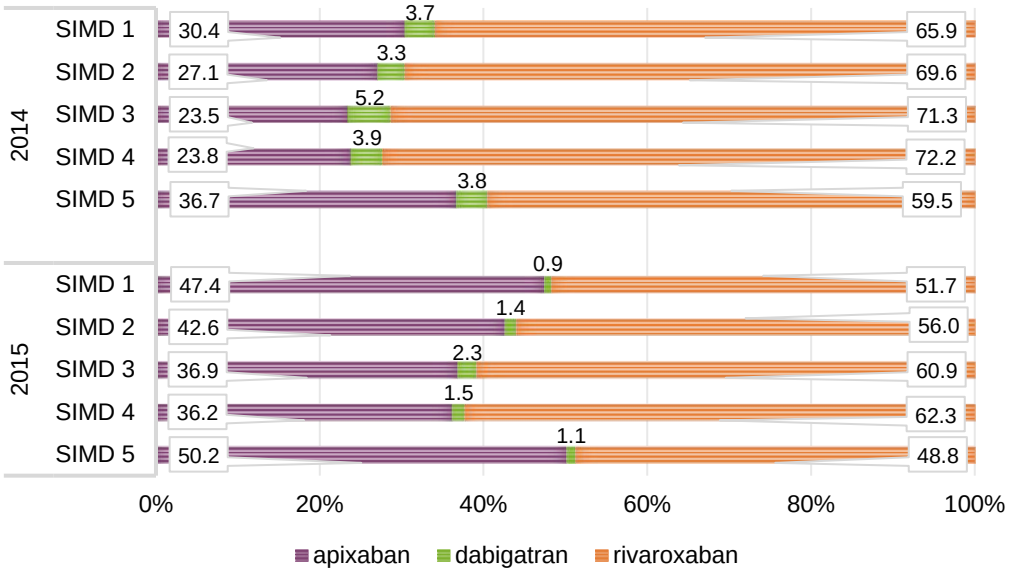
5.3.4.3 Level of deprivation

Differences among patients starting oral anticoagulation with either a VKA or a DOAC were not very pronounced with respect to level of deprivation; in 2015, the proportion of patients receiving a DOAC as drug of first choice ranged from 53.2% to 59.7% as pictured in figure 5.16.

SIMD – Scottish Index of Multiple Deprivation; 1 included the most deprived 20% of the population, while 5 the less deprived 20%

Figure 5.16: Share of patients initiating OAC treatment with a DOAC 2013 - 2015, by level of deprivation and calendar year [%]

Among the patients being initiated on DOAC treatment – including both OAC-naïve patients as well as those previously treated with a VKA – a majority received rivaroxaban; nevertheless, in 2015, apixaban was used in 50.2% of patients in the least deprived areas (see also figure 5.17 for details).



SIMD – Scottish Index of Multiple Deprivation; 1 included the most deprived 20% of the population, while 5 the less deprived 20%

Figure 5.17: Share of patients initiating DOAC treatment with each drug in 2014 compared to 2015, by level of deprivation [%]

5.4 Discussion

This was the first study to present a comprehensive description of OAC use nationally for Scotland, and one of an increasing number of studies analysing recent prescribing patterns on a national level – either including all patients regardless of indication (Barnes et al., 2015, Hanemaaijer et al., 2015, Loo et al., 2017, Protty & Hayes, 2017, Weitz et al., 2015), or focusing on patients with a diagnosis of AF (Gadsbøll et al., 2017, Kjerpeseth et al., 2017, Komen et al., 2017).

Findings are in general in line with other published research: the number of patients being treated with OACs increased over time; a majority of all patients newly starting oral anticoagulant treatment in 2015 received a DOAC rather than a VKA; and the DOAC used most commonly for treatment initiation was rivaroxaban. In Scotland, there were however noticeable regional differences in prescribing practice.

5.4.1 Main findings

The annual number of OAC prescriptions issued in 2015 was approximately 53% higher than in 2009, and is in line with an increase of patients newly initiating OAC treatment of more than 60% in 2015 as compared to 2010. By the end of the study period, 16.3% of all OAC prescriptions dispensed to patients were prescriptions for either apixaban, dabigatran, or rivaroxaban. Between 2010 and 2015, the annual number of patients initiating treatment with a VKA decreased by 29% (from 12,622 in 2010 to 8,953 in 2015), while the number of patients receiving a DOAC as first drug increased almost 100-fold – from 124 patients in 2010 (1.0% of all patients starting oral anticoagulant therapy), to 11,641 patients in 2015 (56.5%); changing preferences – prescribing DOACs rather than VKAs to previously OAC-naïve patients – became noticeable in 2013, when the number of new VKA patients first started to decline.

Similar findings have been reported from other studies. The number of patients being treated with OACs – irrespective of indication – increased not only throughout Britain, but also in the Netherlands, Canada, and the US; DOAC use increased in all these countries, whereas use of VKAs increased in Wales and the Netherlands but decreased in England, Canada, and the US – albeit to differing degrees (Barnes et al., 2015, Hanemaaijer et al., 2015, Loo et al., 2017, Protty & Hayes, 2017, Weitz et al., 2015). The share of DOAC prescriptions among all OAC prescriptions dispensed

annually was however higher in other countries than in Scotland: while in Scotland 16.3% of OAC prescriptions dispensed in 2015 were DOAC prescriptions, this share was 33% in Canada by June 2014; in Wales, 32% of prescribing in December 2015 has been attributed to DOACs (Protty & Hayes, 2017, Weitz et al., 2015). Although the exact reasons for these differences are unknown, they might partially be attributable to differences in methodology; the study conducted in Wales for example (Protty & Hayes, 2017) analysed prescribing based on DDDs rather than absolute prescription numbers. Nevertheless, diverging practices with regards to switching existing patients from a VKA to a DOAC might also have contributed: while the DOAC prevalence in the Sottish patient population for instance increased considerably during the study period due to an increase in DOAC incidence, the VKA prevalence did not decrease at a similar rate, potentially indicating that most patients in Scotland – once adjusted to VKA treatment – did not change to a DOAC; practices in other countries may differ depending on treatment guidelines, health care resources (especially anticoagulation services), and individuals' preferences.

Focusing on patients with AF, studies conducted in three Scandinavian countries (Denmark, Norway, and Sweden) also reported an overall increase in patients being treated with OACs; VKA use decreased over time, and DOAC use increased, in all three countries. Of all AF patients initiating OAC treatment, a huge majority received a DOAC: 72.6% in June 2015 in Denmark (Gadsbøll et al., 2017); 82% in 2015 in Norway (Kjerpeseth et al., 2017); and more than 80% since November 2015 in the Stockholm region in Sweden (Komen et al., 2017). These findings are however not directly comparable to the results from this study, as all patients receiving OACs in Scotland have been included regardless of indication (due to the unavailability of this information in PIS).

While rivaroxaban was the most commonly used DOAC in Scotland throughout the study period – albeit with fluctuating shares among all new DOAC patients across calendar years (between 52.6% in 2011 and 95.6% in 2010) – the usage of both dabigatran and apixaban changed considerably over time, as highlighted in figure 5.5: dabigatran use reached its peak in 2011, having been prescribed to 47.4% of all patients initiating DOAC treatment, and dropped to a share of only 1.5% in 2015, whereas the proportion of patients receiving apixaban continually increased, from 10.1% of DOAC incident patients in 2013 to 42.5% in 2015.

These findings broadly mirror the distribution of individual drugs among patients initiating DOAC treatment in other countries: rivaroxaban was the most commonly used DOAC – and dabigatran the least – in a number of studies conducted on a national level. In England for instance, rivaroxaban accounted for 64.8% of all OAC prescriptions in 2015, apixaban for 29%, and dabigatran for 5.9% (Loo et al., 2017); findings were similar in Wales, with rivaroxaban, apixaban, and dabigatran accounting for 61%, 29%, and 10% of DOAC prescriptions in December 2015, respectively (Protty & Hayes, 2017). In contrast, among AF patients in Norway, apixaban was used to initiate DOAC treatment in the majority of cases (59.4%) in 2015, followed by rivaroxaban and dabigatran with 29.8% and 10.8% (Kjerpeseth et al., 2017); apixaban was also the most commonly used DOAC in AF patients in Sweden (Komen et al., 2017). Observed differences between results from the UK (including Scotland) as compared to Norway and Sweden might at least partially be attributable to the fact that the British studies included all patients irrespective of indication, while the Scandinavian studies only comprised patients with AF; if treatment guidelines for different conditions differed, with rivaroxaban potentially being used primarily in patients with indications other than AF, focusing on AF patients would consequently lead to findings of higher rates of apixaban use.

5.4.2 Regional variation in Scotland

Regional differences in prescribing trends in Scotland were remarkable, particularly with respect to Health Boards. While approximately a quarter of patients newly initiating OAC treatment in 2015 in Lanarkshire (26.1%) received a DOAC, this proportion was three times higher in Greater Glasgow & Clyde (78.1%); similarly, the choice of drug differed considerably, with apixaban for instance accounting for 85.7% of all DOAC initiations in Lothian but only 5.7% in Fife, and dabigatran losing importance in almost all Health Boards except Dumfries & Galloway (7.5% of new DOAC patients in 2015). These variations in OAC treatment between Health Boards are most likely a reflection of diverging local treatment recommendations; although Health Boards are expected to follow advice regarding treatment options published by SIGN and/or NICE, they have discretion with regards to local priorities and provisions of care (Steel & Cylus, 2012) – and considering that current guidelines are rather limited when it comes to choosing one DOAC over another, it is not unexpected to see variation. However, without concrete recommendations for a specific drug in

any given circumstance, the choice of OAC on a local level is most likely based on prior experiences and personal preference; more specificity in guidelines, supported by clinical evidence, might eventually lead to local treatment guidelines being more similar to each other, and thus potentially result in a reduction of treatment variation.

Differences in both OAC initiation with a DOAC rather than a VKA as well as the drug of first choice when starting DOAC treatment were less sizeable across areas according to the urban/rural classification system than between Health Boards, but still noticeable: in 2015, highest rates of DOAC use were observed in very remote small towns (67.8%) and very remote rural areas (65.1%); simultaneously, apixaban use was least common in these regions (with shares of 4.8% and 11.1%, respectively), and dabigatran was used as first drug mainly in remote rural (4.4%) and very remote rural (3.5%) areas. As Health Boards and urban/rural areas partially overlap – most Health Boards for example comprise both small towns as well as rural areas – reasons for the observed differences are difficult to discern. In addition to diverging treatment guidelines as issued by the relevant Health Boards, the relatively higher use of DOACs in very remote areas might also be due to the convenience of DOACs as compared to VKAs; considering the difficulties of regular INR testing and dose adjustments when the nearest health care facility is not within easy reach, initiating OAC treatment with a DOAC removes some of the inconvenience of anticoagulant therapy for patients, and potentially also alleviates the burden for small local facilities. A similar proposition has been made with regards to variation in OAC prescribing between Canadian provinces (Weitz et al., 2015); studies specifically analysing OAC treatment variation based on geographical aspects are nevertheless scarce thus far.

Other studies, focusing on a range of diverse medications, suggested that regional variation in prescribing might potentially be attributable to differences in disease prevalence, patients' characteristics, treatment traditions, and/or patient knowledge/health seeking behaviour (Arnlind et al 2010, Neovius et al, 2011, Vlahović-Palčevski et al, 2016). Although it could, for example, be possible that AF prevalence and patient characteristics differ slightly between urban and rural areas in Scotland, these differences alone would not account for the observed deviations in prescribing patterns; information about other factors potentially influencing OAC treatment decisions was however not available.

5.4.3 Socio-demographic aspects

While differences in OAC treatment initiation were minor between sexes, two findings with regards to patient age at time of treatment initiation should be pointed out. First, the share of patients receiving a DOAC among all patients newly initiating OAC treatment were highest in the youngest and the oldest age groups, with 61.4% in patients under the age of 55 and 64.9% in patients aged 85 years or older in 2015; and second, apixaban was used least in patients under 55 years of age (24.1% in 2015, as compared to proportions ranging from 41.5% to 47.3% in the other age groups). These findings might at least partially be due to the underlying diagnoses: as the presence of AF as well as the general risk of stroke increase with age, older patients are more likely to be treated long-term with OACs for these reasons while younger patients have potentially been treated for a DVT. This could explain both the higher percentage of patients younger than 55 years initiating treatment with a DOAC (based on their convenience – removes the burden of adjusting VKA dosing, which is disproportionally higher when treatment is intended to be short-term only), as well as the low share of apixaban in this age group (apixaban might be recommended in guidelines mostly for use in AF patients). In patients aged 85 years or older, the convenience of DOAC treatment could also play an important role when choosing DOACs over VKAs; however, the lower level of drug-drug and drug-food interactions of DOACs in comparison to warfarin most likely factors in as well. With increasing age, the amount of medication taken by patients usually increases, leading to higher probabilities of adverse events due to drug-drug interactions; in addition, polypharmacy – especially in combination with forgetfulness or dementia – could result in patients taking their drugs more erratically. Hence, having a simple dosing schedule and removing the necessity of constant therapeutic drug monitoring might be seen as advantages. Nevertheless, as the indications for OAC treatment in patients included in this study were unavailable, the exact reasons for differences based on patients' age at time of first prescription remain unknown.

5.4.4 Methodological considerations

This study utilised nation-wide, patient-level data with respect to all prescriptions that have been dispensed in the community; as the Scottish NHS is tax-funded and every resident is entitled to health care, it therefore covers the entire population. There are, however, a number of limitations. First of all, because prescription data was derived

from PIS, medication dispensed in secondary care as well as prescriptions issued but not redeemed by the patient were not included; this may have resulted in missing out a small number of patients, but should not have affected the overall results due to the large volume of prescriptions issued and dispensed in primary care. Second, as no indication for treatment was available, patients receiving an OAC during the study period irrespective of diagnosis have been included, resulting in the presentation of basic descriptive statistics rather than conducting any hypothesis testing; in addition, missing indications make the study results less comparable to findings from other studies focussing for example on patients with AF. Third, despite including level of deprivation in the analysis, the nature of the measurement used (SIMD) – which is an area rather than an individual indicator of deprivation – meant it was unsuitable for comparison with other studies. And lastly, due to the data available for this study, the reasoning behind the choice of specific treatment options remains unknown.

5.5 Conclusion

Generally speaking, the number of patients being treated with OACs is increasing – not only in Scotland, but also in a range of other countries across Europe as well as in North America. OACs are frequently used for long-term treatment, and the major indication for prolonged treatment is the prevention of stroke in patients with atrial fibrillation; with ageing populations, heightened awareness of the condition, and possibly a reduction of under-treatment of AF patients (based on the availability of DOACs), this trend could become even more pronounced in the near future.

Prescribing trends over time indicate not only an overall increase in the use of OACs in general, but – more importantly – an increasing utilisation of DOACs, while VKAs seem to have fallen out of favour. Increasing use of DOACs in Scotland roughly coincided with the introduction of DOACs in AF treatment guidelines: an updated guideline for the prevention of stroke in patients with AF, issued by the European Society of Cardiology, incorporated a recommendation for the use of DOACs in 2012 (Camm et al., 2012); guidelines published by NICE and SIGN (NICE, 2014a, SIGN, 2014), including DOAC recommendations, followed in 2014.

Considering the speed with which DOACs have started to replace VKAs, it is not completely inconceivable that DOACs might eventually all but supplant warfarin in

some indications. The major assumption made when introducing DOACs was that DOACs are as effective and safe in clinical practice as VKAs for the prevention of strokes in patients with AF, as efficacy and safety of DOACs have been proven in clinical trials. There are, nevertheless, some aspects of this rapid change in treating patients with oral anticoagulants that require further scrutiny: direct comparisons between the DOACs for instance are lacking, meaning that no clear guidance for which drug to choose in any given situation is available; and many very elderly patients (over the age of 85 years) initiating OAC treatment in Scotland now receive a DOAC instead of warfarin, even though the average age of participants in the clinical trials upon which approval were granted was much lower (Connolly et al., 2009, Granger et al., 2011, Patel et al., 2011).

Despite a number of studies analysing prescribing patterns of OACs over time having been published, comparisons between studies were constricted by noticeable differences in methodology – in terms of data sources (ranging from outpatient office visit audits to national databases covering prescriptions dispensed in primary care) and analytical techniques, but also with respect to the format of results. While some studies for example reported trends in prescription numbers and the share of DOACs among prescriptions issued (Loo et al., 2017, Protty & Hayes, 2017, Weitz et al., 2015), other studies focused on patient numbers, and highlighted the proportion of new patients initiating treatment with a DOAC instead of a VKA (Gadsbøll et al., 2017, Kjerpeseth et al., 2017, Komen et al., 2017); comparability of findings was further complicated by diverging inclusion criteria (e.g. all patients versus patients with a diagnosis of AF only), as well as by stratifications of results for instance by short term versus long-term DOAC use (Hanemaaijer et al., 2015), or by physician specialty (Weitz et al., 2015) – although most studies at least gave a brief summary of overall results. Socio-demographic aspects of patients have also been reported using unstandardized and difficult-to-compare formats, if at all. Hence, a consolidation of methods would enable easier comparison of results across studies.

Chapter 6 – Baseline characteristics: patients with atrial fibrillation receiving oral anticoagulants

The main purpose of this chapter is to give an overview of the study population used for subsequent analyses (utilisation, chapter 7; and clinical effectiveness and safety, chapter 8) by describing patients' baseline characteristics. Along with a description of how the study population was selected, this chapter also provides methodological details pertaining patients' baseline characteristics, in addition to the general study specifics as outlined in chapters 3 and 4.

6.1 Methods

This study has been designed as a retrospective cohort study, using routinely collected administrative data. As described in section 3.4, two patient cohorts have been identified within the available datasets: patients having received at least one prescription for any oral anticoagulant (acenocoumarol, phenindione, warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban) between January 2009 and December 2015, identified in PIS; and patients with a diagnosis of AF, confirmed in secondary care between January 1997 and December 2015, identified in SMR01 (for a description of the data sources, see also section 4.1). The study period spanned from January 2009 to December 2015.

6.1.1 Study population

The specific study population used for further analyses consisted of patients who are part of both cohorts, i.e. patients with a diagnosis of AF who received at least one prescription for any OAC. As both the utilisation and the subsequent outcomes analyses focused on direct oral anticoagulants rather than all OACs available, inclusion of patients has further been refined to include only those patients with at least one prescription for any DOAC (apixaban, dabigatran, rivaroxaban, edoxaban); prescriptions for rivaroxaban 2.5mg have however been disregarded as this strength is exclusively indicated for patients with acute coronary syndrome. Patients were excluded when they had a diagnosis or surgical procedure indicating valvular disease or heart valve replacement, or a diagnosis of VTE during a six month time period immediately preceding their first DOAC prescription – representing the major alternative indications for long-term use of oral anticoagulants. Patients who received a first prescription for any DOAC prior to the drug's date of SMC approval for stroke prevention in AF patients in Scotland (dabigatran: 05.08.2011, rivaroxaban: 13.01.2012, apixaban: 11.01.2013, edoxaban: 09.10.2015) or after their individual

study end date have also been excluded, as this likely indicates alternative reasons for anticoagulant treatment and administrative errors, respectively. For an overview of all specific inclusion and exclusion criteria, see table 6.1; diagnostic codes have been chosen based on the literature (Berry et al., 2013, Friberg et al., 2012, Larsen et al., 2016, Melgaard et al., 2015, Olesen et al., 2011b, Public Health England, 2011, Quan et al., 2005, SIGN, 2012, Sood et al., 2014).

Table 6.1: Study population inclusion and exclusion criteria

Study population selection	Method of identification
1. Inclusion criteria (SMR01, PIS)	
Atrial fibrillation	***ICD-10* code** I48
Direct oral anticoagulant	***BNF name*** apixaban, dabigatran etexilate, rivaroxaban, edoxaban
2. Exclusion criteria (SMR00, SMR01, PIS)	
Valvular disease or heart valve replacement	***ICD-10* codes** I05, I06, I08, I34, I35, Q23, Z95.2 – Z95.4 ***OPCS-4* codes** K25.2 – K25.4, K26.2 – K26.4, K29.2 – K29.4
VTE 6 months prior to first prescription	***ICD-10* codes** I26, I63.6, I67.6, I80.1 – I80.9, I81, I82.2-I82.9
Index prescription prior to drug's SMC approval for the indication of stroke prevention in patients with AF	***Date of first recorded DOAC prescription prior to*** *Dabigatran: 05.08.2011* *Rivaroxaban: 13.01.2012* *Apixaban: 11.01.2013* *Edoxaban: 09.10.2015*
Rivaroxaban 2.5mg	***BNF name:** rivaroxaban & **BNF strength:** "2.5"*

AF – atrial fibrillation; BNF – British National Formulary; ICD-10 – International Classification of Disease, 10th edition; OPCS-4 – Office of Population Censuses and Surveys procedural codes, 4th revision; SMC – Sottish Medicines Consortium; VTE – venous thromboembolism

A patient's index date was the date of first recorded prescription for any DOAC, and age and sex at baseline have been determined based on CHI records. In order to assess patients' baseline characteristics with regards to comorbidities, hospital and outpatient clinic records spanning five years prior to the index date have been used, based on a sensitivity analysis testing different lengths of baseline periods; while using a period shorter than 5 years increased the probability of not capturing all relevant comorbidities, including records going back more than 5 years did not considerably change results any further. Disease related information has been taken from SMR01 and SMR00, and comprised all diagnostic fields. A time period of six months before the index date, chosen to ensure that all relevant concomitant medications have been captured while excluding outdated prescriptions (taking into

account prescribing practices in Scotland), has been applied to define concomitant medication; prescribing data stemmed from PIS.

6.1.2 Comorbidities

Disease-related data consisted of up to ten character variables containing ICD-10 codes: main condition and five additional conditions covering in-patient hospital episodes (SMR01); and up to four referral reasons covering outpatient clinic appointments (SMR00). Admission (SMR01) or appointment dates (SMR00) were available in the format *yyyy-mm-dd* for each episode.

Binary variables indicating the presence of specific diseases of interest at baseline – congestive heart failure, hypertension, diabetes, prior stroke/transient ischaemic attacks, vascular disease, renal disease, liver disease, prior major bleeds, pulmonary embolism, and cancer – were created based on ICD-10 codes as recorded in the available records (see also table 6.2).

As a general indicator of comorbidity, a Charlson comorbidity index has been calculated for every patient. The Charlson comorbidity index (Charlson et al., 1987), similar to an earlier developed method by Kaplan and Feinstein (Kaplan & Feinstein, 1974), was originally designed so as to account for diseases present in patients when calculating mortality risks, and has since been used in a variety of studies to adjust clinical outcomes for comorbidities. An updated version using ICD-10 codes has previously been published (Quan et al., 2005), and the validity of using ICD-10 codes extracted from administrative databases to calculate Charlson scores has been established (Thygesen et al., 2011). The codes used to calculate the Quan-Charlson score, which have also been used in this study, can be found in appendix II.

In addition to the Charlson score, $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores – designed specifically to assess stroke and bleeding risks in patients with atrial fibrillation (Lip, 2013a, Pisters et al., 2010), and described in more detail in section 2.3.2 – were calculated for each patient at baseline, using both hospital and prescription records. ICD-10/BNF codes used for calculation were selected based on a review of the literature (Allan et al., 2016, Larsen et al., 2013, Larsen et al., 2016, Olesen et al., 2011a), and are listed in table 6.2.

Table 6.2: Codes used for identification of comorbidities and calculation of risk scores

$CHADS_2$/CHA_2DS_2-VASc scores (SMR00, SMR01)	
Congestive heart failure	**ICD-10**: I11.0, I13.0, I13.2, I50
Hypertension	**ICD-10**: I10 – I15
Diabetes mellitus	**ICD-10**: E10, E11, E13, E14, G59.0, G63.2, H28.0, H36.0, M14.2, N08.3, O24.0, O24.1, O24.3
Prior stroke/TIA	**ICD-10**: I63, I64, G45.8, G45.9, G46.3 – G46.7
Vascular disease [1]	**ICD-10**: I20 – I22, I70, I73.1, I73.8, I73.9, I74
HAS-BLED score (SMR00, SMR01, PIS)	
Hypertension	**ICD-10**: I10 – I15
Renal disease	**ICD-10**: I12, I13, N00 – N05, N07, N11, N14, N17 – N19, Q61
Liver disease	**ICD-10**: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.5 – K76.7
Prior stroke/TIA	**ICD-10**: I63, I64, G45.8, G45.9, G46.3 – G46.7
Prior major bleeding	**ICD-10**: D62, H11.3, H35.6, H43.1, I60 – I62, J94.2, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0 – K92.2, N02, N95.0, R04, R31, R58
Medication usage predisposing to bleeding	**BNF**: 02.09, 10.01.01
Alcohol usage	**ICD-10**: E52, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, T51, Z71.4, Z72.1 **BNF**: 04.10.01
Additional disease codes (SMR00, SMR01)	
Pulmonary embolism	**ICD-10**: I26
Cancer	**ICD-10**: C00 – C97

BNF – British National Formulary; ICD-10 – International Classification of Disease, 10th edition; PIS – Prescribing Information System; SMR00 – Scottish Morbidity Records, Outpatient attendance dataset; SMR01 – Scottish Morbidity Records, Inpatient and day case dataset; TIA – transient ischaemic attack; VKA – vitamin K antagonist

[1] CHA_2DS_2-VASc score only

As records from primary care as well as laboratory data were not available for this study, all calculated scores (Charlson, $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED) are estimates only, potentially missing out on a number of existing comorbidities not recorded during individual hospital episodes.

6.1.3 Concomitant medication

All prescriptions for study participants as covered in the main BNF chapters 1 – 15 have been included, regardless of drug class and indication, except emollients (BNF section 13.02), sunscreen (13.08), and shampoo (13.09).

Binary variables indicating the concomitant use of specific drugs at baseline have been created based on drugs dispensed, using BNF codes and/or item names as listed in table 6.3. Specific drugs have been chosen for a number of reasons: to provide further information regarding antithrombotic therapy, including VKAs, parenteral anticoagulants, antiplatelet drugs (other than aspirin), and aspirin (all uses); as a possible proxy for any disease of interest – either AF itself, or any of the comorbidities as listed in section 6.1.2 – as well as frailty more generally (antiarrhythmic drugs, digoxin, nitrate, statins, drugs affecting the renin-angiotensin system, beta-blocker, diuretics, antidiabetic drugs, analgesics, hypnotics); or because their concomitant use could potentially affect the safety of DOAC use by increasing the risk of bleeding (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRIs)).

Table 6.3: Codes and/or drug names used for identification of concomitant medication in PIS

Drugs necessitating caution when used concomitantly with DOACs	
VKA	acenocoumarol, phenindione, warfarin
Parenteral anticoagulants	**BNF**: 02.08.01
Antiplatelet drugs	**BNF**: 02.09, excluding “aspirin”
NSAIDs	**BNF**: 10.01.01
SSRI	**BNF**: 04.03.03
Other common concomitant medication	
Antiarrhythmic drugs	**BNF**: 02.03.02
Nitrates	**BNF**: 02.06.01
Statins	atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin
Drugs affecting the renin-angiotensin system [1]	**BNF**: 02.05.05
Beta-blocker	**BNF**: 02.04
Diuretics	**BNF**: 02.02
Antidiabetic drugs	**BNF**: 06.01.01 & 06.01.02
Analgesics	**BNF**: 04.07.01 & 04.07.02, excluding aspirin
Hypnotics	**BN**: 04.01

BNF – British National Formulary; DOAC – direct oral anticoagulant; NSAID – non-steroidal anti-inflammatory drug; PIS – Prescribing Information System; SSRI – selective serotonin reuptake inhibitor; VKA – vitamin K antagonist

[1] angiotensin-converting enzyme (ACE) inhibitors & angiotensin-II (AT-II) receptor antagonists

In addition to the total number of different drugs used concomitantly, calculated by counting the different BNF item names appearing on prescriptions, concomitant drug use at baseline was recoded into a categorical variable with three levels (0-4, 5-9, 10+ different drugs). A binary variable indicating polypharmacy (0=less than 5 different drugs, 1=5 or more different drugs) was also introduced for all patients.

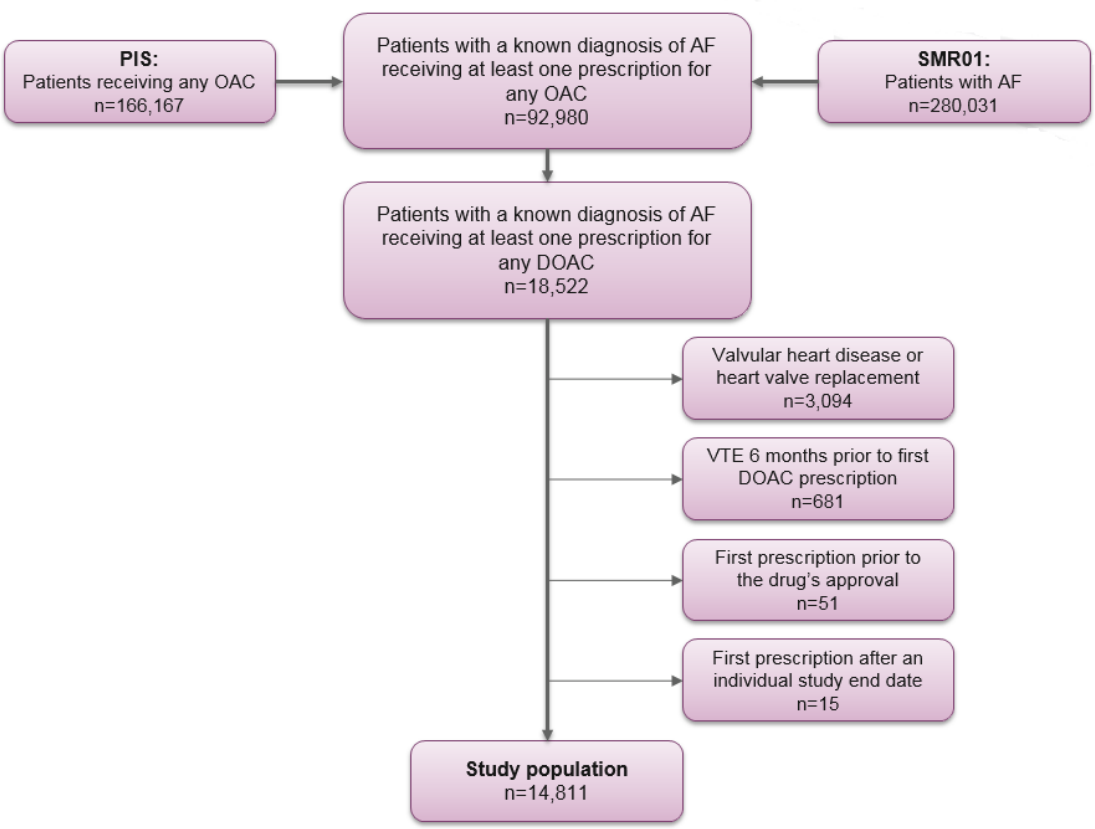
6.1.4 Statistical analysis

Statistical tests were conducted in order to compare patients' baseline characteristics between individual DOACs. For continuous variables, one-way ANOVA tests were applied; for categorical variables, chi-square tests were used. Differences between drugs identified through ANOVA were analysed further using Tukey's test. The applied level of significance was 0.05.

6.2 Results

A total of 92,980 patients with a diagnosis of AF, confirmed in secondary care, were identified in PIS as having received at least one prescription for any oral anticoagulant – either a VKA (acenocoumarol, phenindione, warfarin), or a DOAC (apixaban, dabigatran, or rivaroxaban) – between January 2009 and December 2015, of which 18,522 received at least one prescription for any DOAC. After applying all exclusion criteria, 14,811 patients were included in the study; the selection process is depicted in figure 6.1.

A large majority of all patients initiated treatment with a factor Xa inhibitor, either apixaban (42.4%) or rivaroxaban (50.0%), and approximately half of all patients (47.3%) started treatment in 2015; see also figure 6.2 for the distribution of patients by individual drug and year of first prescription. Table 6.4 gives an overview of patients' baseline characteristics overall and by drug.



AF – atrial fibrillation; DOAC – direct oral anticoagulant; OAC – oral anticoagulants; PIS – Prescribing Information System; SMR01 – Scottish Morbidity records, Inpatient and day case dataset; VTE – venous thromboembolism

Figure 6.1: Identification of study population based on inclusion and exclusion criteria, January 2009 to December 2015

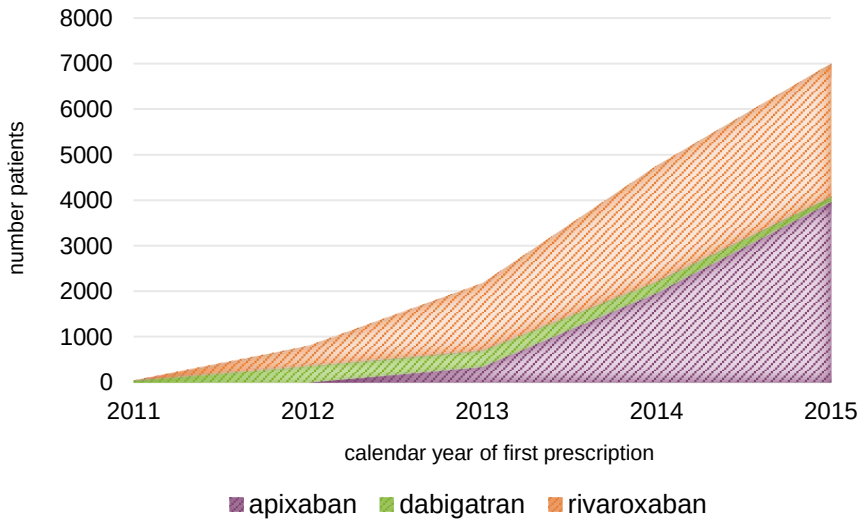


Figure 6.2: Distribution of DOAC treatment initiation by drug and calendar year

Table 6.4: DOAC patients' baseline characteristics, overall and by first drug prescribed

	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value
Calendar year of first prescription [number patients] (%)					
2011	50 (0.3)		50 (4.4)		
2012	809 (5.5)		360 (31.9)	449 (6.1)	
2013	2,182 (14.7)	342 (5.5)	357 (31.6)	1,483 (20.0)	
2014	4,766 (32.2)	1,968 (31.4)	250 (22.1)	2,548 (34.4)	
2015	7,004 (47.3)	3,963 (63.2)	112 (9.9)	2,929 (39.5)	
Female (%)	6,748 (45.6)	2,920 (46.5)	423 (37.5)	3,405 (46.0)	<0.001
Age at first prescription [years] (%)					<0.001
Less than 55	858 (5.8)	405 (6.5)	100 (8.9)	353 (4.8)	
55 – 64	1,889 (12.8)	832 (13.3)	200 (17.7)	857 (11.6)	
65 – 74	4,113 (27.8)	1,715 (27.3)	348 (30.8)	2,050 (27.7)	
75 – 84	5,291 (35.7)	2,251 (35.9)	324 (28.7)	2,716 (36.7)	
85 or older	2,660 (18.0)	1,070 (17.1)	157 (13.9)	1,433 (19.3)	
Mean age [years] (SD)	74.1 (11.3)	73.7 (11.5)	71.1 (12.0)	74.8 (11.0)	<0.001
Prior VKA use [number patients] (%)	5,575 (37.6)	1,831 (29.2)	501 (44.4)	3,243 (43.8)	<0.001
Mean Charlson score (SD)	1.33 (1.72)	1.36 (1.74)	1.06 (1.50)	1.34 (1.73)	<0.001
Mean $CHADS_2$ score (SD)	1.48 (1.28)	1.48 (1.26)	1.26 (1.23)	1.51 (1.29)	<0.001
Mean CHA_2DS_2-VASc score (SD)	2.93 (1.71)	2.92 (1.70)	2.52 (1.75)	2.99 (1.70)	<0.001
Mean HAS-BLED score (SD)	2.05 (1.17)	2.10 (1.17)	1.88 (1.16)	2.03 (1.17)	<0.001
Median number different drugs (IQR)	10 (6 – 13)	10 (6 – 14)	8 (5 – 12)	10 (7 – 13)	<0.001
Polypharmacy (%) [1]	87.2	86.8	82.6	88.2	<0.001
Median time of follow-up [days] (IQR)	346 (167 – 597)	260 (122 – 435)	867 (535 – 1168)	403 (198 – 673)	
Median number DOAC prescriptions (IQR)	7 (3 – 13)	6 (3 – 10)	13 (5 – 23)	8 (4 – 15)	
Only one DOAC prescription (%)	1,505 (10.2)	725 (11.6)	100 (8.9)	680 (9.2)	
Number different DOACs (%)					<0.001
1	14,242 (96.2)	6,188 (98.6)	917 (81.2)	7,137 (96.3)	
2 or 3	569 (3.8)	85 (1.4)	212 (18.8)	272 (3.7)	

DOAC – direct oral anticoagulant; IQR – interquartile range; SD – standard deviation; VKA – vitamin K antagonist

[1] Using 5 or more different drugs concomitantly

The mean age of patients at time of first DOAC prescription was 74.1 years (SD 11.3), and 45.6% were female. Approximately a third of all patients (37.6%) were treated with VKAs during the six month period prior to DOAC initiation. Patients' characteristics differed however between individual drugs: mean age at first prescription was lowest for dabigatran and highest for rivaroxaban, with 71.1 years (SD 12.0) and 74.8 years (SD 11.0), respectively; all individual comparisons were statistically significant ($p<0.001$). The share of women was considerably lower among dabigatran patients (37.5%) in comparison to patients initiating treatment with either apixaban (45.6%) or rivaroxaban (46.0%); the proportion of patients previously treated with VKAs prior to being prescribed a DOAC was similar for dabigatran (44.4%) and rivaroxaban (43.8%), but significantly lower among apixaban patients (29.2%).

Overall median follow-up time was 346 days (IQR 167 – 597); 10.2% of patients received only one DOAC prescription, while the median number of DOAC prescriptions issued to patients during the study period was 7 (IQR 3 – 13). A small minority of patients received prescriptions for more than one DOAC (3.8%) – nevertheless, differences between the individual drugs were sizable, ranging from 1.4% among patients with apixaban as drug of first choice to 18.8% among patients initially prescribed dabigatran.

6.2.1 Comorbidities

The mean Charlson score was 1.33 (SD 1.72), and was significantly lower among patients initiating treatment with dabigatran (1.06, SD 1.50) than among either rivaroxaban (1.34, SD 1.73; $p<0.001$) or apixaban (1.36, SD 7.41; $p<0.001$) patients. The majority of patients (66.5%) had a Charlson score less than 2, ranging from 65.5% (apixaban) to 72.2% (dabigatran); see figure 6.3 for the distribution of Charlson score by drug at baseline, and table 6.5 for details.

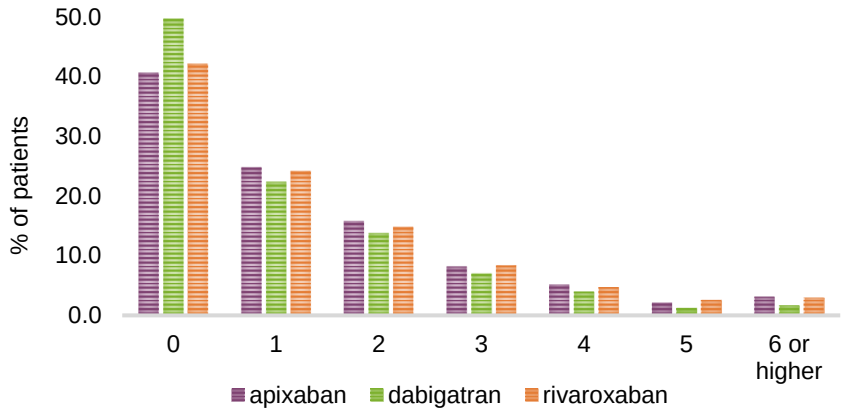


Figure 6.3: Distribution of Charlson scores at baseline, by drug [%]

The mean $CHADS_2$ and CHA_2DS_2-VASc scores among the study population were 1.48 (SD 1.28) and 2.93 (SD 1.71), respectively; both stroke risk scores were lowest among dabigatran patients, with a mean $CHADS_2$-score of 1.26 (SD 1.23) and a mean CHA_2DS_2-VASc score of 2.52 (SD1.75), and highest for rivaroxaban patients – albeit with only minor differences between the rivaroxaban and apixaban groups. Consequently, individual comparisons showed significant differences in both scores between dabigatran and apixaban ($p<0.001$) as well as between dabigatran and rivaroxaban patients ($p<0.001$). Most patients (78.9%) had a CHA_2DS_2-VASc score of 2 or higher – shares ranged from 68.6 % (dabigatran) to 80.5% (rivaroxaban). Figures 6.4 and 6.5 depict the distribution of stroke risk scores at baseline by drug; for additional details, see table 6.5.

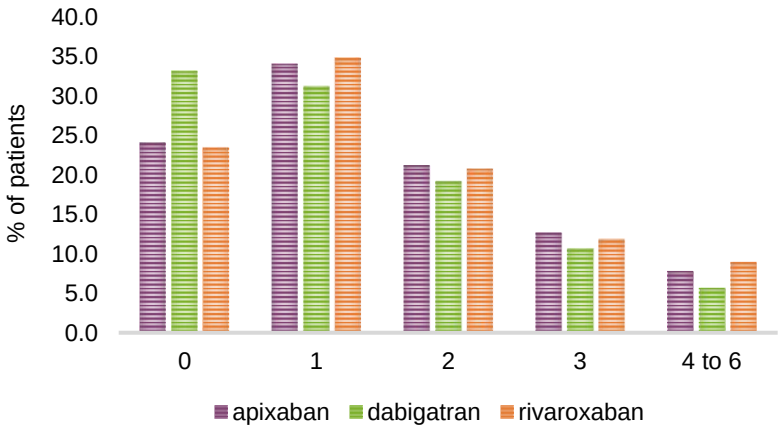


Figure 6.4: Distribution of $CHADS_2$ scores at baseline, by drug [%]

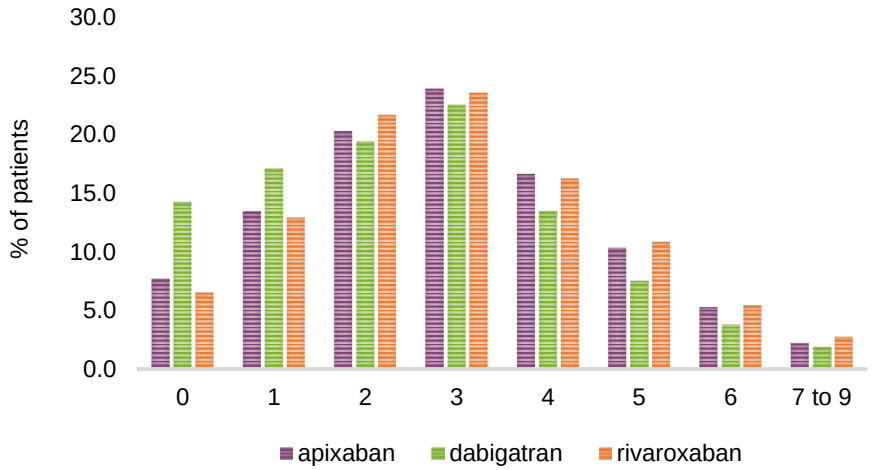


Figure 6.5: Distribution of CHA_2DS_2-VASc scores at baseline, by drug [%]

The mean HAS-BLED score was 2.05 (SD 1.17), and was again lowest among dabigatran patients with a mean of 1.88 (SD 1.16); in contrast to the stroke risk scores, the bleeding risk score was highest in the apixaban group. All individual differences were statistically significant (p<0.001). See also figure 6.6 for the distribution of HAS-BLED scores at baseline by drug, and table 6.5 for details.

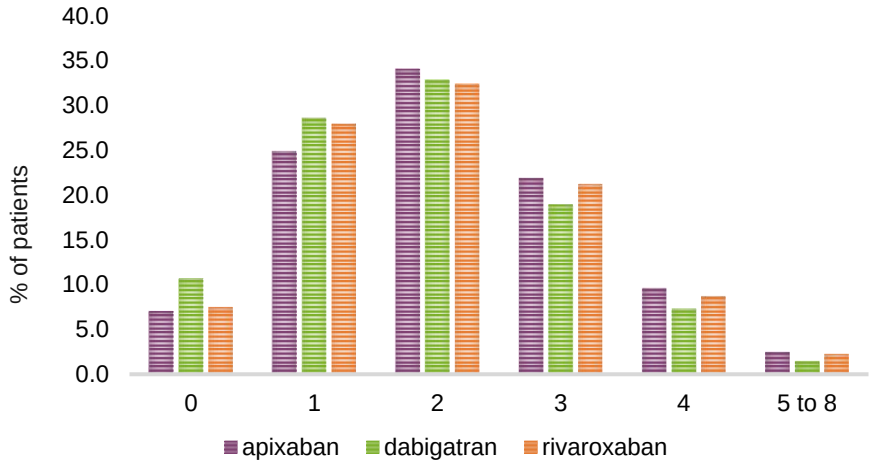


Figure 6.6: Distribution of HAS-BLED scores at baseline, by drug [%]

Table 6.5: Comorbidity/risk scores and concomitant medication at baseline, overall and by drug

	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)
Charlson score [number patients] (%)				
0	6,235 (42.1)	2,551 (40.7)	562 (49.8)	3,122 (42.1)
1	3,608 (24.4)	1,558 (24.8)	253 (22.4)	1,797 (24.3)
2	2,245 (15.2)	991 (15.8)	156 (13.8)	1,098 (14.8)
3	1,218 (8.2)	513 (8.2)	80 (7.1)	625 (8.4)
4	724 (4.9)	325 (5.2)	45 (4.0)	354 (4.8)
5	344 (2.3)	137 (2.2)	14 (1.2)	193 (2.6)
6 or higher	437 (3.0)	198 (3.2)	19 (1.7)	220 (3.0)
$CHADS_2$ score [number patients] (%)				
0	3,626 (24.5)	1,513 (24.1)	374 (33.1)	1,739 (23.5)
1	5,070 (34.2)	2,137 (34.1)	352 (31.2)	2,581 (34.8)
2	3,092 (20.9)	1,333 (21.2)	217 (19.2)	1,542 (20.8)
3	1,799 (12.1)	797 (12.7)	121 (10.7)	881 (11.9)
4 – 6	1,224 (8.3)	493 (7.9)	65 (5.8)	666 (9.0)
CHA_2DS_2-VASc score [number patients] (%)				
0	1,133 (7.6)	485 (7.7)	161 (14.3)	487 (6.6)
1	1,995 (13.5)	845 (13.5)	193 (17.1)	957 (12.9)
2	3,095 (20.9)	1,272 (20.3)	219 (19.4)	1,604 (21.6)
3	3,498 (23.6)	1,501 (23.9)	254 (22.5)	1,743 (23.5)
4	2,400 (16.2)	1,045 (16.7)	152 (13.5)	1,203 (16.2)
5	1,540 (10.4)	650 (10.4)	85 (7.5)	805 (10.9)
6	781 (5.3)	333 (5.3)	43 (3.8)	405 (5.5)
7 – 9	369 (2.5)	142 (2.3)	22 (1.9)	205 (2.8)
HAS-BLED score [number patients] (%)				
0	1,119 (7.6)	442 (7.0)	121 (10.7)	556 (7.5)
1	3,952 (26.7)	1,561 (24.9)	323 (28.6)	2,068 (27.9)
2	4,906 (33.1)	2,136 (34.1)	371 (32.9)	2,399 (32.4)
3	3,157 (21.3)	1,372 (21.9)	214 (19.0)	1,571 (21.2)
4	1,334 (9.0)	604 (9.6)	83 (7.4)	647 (8.7)
5 - 8	343 (2.3)	158 (2.5)	17 (1.5)	168 (2.3)
Number different concomitant drugs [number patients] (%)				
0 – 4	1,896 (12.8)	826 (13.2)	197 (17.4)	873 (11.8)
5 – 9	5,462 (36.9)	2,209 (35.2)	462 (40.9)	2,791 (37.7)
10 or more	7,453 (50.3)	3,238 (51.6)	470 (41.6)	3,745 (50.5)

DOAC – direct oral anticoagulant

Of those conditions included in the CHA_2DS_2-VASc score (congestive heart failure, hypertension, diabetes, prior stroke/TIA, vascular disease), hypertension was the most common, present in 36.7% of patients; 14.1% of patients had a history of prior stroke and/or transient ischaemic attacks. In addition, 14.3% of patients had a diagnosis of kidney disease, and 9.4% had experienced major bleeds prior to DOAC initiation. For details, see table 6.6.

Table 6.6: Comorbidities at baseline, overall and by first drug prescribed

Number patients (%)	**DOAC (n=14,811)**	**Apixaban (n=6,273)**	**Dabigatran (n=1,129)**	**Rivaroxaban (n=7,409)**	**p-value**
Congestive heart failure [1], [2]	2,080 (14.0)	931 (14.8)	128 (11.3)	1,021 (13.8)	0.005
Hypertension [1], [2], [3]	5,442 (36.7)	2,273 (36.2)	391 (34.6)	2,778 (37.5)	>0.05
Diabetes mellitus [1], [2]	2,245 (15.2)	964 (15.4)	150 (13.3)	1,131 (15.3)	>0.05
Prior stroke/TIA [1], [2], [3]	2,092 (14.1)	909 (14.5)	138 (12.2)	1,045 (14.1)	>0.05
Vascular disease [2]	2,603 (17.6)	1,079 (17.2)	164 (14.5)	1,360 (17.6)	0.004
Renal disease [3]	2,122 (14.3)	957 (15.3)	98 (8.7)	1,067 (14.4)	<0.001
Liver disease [3]	31 (0.2)	13 (0.2)	*	18 (0.2)	>0.05
Prior major bleed [3]	1,399 (9.4)	595 (9.5)	117 (10.4)	687 (9.3)	>0.05
Pulmonary embolism	169 (1.1)	60 (1.0)	9 (0.8)	100 (1.3)	>0.05
Cancer	1,293 (8.7)	556 (8.9)	91 (8.1)	646 (8.7)	>0.05

DOAC – direct oral anticoagulant; TIA – transient ischaemic attack

[1] Included in $CHADS_2$ score; [2] included in CHA_2DS_2-VASc score; [3] included in HAS-BLED score;
* **–** less than five patients

6.2.2 Concomitant medication

Polypharmacy was widespread, with 87.2% of patients being treated with five or more different drugs prior to DOAC initiation. The median number of different drugs issued to patients during the six-month baseline period was 10 (IQR 6 – 13), and approximately half of all patients (50.3%) received ten or more different drugs.

Most prevalent concomitant medications were beta-blockers (issued to 67.6% of patients), statins (56.1%), drugs affecting the renin-angiotensin system such as ACE inhibitors and AT-II receptor antagonists (52.5%), analgesics (50.9%), and diuretics

(46.8%); 34.5% of patients were treated with aspirin, while 12.0% received prescriptions for antiplatelet drugs other than aspirin. Details are provided in table 6.7.

Table 6.7: Concomitant medication at baseline, overall and by first drug prescribed

Number patients (%)	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value
VKA	5,575 (37.6)	1,831 (29.2)	501 (44.4)	3,243 (43.8)	<0.001
Parenteral anticoagulants	230 (1.6)	65 (1.0)	18 (1.6)	147 (2.0)	<0.001
Antiplatelet drugs	1,773 (12.0)	872 (13.9)	94 (8.3)	807 (10.9)	<0.001
Aspirin	5,115 (34.5)	2,398 (38.2)	424 (37.6)	2,293 (30.9)	<0.001
NSAIDs	1,066 (7.2)	490 (7.8)	95 (8.4)	481 (6.5)	0.003
SSRI	1,504 (10.2)	656 (10.5)	103 (9.1)	745 (10.1)	>0.05
Anti-arrhythmic drugs	1,246 (8.4)	586 (9.3)	127 (11.2)	533 (7.2)	<0.001
Digoxin	3,538 (23.9)	1,493 (23.8)	288 (25.5)	1,757 (23.7)	>0.05
Nitrates	2,356 (15.9)	1,004 (16.0)	160 (14.2)	1,192 (16.1)	>0.05
Statins	8,311 (56.1)	3,587 (57.2)	591 (52.3)	4,133 (55.8)	0.008
ACE inhibitors & AT-II antagonists	7,782 (52.5)	3,309 (52.7)	573 (50.8)	3,900 (52.6)	>0.05
Beta-blocker	10,011 (67.6)	4,398 (70.1)	713 (63.2)	4,900 (66.1)	<0.001
Diuretics	6,926 (46.8)	2,884 (46.0)	467 (41.4)	3,575 (48.3)	<0.001
Antidiabetic drugs	2,197 (14.8)	915 (14.6)	155 (13.7)	1,127 (15.2)	>0.05
Analgesics	7,543 (50.9)	3,230 (51.5)	476 (42.2)	3,837 (51.8)	<0.001
Hypnotics	1,693 (11.4)	721 (11.5)	124 (11.0)	848 (11.4)	>0.05

ACE – angiotensin converting enzyme; AT-II – angiotensin-II receptor; DOAC – direct oral anticoagulant; NSAID – non-steroidal anti-inflammatory drug; SSRI – selective serotonin reuptake inhibitor; VKA – vitamin K antagonist

6.3 Discussion

Although observational studies analysing the usage of DOACs in patients with atrial fibrillation vary considerably – in terms of context and sample size, but also with respect to study purpose – baseline characteristics of patients with AF in Scotland initiating DOAC therapy were broadly comparable to previously published findings: patients are in general elderly and have a range of comorbidities; a small majority of patients are male; and a sizable share of patients in Scotland were treated with vitamin K antagonists prior to DOAC initiation. However, results differ substantially

between individual studies, particularly regarding comorbidities; in addition, there are noticeable differences between the study population and the patients included in the three clinical trials upon which approvals for DOACs were granted.

6.3.1 Other observational studies

When combining all patients regardless of which drug they were initiated on, the overall DOAC population included in this study – with a mean age of 74.1 years and comprising 45.6% women – was similar to the DOAC patients (n=914) included in a study previously conducted in England, where the mean age was 74.5 years and 39.5% of patients were female. CHA_2DS_2-VASc scores were slightly higher in Scotland with a mean of 2.93 as compared to 2.8 in England; in contrast, mean Charlson scores were lower in Scotland (1.33 versus 1.7), and the proportion of patients diagnosed with hypertension, diabetes, and prior stroke were also considerably lower – 36.7%, 15.2%, and 14.1% compared to 60.6%, 20.1%, and 25.1%, respectively (Martinez et al., 2016). At least some of these differences in comorbidities might be due to differences in the data available though: while the Clinical Practice Research Datalink (CPRD) database used for the English study contains primary care data, medical records were only available from secondary care for this study, likely resulting in an underestimation of conditions such as hypertension and diabetes that are usually diagnosed and treated in primary care.

When stratifying patients by their index drug, the mean ages of patients in this study were 73.7 years (apixaban), 71.1 years (dabigatran), and 74.8 years (rivaroxaban); the proportion of female patients were 46.5%, 37.5%, and 46.0% for patients starting treatment with apixaban, dabigatran, and rivaroxaban, respectively. These results match previously published study findings: among apixaban patients, the mean patient age ranged from 70 to 78.0 years, and the share of women from 42% to 58.5% (Al-Khalili et al., 2016, Deitelzweig et al., 2017, Forslund et al., 2016, Hernandez et al., 2017, Olesen et al., 2015, Shiga et al., 2015); for patients treated with dabigatran, mean age ranged from 70 to 76.8 years, and between 26% and 53.0% of patients were female (Coleman et al., 2016, Deitelzweig et al., 2017, Forslund et al., 2016, Gorst-Rasmussen et al., 2015, Hernandez et al., 2017, Olesen et al., 2015, Shiga et al., 2015); and among patients initiating treatment with rivaroxaban, mean age ranged from 70 to 77.2 years, and between 32% and 57.3% of patients were women (Al-Khalili et al., 2016, Coleman et al., 2016, Deitelzweig et al., 2017, Forslund et al.,

2016, Hernandez et al., 2017, Olesen et al., 2015, Shiga et al., 2015). In contrast, study populations differed with respect to prior treatment with VKAs. A little over a third of all patients (37.3%) included in this study were treated with VKAs during the baseline period, ranging from 29.2% of apixaban patients to 44.4% of dabigatran patients. Few other studies have reported on VKA use prior to DOAC initiation, with widely differing findings: in a small study (n=350) based on a single hospital unit in Sweden, 24% and 14% of apixaban and rivaroxaban patients, respectively, have previously been treated with VKAs (Al-Khalili et al., 2016); whereas the share among rivaroxaban patients (n=1,204) contained within a regional DOAC registry in Germany was 39.3% (Beyer-Westendorf et al., 2015). However, the majority of studies only included OAC-naïve patients – usually in order to compare uptake and/or adherence between patients newly initiating DOACs to those starting warfarin (Forslund et al., 2016, Hernandez et al., 2017, Martinez et al., 2016, Olesen et al., 2015, Shiga et al., 2015, Yao et al., 2016). While limiting study populations to OAC-naïve patients might indeed be necessary for the purpose of comparing for example adherence to VKAs and DOACs, including all patients in the analysis – regardless of prior VKA status – would most likely be beneficial when comparing individual DOACs to each other: not only would this increase sample sizes; study populations would also be a better representation of actual treatment population, considering that switching patients from warfarin to a DOAC might become more frequent over time.

As with most other baseline characteristics, findings with regards to comorbidities varied across studies. Although most observational studies generally calculated CHA_2DS_2-VASc scores and presented data with regards to individual comorbidities, not all studies reported mean score values; where available, mean CHA_2DS_2-VASc scores were usually higher than those found here – 3.0 to 4.68 for apixaban, 2.7 to 4.3 for dabigatran, and 3.1 to 4.55 for rivaroxaban patients, compared to 2.92, 2.52, and 2.99 in Scotland, respectively (Coleman et al., 2016, Deitelzweig et al., 2017, Forslund et al., 2016, Gorst-Rasmussen et al., 2015, Hernandez et al., 2017, Olesen et al., 2015). The proportion of patients who were diagnosed with heart failure or diabetes, as well as those with a history of stroke and/or TIA, were within the ranges found in other studies; findings differed considerably between studies though. In contrast, hypertension was much less common in this study than reported elsewhere; while the share of patients with a known diagnosis of hypertension among patients initiating DOAC treatment were 36.2% (apixaban), 34.6% (dabigatran), and 37.5%

(rivaroxaban) in this study, findings from other studies ranged from 45.1% to 93.6%, 43.5% to 88.9%, and 45.5% to 91.8%, respectively (Al-Khalili et al., 2016, Beyer-Westendorf et al., 2015, Coleman et al., 2016, Forslund et al., 2016, Hernandez et al., 2017, Olesen et al., 2015, Shiga et al., 2015, Yao et al., 2016). Discrepancies in reported comorbidities could, however, at least partially be attributable to differences in data availability; the presence of hypertension for instance might have been underestimated in this study as this information has been extracted solely from hospital discharge records – with implications for the stroke risk scores as well, as both the $CHADS_2$ and the CHA_2DS_2-VASc scores include hypertension as one of their indicators.

As opposed to comorbidities, few studies have reported on concomitant medication at baseline, and results diverged considerably. A Danish study for example – using administrative patient registry data, including 8,709 AF patients who were initiated on DOAC treatment between August 2011 and October 2013 – found aspirin use at comparable levels to AF patients in Scotland initiating treatment with apixaban and dabigatran; usage among rivaroxaban patients was however higher than in Scotland, with 30.9% versus 42.3% (Olesen et al., 2015). The Danish study also reported higher percentages of patients receiving prescriptions for NSAIDs across all DOACs (between 14.4% and 15.1%, as compared to 6.5% to 8.4%); similarly, a large US study analysing a sample of Medicare beneficiaries newly diagnosed with AF and starting treatment with any OAC between January 2013 and December 2014 (n=21,265) found higher levels of NSAID use during a 6-month period prior to DOAC initiation for all DOACs, ranging from 11.6% to 12.7% (Hernandez et al., 2017, Olesen et al., 2015). In contrast, percentages of patients using a range of other drugs were considerably lower in Denmark than in Scotland, regardless of DOAC: between 7.8% (dabigatran) and 9.2% of patients (rivaroxaban) were prescribed digoxin in Denmark, as compared to 23.7% (rivaroxaban) to 25.5% (dabigatran) in Scotland; and the proportion of patients in Denmark using beta-blockers ranged from 39.1% to 44.2%, and between 32.0% and 33.5% of patients were treated with statins, whereas these shares were 63.2% to 70.1% and 52.3% to 57.2% in Scotland, respectively (Olesen et al., 2015). The higher rates of treatment with digoxin, beta-blockers and statins in Scotland could be indicative of an overall unhealthier patient population, even though this was not mirrored in recorded levels of comorbidities; alternatively, these discrepancies could be a reflection of diverging treatment guidelines (e.g. using

different blood pressure thresholds when prescribing medication, or using alternative drugs for similar indications) – exact reasons for these diverse findings remain however unclear.

6.3.2 Clinical trials

Compared to the phase III clinical trials upon which approval for DOACs were granted, this study's population was slightly older (except from patients starting treatment with dabigatran), and had a higher share of female patients: the mean age in the RELY trial (dabigatran) was 71.5 years, while median ages in the ARISTOTLE (apixaban) and ROCKET-AF (rivaroxaban) studies were 70 and 73 years, respectively; the proportion of female patients ranged from 35.5% (ARISTOTLE) to 39.7% (RELY). In contrast, the proportion of patients who were treated with VKAs prior to trial inclusion were considerably higher than observed in this study; while 29.2%, 44.4%, and 43.8% of apixaban, dabigatran, and rivaroxaban patients in this study were previously treated with warfarin, proportions in the clinical trials were 57.1% (ARISTOTLE), 50.2% (RELY), and 62.3% (ROCKET-AF). However, definitions for prior use of VKAs differed between studies: while prior VKA use was defined as having used a VKA for more than 30 consecutive days in ARISTOTLE, a total lifetime use of more than 60 days was considered prior long-term VKA use in RELY; no definition was provided for ROCKET-AF (Connolly et al., 2009, Granger et al., 2011, Patel et al., 2011).

All major comorbidities (prior stroke, heart failure, diabetes, and hypertension) were much less common in the study population than in the respective clinical trials; consequently, $CHADS_2$ scores were noticeably higher in the trial populations – with means of 2.1, 2.2, and 3.48 for apixaban, dabigatran, and rivaroxaban in the RCTs, as compared to 1.48, 1.26, and 1.51 in the population as included in this study, respectively (Connolly et al., 2009, Granger et al., 2011, Patel et al., 2011). Discrepancies in baseline comorbidities were most pronounced in comparison to ROCKET-AF: whereas only 14.1% of rivaroxaban patients in this study for instance previously experienced a stroke, the proportion among ROCKET-AF participants was 54.9%; 62.6% of patients participating in ROCKET-AF had a diagnosis of heart failure, 40.4% had diabetes, and 90.3% had hypertension. Differences in comorbidities, even though potentially influenced by the possible underestimation of e.g. hypertension and diabetes mellitus in this study due to data constrains, can however at least partially be explained by the inclusion criteria in place for the trials: in order to be eligible for

inclusion in ROCKET-AF, either a history of stroke or the presence of at least one of these conditions in addition to an age of at least 75 years (or two of the medical conditions if a patients' age was below 75) was required, and the majority of patients enrolled were mandated to have at least three risk factors for stroke – thus purposely selecting a very high-risk population. Similar inclusion criteria were in place for the other trials, although with less stringent pre-selections of high-risk participants; for both the apixaban and dabigatran trials, only either the presence of one of the aforementioned conditions, or an age above 75 years were required in lieu of a history of stroke, resulting in lower shares of patients having diabetes (25.0% ARISTOTLE, 23.1% RELY), heart failure (35.5% ARISTOTLE, 31.8%, RELY), and hypertension (87.3% ARISTOTLE, 78.9% RELY) as compared to ROCKET-AF.

In contrast to deliberately including patients with high risks of stroke, patients with high risks of bleeding events – such as patients with a history of major bleeding including relevant gastro-intestinal bleeds, patients who recently had surgery, or those with uncontrolled hypertension – were excluded from both the ROCKET-AF and the RE-LY trial, and HAS-BLED scores or a comparable compound measurement of bleeding risk have not been reported (Connolly et al., 2009, Patel et al., 2011). Among the RCTs conducted with DOACs, only the ARISTOTLE trial did not exclude patients based on their potential bleeding risk – hence, 16.7% of patients had a history of bleeding prior to apixaban initiation during the trial (Granger et al., 2011). By excluding patients with an elevated risk of bleeds, actual bleeding risks associated with DOAC treatment in real life could therefore have potentially been underestimated. In this study for example, the mean HAS-BLED scores ranged from 1.88 (dabigatran) to 2.10 (apixaban), generally indicating at least a median risk of bleeding among patients; indeed, only between 7.0% and 10.7% of patients had a low risk of bleeding (with a HAS-BLED score of 0), while 27.9% of dabigatran patients, and 32.2% and 34.0% of patients initiating treatment with rivaroxaban and apixaban, respectively, had a high risk, with HAS-BLED scores of 3 or higher.

Even though comorbidities at baseline differed considerably between the population included in this study and the participants enrolled in the clinical trials, differences in concomitant medication were seemingly mostly minor: amiodarone use among the study population was similar to the trials, where reported; usage of beta-blockers was lower in ARISTOTLE than found here (63.6% versus 70.1%), while similar in RELY

and ROCKET-AF; 8.2% of participants in ARISTOTLE were treated with NSAIDs at baseline, as compared to 7.8% of apixaban patients included in this study; and approximately a third of patients included in the clinical trials were using aspirin at baseline (31.3% in ARISTOTLE, 38.7% in RELY, and 36.3% in ROCKET-AF). Statin use was however higher among the study population than in all three respective trials, ranging from 52.3% (dabigatran) to 57.2% (apixaban), in contrast to 43.0% to 45.0% in the trials (Connolly et al., 2009, Granger et al., 2011, Patel et al., 2011). Nevertheless, all trials had some restrictions in place with regards to concomitant medication: concomitant aspirin use for example was only allowed up to daily dosages of 100mg / 165mg in ROCKET-AF and ARISTOTLE, respectively; and patients with chronic use of NSAIDs were excluded from ROCKET-AF. As both aspirin and NSAIDs are available without a prescription – at least at low doses – in many countries, including Scotland, usage of these drugs could have been underestimated in this study and might, consequently, be considerably higher in real-world populations than among the participants in the clinical trials – with potential implications on treatment outcomes.

6.4 Conclusion

Baseline characteristics of patients with AF initiating DOAC treatment were broadly similar across observational studies conducted across a range of diverse settings, even though differences in context and data availability might have affected the degree to which comorbidities and concomitant medication within a study population were captured. In contrast, differences between clinical trial participants and real-world patients as included in this study were considerable, especially with regards to comorbidities; while these differences might have been impacted to a certain extent by data constraints (as no primary care or laboratory records were available for this study), specific selection criteria as applied in the RCTs have most definitely contributed.

Due to the selection criteria as applied in the trials (i.e. predominantly including patients with relatively high risks of stroke), specific conditions at baseline – most prominently heart failure, hypertension, and a history of stroke – were for instance more common in the RCTs than in this study and, consequently, comorbidity scores based on these conditions such as the $CHADS_2$ score were higher. In contrast, other

diseases which could potentially affect the effectiveness and safety of DOAC treatment might have been underrepresented; all trials for example restricted the inclusion of patients with liver disease, kidney disease, and cancer, albeit to different degrees, while ROCKET-AF and RE-LY also excluded patients with an increased risk of bleeding events. In addition, the relatively high levels of concomitant drug use in patients in clinical practice could pose a rather different risk than in a tightly controlled trial environment – where drug use is potentially restricted, and the occurrence of any adverse events is monitored.

Chapter 7 – Utilisation of direct oral anticoagulants

This chapter summarises the results from the DOAC utilisation analysis, and as such provides answers to study objective 2 as outlined in section 3.2 (to evaluate the quality of drug use by determining drug utilisation patterns in AF patients in Scotland). It first gives a detailed overview of drug utilisation studies, including definitions of major concepts and explanations of the main measurements used, and highlights some crucial methodological issues, before describing the most important study-specific aspects. The results presented and discussed here only relate to the usage of DOACs – i.e. discontinuation, persistence, and adherence; for patients' baseline characteristics, see chapter 6.

7.1 Definitions of concepts

Drug utilisation studies are commonly conducted to analyse the usage of drugs in clinical practice, and results are frequently used to compare uptake and utilisation of drugs over time and/or between regions. In addition, findings can potentially be used to improve the accuracy of drug exposure estimates when investigating treatment outcomes in clinical practice as compared to clinical trials.

However, the terminology applied to describe the use of drugs is not standardised and has been subject to changes over time, resulting in a sometimes confusing array of diverging definitions (Vrijens et al., 2012). In addition, a wide range of diverse measures potentially useful for analysing drug utilisation has been proposed over time, but no "gold standard" for how to optimally summarise the use of drugs has been agreed upon yet; instead, several different definitions and methods of calculation can be found for measurements commonly used in utilisation studies (Caetano et al., 2006, Lehmann et al., 2014).

For the purpose of this study, the taxonomy proposed by the Ascertaining Barriers for Compliance (ABC) project in cooperation with the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) has been used to describe the different parts and aspects of drug utilisation (Vrijens et al., 2012), while definitions and methods of calculation for adherence measures are based on a systematic literature review aimed at facilitating standardisation (Hess et al., 2006).

7.1.1 Describing treatment adherence

Adherence to drug treatment has been defined by the WHO in 2003 as "[…] *the extent to which a person`s behaviour* […] *corresponds with agreed recommendations from a health care provider*." (WHO, 2003a). An alternative current version, supported by ESPACOMP, defines treatment adherence as "[…] *the process by which patients take their medications as prescribed* […]" (Vrijens et al., 2012), thereby emphasising its changeable, processual character. "Adherence", regardless of the specific definition applied, has started to replace the older term "compliance", introduced some 40 years ago, as it is thought of better reflecting a patient's autonomy in decision-making and being less judgemental (Acri & Gross, 2012).

Adherence to medicine as a process consists of three different parts, each representing a distinctive aspect: initiation; implementation; and discontinuation (Vrijens et al., 2012). While initiation and discontinuation indicate the start and end of a therapy, respectively, implementation illustrates the extent to which a patient's drug taking behaviour matches the instructions given by the prescriber. In addition, persistence describes the period of time between initiation and discontinuation of treatment; figure 7.1 gives an overview of the complete process.

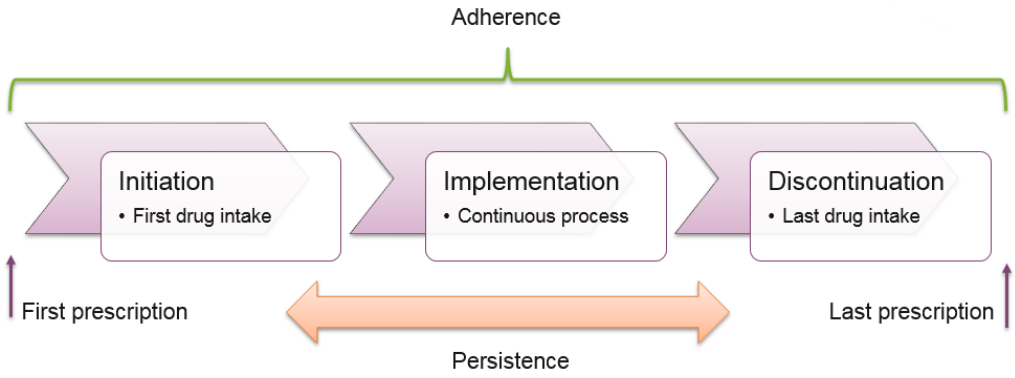


Figure 7.1: Adherence to medication – framework; adapted from Vrijens et al., 2012

Based on this taxonomy, non-adherence can be divided into three different categories: first, failure to initiate treatment in a timely fashion, or at all; second, deviation from prescribed treatment schedules, either regarding dosing or with respect to timing of drug intake; and third, premature discontinuation (Vrijens et al., 2012). Failure to initiate treatment – meaning, basically, that a patient never received

the drug because they did not fill in a prescription for the first time – is also called primary non-adherence, while secondary non-adherence encompasses all other instances of patients not taking medication as prescribed (Blix, 2016).

7.1.2 Measuring adherence

The aim of measuring adherence is the attempt to quantify a patient´s drug taking behaviour in three respects: intensity, continuity, and duration – how much of a drug does a patient take, how frequently, and for how long? The implementation phase of adherence is the key to answering mainly the first two aspects, while analysing discontinuation and persistence addresses the latter.

Adherence to medication can be measured directly or indirectly. Direct methods measure the intake of a drug, for example via using biological markers or drug assays; however, measuring adherence directly is a complex endeavour, and for practical reasons direct measures are rarely used to assess adherence. In contrast, indirect methods – measuring a patient's possession of a drug rather than actual intake – are much easier to apply. Methods include patients´ self-reporting, electronic devices, and pill counts; nowadays, indirect measurement of adherence is usually conducted by analysing administrative data such as electronic prescribing records, which allows for much larger sample sizes. Nevertheless, indirect methods also have disadvantages, from recall bias (self-reporting) to missing information (pharmacy claim databases). In addition, possession of medication can only ever be a proxy to drug intake, and is subject to a range of assumptions – not least that patients indeed do take the drugs they received (Hansen et al., 2009, Lehmann et al., 2014, Vrijens & Heidbuchel, 2015).

The minimum of basic values needed to answer the main questions with respect to patients' adherence to treatment are a) quantity prescribed and/or dispensed; and b) time interval between treatment initiation and discontinuation, or between individual prescriptions. Depending on the variables available for a study, a wide variety of measures can be calculated, particularly with regards to the implementation phase. Even though several of the adherence (implementation) measures are sometimes used interchangeably, they all measure slightly different aspects; and to complicate things further, numerous variations of some of the more well-known measurements have been used, with measurements based on diverging definitions. In addition,

studies quite frequently simply dichotomise adherence by introducing an arbitrary cut-off point for perceived non-adherence, based on a selection of available measures (Caetano et al., 2006, Hudson et al., 2007, Lehmann et al., 2014). Although measuring persistence has also not been standardised, the differences in methodology are not quite as pronounced as is the case for adherence. Nevertheless, the two main methods used for calculating persistence – the refill-gap and anniversary methods, as described subsequently – may lead to significantly diverging results due to differences in underlying definitions and assumptions (Gregoire & Moisan, 2016). Consequently, it is crucial that studies analysing the utilisation of drugs offer definitions of the concepts used, as well as detailed explanations of the measurements applied.

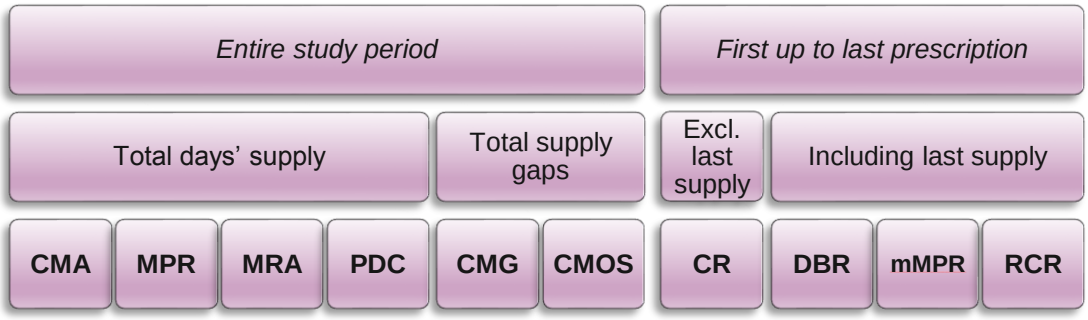
Due to the availability of a wide range of diverse measurements, all measuring different aspects of adherence, it has been proposed that triangulation of methods – applying at least two different measurements – is necessary in order to enhance validity and reliability of results (Caetano et al., 2006, Lehmann et al., 2014).

7.1.2.1 Measurements of adherence (implementation)

When analysing adherence, the period of drug intake in question can either be a complete study period, a specific part of a study period, or an individual prescription interval. While many commonly used measurements – e.g. medication possession ratio (MPR), medication refill adherence (MRA), or proportion of days covered (PDC) – describe the availability of drugs over the entire period of study participation regardless of when the last prescription was issued to a patient, some measurements such as the compliance rate (CR) or the refill compliance rate (RCR) only include the time between first and last recorded prescription. A modified version of the medication possession ratio (mMPR) covers the period between first prescription and presumed end of last recorded prescription (Hess et al., 2006).

Most measurements base their calculations on the total days´ supply prescribed during the study period, including some of those who do not include the period of time after the last recorded prescription (mMPR, but also RCR and days between refills (DBR)); an exception is the compliance rate, where the supply dispensed at the last recorded prescription is excluded from calculations. In contrast, two measurements are based on supply gaps: continuous measure of medication acquisition (CMG), and

continuous multiple interval measure of oversupply (CMOS). While CMOS allows for oversupply, negative values – indicating that days` supply exceeds the number of days a patient has been included in the study – are truncated when calculating CMG. Oversupply is also truncated when calculating PDC, resulting in a maximum value of 100%; other differences between individual measures are minor (Hess et al., 2006). Figure 7.2 gives an overview.



CMA – continuous measure of medication acquisition; CMG – continuous measure of medication gaps; CMOS – continuous multiple interval measure of oversupply; CR – compliance rate; DBR – days between fills adherence rate; mMPR – modified medication possession ratio; MPR – medication possession ratio; MRA – medication refill adherence; PDC – proportion of days covered; RCR – refill compliance rate.

Figure 7.2: Adherence to medication – proposed measurements. (Hess et al., 2006)

Unlike the aforementioned aggregate measurements, the continuous single-interval measure of medication availability (CSA) is based on the number of days between subsequent prescriptions, and thus gives a much more detailed picture of adherence (Hess et al., 2006).

The specific measurements used in this study are discussed further in section 7.3.2.

7.1.2.2 Measurements of discontinuation and persistence

In the taxonomy promoted by ESPACOMP, discontinuation of treatment is defined as the end of treatment (Vrijens et al., 2012). However, drug utilisation studies only cover a finite time period, and the actual end of drug treatment will be unknown in many cases; therefore, discontinuation is usually based on treatment gaps (refill-gap method): patients are presumed to have discontinued treatment when the time period between prescriptions not covered by a sufficient drug supply exceeds a pre-specified, admissible gap length. Patients are censored after the first identified discontinuation event, and discontinuation rates are calculated by dividing the number

of patients having discontinued treatment at the end of the study by the total number of patients initiating treatment (Gregoire & Moisan, 2016). Admissible gaps can be defined depending on e.g. the drug in question (taking into account, for instance, a drug's half-life) and/or observed prescribing practices (such as the average supply per prescription), and may vary considerably between studies; these differences need to be considered when comparing results, as definitions of admissible gaps and grace periods have a direct impact on discontinuation rates.

Treatment persistence is frequently defined based on discontinuation: crude persistence rates are calculated by dividing the number of patients not having discontinued treatment at the end of the study by the total number of patients initiating treatment (Gregoire & Moisan, 2016). In effect, the persistence rate calculated using this approach will be the equivalent of (100% – discontinuation rate). A similar method can be applied when calculating persistence after certain time periods; when e.g. attempting to identify the share of patients still on treatment one year after initiation, the number of patients not having discontinued after 12 months should be divided by the number of patients initiating treatment with a minimum time of follow-up of 12 months.

However, two aspects need to be taken into consideration so as to ensure estimations for discontinuation as well as persistence are as accurate as possible. First, the timing between prescriptions does not necessarily match the supply dispensed at each occasion, for a number of reasons – patients might, for instance, order a prescription in due time before they run out of medication, i.e. a previous oversupply might have to be taken into account when identifying discontinuation events. And second, patients might interrupt treatment only temporary, and eventually re-initiate therapy (e.g. unplanned "drug holidays" decided by the patient; planned short-term interruptions of OAC treatment due to surgical interventions; or discontinuation and subsequent re-initiation of treatment due to changes in underlying disease states, etc.); this means that patients who re-start treatment after a temporary interruption would be misclassified as having stopped treatment while this in fact has not been the case. To account for intermediary treatment interruptions, persistence at pre-specified points in time can alternatively be calculated using the anniversary method; with this approach, patients are deemed persistent at the pre-specified point in time when a

prescribed drug supply covers the anniversary date (e.g. 1 year after initiation) of the index prescription (Gregoire & Moisan, 2016).

The specific measurements used in this study are discussed further in section 7.3.2.

7.2 Purpose of this study

In order to prevent strokes, many AF patients are treated with oral anticoagulants on a long-term basis. Warfarin, a vitamin K inhibitor, has been used for this purpose for decades; its utilisation has been studied widely, suggesting under-usage of anticoagulants in certain patient groups (Díez-Manglano et al., 2014, Fornari et al., 2007, Ogilvie et al., 2010, Ogilvie et al., 2011, Pinheiro Sá et al., 2016), but also issues related to patients' adherence to treatment including irregular or intermittent drug intake (Ewen et al., 2014, Skeppholm & Friberg, 2014). Although non-adherence to treatment is widespread among drugs used for cardiovascular diseases (Cotté et al., 2014, Kolandaivelu et al., 2014, Schulz et al., 2016), non-adherence to warfarin treatment seems to be particularly common, and high discontinuation rates of warfarin treatment have been reported in both clinical trials and observational studies (Ewen et al., 2014, Fang et al., 2010, O'Brien et al., 2014). Poor adherence has been ascribed to a variety of issues, ranging from the occurrence of bleeding events to the inconvenience of warfarin treatment (Cotté et al., 2014, Kaariainen et al., 2013, Lip & Shantsila, 2013, Nutescu et al., 2011).

As non-adherence to VKA treatment negatively affects treatment outcomes (Cotté et al., 2014, Morgan et al., 2009, Schein et al., 2016, Sherwood et al., 2014), efforts to replace warfarin with easier-to-use, more patient-friendly drugs have resulted in the introduction of DOACs. DOACs have easier dosing schemes and in theory do not require monitoring, primarily because their therapeutic windows are much wider and interactions with other drugs and food ingredients are shown to be less likely than with warfarin (Deitelzweig, 2014, Scaglione, 2013) – factors that might potentially lead to an improvement in patients' adherence to these drugs as compared to warfarin. However, concerns have been raised about the potential impact of the absence of monitoring, as well as the presence of multi-morbidity and polypharmacy, on DOAC treatment adherence (Di Minno et al., 2014, Jaspers Focks et al., 2016, Piccini et al., 2016, Rodriguez et al., 2013, Sanfélix-Gimeno et al., 2015).

Knowledge about patients' adherence to DOACs in clinical practice is still limited though. Studies conducted thus far have been disparate in sample size, follow-up period, and methodology; the use of a variety of definitions and measurements, with methods of calculation differing, complicates comparisons of results across studies. Moreover, studies commonly focused on a specific aspect of utilisation, and frequently reported on DOACs as a group (Martinez et al., 2016, Pottegård et al., 2014) – or, when analysing utilisation by individual drug, regularly did not report on all DOACs (Beyer-Westendorf et al., 2015, Gorst-Rasmussen et al., 2015, Schulman et al., 2013, Thorne et al., 2014). In addition, even though treatment with DOACs is in general deemed to be as effective and safe as with warfarin (Connolly et al., 2009, Giugliano et al., 2013, Granger et al., 2011, Patel et al., 2011), the effect of non-adherence to treatment on bleeding risk and stroke incidence among AF patients has been addressed but as yet not intensely studied (Sanfélix-Gimeno et al., 2015, Yao et al., 2016).

The *purpose* of this study was therefore twofold: first, to report on the use of DOACs for stroke prevention in patients with a diagnosis of AF, confirmed in secondary care, in Scotland; and second, to assess the differences between the various measures of adherence as applied to the same set of patients.

7.3 Methods and material

This section is mainly intended to give a detailed description of the specific adherence measurements applied; it also gives a brief summary of the study, including the study population and variables used for analysis. The overall study design, its settings, and the data sources are explained in sections 3.4., 3.3 and 4.1, respectively, together with a more in-depth description of the data itself in section 4.2.

7.3.1 Summary of study specifics

7.3.1.1 Study population

The study population comprised patients with a diagnosis of AF, confirmed in secondary care, who received at least one prescription for any DOAC; patients with heart valve replacements, a diagnosis of mitral stenosis, or a VTE six months prior to DOAC initiation were excluded (the exclusion criteria are described in detail in section 6.1). A patient's index date for study inclusion was the date of first recorded

prescription for any DOAC; their individual end date of follow-up was either date of death or removal from a Scottish GP registry for other reasons (e.g. emigration), or the study end date (December 31st, 2015), whichever occurred first.

7.3.1.2 Variables

A limited number of variables has been used for this analysis, comprising basic socio-demographic aspects and prescription-related information. In addition to the variables which were readily available in the datasets, a range of derivative variables has been created.

Socio-demographic data included patient sex as a binary variable (1=m, 2=f); and age at time of prescription. Along with the continuous measure of age in years, patient age at time of first prescription has been recoded into a categorical variable, comprising five separate age groups (<55, 55 – 64, 65 – 74, 75 – 84, 85+ years).

Details with regards to prescribed/dispensed items included year and date of prescription; item name and dose; dispensed quantity; and amount and frequency of drug intake, which were originally derived from dose instructions. Prescription dates were recorded in the format *yyyy-mm-dd;* item name was a character variable, while all other variables were numeric.

Days' supply per prescription has been calculated primarily based on dispensed quantity and BNF dose instructions (i.e. rivaroxaban, once daily: days' supply = quantity dispensed; apixaban & dabigatran, twice daily: days' supply = quantity dispensed / 2). However, prescribing dose instructions – or, to be more specific, the derived variables of amount and frequency – have been used for verification; in those cases where the number of days' supply using dose instructions for calculation deviated from calculations based on standard dosing, these numbers have been used instead. Total days' supply for a patient has been calculated by summing up a patients' supply for all prescriptions received.

7.3.2 Measurements

In order to gain an adequate understanding of how DOACs were utilised in AF patients in Scotland during the study period, this study made use of a variety of measures, including adherence and persistence to and discontinuation of prescribed treatment.

Table 7.1 provides an overview of the main measures used, including definitions and equations where appropriate; selection of measurements has been made based on a review of the literature, ensuring that all major aspects of utilisation were covered. All discontinuation rates were based on admissible gaps, while persistence has been calculated using both the refill-gap method as well as the anniversary method, as described subsequently.

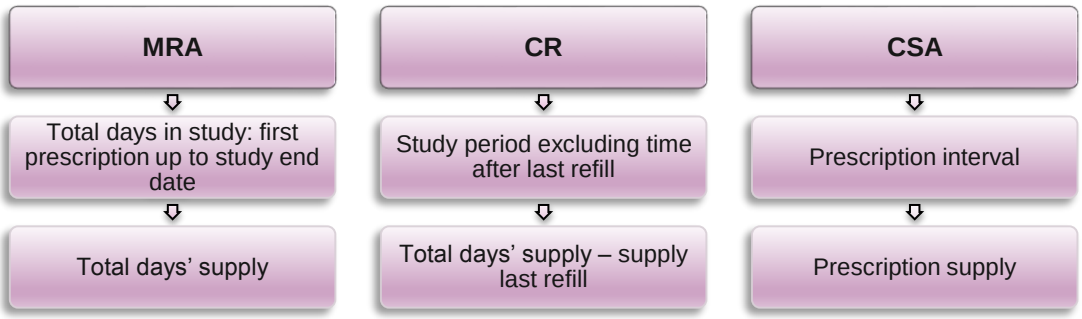
Table 7.1: Utilisation measurements as used in this study, definitions and calculation methods

Measurement		Definition	Calculation
Adherence (Hess et al., 2006)	*Medication Refill Adherence (**MRA**)*	Exposure to medication covering the time period of treatment	(total days' supply / total days in study) * 100
	*Compliance Rate (**CR**)*		((total days' supply - last refill) / days first up to, but not including last refill) * 100
	*Continuous, single-interval measure of medication availability (**CSA**)*	Exposure to medication covering the time period between individual dispensations	(Days' supply per dispensing / days in dispensing interval) * 100
Discontinuation (Gregoire & Moisan, 2016)	*Discontinuation rate (basic refill-gap method)*	Patients discontinuing treatment (i.e. supply gap between prescriptions exceeding 28 days)	(Patients discontinuing treatment / patients initiating treatment) * 100
	Discontinuation rate (taking into account oversupply)		
	Cessation rate (allowing for treatment interruptions)	Patients ceasing treatment (i.e. no further prescription for any DOAC during the study period)	(Patients ceasing treatment / patients initiating treatment) * 100
Persistence (Gregoire & Moisan, 2016)	*Overall study persistence (**refill-gap method**)*	Patients still on treatment at the end of the study period	(Patients not having discontinued treatment / patients initiating treatment) *100
	*Persistence after 6, 12, 18, 24, 30 & 36 months (**refill-gap method**)*	Patients still on treatment 6, 12, 18, 30 & 36 months after initiation	(Patients not having discontinued treatment during a specific time period / patients with sufficient follow-up time) * 100
	*Persistence after 6, 12, 18, 24, 30 & 36 months (**anniversary method**)*		(Patients with drug supply covering the anniversary date / patients with sufficient follow-up time) * 100

CR – compliance rate; CSA – continuous single-interval measure of medication availability; DOAC – direct oral anticoagulant; MRA – medication refill adherence

7.3.2.1 Adherence

As mentioned previously, a variety of different measurements can potentially be calculated in order to express adherence to treatment; these measures are sometimes used interchangeably, although they all give slightly diverging results due to different methods of calculation. As this makes it difficult to compare results from individual studies, three different adherence measures have been calculated here, selected based on the literature (Hess et al., 2006): CR; MRA; and CSA. Figure 7.3 provides an overview of the applied measures.



CSA – continuous, single-interval measure of medication availability; CR – compliance rate; MRA – medication refill adherence

Figure 7.3: Differences between adherence measures as applied in this study

The MRA gives an overall adherence percentage and is a widely used measurement, mainly due to its simplicity and the restricted range of data needed for its calculation (Hess et al., 2006); however, the term "medication refill adherence" may be used differently depending on context (Vink et al., 2009). In contrast to MRA, the last observation and the time afterwards are excluded when calculating a CR. The CSA is calculated using individual prescriptions, whereas the other measures are based on aggregate figures for each patient. In addition to the median, both MRA and CR have also been dichotomised, categorising patients as either adherent or non-adherent by applying a commonly used threshold of 80% (Gregoire & Moisan, 2016).

Treatment duration from first up to, but not including, the last prescription, has been calculated by subtracting the date of the first prescription from the date of the last prescription. For total duration of study participation, the study end date has been used instead of the date of last prescription; this duration is equivalent to a patients´

time of follow-up. The interval between subsequent prescriptions for each patient has been calculated by subtracting the date of prescription from the date of the following prescription.

All patients who received at least two prescriptions for any DOAC have been included in the analysis of adherence to DOAC treatment in general, and days' supply is based on all available prescriptions regardless of which drug was prescribed. In contrast, for calculations regarding individual drugs, only patients with at least two recorded prescriptions for their index drug (the first drug prescribed) have been included; days' supply is based solely on prescriptions for this specific drug.

7.3.2.2 Discontinuation

Discontinuation, as a measure of stopping and/or interrupting treatment, has been defined as the presence of a period of more than 28 days without drug supply. An admissible gap of 28 days was decided upon a) a review of the literature (Acurcio et al., 2016, Beyer-Westendorf et al., 2015, Flynn et al., 2012, Sherwood et al., 2014); and b) summary statistics of the data (median number of days' supply per prescription: 28 (IQR 28 – 56); median number of days between consecutive prescriptions: 31 (IQR 27 – 53).

Two variations of identifying discontinuation have been used: first, based on a gap of more than 28 days following the assumed end of an individual prescription, regardless of previous oversupply; and second, based on a gap of more than 28 days in between prescriptions since treatment initiation, taking into account previous drug oversupply (Gregoire & Moisan, 2016).

In the first instance, supply gaps have been identified by subtracting the obtained days' supply from the number of days between the respective prescription and the following prescription; in cases where the prescription in question was the last prescription recorded for this patient, the study end date has been used instead. By definition, discontinuation events have occurred if the difference between number of days and number of drugs' supply exceeded 28. In the second instance, the definitive presence of a supply gap has been verified by comparing the cumulative supply received up to and including the prescription directly preceding the identified discontinuation event to the cumulative number of days between the index date and

the date of the first prescription following the discontinuation event, if applicable; a discontinuation event was identified only if the difference between cumulative number of days and cumulative days' supply exceeded 28. The supply end date for patients discontinuing treatment has in both variants been calculated by adding the last days' supply, received at the prescription directly preceding the identified discontinuation event, to the date of that prescription.

Discontinuation rates, based on censoring patients after the first recorded discontinuation event, have for both versions been calculated by dividing the number of patients discontinuing treatment by the number of all patients initiating treatment, expressed as a percentage.

In order to account for patients re-initiating treatment after having discontinued temporarily for unknown reasons, a cessation rate has been introduced, including only patients categorised as having stopped treatment. Patients have been regarded as having stopped treatment when, following a discontinuation event, no subsequent prescriptions were recorded. The supply end date for patients ceasing treatment has been calculated by adding the days' supply at last recorded prescription to the date of the prescription. The cessation rate has been calculated by dividing the number of patients stopping treatment by the total number of patients initiating treatment, expressed as a percentage; this rate includes patients who interrupted treatment temporarily but eventually stopped taking DOACs.

7.3.2.3 Persistence

Persistence has been calculated in two different ways.

First, using the refill-gap method, persistence has been assessed for the complete study period, as well as for time periods of 6, 12, 18, 24, 30, and 36 months after treatment initiation; these rates were all based on the discontinuation rate taking into account oversupply as described in the previous section, and identified the proportion of patients not having discontinued treatment during a set time period. Persistence rates have been calculated by dividing the number of patients not discontinuing treatment during the study period/during specified follow-up periods by the number of patients initiating treatment, expressed as a percentage; while all patients have been

included to calculate overall study persistence, only patients with a sufficient length of follow-up have been included for the analysis of specific time periods.

In line with the literature (Gregoire & Moisan, 2016), persistence has also been calculated using the anniversary method so as to allow for temporary treatment interruptions. In contrast to the refill-gap method, patients were not censored after a first discontinuation event when using the anniversary method; all patients were included in the analysis, regardless of whether or not discontinuation occurred. With this method, persistence was assessed at specific points in time (anniversary dates) after treatment initiation rather than for defined periods of time.

Anniversary dates have been calculated by adding 6, 12, 18, 24, 30, and 36 months to the index date. Persistence at these time points has then been evaluated by identifying the prescriptions directly preceding the anniversary dates, subtracting the prescription dates from the anniversary dates, and comparing the intervals between these dates (in days) to the quantities prescribed. Patients have been considered persistent to treatment when the quantity prescribed was sufficient to cover the time period between the prescription and the anniversary date in question, or if the supply gap between an assumed end of drug supply provided to the patient and the anniversary date did not exceed 28 days.

Persistence rates 6, 12, 18, 24, 30, and 36 months after treatment initiation have been calculated by dividing the number of patients in possession of sufficient supply to cover the respective anniversary date by the number of patients having initiated treatment, expressed as a percentage; analyses for each period of specified length has been restricted to patients with a sufficient length of follow-up.

7.3.3 Statistical analysis

All adherence measurements have been calculated for DOACs as a group, as well as for each drug individually. In addition to crude overall rates comprising all patients, results have been stratified by sex and age group whenever patient numbers allowed.

Statistical tests have been conducted in order to compare the main adherence measures between individual DOACs, as well as between patient sexes and different age groups. For continuous variables, means between sexes have been compared

using two-sample t-tests; for comparisons between individual DOACs and age groups, one-way ANOVA tests have been applied. For differences in nominal variables between drugs, sexes, and/or age groups, chi-square tests have been used. The applied level of significance was 0.05.

Time to discontinuation has been assessed using Kaplan-Meier time to event survival analysis, for all DOACs combined as well as for each drug individually. To enable comparisons between discontinuation with censoring patients after a first event and allowing for temporary treatment interruptions, separate analyses have been conducted, based on discontinuation and cessation respectively.

Sensitivity analyses with regards to discontinuation and persistence included using alternative admissible gaps of 14, 56 and 84 days, in order to account for uncertainty regarding temporary treatment interruptions; these alternative periods have been chosen based on considerations regarding pharmacological drug profiles as well as prescribing practices and available package sizes in Scotland, and attempted to take potentially expected patient behaviour into consideration.

7.4 Results

7.4.1 Adherence

Of the 14,811 patients treated with DOACs during the study period, 13,306 patients (89.8%) received at least two prescriptions for any DOAC; 13,165 patients (88.9%) received at least two prescriptions for the first DOAC prescribed. All measurements gave comparable results and indicated high adherence to DOAC treatment, albeit with differences between individual drugs. Adherence remained stable over time when looking at six months intervals rather than assessing patients' entire treatment periods. For details see tables 7.2 (measurements based on the study period) and table 7.3 (measures based on intervals between individual prescriptions).

Table 7.2: Adherence to DOAC treatment based on different definitions of the follow-up period used for calculation, overall and by drug

	DOAC (n=13,306)	Apixaban (n=5,518)	Dabigatran (n=986)	Rivaroxaban (n=6,661)	p-value
Median number days of follow-up (IQR) [1]	374 (199 – 624)	288 (160 – 456)	882 (549 – 1178)	430 (227 – 694)	
Median number days' supply/follow-up (IQR) [1]	336 (168 – 560)	280 (157 – 425)	543 (196 – 900)	364 (196 – 616)	
MRA > 80% (%) [2]	81.9	84.3	56.5	80.9	<0.001
Median MRA (IQR) [2]	102.3 (90.1 – 112.5)	103.3 (91.2 – 115.1)	90.3 (41.4 – 103.3)	102.0 (89.6 – 110.9)	<0.001
Median MRA over time (IQR) [3]					
0-6 months	114.8 (98.4 – 112.4)	114.8 (97.3 – 122.4)	110.9 (82.0 – 122.4)	122.4 (107.1-122.4)	
7-12 months	112.7 (102.4 – 125.0)	111.9 (101.2 – 124.4)	112.1 (100.0 – 125.0)	112.8 (103.7 – 124.8)	
13-18 months	110.7 (101.8 – 124.4)	111.4 (101.8 – 124.4)	111.1 (100.6 – 123.5)	110.1 (101.8 – 123.8)	
19-24 months	112.0 (102.4 – 125.8)	109.5 (101.2 – 125.1)	111.1 (100.0 – 126.5)	112.0 (102.4 – 125.8)	
25-30 months	112.0 (102.4 – 125.8)	110.7 (103.7 – 118.1)	110.9 (98.9 – 125.0)	112.0 (103.1 – 125.1)	
31-36 months	112.8 (102.4 – 126.1)	n/a	111.1 (101.4 – 126.1)	113.4 (102.3 – 125.3)	
Median number days of follow-up (IQR) [4]	288 (160 – 456)	226 (106 – 392)	516 (158 – 918)	321 (139 – 596)	
Median number days' supply/follow-up (IQR) [4]	280 (126 – 518)	224 (112 – 392)	507 (150 – 840)	315 (140 – 588)	
CR > 80% (%) [2]	90.5	91.1	85.1	91.8	<0.001
Median CR (IQR) [2]	102.3 (95.2 – 111.5)	102.8 (94.8 – 113.5)	100.2 (91.6 – 107.7)	102.4 (96.6 – 110.9)	>0.05
Median CR over time (IQR) [3]					
0-6 months	105.0 (96.0 – 116.0)	103.7 (94.9 – 114.8)	103.5 (92.0 – 115.9)	106.1 (97.7 – 116.7)	
7-12 months	100.0 (94.9 – 107.7)	100.0 (94.1 – 107.6)	100.8 (93.1 – 109.1)	100.0 (94.9 – 107.7)	
13-18 months	100.0 (94.1 – 107.1)	100.3 (94.1 – 108.1)	100.7 (90.9 – 108.1)	100.0 (94.9 – 105.7)	
19-24 months	100.0 (94.2 – 106.7)	100.0 (93.3 – 105.9)	100.8 (92.1 – 109.3)	100.0 (94.8 – 105.7)	
25-30 months	100.0 (94.1 – 107.1)	100.7 (94.9 – 106.2)	100.0 (91.1 – 107.9)	100.0 (94.9 – 106.3)	
31-36 months	100.0 (94.1 – 107.1)	n/a	100.0 (92.7 – 106.8)	100.0 (94.1 – 106.7)	

CR – compliance rate; DOAC – direct oral anticoagulant; IQR – interquartile range; MRA – medication refill adherence

[1] Follow-up period from the date of first prescription up to the end of the study period
[2] Includes all patients with at least two prescriptions during the follow-up period
[3] Includes only patients with sufficient follow-up time to cover the respective prescription period
[4] Follow-up period from the date of first prescription up to the date of last prescription

7.4.1.1 Medication Refill Adherence (MRA)

The median number of days of follow-up for patients treated with any DOAC who received at least two prescriptions was 374 (IQR 199 – 624), and the median number

of days' supply dispensed to patients during follow-up was 336 (IQR 168 – 560). Overall median MRA was 102.3% (IQR 90.1 – 112.5), with no significant difference between sexes (p>0.05); stratified by age group, median MRAs ranged from 96.0% (IQR 56.7 – 108.5) among patients younger than 55 years to 103.7% (IQR 94.0 – 113.7) among those aged 65 to 74 years (p<0.001). When applying a threshold of 80% to the MRA, 81.9% of all patients were adherent to treatment – ranging from 64.0% (patients younger than 55 years) to 85.5% (patients aged 65 to 74 years).

The median time of follow-up differed substantially between drugs, ranging from 288 days (IQR 160 – 456) for patients treated with apixaban to 882 days (IQR 549.2 – 1177.5) for patients treated with dabigatran; median number of days' supply were 280 (IQR 156.5 – 424.8) and 542.5 (IQR 196 – 899.5), respectively. Median MRAs were considerably lower among patients treated with dabigatran (90.3%, IQR 41.4 – 103.3) as compared to both apixaban (103.3%, IQR 91.2 – 115.1) and rivaroxaban (102.0%, IQR 89.6 – 110.9). Similar to DOACs overall, no differences were observed between sexes but between age groups, with median MRA lowest in the youngest age group and highest among patients aged 65 to 74 years, regardless of drug. While 84.3% of apixaban patients and 80.9% of rivaroxaban patients were adherent to treatment, only 56.5% of dabigatran patients had an MRA > 80%; detailed results by patient sex and age group can be found in appendix II.

7.4.1.2 Compliance Rate (CR)

Taking into account only the time period up to but not including the last recorded prescription, the median number of days of follow-up for patients treated with any DOAC was 288 (IQR 127 – 532), and the number of days' supply dispensed during this time was 280 (IQR 126 – 518). The overall median CR was 102.3% (IQR 95.2 – 111.5), with no significant difference between sexes (p>0.05); stratified by age group, median CRs ranged from 97.5% (IQR 84.0 – 106.2) among patients younger than 55 years to 104.6% (IQR 97.4 – 116.5) among patients aged 85 years or older (p=0.003). Using an 80% threshold, 90.5% patients were adherent to treatment – with a minimum of 78.4% in the youngest age group and a maximum of 92.5% in the oldest.

Length of follow-up differed by drug, with a minimum of 226 days (IQR 106 – 392) for apixaban and a maximum of 515.5 days (IQR 158.2 – 917.8) for dabigatran patients; median number of days' supply dispensed up to but not including the last recorded

prescription were 224 days (IQR 112 – 392) and 507 (IQR 150 – 840) for apixaban and dabigatran, respectively. Median CRs did not differ significantly between individual drugs, ranging from 100.2% (IQR 91.6 – 107.7) for dabigatran to 102.8% (IQR 94.8 – 113.5) for apixaban; however, a considerably lower share of dabigatran patients were adherent to treatment (85.1%) as compared to patients being treated with either apixaban or rivaroxaban, with 91.1% and 91.8%, respectively. For differences between patient sex and age groups, see appendix II.

7.4.1.3 Continuous, single-interval measure of medication availability (CSA)

For DOACs overall, the median time interval between individual prescriptions was 31 days (IQR 27 – 53), and the median days' supply per prescription was 28 (IQR 28 – 56). The median length of supply gaps between subsequent prescriptions was 0 (IQR -6 – 4 days), resulting in a median CSA of 100.0% (IQR 90.3 – 119.1). Results by drug were almost identical; see table 7.3 for details.

Table 7.3: Adherence to DOAC treatment based on individual prescriptions, overall and by drug

	DOAC (n=13,306)	**Apixaban (n=5,518)**	**Dabigatran (n=986)**	**Rivaroxaban (n=6,661)**
Median number days between prescriptions (IQR)	31 (27 – 53)	31 (26 – 52)	32 (27 – 55)	31 (27 – 53)
Median number days' supply/prescription (IQR)	28 (28 – 56)	28 (28 – 56)	30 (30 – 60)	28 (28 – 56)
Median number gap days between prescriptions (IQR)	0 (-6 - 4)	0 (-6 – 4)	0 (-5 – 5)	0 (-6 – 4)
***Median CSA (IQR)** [1]*	100.0 (90.3 – 119.1)	100.0 (90.3 – 121.7)	100.0 (88.2 – 115.4)	100.0 (90.3 – 116.7)
***Median CSA over time (IQR)** [2]*				
0-6 months	103.7 (90.9 – 130.4)	101.8 (90.3 – 127.3)	103.4 (88.2 – 130.4)	103.7 (93.3 – 133.3)
7-12 months	100.0 (90.3 – 115.4)	100.0 (90.3 – 114.3)	103.5 (90.3 – 117.7)	100.0 (90.3 – 114.3)
13-18 months	100.0 (90.3 – 114.3)	100.0 (90.3 – 116.7)	100.0 (90.3 – 115.4)	100.0 (91.8 – 112.0)
19-24 months	100.0 (90.3 – 112.0)	100.0 (90.3 – 114.3)	103.0 (89.1 – 115.4)	100.0 (90.3 – 112.0)
25-30 months	100.0 (91.8 – 113.2)	100.0 (90.9 – 109.8)	100.0 (89.1 – 112.0)	100.0 (93.3 – 112.0)
31-36 months	100.0 (90.9 – 113.2)	n/a	100.0 (90.3 – 113.7)	100.0 (91.8 -112.0)

CSA – continuous, single-interval measure of medication availability; DOAC – direct oral anticoagulant; IQR – interquartile range

[1] Includes all patients with at least two prescriptions during the study period.
[2] Includes only patients with sufficient follow-up time to cover the respective prescription period.

7.4.2 Discontinuation

Discontinuation rates differed significantly between individual drugs; in addition, there were considerable differences between rates depending on the method used for calculation.

7.4.2.1 Using a basic refill-gap method

When looking at DOACs in general – regardless of which DOAC has been used, and disregarding switches between individual drugs – 6,137 patients (41.4%) discontinued treatment during the study period, and the median time to discontinuation was 461 days (95% CI 445 – 485 days). There was no significant difference between sexes ($p>0.05$), but discontinuation rates differed significantly between age groups – spanning from 37.3% among patients aged 65 to 74 years up to 53.1% among patients younger than 55 years ($p<0.001$). See also table 7.4 for details.

Table 7.4: Discontinuation rates calculated using a basic refill-gap method with an admissible gap of 28 days, overall and by drug

[%]	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value [1]
All patients	41.4	34.5	73.9	44.6	<0.001
By patient sex					
Male	41.7	34.0	75.9	44.3	
Female	41.1	35.0	70.4	44.9	
p-value [2]	>0.05	>0.05	>0.05	>0.05	
By age group					
Less than 55	53.1	46.7	89.0	52.7	
55 – 64	41.3	30.8	80.0	44.9	
65 – 74	37.3	30.8	69.3	39.7	
75 – 84	41.3	33.9	71.6	46.0	
85 or older	44.4	39.9	71.3	46.6	
p-value [3]	<0.001	<0.001	<0.001	<0.001	

DOAC – direct oral anticoagulant

[1] For differences between drugs.
[2] For differences between sexes.
[3] For differences between age groups.

For individual DOACs, a total of 6,300 patients discontinued treatment with the first drug prescribed, and discontinuation rates differed significantly between drugs: 34.5% among patients treated with apixaban, 44.6% in the rivaroxaban group, and 73.9% for those receiving dabigatran (p<0.001). Median time to discontinuation was considerably shorter for dabigatran (211 days, 95% CI 185 – 252 days) than for both apixaban (464 days, 95% CI 438 – 498 days) and rivaroxaban (462 days, 95% CI 439 – 490 days). Discontinuation rates for individual drugs did not differ significantly between sexes; patterns of differences between age groups were similar to those found for DOACs overall, with rates lowest among patients aged 65 to 74 years and highest among those aged 55 years or younger for all drugs. Figure 7.4 presents Kaplan-Meier survival curves with 95% confidence intervals for discontinuation of treatment, for DOACs overall as well as for individual drugs.

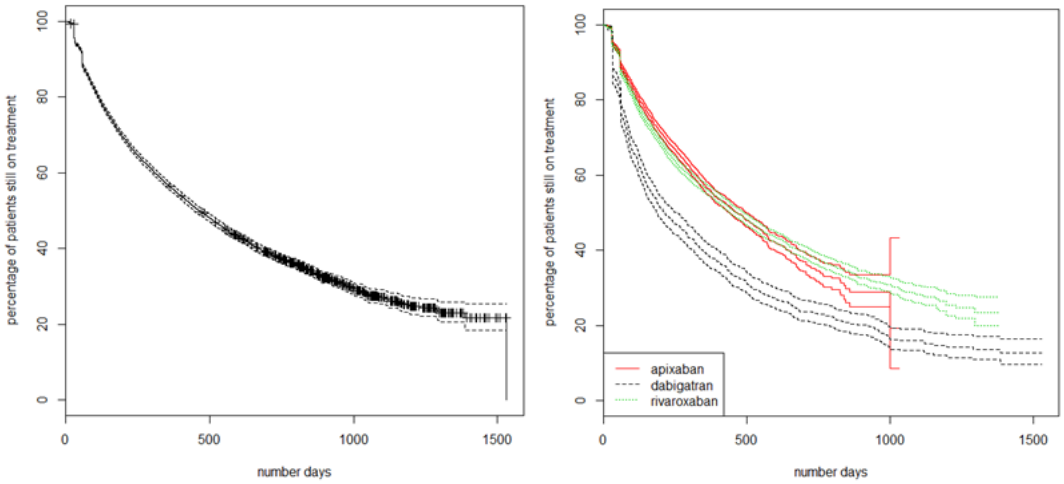


Figure 7.4: Kaplan-Meier survival curves – time to discontinuation of DOAC treatment, admissible gap 28 days, overall and by drug

7.4.2.2 Using a refill-gap method and taking into account oversupply

When adjusting for previous oversupply, discontinuation rates were all considerably lower than those found when using the basic refill-gap method; general patterns did however not change. A total of 4,520 patients discontinued treatment, resulting in an overall DOAC discontinuation rate of 30.5%; median time to discontinuation was 979 days (95% CI 889 – 1,086 days). Discontinuation rates were slightly lower for women than for men (29.2% vs 31.6%, p=0.001), and differed significantly between age

groups, ranging from 26.8% among patients aged 65 to 74 years to 46.2% among patients younger than 55 years (p<0.001); see also table 7.5.

Table 7.5: Discontinuation rates calculated using the refill-gap method with an admissible gap of 28 days and taking into account previous oversupply, overall and by drug

[%]	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value [1]
All patients	30.5	24.9	63.3	33.3	<0.001
By patient sex					
Male	31.6	25.3	65.6	33.8	
Female	29.2	24.4	59.6	32.7	
p-value [2]	0.001	>0.05	0.050	>0.05	
By age group					
Less than 55	46.2	40.2	82.0	45.9	
55 – 64	32.3	24.6	73.0	33.6	
65 – 74	26.8	22.2	56.0	29.0	
75 – 84	29.3	23.0	59.6	34.1	
85 or older	32.4	27.7	63.1	34.8	
p-value [3]	<0.001	<0.001	<0.001	<0.001	

DOAC – direct oral anticoagulant

[1] For differences between drugs.
[2] For differences between sexes.
[3] For differences between age groups.

Discontinuation rates also differed significantly between drugs: 4,744 patients discontinued treatment with the first drug prescribed – 24.9% of apixaban patients, 33.3% of patients receiving rivaroxaban, and 63.3% of patients initiating treatment with dabigatran (p<0.001). Median time to discontinuation was again shortest for dabigatran (298 days, 95% CI 242 – 342 days) and longest for rivaroxaban (1,001 days, 95% CI 858 – 1,121 days). Relative differences between sexes and age groups for all three drugs were similar to differences between overall DOAC discontinuation rates. Figure 7.5 shows Kaplan-Meier survival curves with 95% confidence intervals for discontinuation of treatment, adjusted for previous drug oversupply, for DOACs overall as well as by drug.

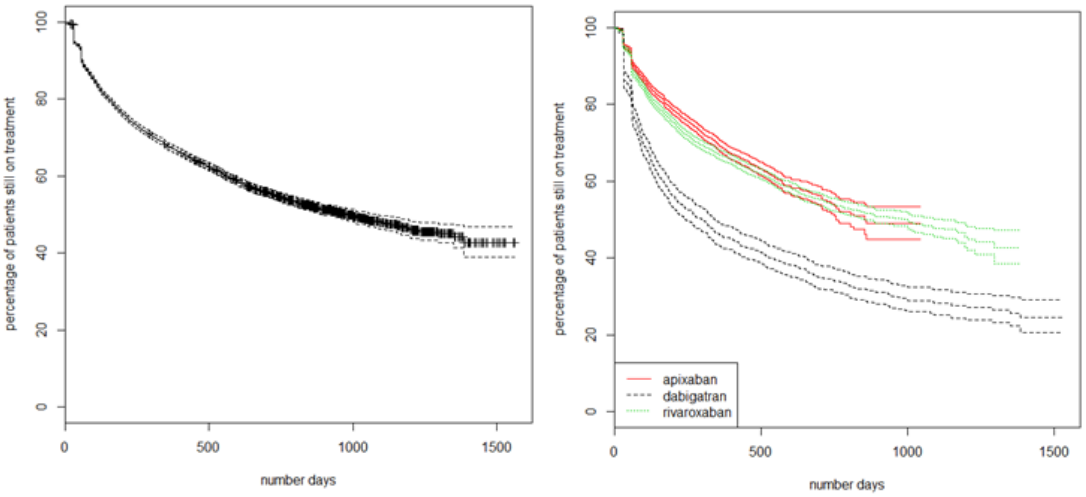


Figure 7.5: Kaplan-Meier survival curves – time to discontinuation of DOAC treatment, admissible gap 28 days and taking into account previous drug oversupply, overall and by drug

7.4.2.3 Allowing for temporary treatment interruptions

Of all patients discontinuing treatment with any DOAC – based on calculations taking into account previous drug oversupply – 50.0% re-initiated treatment at least temporarily, i.e. they subsequently received at least one additional prescription for any DOAC; however, by study conclusion, 3,307 patients had stopped receiving DOAC prescriptions, resulting in a cessation rate of 22.3%. Similar to discontinuation in general, no difference was observed between sexes ($p>0.05$) but between age groups ($p<0.001$), with a range of cessation rates from 17.0% among patients aged 65 to 74 years to 33.2% among those younger than 55 years (table 7.6).

Accounting for re-initiations, the share of patients who eventually ceased treatment with their index drug ranged from 19.3% for apixaban to 50.9% for dabigatran ($p<0.001$); cessation rates among age groups differed significantly, similar to findings from DOACs overall (with rates highest among patients younger than 55 years, and lowest among those aged 65 to 74 years), while no differences between sexes were observed – with the exception of patients initiating treatment with rivaroxaban, where female patients had a slightly higher cessation rate (26.8%, compared to 24.4% among men; $p=0.017$). Kaplan-Meier survival curves with 95% confidence intervals of patients ceasing treatment are shown in figure 7.6.

Table 7.6: Cessation rates allowing for temporary treatment interruptions, overall and by drug

[%]	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value [1]
All patients	22.3	19.3	50.9	25.5	<0.001
By patient sex					
Male	22.1	18.9	52.3	24.4	
Female	22.7	19.8	48.7	26.8	
p-value [2]	>0.05	>0.05	>0.05	0.017	
By age group					
Less than 55	33.2	30.4	68.0	34.0	
55 – 64	19.4	15.5	58.0	20.2	
65 – 74	17.0	14.9	41.7	20.0	
75 – 84	22.0	18.3	49.1	26.8	
85 or older	29.8	27.1	55.4	32.2	
p-value [3]	<0.001	<0.001	<0.001	<0.001	

DOAC – direct oral anticoagulant

[1] For differences between drugs.
[2] For differences between sexes.
[3] For differences between age groups.

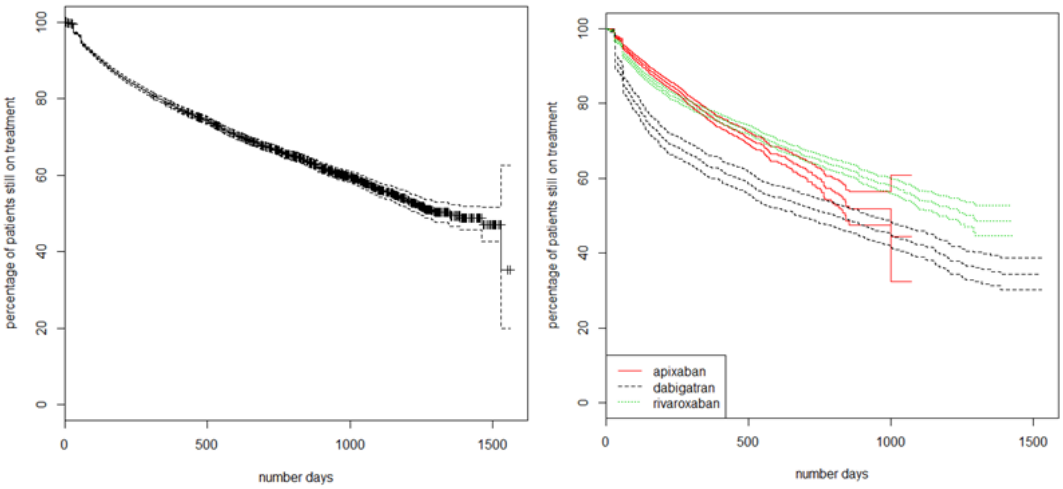


Figure 7.6: Kaplan-Meier survival curves – time to cessation of DOAC treatment, overall and by drug

7.4.3 Switching between drugs after first treatment discontinuation

After having discontinued DOAC treatment (based on the refill-gap method, adjusting for previous drug oversupply), 2,578 patients (57.0%) eventually re-initiated treatment with any oral anticoagulant during the study period – mostly with DOACs, either directly or after temporarily switching to a VKA (see also figure 7.7).

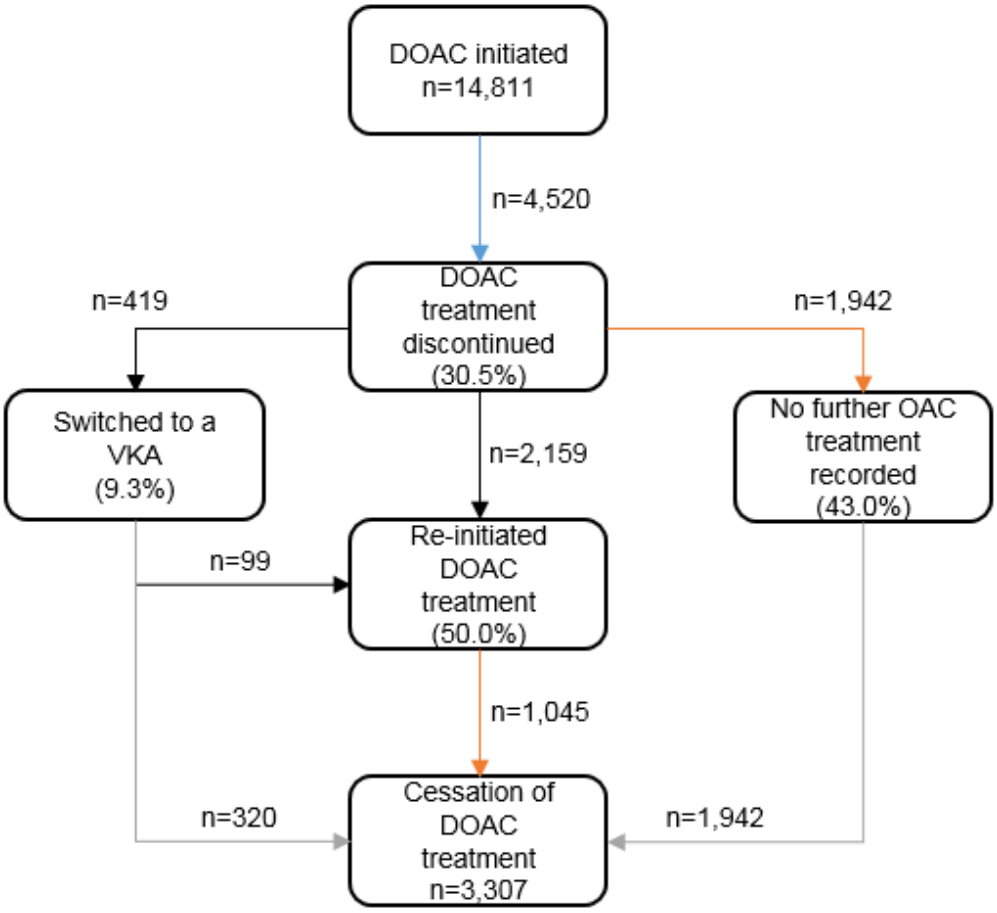


Figure 7.7: Patients' treatment options after DOAC discontinuation, based on refill-gap method taking into account previous drug oversupply

In total, 2,024 patients (42.7%) restarted with the same drug after temporarily interrupting treatment: 48.0% of apixaban, 41.0% of rivaroxaban, and 36.8% of dabigatran patients. Figure 7.8 shows the drug of first choice used to re-initiate oral anticoagulant treatment after discontinuation with the index drug, highlighting the differences between the individual DOACs.

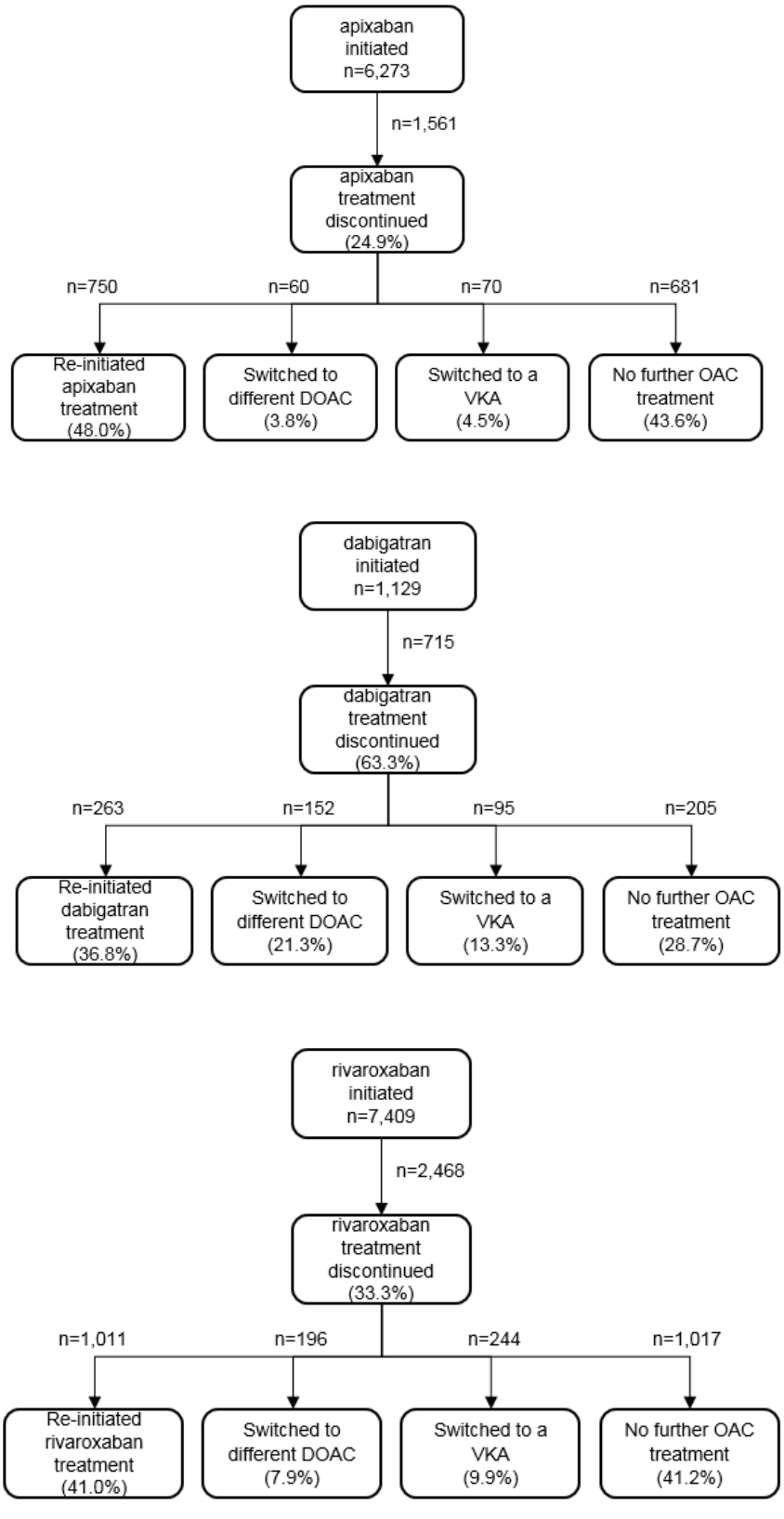


Figure 7.8: Drug of choice after first treatment discontinuation, by index drug

7.4.4 Persistence

7.4.4.1 Using the refill-gap method, based on discontinuation

Using the refill-gap method (taking into account previous drug oversupply), crude overall persistence with DOAC treatment during the study period was 69.5%. In accordance with discontinuation rates, persistence rates differed significantly between drugs, ranging from 36.7% among dabigatran patients to 75.1% for patients receiving apixaban (p<0.001); see also table 7.7 for detailed results by patient sex and age group (additional results based on the other methods of calculating discontinuation – without accounting for previous oversupply, and taking temporary interruptions into consideration – can be found in appendix II).

Table 7.7: Persistence rates based on the refill-gap method with an admissible gap of 28 days and taking into account previous oversupply, overall and by drug

[%]	DOAC (n=14,811)	Apixaban (n=6,273)	Dabigatran (n=1,129)	Rivaroxaban (n=7,409)	p-value [1]
All patients	69.5	75.1	36.7	66.7	<0.001
By patient sex					
Male	68.4	74.7	34.4	66.2	
Female	70.8	75.6	40.4	67.3	
p-value [2]	0.001	>0.05	0.05	>0.05	
By age group					
Less than 55	53.8	59.8	18.0	54.1	
55 – 64	67.7	75.4	27.0	66.4	
65 – 74	73.2	77.8	44.0	71.0	
75 – 84	70.7	77.0	40.4	65.9	
85 or older	67.7	72.3	36.9	65.2	
p-value [3]	<0.001	<0.001	<0.001	<0.001	

DOAC – direct oral anticoagulant

[1] For differences between drugs.
[2] For differences between sexes.
[3] For differences between age groups.

Persistence 6 months after treatment initiation regardless of switches between individual drugs was 76.6%, decreasing to 40.1% after 36 months. Gender differences increased over time, with female patients more likely to stay on treatment than male

patients; while 77.5% of women were persistent after 6 months and 47.6% after 36 months, proportions among men were 75.9% and 35.1%, respectively. Patients aged 65 to 74 years had the highest persistence rates throughout, whereas patients younger than 55 years of age had the lowest.

Persistence rates also differed significantly by drug: 6 months after treatment initiation, 57.3% of dabigatran patients were still persistent – in contrast to 75.9% of rivaroxaban and 79.1% of apixaban patients ($p<0.001$). Persistence declined over time for all three drugs, albeit to a different extent; after 30 months, persistence in the dabigatran group has decreased to 28.7%, while rates for patients treated with rivaroxaban and apixaban were 52.0% and 61.9%, respectively. Differences between sexes and age groups for individual groups were similar to overall findings, albeit with minor differences between drugs; see also appendix II for detailed results. Table 7.8 lists persistence rates, based on the refill-gap method allowing for previous drug oversupply, by time period.

7.4.4.2 Using the anniversary method

Using the anniversary method, overall persistence with DOAC treatment was 85.6% after 6 months, decreasing to 69.7% 36 months after treatment initiation. A decrease in persistence over time was more pronounced in male patients, resulting in a lower rate of 65.9% after 3 years as compared to 75.5% among women; patterns of differences between age groups stayed constant over time, with patients aged 65 to 74 years having the highest persistence rates regardless of how much time has elapsed since treatment initiation, and patients aged younger than 55 years having the lowest rates throughout.

Persistence differed significantly between drugs, ranging from 69.1% among dabigatran patients to 88.3% among apixaban patients after 6 months of treatment ($p<0.001$), and decreasing to 49.4% and 81.0% after 30 months, respectively ($p<0.001$). Differences between sexes and age groups were comparable to overall findings, with minor differences between individual drugs; results by patient sex and age group can be found in appendix II. Persistence rates by time period based on the anniversary method are shown in table 7.8.

Table 7.8: Persistence with DOAC treatment over time, overall and by drug

	DOAC	Apixaban	Dabi-gatran	Riva-roxaban	p-value
Patients with at least 6 months follow-up time	10,793	4,026	1,047	5,720	
Persistence rate after 6 months – refill-gap method (%)	76.6	79.1	57.3	75.9	<0.001
Persistence rate after 6 months – anniversary method (%)	85.6	88.3	69.1	83.8	<0.001
Patients with at least 12 months follow-up time	7,075	2,128	956	3,991	
Persistence rate after 12 months – refill-gap method (%)	66.2	68.9	45.8	66.1	<0.001
Persistence rate after 12 months – anniversary method (%)	80.6	83.6	61.8	78.6	<0.001
Patients with at least 18 months follow-up time	4,383	908	830	2,645	
Persistence rate after 18 months – refill-gap method (%)	59.7	61.7	40.1	61.1	<0.001
Persistence rate after 18 months – anniversary method (%)	78.2	81.3	57.5	77.2	<0.001
Patients with at least 24 months follow-up time	2,516	277	678	1,561	
Persistence rate after 24 months – refill-gap method (%)	52.9	60.3	33.6	55.3	<0.001
Persistence rate after 24 months – anniversary method (%)	75.6	80.9	53.8	76.0	<0.001
Patients with at least 30 months follow-up time	1,342	42	516	784	
Persistence rate after 30 months – refill-gap method (%)	47.0	61.9	28.7	52.0	<0.001
Persistence rate after 30 months – anniversary method (%)	72.7	81.0	49.4	76.0	<0.001
Patients with at least 36 months follow-up time (%)	679	0	338	341	
Persistence rate after 36 months – refill-gap method (%)	40.1	n/a	23.4	49.0	<0.001
Persistence rate after 36 months – anniversary method (%)	69.7	n/a	46.4	75.1	<0.001

7.4.5 Sensitivity analyses

Sensitivity analyses of length of admissible gap showed considerable changes in discontinuation rates: while reducing the admissible gap to 14 days resulted in an

increase of the overall discontinuation rate (based on the refill-gap method, taking into account previous drug oversupply) from 30.5% to 42.8%, increasing the gap to 56 days led to a DOAC discontinuation rate of 20.2%, dropping further to 16.1% when applying an extensive grace period of 84 days. In addition, with a lengthening of the admissible gap, the differences between the two methods of calculating discontinuation (with and without taking into account previous drug oversupply) decreased. Cessation rates were also affected by changes in admissible gaps, but to a lesser degree; a reduced length of 14 days increased overall cessation from 22.3% to 29.8%, and increasing the admissible gap to 56 and 84 days resulted in decreased DOAC cessation rates of 15.6% and 13.1%, respectively. Results for all drugs and gap lengths can be found in appendix II.

As persistence is based on discontinuation when using the refill-gap method, changes in admissible gaps had a comparable effect on these persistence rates than it had on discontinuation rates. In contrast, findings based on the anniversary method were only marginally affected: decreasing the admissible gap to 14 days decreased 6-months DOAC persistence from 85.6% to 82.9%, and 1-year persistence from 80.6% to 77.8%; increasing the gap to 56 days resulted in a 6-months DOAC persistence rate of 88.7%, and a 1-year persistence of 82.6%. For detailed results for all gap lengths as well as by individual drug, see appendix II.

7.5 Discussion

This was the first study in Scotland using linked data from PIS and SMR01 to analyse discontinuation, persistence, and adherence to DOAC treatment, and one of a small number of studies analysing routinely collected data at a national level (Gorst-Rasmussen et al., 2015, Yao et al., 2016). Additionally, this is one of the first studies to apply the ESPACOMP framework for drug utilisation studies (Vrijens et al., 2012) in combination with proposed standardised measurements for drug adherence (Hess et al., 2006); it encompasses all dimensions of drug utilisation rather than focusing on a single aspect, and therefore gives a comprehensive picture of how DOACs are used in clinical practice.

7.5.1 Main findings

Main findings are, by and large, comparable to other research: adherence to DOAC treatment is overall good (Al-Khalili et al., 2016, Forslund et al., 2016, Gorst-Rasmussen et al., 2015); discontinuation of treatment varies significantly between individual DOACs (Al-Khalili et al., 2016, Coleman et al., 2016, Shiga et al., 2015, Simons et al., 2016); and persistence declines over time (Coleman et al., 2016, Martinez et al., 2016). Nevertheless, switches from DOACs to VKAs were slightly less common than in other previous observational studies (Beyer-Westendorf et al., 2015, Pottegård et al., 2014, Shiga et al., 2015).

Adherence to medication was high for all drugs, and did not considerably decline over time. Treatment gaps were rare, with patients generally having enough medication to cover the treatment period; median MRA, and median CR during the first six months of treatment, indicated over- rather than undersupply of drugs, although these findings might be due to the timing of prescriptions. High adherence to DOAC treatment has been shown before: two studies, each conducted in a single health care centre (one in Sweden and one in Canada) and using measurements comparable to the CR, found median adherence rates of 99.7% for dabigatran, and 100% for rivaroxaban and apixaban (Al-Khalili et al., 2016, Schulman et al., 2013); results differed however considerably between the various studies that have been published thus far, potentially because calculation methods for adherence and analysable time-periods varied. Moreover, results have frequently been reported in dichotomised form, with a threshold of 80% of the calculated measurement used to identify adherent patients; findings using this approach ranged from 38.5% to 92.0% for dabigatran (Forslund et al., 2016, Gorst-Rasmussen et al., 2015, Schulman et al., 2013, Shore et al., 2014, Yao et al., 2016), 50.5% to 96% for rivaroxaban (Al-Khalili et al., 2016, Forslund et al., 2016, Yao et al., 2016), and 61.9% to 95% for apixaban (Al-Khalili et al., 2016, Forslund et al., 2016, Yao et al., 2016) – placing the findings of this study, with proportions of patients with a CR>80% of 56.5%, 80.9%, and 84.3% for dabigatran, rivaroxaban, and apixaban respectively, in the middle of each scale. Comparing the findings obtained here by using three different adherence measurements, applied to the study data, illustrates how differences in calculation methods can impact the results; these observations most certainly raise concerns regarding comparability and generalisability of findings, especially when methods are not clearly described.

The crude discontinuation rate and 12 months persistence to DOAC treatment in Scotland were 30.5% and 80.6%, respectively (with discontinuation based on a refill-gap method taking into account previous drug oversupply, and persistence calculated using the anniversary method), and similar rates have been reported before (Beyer-Westendorf et al., 2015, Martinez et al., 2016, Shiga et al., 2015, Thorne et al., 2014). However, most studies reporting on discontinuation and/or persistence either did not explicitly describe how rates have been calculated, or did not clearly distinguish between the different concepts of discontinuation and persistence – treatment persistence is for example sometimes interpreted as the duration between treatment initiation and discontinuation and analysed using Kaplan-Meier survival models (Shiga et al., 2015, Simons et al., 2016), while other studies define being persistent as "not having discontinued treatment" and determine persistence rates by calculating (1 – discontinuation rate) (Beyer-Westendorf et al., 2015). In addition, most studies did not specify whether or not previously received drug oversupply was taken into consideration; findings in this study do differ however depending on how rates were calculated – with discontinuation rates being considerably lower, and persistence rates higher, when oversupply has been accounted for. Moreover, 50.0% of patients discontinuing treatment subsequently received at least one additional prescription for any DOAC, i.e. they eventually resumed treatment. When allowing for treatment interruptions by using only the number of patients where no subsequent DOAC prescriptions were recorded – a figure considerably influenced by length of follow-up, as more patients might reinitiate treatment over time – the crude DOAC discontinuation rate was 22.3%, highlighting that the method of calculation where patients are censored after the occurrence of a first discontinuation event likely leads to an overestimation of discontinuation. This lower discontinuation (cessation) rate is also more in agreement with the persistence rates found in this study, calculated using the anniversary method which is insensitive to periods of treatment interruptions (Gregoire & Moisan, 2016).

Although many studies reported on DOACs as a group rather than separately by individual drugs, the results from this study confirm previous findings indicating sizable differences between individual drugs: generally speaking, discontinuation rates were highest – and persistence rates lowest – among dabigatran patients, and discontinuation rates were lowest – and persistence rates highest – among patients initiating apixaban treatment. Differences in rates for individual drugs across studies

were however sizeable – potentially influenced by differences in methodology, similar to findings reported for DOACs overall. At 63.3%, the discontinuation rate (based on an admissible gap of 28 days and taking into account previous drug oversupply) in this study was significantly higher among dabigatran patients than for patients being treated with either rivaroxaban (33.3%) or apixaban (24.9%); 12 months persistence rates (calculated using the anniversary method) were 61.8%, 78.6%, and 83.6% for dabigatran, rivaroxaban, and apixaban, respectively. Previously reported 12 months persistence rates by drug were comparable, with findings ranging from 44.7% to 74.4% for dabigatran compared to 60.1% to 83.7% for rivaroxaban, and up to 85.9% for apixaban (Coleman et al., 2016, Forslund et al., 2016, Martinez et al., 2016, Thorne et al., 2014,). In contrast, discontinuation rates by drug were lower in other studies – ranging from 13% to 18% for apixaban, from 17% to 28% for rivaroxaban, and from 30.4% to 34% for dabigatran (Al-Khalili et al., 2016, Shiga et al., 2015, Thorne et al., 2014).

The percentage of patients switching to VKA treatment after DOAC discontinuation as observed in this study (9.3%) was slightly higher than in England (6.0%) but slightly lower than in Japan (15.2%), and comparable to the one year follow-up EORP-AF pilot registry (11.8%). The share of patients switching from DOACs to a VKA was however noticeably higher in a Danish study, where 51.2% of previously OAC-naïve patients commenced with a VKA within 6 months of DOAC treatment initiation (Lip et al., 2014b, Martinez et al., 2016, Pottegård et al., 2014, Shiga et al., 2015). While some of these differences might potentially be due to small sample sizes (the Japanese study comprised 401 DOAC patients, and the English study 914; Danish data relates to 389 patients), the timing of the studies has nevertheless most likely also affected findings. The Danish study, for instance, was conducted between August 2011 and June 2013 (Pottegård et al., 2014), and consequently included mainly patients initiating treatment with dabigatran (as dabigatran was the first DOAC to gain market access for the indication of stroke prevention in patients with AF throughout Europe) – and among all DOAC patients, those initiating treatment with dabigatran are seemingly most likely to discontinue treatment. Hence, observing a higher percentage of patients switching to warfarin – in contrast to studies comprising mostly patients initiating treatment with either apixaban or rivaroxaban – is not completely surprising, especially considering that physicians would not have been very familiar yet with either drug during the Danish study period. Individual patients'

and physicians preferences as well as clinical guidelines, especially with respect to treatment changes following adverse drug events, might also have played a role.

Reasons for discontinuation treatment are numerous, and potentially include a wide range of aspects – not all of which have been properly understood. Cessation of DOAC treatment has often been attributed to changes in underlying disease severity including restoration of sinus rhythm, worsening kidney function, and side-effects including bleeding events or, particularly in case of dabigatran, gastro-intestinal disturbances (Beyer-Westendorf et al., 2015, Shiga et al., 2015, Thorne et al., 2014); in addition, behavioural factors rooted in patients' lack of knowledge about the drugs prescribed and/or negative attitudes towards anticoagulant treatment, which could be present among both patients and physicians, would potentially have to be considered as well. Due to the data available for this study, specific reasons for discontinuation of DOACs in general, as well as switching between DOACs and warfarin in particular, among the study population remain however unknown.

7.5.2 Methodological considerations

This study has a number of limitations. First of all, by identifying eligible patients to be included in the study in secondary care, patients diagnosed and treated exclusively in primary care were not captured – particularly those with less severe representations of the condition. A recent study, conducted in England, identified that 42.1% of AF patients had an initial diagnosis in primary care (Allan et al., 2016); however, as many of these patients are relatively elderly, a proportion might subsequently have been admitted to hospital, hence reducing the percentage of patients not included in this study. As patient characteristics as well as major trends with respect to the main study findings were largely similar across observational studies despite differences in how these patients have been identified – using administrative databases covering primary (Martinez et al., 2016) or secondary care records (Gorst-Rasmussen et al., 2015), health insurance claims (Coleman et al., 2016, Yao et al., 2016), or referrals to a single health-care facility (Al-Khalili et al., 2016, Schulman et al., 2013) – not including all potentially eligible patients is not anticipated to have had a large impact on findings with regards to adherence, discontinuation, or persistence.

Second, the data used for analysis has not been collected for the specific purpose of this study but was gathered routinely in daily care. Consequently, not all desirable

information was present; in particular, no indication for why drugs were prescribed was available. This might have resulted in the inclusion of patients who had AF but were treated with DOACs for other reasons, potentially leading to imprecisions in results due to diverging anticipated treatment lengths and dosing schedules. Especially persistence to medication might have been underestimated, considering that treatment with DOACs for other indications might not necessarily be intended to be long-term – including, for instance, treatment with any DOAC for up to six months due to deep vein thrombosis, or short-term treatment of patients scheduled for catheter ablation or cardioversion. The effect of potentially including patients who have been treated for reasons other than AF on discontinuation and persistence was, however, likely small, as patients with a recorded diagnosis of DVT prior to treatment initiation have been excluded from the study; in addition, dose instructions as recorded by the prescriber have been used supplementary to drug supply based on standard dosing guidelines to limit the potential impact of variations in dosing schedules on adherence.

And finally, as prescription records do not cover secondary care, in-patient periods were not captured; this might have impacted adherence and persistence, as hospital days could have appeared to be treatment interruptions. Sensitivity analyses of the lengths of admissible gaps and the additional measurement of treatment cessation have however been used to account for the potential effect of in-patients episodes on discontinuation and persistence.

This study has nevertheless also several strengths: access to health care is universal, and electronic health records in Scotland cover the entire population; due to the presence of a unique patient identifier, records can easily and reliably be linked, resulting in the availability of a large variety of variables including those essential for calculating adherence to medication; and PIS and SMR01 have previously been used for research, and validity and accuracy of the data have been established (Alvarez-Madrazo et al., 2016, ISD Scotland, 2016b). Furthermore, by using a coherent framework underpinning the study as well as covering all facets of adherence – including triangulation of analytical methods – this study offered an unprecedentedly comprehensive overview of DOAC utilisation, with the potential to increase comparability of findings across studies. With the provisioning of routinely collected administrative health data of high quality and granularity, Scotland is part of a small

group of countries exceedingly qualified for conducting drug utilisation studies; PIS in particular represents a very valuable resource for this kind of research. Implementing standardised methods for analysing adherence, discontinuation, and persistence would be a logical next step to further improve the quality of research and the usefulness of findings – the most suitable specific measurements to be used for analysis naturally depend on the drugs studied and the question posed, but should nevertheless include at least one measure for each dimension of adherence.

7.6 Conclusion

New drugs usually get approval based on perceived advantages over well-established therapeutic alternatives. In the case of the DOACs, a major advancement is most certainly the easier dosing schedule in comparison to warfarin; as the complexity of warfarin therapy is considered one of the reasons for patients' non-adherence to treatment, the introduction of DOACs was thought to improve adherence to long-term anticoagulant treatment – and, bearing in mind the consequences of inadequate anticoagulation, hopefully in better treatment outcomes (Cotté et al., 2014, Kneeland & Fang, 2010, Schein et al., 2016).

In Scotland, adherence to DOAC treatment among patients with AF was high, and switching from DOAC to warfarin was low. Discontinuation rates were variable between the different drugs, but treatment interruptions were often temporary and persistence rates were comparable to those of warfarin (Johnson et al., 2016). However, some questions remain unanswered; analysing the underlying reasons for treatment discontinuation, for example, was outside the scope of this work.

Although several studies analysing the utilisation of DOACs in a population of patients with AF have been published thus far, study specifics – including study focus (e.g. DOACs in general or individual drugs; adherence, discontinuation, or persistence, and/or various combinations thereof), study designs, sample sizes, follow-up periods, and analytical methods – differed considerably, impeding the direct comparison of findings. To decrease the inconsistencies in drug utilisation methodology impacting the comparability of results across studies, the use of a coherent framework – using a combination of discontinuation, persistence and adherence – and the standardisation of measurements is strongly advocated.

Chapter 8 – Clinical effectiveness and safety

By summarising the results of the outcomes study, this chapter provides answers with regards to study objective 3, as outlined in section 3.2: to analyse the clinical effectiveness and safety associated with different DOACs in patients with AF in Scotland. The results presented and discussed here relate to the comparative clinical effectiveness and safety of DOACs – i.e. the risks of stroke and other thromboembolic events, death, and major bleeding; for patients' baseline characteristics, see chapter 6.

8.1 Introduction

Clinical trials are the current gold standard when trying to determine a drug's safety and efficacy, and are mandatory requirements for the approval of new drugs. RCTs are however frequently subject to criticism, especially with regards to transferability of results into real life contexts. In contrast to clinical trials for example, where study participation is usually restricted on the basis of very specific inclusion and exclusion criteria, patients in clinical practice are potentially older, with more comorbidities and a wider range of concomitant medications (Kennedy-Martin et al., 2015, Rothwell, 2005) – and comorbidities as well as concomitant medication can have considerable impact on treatment outcomes. While multi-morbidity for instance could indicate overall ill-health and frailty and thus might, in itself, be a risk factor for unfavourable disease outcomes, specific health conditions could potentially influence the severity of a disease and/or its impact on patients; and pre-existing conditions and/or other medication might directly affect the effectiveness and safety of drug treatment.

Observational pharmacoepidemiological studies, analysing treatment outcomes in real-world patients, are therefore crucial supplements to clinical trials in order to ensure that the benefits of drug treatment outweigh the risks, and that patients receive the most appropriate treatment option given their individual circumstances.

8.1.1 Observational studies to analyse drug treatment outcomes

Observational studies analysing outcomes of drug treatment are quite different from RCTs, in more than one respect; patients are for instance not as tightly monitored as would be the case during a clinical trial, with potential effects on adherence to treatment as well as timely discovery of side effects and/or adverse drug reactions.

Most importantly though, no randomisation of treatment takes place – with important implications for analysing and interpreting results.

Whereas participants in RCTs are allocated to different treatment groups randomly and, usually, neither patients nor trial personnel know which substance they are receiving (meaning that differences between treatment groups in clinical trials are minimised and down to chance), physicians in clinical practice make deliberate decisions to treat an individual patient with a specific drug. Hence, patients being treated with one drug might be inherently different from patients treated with another one – based on, for example, patient's characteristics or pre-existing conditions.

Consequently, associations between an exposure (e.g. to a drug) and the outcome of interest (e.g. stroke) found in observational studies could potentially be due to a third factor – linked to both exposure and outcome – rather than being causal. If, for instance, male patients are more likely to have a stroke but are also more likely to be treated with a certain drug, findings associating this particular drug with a higher risk of stroke need to take this confounding into consideration in order to ensure validity of results. Frequently used methods to account for confounding include, for example, stratification by different levels of potential confounding factors (e.g. analysing data separately for men and women), or adjusting for the confounding effect by including the relevant factors in a multivariate statistical model.

8.1.2 Defining drug exposure

Generally speaking, observational studies commonly make use of two divergent approaches to analysing outcomes of drug treatment: first, ever/never analyses, where drug exposure is normally defined as either "*yes"* or "*no"*; and second, dose-response analyses, taking into account duration and/or intensity of drug intake. Though representing related concepts, these analyses answer slightly different questions: while ever/never analyses provide evidence whether different drugs lead to different treatment outcomes – whether, for instance, one drug is more effective in preventing strokes than another – dose-response analyses can e.g. be used to evaluate potential changes in treatment effects over time.

In order to define drug exposure in dose-response analyses, DDDs are the most frequently used measurement. DDDs, the "defined daily dose" – indicating the

assumed average adult dose (WHO Collaborating Centre for Drug Statistics Methodology, 2016) – have been assigned to the majority of drugs taken orally, based on their main indication; DOACs for instance have been assigned DDDs based on the treatment of patients with AF (dabigatran: 0.3g, rivaroxaban: 20mg, apixaban: 10mg, edoxaban: 60mg). However, actual dosing might differ depending on, for example, patient age, weight, concomitant medication, and kidney and/or liver function; DDDs are therefore not necessarily in agreement with prescribed doses, and hence should be regarded as estimates only (ibid).

As an alternative to DDDs, the "days' supply" may be used: days' supply indicates the number of days a patients was exposed to a drug, based on dispensed quantities and standard dosing and/or prescribers' dose instructions, depending on data availability. Although presumably more accurate than DDDs (Sinnott et al., 2016), the accuracy of days' supply as a measurement of drug exposure depends on the quality of data available for its calculation, and is in addition subject to a range of assumptions – not least that patients took medication as prescribed. In addition, days' supply might be difficult to calculate if dosing is not standardised; while it is for instance relatively straightforward to identify days' supply based on prescription data for drugs such as DOACs, with a fixed dosing schedule of one or two tablets a day (depending on the drug in question), calculating days' supply for warfarin patients is impeded by not only wide inter-individual differences in dosing based on patients' general response to treatment, but also by potentially sizable differences in an individual patient's dosing schedule over time due to changing circumstances (e.g. changes in concomitant medication and/or comorbidities necessitating adjustment of daily warfarin dose).

8.2 Purpose of this study

VKAs such as warfarin have been used to prevent strokes in patients with AF for decades; although bleeding events as a consequence of anticoagulation are not uncommon, warfarin has proven to be sufficiently safe and effective for this indication. VKA treatment has however limitations: it can be inconvenient for patients as it requires constant monitoring; and there are frequently cases, particularly when patients are frail or very elderly, when warfarin treatment is not initiated despite the presence of multiple risk factors (Cowan et al., 2013, Holt et al., 2012).

Thus, new drugs have been developed, promising to be as safe and effective as warfarin while offering a more convenient therapeutic option. Clinical trials, comparing these DOACs – dabigatran, rivaroxaban, apixaban, and edoxaban – with warfarin (Connolly et al., 2009, Giugliano et al., 2013, Granger et al., 2011, Patel et al., 2011), have proven their safety and efficacy; consequently, they have now been approved for stroke prevention in patients with AF, and are increasingly prescribed to patients in many countries, including Scotland.

Several health conditions, commonly present in patients with AF in clinical practice, can however potentially influence the effectiveness and safety of DOAC treatment. Cardiovascular disease and diabetes e.g. increase the stroke risk among AF patients (Lip, 2013a); cancer has been linked to an increase in bleeding incidences (Prandoni et al., 2002); and kidney and/or liver disease can have sizeable effects on drug metabolism (Dempfle, 2014) – thus theoretically representing contraindications for particular drugs, or at least warranting caution. Concomitant medication may pose additional challenges; certain drugs with an inherent risk of bleeding themselves (e.g. aspirin, NSAIDs, SSRI) possibly further increase the bleeding risk among patients taking OACs (Lamberts et al., 2014, Quinn et al., 2014, Steinberg et al., 2013), while the general risk of drug-drug interactions increases with the number of drugs taken simultaneously. Furthermore, non-adherence to cardiovascular drug treatment in real life is wide-spread (Kolandaivelu et al., 2014, Schulz et al., 2016) even though non-adherence has been linked to an increase in unwanted treatment outcomes (Bansilal et al., 2016, Ho et al., 2009). Concerns have therefore been raised about the potential impact of multi-morbidity, polypharmacy, and non-adherence on DOAC treatment outcomes in clinical practice (Jaspers Focks et al., 2016, Piccini et al., 2016, Yao et al., 2016).

Nevertheless, real world data is still scarce; moreover, no clinical trials directly comparing the different DOACs have been conducted. Hence, the *purpose* of this study was to analyse the clinical effectiveness and safety of DOACs in real life patients with a diagnosis of atrial fibrillation, confirmed in secondary care in Scotland. More specifically, the objectives of this study were to compare the risks of stroke, cardiovascular death, and major bleeding events in patients exposed to the different DOACs with each other; and to examine the impact of treatment duration on outcomes by using two different analytical methods: first, an ever/never analysis, comparing

outcomes based on general exposure/non-exposure to individual drugs; and second, a dose-response analysis, examining outcomes based on cumulative duration of drug exposure.

8.3 Methods and material

This section is intended to give a detailed description of the specific methodology applied for analysing the outcomes of DOAC treatment; it also gives a brief summary of the study, including the study population and variables used for analysis. The overall study design, its setting, and the data sources are explained in sections 3.4, 3.3 and 4.1, together with a more in-depth description of the data itself in section 4.2.

8.3.1 Summary of study specifics

This study has been designed as a retrospective cohort study, using routinely collected administrative data. The study period spanned from January 2009 to December 2015.

The study population comprised patients with AF, either diagnosed or confirmed in secondary care, who started treatment with any DOAC available in Scotland during the study period (apixaban, dabigatran, rivaroxaban). Patients where alternative indications for OAC treatment were present (i.e. heart valve replacements, mitral stenosis, or a VTE during the 6-month period directly preceding the date of DOAC initiation) were excluded; specific inclusion and exclusion criteria are detailed in section 6.1. In addition, patients were also required to have a follow-up period of at least one day to enable analyses; for the purpose of the dose/response analysis only, the study population has been restricted to patients who were exclusively treated with a single DOAC in order to allow a straightforward analysis of treatment effects of individual drugs over time.

A patient's index date for study inclusion was the date of first recorded prescription for any DOAC. Patients were followed up until the investigated outcomes occurred, the patient died or was removed from a Scottish GP register for other reasons, or the study end date (December 31st, 2015), whichever happened first. For the ever/never analysis, patients were censored at the time of first treatment discontinuation; time to first discontinuation was calculated using the refill-gap method, with an admissible

supply gap of 28 days and adjusting for previous oversupply (as explained in section 7.3). Censoring for discontinuation included patients switching from their index drug to a different DOAC.

Person time at risk was measured in years; patients contributed person time at risk starting from the date of first DOAC prescription until the end of follow-up. For patients being censored due to either switching drugs or discontinuing treatment with their index drug more generally, the end of follow-up was determined by adding the dispensed days' supply at the last prescription prior to censoring to the date of this prescription.

8.3.2 Definition of drug exposure

As the effects of drug treatment might change depending on the level of exposure, drug exposure has been defined in two different ways for the purpose of this study: first, whether a patient has ever been treated with a specific DOAC; and second, for how long patients have been treated with their index drug, expressed as a categorical variable based on the cumulative days' supply patients received during follow-up.

For the ever/never analysis, exposure to specific DOACs was defined as either yes or no. As all patients included in the study have been treated with only one of the DOACs during follow-up, a categorical variable with three levels (apixaban, dabigatran, rivaroxaban) – based on the drug used to initiate DOAC treatment – was used to indicate drug exposure (*first_item*); hence, patients initiating treatment with one drug were compared to patients using either of the other drugs. By focusing solely on the first treatment episode, differences in discontinuation rates and persistence to treatment between the different DOACs have been taken into account. Due to the censoring of patients at time of first treatment discontinuation and/or switch between drugs, all patients were continuously exposed to their index drug throughout their respective follow-up periods.

In order to assess dose-response relationships among DOACs, cumulative duration of treatment was calculated using days' supply; days' supply itself was previously calculated based on dispensed quantity and standard dose instructions/prescribing instructions (as used in the utilisation study; for details, see section 7.3). Cumulative days' supply has then been recoded into a categorical variable with 5 levels, as shown

in table 8.1: 0-3 months; 3-6 months; 6-12 months; 12-18 months; and 18 months or longer (*exp_level*). Limits were chosen based on observable treatment patterns (common treatment durations for DOACs include, for instance, up to 6 or 12 months for patients with DVTs), as well as data availability (with few patients exposed to DOACs – especially apixaban – for 24 months or longer). For use in the statistical analysis, observations indicating a change in exposure level were retained, resulting in a dataset used for analysis comprising at least one and at most five records for every patient, depending on the number of changes in exposure level observed. Each record represented a treatment interval based on a specified level of exposure, and included start and end times for this interval as well as a status variable indicating whether an outcome of interest has occurred at the end. As patients might not have been perfectly adherent or could have had intermittent periods of treatment interruptions, cumulative days' supply did not necessarily exactly match the number of days of follow-up for each patient; a patient could, for example, have received five prescriptions with a 28 days' supply within a 7-month period – meaning that this patient would still be at the 3-6 months exposure level, regardless of the theoretically longer treatment duration.

Table 8.1: Cumulative days' supply and corresponding level of drug exposure

Exposure level	Cumulative days' supply
0 – 3 months	0 – 91
3 – 6 months	92 – 183
6 – 12 months	184 – 365
12 – 18 months	366 – 548
18 months or more	549 and above

8.3.3 Definition of endpoints

Treatment outcomes have been divided into two separate categories: effectiveness outcomes, and safety outcomes. In order to facilitate comparisons with results originating from the major clinical trials regarding the DOACs dabigatran, rivaroxaban, and apixaban (Connolly et al., 2009, Granger et al., 2011, Patel et al., 2011), similar outcomes and definitions thereof have been used as far as possible.

The primary effectiveness outcomes comprised stroke – all stroke (a composite of ischaemic and haemorrhagic strokes), as well as ischaemic stroke separately – systemic embolism, and death due to cardiovascular reasons as main clinical endpoints, comparable to the three clinical trials. Also similar to the trials, additional outcomes in this category were pulmonary embolism, transient ischaemic attack, myocardial infarction, and all-cause mortality; as well as composite effectiveness outcomes comprising a) ischaemic stroke and systemic embolism; and b) all stroke, systemic embolism, and transient ischaemic attack.

Safety outcomes all related to bleeding events, categorised as either major or non-major/minor bleeding in the clinical trials. According to the International Society of Thrombosis and Haemostasis, major bleedings are characterised by either being fatal; occurring in a critical area or organ (e.g. intracranial, pericardial); or leading to a transfusion of two or more units of blood (Schulman & Kearon, 2005). However, due to the data available for this study, bleeding outcomes in this study have been divided into haemorrhagic stroke (comprising both intracranial and subarachnoid haemorrhages); other major bleeds, including other non-traumatic intracranial haemorrhages as well as haemorrhages occurring within the chest or the respiratory or urinary tract; and gastro-intestinal bleeding. A composite outcome of all bleeds – comprising haemorrhagic stroke, other major bleeds, and gastro-intestinal bleeding – has been added in order to evaluate the overall risk of bleeding.

Endpoints (except death) have been identified in SMR01/SMR00, using all available diagnostic codes (main diagnosis and up to five additional diagnosis, and up to four referral reasons, respectively); cause of death has been identified in NRS, using main and underlying reason of death to identify death due to cardiovascular events. ICD-10 codes used to identify clinical endpoints within the datasets have been chosen based on the literature (Alotaibi et al., 2015, Larsen et al., 2013, Melgaard et al., 2015, Sood et al., 2014, Valkhoff et al., 2014, Woodfield et al., 2015), and are listed in table 8.2.

Table 8.2: ICD-10 codes used to identify study endpoints

Endpoint/outcomes	Diagnostic codes
1. Clinical effectiveness	
Stroke, all	I60, I61, I63, I64
Ischaemic stroke	I63, I64
Transient ischaemic attack	G45.8, G45.9
Systemic embolism	I74
Pulmonary embolism	I26
Myocardial infarction	I21, I22
Death, cardiovascular	I11, I13, I20-I26, I46, I47, I49, I50, I60, I61, I63, I64, I67, I73, I74
2. Safety	
Haemorrhagic stroke	I60, I61
Other major bleeds	D62, H11.3, H35.6, H43.1, I62, J94.2, N02, N95.0, R04, R31, R58
Gastro-intestinal bleeds	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0 – 92.2

Patients were censored after a first recorded event; however, all outcomes were analysed separately – meaning that while patients could have been subject to two different outcome events (e.g. a transient ischaemic attack and a myocardial infarction, or a stroke and a major bleed), repeat events (i.e. a second stroke after having already suffered a stroke since initiating DOAC treatment) have not been included in the analysis. More specifically, this means that a patient with both a stroke and a major bleed has been included in the stroke analysis up to the time of first stroke, and in the major bleed analysis up to the time of first major bleed; if the stroke came first, the major bleed analysis was not censored at the time of stroke.

The time to event was calculated based on the date of first prescription and date of admission/date of death (as applicable), and has been expressed in days.

8.3.4 Covariates

In order to account for confounding, multivariate analysis – adjusting results for confounding factors – has been applied. Variables to be used as covariates in the survival models were chosen based on observed geographical variations in

prescribing patterns across Scotland as well as differences in patients' baseline characteristics (as detailed in chapters 5 and 6 respectively), and comprised patient sex and age at time of first prescription; Health Board of residence and location based on the urban/rural classification; the Scottish Index of Multiple Deprivation (SIMD); and indicators for comorbidities, concomitant medication, and stroke, as well as bleeding risks (table 8.3 gives an overview). All covariates were fixed at baseline.

Table 8.3: Covariates included in multivariate analysis to adjust for confounding

Variable	Data source	Format
Patient sex	CHI	Binary
Patient age at first prescription	CHI, PIS	Continuous
Health Board of residence	PIS	Categorical
Urban/rural classification	PIS	Categorical
Scottish Index of Multiple Deprivation	PIS	Categorical
Charlson score	SMR	Numerical
CHA_2DS_2-VASc score	SMR	Numerical
HAS-BLED score	SMR, PIS	Numerical
Polypharmacy	PIS	Binary

CHI – Community Health Index; PIS – Prescribing Information System; SMR – Scottish Morbidity Records

8.3.4.1 Socio-demographic factors

Variables with regards to socio-demographic factors were mostly readily available in the datasets, and comprised patient sex and age at time of first prescription; two variables describing patients' geographical area of residence; and the level of deprivation. While patient sex was a binary variable (1=male, 2=female), taken directly from CHI, patient age at time of first DOAC prescription was continuous, and has been derived from patient date of birth and date of index prescription as recorded in CHI and PIS, correspondingly. Health Board, urban/rural classification, and SIMD were all categorical variables, with 14, 8, and 5 levels, respectively, gathered from PIS (see also section 4.2 for a more in-depth description).

8.3.4.2 Comorbidities and concomitant medication

The scores used to adjust for comorbidities and other risk factors potentially influencing treatment outcomes were all numerical, and included the Charlson score (as an indicator of comorbidity in general), and CHA_2DS_2-VASc and HAS-BLED scores (quantifying the risk of having a stroke and experiencing a bleeding event, respectively); for a description of how these scores have been calculated, see section 6.1. In addition, a dichotomised variable indicating whether a patient was subject to polypharmacy at baseline – taking five or more different drugs concomitantly – has been included (0=no, 1=yes).

8.3.5 Statistical analysis

Statistical analysis has been conducted using Cox proportional hazard models, with time to event measured in days. The main explanatory variable was drug exposure, either in absolute terms (yes/no) or as a time-dependent categorical variable (detailing the cumulative level of exposure over time); binary variables (0=no, 1=yes) indicated the occurrence of an outcome of interest.

Using the R software (R Core Team, 2016), models have been written in the general forms:

$$coxph(Surv(time.event, endpoint) \sim exposure + covariates)$$

$$coxph(Surv(time.start, time.stop, endpoint) \sim exposure + covariates)$$

Models represent the ever/never analysis and the dose-response analysis, respectively; more detailed R code can be found in appendix III.

The applied level of statistical significance was 0.05.

8.4 Results

8.4.1 Ever / never analysis

Of the 14,811 AF patients initiating treatment with any DOAC during the study period, 94 patients have been excluded either due to having been treated with more than one DOAC simultaneously (n=71), or because they received a first prescription for a

DOAC on the last day of their follow-up period (n=23). Hence, 14,717 patients have been included in the ever/never analysis: 6,250 patients (42.5%) having been treated with apixaban, 1,116 (7.6%) with dabigatran, and 7,351 (49.9%) with rivaroxaban.

8.4.1.1 Crude incidence rates

When focusing on the first treatment period of patients (i.e. censoring patients at first discontinuation of treatment/when switching index drug), 193 ischaemic strokes, 18 systemic embolisms, and 616 deaths due to cardiovascular reasons occurred during the study period, in addition to 55 haemorrhagic strokes, 229 gastro-intestinal bleeds, and 368 other bleeding events. Table 8.4 gives an overview of crude incidence rates, overall and by drug, for all outcomes except composites.

Table 8.4: Crude incidence rates, overall and by drug

	DOACs (n=14,717)	Apixaban (n=6,250)	Dabigatran (n=1,116)	Rivaroxaban (n=7,351)
Ischaemic stroke				
Number events	193	67	19	107
Person time at risk [years]	11,897	4,082	1,172	6,643
Incidence rate [1]	1.62	1.64	1.62	1.61
Systemic embolism				
Number events	18	5	2	11
Person time at risk [years]	11,958	4,097	1,178	6,682
Incidence rate [1]	0.15	0.12	0.17	0.16
Death, cardiovascular				
Number events	616	197	39	380
Person time at risk [years]	11,958	4,097	1,178	6,682
Incidence rate [1]	5.15	4.81	3.31	5.68
Pulmonary embolism				
Number events	37	7	0	30
Person time at risk [years]	11,955	4,096	1,179	6,681
Incidence rate [1]	0.31	0.17	0.00	0.45
Transient ischaemic attack				
Number events	67	23	4	40
Person time at risk [years]	11,931	4,087	1,178	6,665
Incidence rate [1]	0.56	0.56	0.34	0.60

Table 8.4 continued: Crude incidence rates, overall and by drug

	DOACs (n=14,717)	Apixaban (n=6,250)	Dabigatran (n=1,116)	Rivaroxaban (n=7,351)
Myocardial infarction				
Number events	143	79	7	57
Person time at risk [years]	11,924	4,075	1,175	6,674
Incidence rate [1]	1.20	1.94	0.60	0.85
Death, all cause				
Number events	992	306	61	625
Person time at risk [years]	11,969	4,099	1,179	6,691
Incidence rate [1]	8.29	7.47	5.18	9.34
Haemorrhagic stroke				
Number events	55	17	3	35
Person time at risk [years]	11,966	4,098	1,178	6,689
Incidence rate [1]	0.46	0.41	0.25	0.52
Gastro-intestinal bleeding				
Number events	229	69	22	138
Person time at risk [years]	11,891	4,081	1,169	6,640
Incidence rate [1]	1.93	1.69	1.88	2.08
Other major bleeds				
Number events	368	105	23	240
Person time at risk [years]	11,779	4,053	1,164	6,562
Incidence rate [1]	3.12	2.59	1.98	3.66

[1] per 100 person years

8.4.1.2 Clinical effectiveness

Using multivariate models – adjusting for covariates – no differences between the DOACs were observed with respect to either primary effectiveness outcomes – i.e. stroke (ischaemic stroke, and all stroke), systemic embolism, and death due to cardiovascular reasons – or the composite outcomes (combining strokes, systemic embolism, and/or transient ischaemic attacks). There were, however, differences between drugs regarding three of the secondary effectiveness outcomes: pulmonary embolism; myocardial infarction; and all-cause mortality. Table 8.5 gives an overview of both univariate (unadjusted) as well as multivariate models (adjusted).

Table 8.5: Hazard ratios with 95% confidence intervals for associations between drug of choice and all effectiveness outcomes, unadjusted versus adjusted models

Hazard ratios [95% confidence interval]: univariate models				
Reference: rivaroxaban	***Apixaban***	***p-value***	***Dabigatran***	***p-value***
Ischaemic stroke	0.93 [0.68 – 1.26]	*0.637*	1.06 [0.65 – 1.73]	*0.815*
All stroke	0.91 [0.69 – 1.21]	*0.526*	0.95 [0.60 – 1.50]	*0.828*
Systemic embolism	0.66 [0.23 – 1.92]	*0.449*	1.15 [0.25 – 5.21]	*0.854*
Death, cardiovascular	0.79 [0.66 – 0.94]	*0.007*	0.61 [0.44 – 0.86]	*0.004*
Pulmonary embolism	0.35 [0.15 – 0.80]	*0.012*	n/a	
Transient ischaemic attack	0.84 [0.50 – 1.41]	*0.512*	0.63 [0.22 – 1.76]	*0.374*
Myocardial infarction	2.10 [1.48 – 2.96]	*<0.001*	0.75 [0.34 – 1.66]	*0.483*
All-cause mortality	0.76 [0.66 – 0.87]	*<0.001*	0.57 [0.44 – 0.75]	*<0.001*
Composite A [1]	0.90 [0.67 – 1.21]	*0.498*	1.07 [0.67 – 1.70]	*0.784*
Composite B [2]	0.90 [0.71 – 1.14]	*0.382*	0.93 [0.62 – 1.38]	*0.709*
Hazard ratios [95% confidence interval]: multivariate models				
Reference: rivaroxaban	***Apixaban***	***p-value***	***Dabigatran***	***p-value***
Ischaemic stroke	1.05 [0.68 – 1.63	*0.827*	1.19 [0.70 – 2.02]	*0.524*
All stroke	0.90 [0.61 – 1.32]	*0.582*	1.01 [0.62 – 1.66]	*0.955*
Systemic embolism	0.59 [0.15 – 2.27]	*0.446*	1.56 [0.32 – 7.71]	*0.584*
Death, cardiovascular	0.92 [0.72 – 1.17]	*0.476*	0.72 [0.50 – 1.03]	*0.074*
Pulmonary embolism	0.19 [0.06 – 0.56]	*0.002*	n/a	
Transient ischaemic attack	0.75 [0.38 – 1.48]	*0.403*	0.63 [0.22 – 1.82]	*0.394*
Myocardial infarction	1.71 [1.05 – 2.77]	*0.030*	0.75 [0.33 – 1.71]	*0.490*
All-cause mortality	0.82 [0.68 – 0.99]	*0.043*	0.65 [0.49 – 0.87]	*0.004*
Composite A [1]	0.98 [0.65 – 1.49]	*0.922*	1.19 [0.72 – 1.97]	*0.501*
Composite B [2]	0.86 [0.62 – 1.19]	*0.354*	0.99 [0.64 – 1.52]	*0.964*

[1] ischaemic stroke + systemic embolism; [2] all stroke + transient ischaemic attack + systemic embolism

Patients using rivaroxaban were 5.29 times [95% CI 1.80 – 15.59] more likely than patients being treated with apixaban to experience a pulmonary embolism; in contrast, apixaban patients were more likely to have a myocardial infarction than patients using either rivaroxaban or dabigatran, with hazard ratios of 1.71 [95% CI 1.05 – 2.77] and

2.28 [95% CI 1.00 – 5.21], respectively. The use of rivaroxaban was associated with higher risks of all-cause mortality as compared to both apixaban and dabigatran (apixaban: HR 0.82 [95% CI 0.68 – 0.99], dabigatran: HR 0.65 [95% CI 0.49 – 0.87]). Detailed results are presented in table 8.6.

Table 8.6: Hazard ratios with 95% confidence intervals for significant associations between drug of choice and effectiveness outcomes, including all reference combinations

Hazard ratios [95% confidence interval]: adjusted models only						
	Pulmonary embolism	***p-value***	***Myocardial infarction***	***p-value***	***All-cause mortality***	***p-value***
Apixaban	0.19 [0.06 – 0.56]	*0.002*	1.71 [1.05 – 2.77]	*0.030*	0.82 [0.68 – 0.99]	*0.043*
Dabigatran	n/a		0.75 [0.33 – 1.71]	*0.490*	0.65 [0.49 – 0.87]	*0.004*
Rivaroxaban	1		1		1	
Apixaban	n/a		2.28 [1.00 – 5.21]	*0.050*	1.25 [0.92 – 1.70]	*0.145*
Dabigatran	n/a		1		1	
Rivaroxaban	n/a		1.34 [0.59 – 3.05]	*0.490*	1.53 [1.15 – 2.03]	*0.004*
Apixaban	1		1		1	
Dabigatran	n/a		0.44 [0.19 – 1.00]	*0.050*	0.80 [0.59 – 1.08]	*0.145*
Rivaroxaban	5.29 [1.80 – 15.59]	*0.002*	0.59 [0.36 – 0.95]	*0.030*	1.22 [1.01 – 1.47]	*0.043*

8.4.1.3 Safety

There were no significant differences between DOACs regarding haemorrhagic stroke, but with respect to gastro-intestinal and other bleeds, as well as the composite of all bleeding; see table 8.7 for an overview of findings.

Table 8.7: Hazard ratios with 95% confidence intervals for associations between drug of choice and all safety outcomes, unadjusted versus adjusted models

Hazard ratios [95% confidence interval]: univariate models				
Reference: rivaroxaban	***Apixaban***	***p-value***	***Dabigatran***	***p-value***
Haemorrhagic stroke	0.81 [0.45 – 1.47]	*0.495*	0.48 [0.15 – 1.57]	*0.226*
Gastro-intestinal bleeding	0.75 [0.56 – 1.00]	*0.053*	0.98 [0.62 – 1.54]	*0.936*
Other major bleeds	0.66 [0.52 – 0.83]	*<0.001*	0.59 [0.38 – 0.91]	*0.016*
All bleeds (composite)	0.70 [0.59 – 0.84]	*<0.001*	0.71 [0.52 – 0.96]	*0.027*

Table 8.7 continued: Hazard ratios with 95% confidence intervals for associations between drug of choice and all safety outcomes, unadjusted versus adjusted models

Hazard ratios [95% confidence interval]: multivariate models				
Reference: rivaroxaban	***Apixaban***	***p-value***	***Dabigatran***	***p-value***
Haemorrhagic stroke	0.56 [0.26 – 1.20]	*0.139*	0.44 [0.13 – 1.56]	*0.205*
Gastro-intestinal bleeding	0.68 [0.46 – 0.99]	*0.043*	1.04 [0.64 – 1.70]	*0.869*
Other major bleeds	0.67 [0.49 – 0.91]	*0.010*	0.64 [0.41 – 1.00]	*0.050*
All bleeds (composite)	0.66 [0.52 – 0.83]	*<0.001*	0.75 [0.54 – 1.03]	*0.079*

Gastro-intestinal bleeds as well as other major bleeds were 1.48 [95% CI 1.01 – 2.16] and 1.50 [95% CI 1.10 – 2.03] times more likely among patients using rivaroxaban than among apixaban patients, respectively; the overall bleeding risk – including all bleeding events – was 52% higher among patients being treated with rivaroxaban than among patients receiving apixaban (HR 1.52, 95% CI 1.21 – 1.91). While there were no differences between dabigatran and both apixaban and rivaroxaban with regards to gastro-intestinal bleeds, the risks of other major bleeds was higher among rivaroxaban patients as compared to dabigatran; this finding was however not statistically significant (p=0.05). For a list of hazard rations related to safety outcomes, see table 8.8.

Table 8.8: Hazard ratios with 95% confidence intervals for significant associations between drug of choice and safety outcomes, including all reference combinations

Hazard ratios [95% confidence interval], adjusted models only						
	Gastro-intestinal bleed	***p-value***	***Other major bleed***	***p-value***	***All bleeds***	***p-value***
Apixaban	0.68 [0.46 – 0.99]	*0.043*	0.67 [0.49 – 0.91]	*0.010*	0.66 [0.52 – 0.83]	*<0.001*
Dabigatran	1.04 [0.64 – 1.70]	*0.869*	0.64 [0.41 – 1.00]	*0.050*	0.75 [0.54 – 1.03]	*0.079*
Rivaroxaban	1		1		1	
Apixaban	0.65 [0.38 – 1.10]	*0.105*	1.05 [0.64 – 1.70]	*0.856*	0.88 [0.62 – 1.24]	*0.462*
Dabigatran	1		1		1	
Rivaroxaban	0.96 [0.59 – 1.57]	*0.869*	1.56 [1.00 – 2.45]	*0.050*	1.33 [0.97 – 1.87]	*0.079*
Apixaban	1		1		1	
Dabigatran	1.54 [0.91 – 2.60]	*0.105*	0.96 [0.59 – 1.55]	*0.856*	1.14 [0.81 – 1.61]	*0.462*
Rivaroxaban	1.48 [1.01 – 2.16]	*0.043*	1.50 [1.10 – 2.03]	*0.010*	1.52 [1.21 – 1.91]	*<0.001*

8.4.2 Dose-response analysis

After excluding a further 498 patients who received prescriptions for more than one of the DOACs during the study period, 14,219 patients who were exclusively treated with a single DOAC were included in the dose-response analysis: 6,178 apixaban patients (43.4%), 917 dabigatran patients (6.4%), and 7,124 rivaroxaban patients (50.1%).

The effect of treatment duration on outcomes differed slightly between individual DOACs – albeit to varying degrees, depending on the outcome: statistically significant differences were observed in most effectiveness outcomes (ischaemic stroke and all stroke, death due to cardiovascular reasons and all-cause mortality, and both composite effectiveness outcomes) as well as overall bleeding risk, while trends with respect to transient ischaemic attacks, gastro-intestinal bleeds, and other major bleeds showed similarities between the drugs.

Generally speaking, the risks of strokes (all stroke, as well as ischaemic stroke individually), death due to cardiovascular reasons, and all-cause mortality decreased with increasing treatment duration among apixaban and rivaroxaban patients, and a decreasing risk was also observed for both composite effectiveness outcomes. There was nevertheless variation between these two drugs with respect to strokes – especially regarding ischaemic stroke, with an initial increase in risk among apixaban patients in contrast to a more steady decline among rivaroxaban users –, while the progression of mortality risks more closely matched each other. In contrast, dabigatran exhibited slightly diverging trends, with an initial reduction in risks followed by an increase across all aforementioned effectiveness outcomes. Figures 8.1 to 8.3 show the hazard ratios for these outcomes over time, comparing trends between the different DOACS by using rivaroxaban in the highest exposure category (18 months or more) as reference.

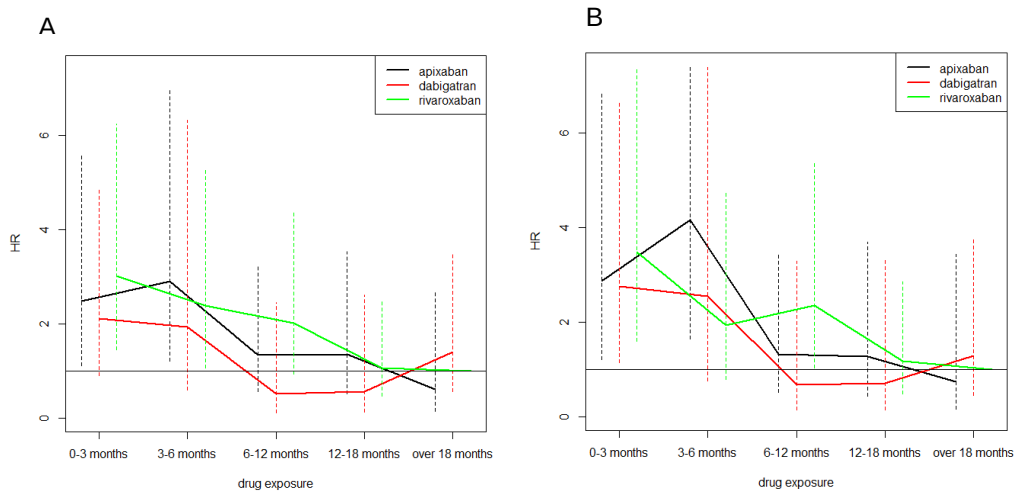


Figure 8.1: Hazard ratios with 95% confidence intervals for all stroke (A) and ischaemic stroke (B) with increasing treatment duration, by drug

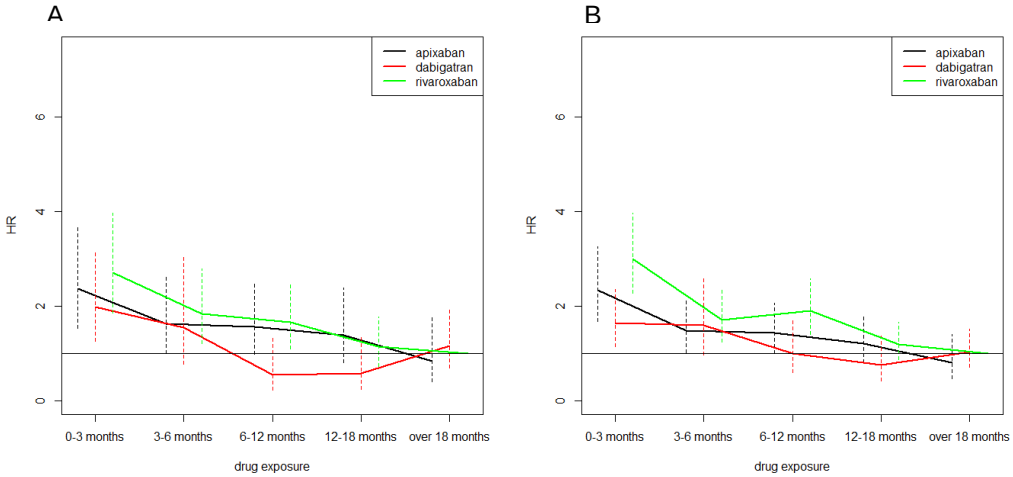


Figure 8.2: Hazard ratios with 95% confidence intervals for death due to cardiovascular causes (A) and all-cause mortality (B) with increasing duration of treatment, by drug

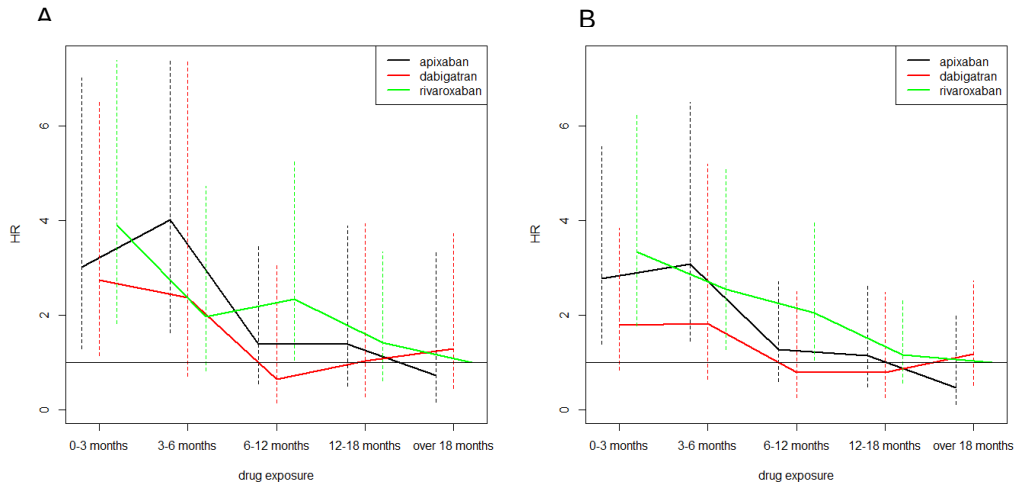


Figure 8.3: Hazard ratios with 95% confidence intervals for composite effectiveness outcomes A (ischaemic stroke + systemic embolism, A) and B (all stroke + transient ischaemic attack + systemic embolism, B) with increasing duration of treatment, by drug

There were neither obvious patterns nor statistically significant differences in trends over time with respect to gastro-intestinal bleeding or other major bleeds with increasing duration of treatment, regardless of drug. However, the overall risk of bleeding differed between drugs; especially with apixaban, the bleeding risk seemed to increase slightly over time (see also figure 8.4).

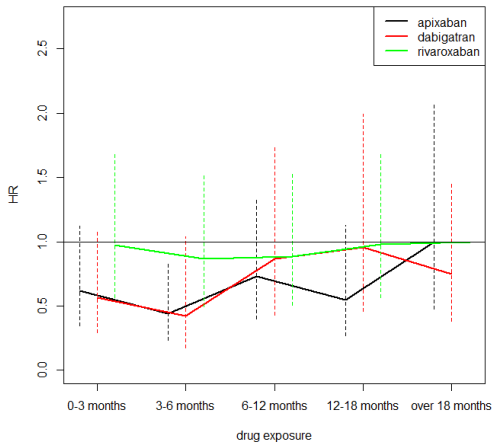


Figure 8.4: Hazard ratios with 95% confidence intervals for all bleeds with increasing duration of treatment, by drug

8.5 Discussion

This was one of the first studies in Scotland using linked data from PIS and SMR01 to analyse the clinical effectiveness and safety of DOAC treatment in patients with AF, and one of a growing number of observational studies directly comparing the individual DOACs – either focusing on safety (Abraham et al., 2017, Lip et al., 2016), or analysing both safety and effectiveness (Deitelzweig et al., 2017, Gorst-Rasmussen et al., 2016, Hernandez et al., 2017, Lai et al., 2017, Noseworthy et al., 2016). In addition, this was the first study to include an analysis of potential changes in DOAC treatment outcomes over time, using drug exposure data obtained from a preceding drug utilisation study (as detailed in chapter 7).

8.5.1 Main findings

The main study findings are, by and large, comparable to previously published results: all DOACs are similarly effective in preventing strokes and systemic embolism; and bleeding risks differ slightly between individual drugs, with apixaban having overall the most favourable bleeding profile. Nevertheless, a number of unexpected results emerged from this study: first, rivaroxaban seems to be associated with an increased risk of all-cause mortality as compared to apixaban and dabigatran; second, patients treated with apixaban appear to have a higher risk of having a myocardial infarction than patients treated with either dabigatran or rivaroxaban; and third, apixaban might potentially be more effective in preventing pulmonary embolisms than rivaroxaban. In addition, findings from the dose-response analysis indicated minor differences between the treatment effects of individual DOACs over time – however, overall trends were largely similar.

8.5.1.1 Comparative clinical effectiveness

In this study, no significant differences between DOACs were found in the risks of strokes, systemic embolism, transient ischaemic attacks, or combinations thereof – in line with the majority of published research. Except from one previous study from the US, where a 28% lower risk of stroke/systemic embolism in patients using apixaban as compared to rivaroxaban patients has been reported (Deitelzweig et al., 2017), other observational studies found no differences in the risk of stroke between dabigatran and rivaroxaban (Gorst-Rasmussen et al., 2016), the combination of

stroke/systemic embolism between apixaban and dabigatran (Deitelzweig et al., 2017) or between any of the DOACs (Noseworthy et al., 2016), or a composite outcome of stroke, systemic embolism and death across all DOACs (Hernandez et al., 2017). These findings principally confirm the conclusions made based on indirect comparisons between DOACs using clinical trial data (Lip et al., 2012, Rasmussen et al., 2012, Schneeweiss et al., 2012), published shortly after the DOACs became available, that the drugs are overall comparable in terms of effectiveness for their main indication – preventing strokes in patients with AF. Reasons for why the findings by Deitelzweig et al (2017) differed slightly are unclear, as both the included patient cohort as well as the study methodology were similar to other published studies.

Unlike the results with regards to primary effectiveness outcomes, which have shown high agreement across studies, findings relating to secondary outcomes were however varied. The risk of all-cause mortality for instance was 53% higher among rivaroxaban patients than among dabigatran patients in this study, and comparable findings have been reported before: 43% in a nationwide Danish study (Gorst-Rasmussen et al., 2016); and 44% in an observational study from Taiwan (Lai et al., 2017). Contrarily, indirect comparisons of DOACs, using clinical trials data, did not hint towards any differences in risk across drugs – neither in all-cause mortality, nor in death from vascular causes (Lip et al., 2012, Rasmussen et al., 2012). Results with respect to comparative risks of myocardial infarction differed even more widely between studies. While this study found higher risks among patients using apixaban as compared to both rivaroxaban and dabigatran patients – with hazard ratios of 1.71 [95% CI 1.05 – 2.77] and 2.28 [95% CI 1.00 – 5.21], respectively –, other studies either found no differences or did not report them (Gorst-Rasmussen et al., 2016, Lai et al., 2017), or suggested higher risks in dabigatran in comparison to apixaban and/or rivaroxaban (Lip et al., 2012, Rasmussen et al., 2012). Moreover, the risks of pulmonary embolism have rarely been analysed; an indirect comparison of apixaban and dabigatran based on clinical trial data found no difference (Lip et al., 2012), whereas the risk of pulmonary embolism in this study was significantly increased in patients using rivaroxaban in contrast to patients being treated with apixaban (HR 5.29 [95% CI 1.80 – 15.59]).

Due to the disparity of secondary outcomes used across studies – both in terms of what has been used, and how it has been defined – and the overall still limited number

of studies directly comparing DOACs thus far, there is only restricted potential to compare results. Consequently, any reasons for observed differences in the risks of all-cause mortality, myocardial infarction and especially pulmonary embolism are virtually impossible to discern – in particular in the absence of additional information such as primary care records and laboratory data, which could have given valuable clues about, for instance, the presence of additional risk factors for cardiovascular events or mortality by providing blood pressure readings, cholesterol levels, or data regarding kidney and/or liver function; these information were however not available for this study.

A suggested explanation for differences in all-cause mortality was selective prescribing for rivaroxaban based on the relatively higher-risk population included in the ROCKET-AF trial (Gorst-Rasmussen et al., 2016); due to the study design and the data available for analysis, unobserved differences in patient characteristics, linked to the prescribing or non-prescribing of specific drugs, were most likely contributing factors. Considering clinical trial results (indicating a slightly higher risk of myocardial infarctions with dabigatran as compared to warfarin) and an earlier report suggesting a lower risk of myocardial infarctions with apixaban as compared to dabigatran (Connolly et al., 2009, Rasmussen et al., 2012), selective prescribing – i.e. initiating patients with prior myocardial infarctions or otherwise increased risks of myocardial infarctions on apixaban rather than dabigatran – could have played a role with regards to these findings as well. Furthermore, pulmonary embolisms were very rare events during the study period (n=37, IR 0.31/100 person-years), and the treatment groups in this study were quite different in size, with considerably less patients having initiated treatment with dabigatran (n=1,116) than with either apixaban (n=6,250) or rivaroxaban (n=7,351) – resulting in no pulmonary embolism having occurred among dabigatran patients during the study period, effectively rendering comparisons between dabigatran and the other DOACs impossible. These study findings regarding secondary effectiveness outcomes (particularly with respect to the risks of pulmonary embolism) should therefore be interpreted with caution – not only in this study, but in similar observational studies as well.

8.5.1.2 Comparative safety

While differences across all DOACs in haemorrhagic strokes were not significant in this study, differences were observed in the other three safety outcomes: the risks of

gastro-intestinal bleeding, other major bleeds, and the overall risk of bleeding were 48%, 50% and 52% higher among patients using rivaroxaban than among apixaban patients, respectively. There were however no differences between apixaban and dabigatran, or rivaroxaban and dabigatran, in any of the safety outcomes.

Similar findings have been reported from other observational studies, albeit with some variation in individual results – mainly pertaining to differences in bleeding risk with regards to dabigatran. Studies published so far for instance highlighted significant differences with regards to gastro-intestinal bleeding, with rates higher for rivaroxaban than for apixaban (Abraham et al., 2017, Deitelzweig et al., 2017, Hernandez et al., 2017) but also for dabigatran (Hernandez et al., 2017, Lai et al., 2017); a higher risk of major bleeding with rivaroxaban in contrast to apixaban (Deitelzweig et al., 2017, Lip et al., 2016, Noseworthy et al., 2016), as well as compared to dabigatran (Noseworthy et al., 2016); and a higher overall bleeding risk among rivaroxaban patients as opposed to patients using apixaban (Deitelzweig et al., 2017, Hernandez et al., 2017) or dabigatran (Gorst-Rasmussen et al., 2016, Hernandez et al., 2017). These findings are, by and large, also in agreement with indirect comparisons based on trial data, suggesting lower risks of major bleeds with apixaban than with rivaroxaban and dabigatran (Lip et al., 2012, Rasmussen et al., 2012, Schneeweiss et al., 2012). As in this study, most other studies did not find any differences in regards to haemorrhagic stroke between DOACs (Deitelzweig et al., 2017, Hernandez et al., 2017, Lai et al., 2017); a 1.79 times higher risk of intracranial bleeding in rivaroxaban patients as compared to patients being treated with dabigatran has been reported in only one study (Noseworthy et al., 2016). In addition, other studies also reported no differences in bleeding events between apixaban and dabigatran (Deitelzweig et al., 2017, Hernandez et al., 2017, Lip et al., 2016).

Although differences in methodology might at least partially explain variations in findings across studies – definitions and clinical codes used to identify outcomes differed, for example –, results with regards to intracranial bleeding could also have been influenced by small numbers of observed events during study periods; nevertheless, specific reasons for these differences across studies remain unknown.

8.5.1.3 Treatment outcomes in relation to duration of treatment

Although results from the dose-response analysis were inconclusive overall, two aspects deserve mentioning. First of all, findings indicated differences between the DOACs in treatment outcomes with increasing treatment duration, with some similarities between apixaban and rivaroxaban but slightly diverging patterns for dabigatran, especially with regards to stroke and mortality. Considering that apixaban and rivaroxaban are both factor Xa inhibitors while dabigatran is a thrombin inhibitor, closer similarities between the former two were likely to be expected; nevertheless, results could have been influenced by differences in sample sizes (with markedly less dabigatran patients (n=917) included in the study than patients using either apixaban, n=6178 or rivaroxaban, n=7124), as well as unobserved differences in patients' characteristics.

And second, the risks of strokes and death appear to decrease over time, whereas the bleeding risks seem to increase slightly with increasing treatment duration. These results might, however, not be rooted in changing effectiveness and/or safety of DOACs with increasing exposure, but could be due to confounding or chance; patients with higher risks of stroke and/or death for instance – e.g. very elderly or frail patients – could stop using DOACs for any number of reasons before an event occurred, resulting in a relatively younger or healthier patient population being exposed to DOACs for longer. Furthermore, the longer patients are exposed to DOACs – with the inherent feature of increasing bleeding risks – the more likely patients are to experience a bleeding event, particularly in a study population where polypharmacy is widespread and the use of other medication impacting the risk of bleeds (such as aspirin or NSAIDs, to mention only the most obvious options) is probable.

Findings should therefore be interpreted with caution – not least because no other studies have published results based on dose-response analyses, using days' supply to define drug exposure levels, before.

8.5.2 Methodological considerations

This study has a number of limitations. First of all, patients to be included in the study have been identified in secondary care only, meaning that patients diagnosed and treated exclusively in primary care – potentially with less severe representations of AF – were not captured. While not including these patients might have resulted in

overestimations of outcome incidence rates, the impact on hazard ratios when comparing DOACs with each other was however most likely small; as current treatment guidelines do not recommend specific DOACs based on varying levels in disease severity, the non-inclusion of patients should have been independent of the drug they received when initiating DOAC treatment.

Second, as the data used for analysis has not been collected specifically for the purpose of this study but stemmed from a limited set of administrative records, not all desirable information was available; identification of endpoints for example had to rely on hospital discharge and death records, with possible implications on the accuracy of findings – particularly regarding bleeding events. Without laboratory data, bleeding events were identified by using only ICD-10 codes, rather than fully applying the definition for major bleeds as recommended by the International Society of Thrombosis and Haemostasis; in addition, bleeds might not have been captured accurately and/or completely in hospital records, potentially resulting in an underestimation of the bleeding risks associated with DOAC use. Furthermore, while the majority of study endpoints represented medical emergencies and in general required hospitalisation, transient ischaemic attacks might have gone unnoticed and, consequently, could have been underreported, also resulting in an underestimation of associated risks.

And finally, as with all observational studies, associations between exposure and outcomes might not have been causal; while efforts have been made to reduce the impact of confounding factors as far as possible, unmeasured confounding could nevertheless have influenced the findings.

8.6 Conclusion

DOACs have gained approval for the indication of stroke prevention in patients with AF based on a limited number of clinical trials, where efficacy and safety of all drugs have been proven; however, no direct comparisons of DOACs in a clinical trials setting have been conducted, and early publications comparing individual drugs relied on indirect methods, using existing data from previously conducted clinical trials. Unsurprisingly, guidelines for using oral anticoagulants are therefore rather limited

when it comes to recommendations for (or against) a specific DOAC in any given situation.

Hence, observational studies have started to provide additional evidence from clinical practice – first by comparing DOAC and VKA treatment outcomes, establishing the clinical effectiveness and safety of DOACs in real-world contexts (Larsen et al., 2016, Nielsen et al., 2017); and increasingly by comparing individual DOACs to each other (Deitelzweig et al., 2017, Gorst-Rasmussen et al., 2016, Hernandez et al., 2017, Lai et al., 2017, Noseworthy et al., 2016).

Generally speaking, this study has mostly confirmed what has been reported before: all DOACs are similarly effective in preventing strokes in patients with atrial fibrillation, but the bleeding profiles differ slightly between drugs – with rivaroxaban showing the highest overall risk of bleeding. Nevertheless, some of the results of this study potentially pose new questions rather than satisfactorily providing additional answers: whether apixaban is better in preventing pulmonary embolisms than rivaroxaban, for example; and whether apixaban actually increases the risk of myocardial infarctions. In addition, potential associations between rivaroxaban exposure and mortality also deserve further attention.

Chapter 9 – Conclusion

The direct oral anticoagulants dabigatran, rivaroxaban, and apixaban have been marketed globally for the prevention of thromboembolic events since 2008, and have been incorporated into a range of clinical guidelines; their main indication is now the prevention of strokes in patients with atrial fibrillation, for which they gained market approval in Scotland from 2011 onwards. Atrial fibrillation is a common arrhythmic disorder especially among the elderly, and a major independent risk factor for strokes – and its overall prevalence is increasing, not least due to demographic developments such as ageing populations. As warfarin, a mainstay in clinical practice for decades, is associated with a range of difficulties, it was hoped that the introduction of DOACs would lead to more eligible patients receiving oral anticoagulants; that patients would be more adherent to DOAC treatment than to warfarin; and that, overall, disease outcomes would eventually be improved – by providing optimal treatment options for every patient.

Even though clinical trials have proven the efficacy and safety of DOACs, the usefulness of treatment guidelines remains limited – when considering oral anticoagulant treatment options for patients with complex medical histories and/or a multitude of concomitant medication in general (as these patients most likely do not match the population included in the clinical trials), but particularly when making recommendations for or against a specific DOAC (as no clinical trials directly comparing individual DOACs have been performed). Information from clinical practice, which could be used to support clinical decision making, is however still scarce; hence, this project comprised three studies to add to the knowledge base: ***first***, to describe the prescribing of DOACs over time; ***second***, to evaluate patients' adherence to DOAC treatment; and ***third***, to analyse the clinical effectiveness and safety of DOACs in patients with atrial fibrillation in Scotland.

9.1 Summary of key findings

Generally speaking, the number of patients being treated with oral anticoagulants is increasing in Scotland – and the introduction of DOACs most certainly influenced these trends. Since 2013, the number of patients initiating anticoagulant treatment with warfarin has been declining, while the number of patients initiating DOAC treatment has steadily been increasing; in 2015, the number of new DOAC patients for the first time exceeded the number of new warfarin patients in Scotland, indicating

that DOACs have quite swiftly been accepted into clinical practice. Nevertheless, not all DOACs have been treated equally: while dabigatran experienced an initial boost in prescribing – most likely due to it being the first DOAC to enter the market – rivaroxaban soon pulled ahead, and is currently the most widely used DOAC; considering the continuing decline in dabigatran prescriptions, the increasing popularity of apixaban, and the introduction of edoxaban as recently as 2015, further changes are likely to be expected.

Three aspects of the observed prescribing trends are of particular importance: *first*, there was huge variety in the prescribing of DOACs in general (as opposed to the continued use of VKAs) as well as with regards to individual DOACs across Health Boards in Scotland, which could be a reflection of the diversity of local treatment guidelines; *second*, uptake of DOACs was particularly swift in very remote areas, potentially linked to the availability and accessibility of health services such as anticoagulation clinics; and *third*, a large percentage of very elderly patients (aged 85 years and older) were initiated on DOACs, probably influenced by the relatively low interaction potential of DOACs as compared to warfarin – considering the high level of medicines use among these patients. The convenience of DOAC treatment – including the easy dosing schedules, and the lack of mandatory monitoring – could also have played a role in the popularity of DOACs in remote areas as well as in a very elderly patient population.

In Scotland, besides being in general elderly, patients with AF starting treatment with any DOAC had a range of comorbidities, and were treated with a large number of concomitant medications – and, most importantly, differed considerably from patients enrolled in the clinical trials comparing DOACs to warfarin.

As the RCTs purposely selected relatively high-risk patients with regards to stroke and other thromboembolic events (albeit to varying degrees), the most important comorbidities in patients with AF – history of prior stroke, hypertension, heart failure and diabetes – were less common among AF patients in Scotland than was the case in the trials, resulting in noticeably lower stroke risk scores; in contrast, by excluding patients with an elevated risk of bleeding events in two of the three pivotal trials, bleeding risks were most likely considerably higher among real-world patients than among clinical trial participants. When trying to transfer the trial results onto patients

in clinical practice, these differences in patient populations need to be kept in mind, as divergences in terms of stroke and bleeding risks could lead to an overestimation of the effectiveness of DOACs, and/or an underestimation of the risks associated with their usage. In addition, a range of other comorbidities which could also affect treatment outcomes (for example kidney disease, liver disease, and cancer) were underrepresented in the clinical trials – thus potentially necessitating a much higher level of scrutiny of patients' medical histories prior to the initiation of DOACs than might be exerted or even anticipated. Polypharmacy – being treated with five or more different drugs concomitantly – might in this context be a good indicator for the complexity encountered in clinical practice: overall, 87.2% of all AF patients in Scotland were subject to polypharmacy prior to initiating DOACs, and the median number of drugs they were treated with was 10 – with, at least theoretically, a high potential of interactions, and possibly relevant implications on the effectiveness and safety of treatment.

Analysing the utilisation of DOACs in patients with AF offered three interesting insights. *First of all*, adherence to DOAC treatment in patients with AF was overall surprisingly good, with patients generally having enough medication to cover treatment periods, and treatment gaps being quite rare. *Second*, discontinuation rates were acceptable considering the high rates of discontinuation observed in patients being treated with warfarin; in addition, treatment interruptions were often temporary, resulting in relatively high persistence rates when taking these interruptions into account – even though persistence declined over time, approximately 80% of patients were still on treatment after one year, and a majority of patients even after 3 years. And *third*, differences between drugs were considerable: patients initiating treatment with dabigatran discontinued treatment more frequently than patients receiving either apixaban or rivaroxaban, and persistence was consequently noticeably lower among dabigatran patients. Generally speaking, these findings suggest that DOACs are an accepted treatment option among patients with AF in Scotland, and do not hint towards any unexpected, major issues regarding treatment adherence – however, differences observed between individual drugs could suggest that dabigatran is less tolerable than the other DOACs.

Despite patients seemingly being least content with using dabigatran – judging from the relatively high discontinuation rates and low persistence in contrast to both

apixaban and rivaroxaban – patients using rivaroxaban exhibited the highest bleedings risks – including gastro-intestinal bleeding as well as other major bleeds.

Unexpectedly, all-cause mortality was also highest among rivaroxaban patients, and rivaroxaban performed worse in preventing pulmonary embolisms than apixaban; in contrast, patients being treated with apixaban appeared to have a higher risk of experiencing a myocardial infarction than those using either dabigatran or rivaroxaban. Nevertheless, all DOACs were similarly effective in preventing strokes and systemic embolisms – hence, when making decisions with regards to the drug of choice for newly initiating patients on DOAC treatment, particular attention should be payed to the presence of risk factors relating to bleeds, potentially going beyond the HAS-BLED score by evaluating a patient's entire medical history, including concomitant medication. Behavioural risk factors such as smoking, alcohol consumption, or a sedentary life-style should potentially also be taken into consideration to a much higher degree, bearing in mind the possible impact of these aspects on morbidity and mortality.

9.2 Strengths and limitations

This project has several strengths: access to health care in Scotland is universal, and electronic health records cover the entire population; records can easily and reliably be linked due to the presence of a unique patient identifier; and the validity and accuracy of the data stored in these records have been established. Therefore, a wealth of reliable, patient-level information has been available for an entire population. Moreover, this project provides an unprecedentedly comprehensive picture of the use of DOACs in patients with AF, covering all facets of drug utilisation – from an in-depth description of prescribing trends, to the analyses of the comparative effectiveness and safety of DOACs in a real-world setting. By combining an array of diverse methods and techniques, this work also offers an insight into the methodological aspects of drug utilisation studies, and could be used as a road map for future projects in Scotland.

Nevertheless, there are also some limitations to consider. *First of all*, as no indication for treatment was available, the description of OAC prescribing practices included all patients who received an oral anticoagulant during the study period regardless of

underlying diagnoses, with potential implications on the comparability of findings to other studies. Furthermore, even though patients with records indicating a reason for being treated with DOACs other than AF have been excluded from the analyses of both DOAC utilisation and treatment outcomes, the inclusion of a small number of patients not having been treated for stroke prevention despite being affected by AF cannot be ruled out; this could potentially have led to imprecisions in results mainly with respect to discontinuation and persistence. *Second*, by identifying eligible patients for inclusion in the studies of drug utilisation and treatment outcomes solely from secondary care records, AF patients diagnosed and treated exclusively in primary care were not captured – most likely those with less severe representations of the condition. While this should not have affected overall results with regards to drug utilisation (adherence, discontinuation, and persistence), not including a potentially substantial proportion of patients with AF in Scotland could have resulted in overestimations of outcome incidence rates. *Third*, as the data used for this research project has not specifically been collected for its purposes but stemmed from a limited set of administrative records, not all desirable information was available; in the absence of GP records, identification of endpoints for the analysis of treatment outcomes for example had to rely on hospital discharge and death records, with possible implications for the accuracy of findings. In addition, the reasoning behind the choice of specific treatment options as well as motivations for discontinuing treatment remain unknown. And *finally*, unmeasured confounding could have influenced the results of the analyses of treatment outcomes – a problem not specific to this project though, but frequently encountered in observational research.

9.3 Implications of this thesis on clinical practice

Considering the enormous burden of thromboembolic events on health systems and patients alike and the potential benefit of OAC treatment, an increase in the proportion of patients with AF being treated with oral anticoagulants can only be commended – even if this implies exposing more patients to the risk of potentially fatal bleeding events, a danger inherent to all OACs. As treatment with DOACs does theoretically not require regular monitoring or dose adjustments and is therefore more convenient for patients than treatment with warfarin, and potentially puts less strain on already stretched health systems, choosing a DOAC over a VKA for patients newly initiating therapy is probably a reasonable approach for the majority of patients; at the very

least, adherence to DOAC treatment has proven to be reasonable, indicating that the simplicity of their dosing schedules could indeed have a positive effect on disease outcomes. In some patient groups – for instance those with very high bleeding risks where no anticoagulation is not a viable option – initiating treatment with a VKA rather than a DOAC might nevertheless be the safer choice, as antidotes and monitoring tests are readily available; alternatively, if patients prefer a DOAC, monitoring of treatment could in the future (once routinely available) be an option – although this would remove one of the obvious advantages DOACs have over warfarin right now.

With all DOACs being equally effective in preventing strokes and systemic embolisms in patients with atrial fibrillation, decisions for or against a specific DOAC probably need to be made on the basis of a wider risk assessment so as to minimise the potential risks of major bleeds, myocardial infarctions, and premature mortality. Most importantly, kidney function should be established prior to choosing a specific drug due to the different extent of renal excretion across DOACs. In order to provide the most suitable option for each patient, it might however also be necessary to evaluate a patients' medical history in much greater detail than is currently most likely the case – including a review of concomitant medication, and possibly also comprising an appraisal of behavioural risk factors that might impact the effectiveness and safety of the chosen drug.

9.4 Recommendations for conducting drug utilisation research

Drug utilisation studies are conducted in order to, for instance, analyse prescribing trends over time, or to evaluate patients' adherence to drug treatment; hence, depending on their aim and objectives, study specifics can deviate widely. While differences in aspects such as study design, sample size and follow-up periods are however easily justifiable and, more often than not, unavoidable, other – methodological – differences are neither inevitable, nor defensible.

Studies analysing drug adherence make use of a variety of definitions and measurements, while also applying differing methods of calculation – resulting in a sometimes confusing array of diverging findings. Comparing results across studies has, therefore, turned out to be challenging; moreover, comparisons were most likely

not always reliable as terms and measurements are sometimes used interchangeably although they in fact measure slightly different things (for example MRA and CR) – or altogether different aspects of adherence (such as discontinuation and persistence).

Hence, in order to decrease the inconsistencies in drug utilisation methodology impeding the direct comparison of findings, a number of recommendations arose from this project: *first*, using a coherent framework of adherence as proposed by ESPACOMP in 2012 (Vrijens et al., 2012) would enable proper distinction between the different aspects of adherence – that is, adherence as a measure of describing the continuous process of drug intake (intensity or quality); discontinuation as a measure of interrupting and/or stopping treatment (continuity); and persistence as a measure of the length of treatment (duration). *Second*, using at least one measurement covering each of these aspects would give a more comprehensive overview of a patient's drug taking behaviour than focusing on only part of this complex issue, and would give a much better insight into potential problems related to drug treatment. *And third*, triangulation – meaning to use more than one method of calculation to measure individual aspects of adherence – would enhance the validity and reliability of results; offering two different sets of results (e.g. both MRA and CR; or persistence based on both the refill-gap method and the anniversary method) would also improve the comparability of findings, considering that the calculation of specific measures might not be possible in every context (e.g. due to data availability). As a last point: properly describing the methods used for analysis – including equations and formulas as well as underlying definitions, as appropriate – should be self-evident, as this fosters transparency, and enables the reproduction of findings.

9.5 Future research

Despite providing a range of useful findings with regards to the use of DOACs in a patient population with AF and, thus, adding to the ever-growing body of knowledge, some questions remained unanswered – moreover, some of the findings emerging from this project posed new questions rather than providing satisfactory answers, thus calling for further research.

Most importantly, potential associations between rivaroxaban exposure and premature mortality, as well as between apixaban exposure and the risk of myocardial

infarctions, deserve further attention; as does the question whether apixaban might be better in preventing pulmonary embolisms than rivaroxaban. While it would be highly desirable if additional clinical trials were to be conducted, directly comparing the DOACs so as to answer these question with a maximum of certainty, this seems highly unlikely to be happening in the foreseeable future; hence, further cohort studies with larger sample sizes than were available thus far would be the next best option – perhaps using combined data from different geographical regions, depending on data availability, comparability, and reliability.

Furthermore, it would be interesting to ascertain whether differences in treatment preferences between urban and rural areas as observed in Scotland are replicated in other countries, and what the specific reasons for these differences are. Differences might, for example, hint towards inequalities in treatment provision due to lack of resources in remote areas, with potential implications for disease outcomes and, thus, health services; so far, any attempts to explain the findings would however be purely speculative, as no further information regarding this topic has been available.

And finally, underlying reasons for discontinuation of DOAC treatment and suboptimal adherence, especially among patients using dabigatran, are still unknown – but would be useful to know in order to optimise decisions with regards to specific treatment options.

9.6 Final conclusion

Pharmacoepidemiology is an important contributor to public health by providing vital information from clinical practice that would otherwise not be available. Its priorities and methods are constantly evolving over time in line with clinical developments, but also in reaction to technological advancements; the adoption of eHealth strategies in a number of countries for instance, in combination with recent revolutions in computing, led to the implementation of vast databases comprising electronic health records of large numbers of patients. Unsurprisingly, pharmacoepidemiological studies nowadays quite frequently use data stemming from these databases for analysis.

While database analysis has several advantages – it is usually easier, faster, and a lot cheaper to analyse already existing data instead of purposely collected research-

specific data – and is therefore most definitely the way forward, some of the pitfalls of using administrative data should be kept in mind. Compatibility of systems is, for instance, not always ensured – not only do systems differ between countries, but sometimes also within countries; primary care facilities for example quite frequently use different software programmes than hospitals. In addition, the nature of the specific data collected and stored in these databases can diverge considerably depending on the structure of a health care system; and, moreover, the way data is recorded and coded can be quite heterogeneous – meaning that combining data in order to conduct cross-regional studies could be rather more complex than anticipated.

Most importantly though, using patient level data (typically without explicit consent of patients) poses ethical issues that are rarely acknowledged. Despite information governance systems being in place in many countries so as to prevent the disclosure of confidential information and the potential identification of individuals through research activities, the possibility of data breaches can never completely be ruled out; in addition, patients are not always in favour or their personal data being used for research for any number of reasons. It is therefore imperative that efforts are made to keep patients and the general public informed about research activities involving the analysis of medical records; that studies conform to the highest standards in terms of research ethics, integrity, and methodology; and that findings of studies are disseminated widely and appropriately.

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Appendices

Appendix I: Project approval

Information Governance certificate, valid October 2014 to October 2016

scriptcpd

Tanja Mueller

Completed a continuing professional development programme in:

SHIP: Information Governance

Via online distance learning

SHIP

Scottish Health Informatics Programme

With a 100% pass rate in the following assessments:

Legal Concepts Assessment
Legal Framework Assessment
Safe Projects Assessment
Safe Data Assessment
Safe Settings Assessment
Safe Outputs Assessment

Certificate issued: 26 October 2014

Certificate valid until: 26 October 2016

Information Governance certificate, valid October 2016 to October 2018

This is to certify that

Tanja Mueller

completed the following e-learning course assessment for Scotland with a score of
100%

Research Data and Confidentiality e-learning course

Covering:
- The concept of confidentiality and how to work within the law
- Principles 1, 2, 7, 8 and section 33 of the Data Protection Act
- Consent and the issues in accessing data for research without consent
- Appropriate disclosure and routes for access without consent
- Accessing data from ONS and the NHS
- Archiving and sharing research data

on Fri Oct 14 2016

Information Services Division
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NHS National Services Scotland

Dr S Alvarez-Madrazo
Research Associate
University of Strathclyde
161 Cathedral Street
GLASGOW
G4 ORE

Date 31 October 2014
Your Ref
Our Ref 28/14

Enquiries to Dr David Brewster
Extension 6092
Direct Line 0131 275 6092
Email david.brewster@nhs.net

Dear Dr Alvarez-Madrazo

Analyses of new anticoagulants in thromboprophylatic treatment for Scotland

Your PAC Application has undergone NSS proportionate governance review and has been approved.

Conditions applied: None

Time period: As specified

Points highlighted: None

The approval is for a period of 5 years from the date of this letter. Any change to the terms of your application, including changes in data user(s), additional data fields or extension of the time period approved must be requested through Susan Kerr, PAC Administrator on 0131 275 6445 or nss.pac@nhs.net.

Please note that the access to data facilitated by this approval is subject to the satisfactory completion of approved information governance training, which must be updated every 3 years.

Please note that the following details about your application will be published under the following headings on the PAC website at http://www.nhsnss.org/pages/corporate/pac_meetings_and_decision_making.php later this year:

No	Title	Type	Summary	Date sent to PAC	PAC Responses	NSS Decision	Date Completed

In order to progress your request please contact the eDRIS team on telephone 0131 275 7333 or email nss.eDRIS@nhs.net.

Yours sincerely

Dr David Brewster
Consultant in Public Health Medicine

cc eDRIS

Project approval, data update – Public Benefit and Privacy Panel, July 2016

Public Benefit and Privacy Panel for Health and Social Care
nss.PBPP@nhs.net
www.informationgovernance.scot.nhs.uk

Professor Marion Bennie
Chief Pharmacist
University of Strathclyde
161 Cathedral Street
G4 0RE

Date: 11th July 2016
Your Ref:
Our Ref: 1516-0514

Dear Professor Bennie,

Re: Application 1516-0514/Bennie: Analyses of new anticoagulants in thromboprophylactic treatment in Scotland (XRB14086)

Thank you for your application for consideration by the Public Benefit and Privacy Panel for Health and Social Care. Your application has undergone proportionate governance review and has been approved, subject to the following conditions:

- Please provide evidence of completed refresher IG training for Dr Geue when this is available

This approval is given to process data as specified in the approved application form, and is limited to this. Approval is valid for the period specified in your application. You are required to notify the Panel Manager of any proposed change to any aspect of your proposal, including purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure, or any other relevant change.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection. In particular you should be aware that once personal data (irrespective of de-identification or other controls applied) has been extracted from NHSS Board(s) and transferred to you, that you will then become the Data Controller as defined by the Data Protection Act (1998).

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (www.informationgovernance.scot.nhs.uk).

I hope that your proposal progresses well,

Yours Sincerely

Jenny Mann
Information Governance Officer
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: nss.PBPP@nhs.net

Appendix II: Supplementary material

Table A1: British National Formulary structure prior to version 70, published in September 2015 (Joint Formulary Committee, 2015a, NHS Business Services Authority, 2017)

Chapter	Section	Subsection	Title
1			Gastro-Intestinal system
2			Cardiovascular system
	02		Diuretics
	03		Anti-arrhythmic drugs
	04		Beta-adrenoceptor blocking drugs
	05		Hypertension and heart failure
	06		Nitrates, calcium-channel blockers, and other antianginal drugs
	08		Anticoagulants and protamine
		01	Parenteral anticoagulants
		02	Oral anticoagulants
	09		Antiplatelet drugs
3			Respiratory system
4			Central nervous system
	01		Hypnotics and anxiolytics
	03		Antidepressant drugs
	07		Analgesics
	10		Drugs used in substance dependence
5			Infections
6			Endocrine system
	01		Drugs used in diabetes
7			Obstetrics, gynaecology, and urinary-tract disorders
8			Malignant disease and immunosuppression
9			Nutrition and blood
10			Musculoskeletal and joint diseases
	01		Drugs used in rheumatic diseases and gout
		01	Non-steroidal anti-inflammatory drugs
11			Eye
12			Ear, nose, and oropharynx
13			Skin
14			Immunological products and vaccines
15			Anaesthesia
18			Preparations used in diagnosis
19			Other drugs and preparations
20			Dressings
21			Appliances
22			Incontinence appliances
23			Stoma appliances

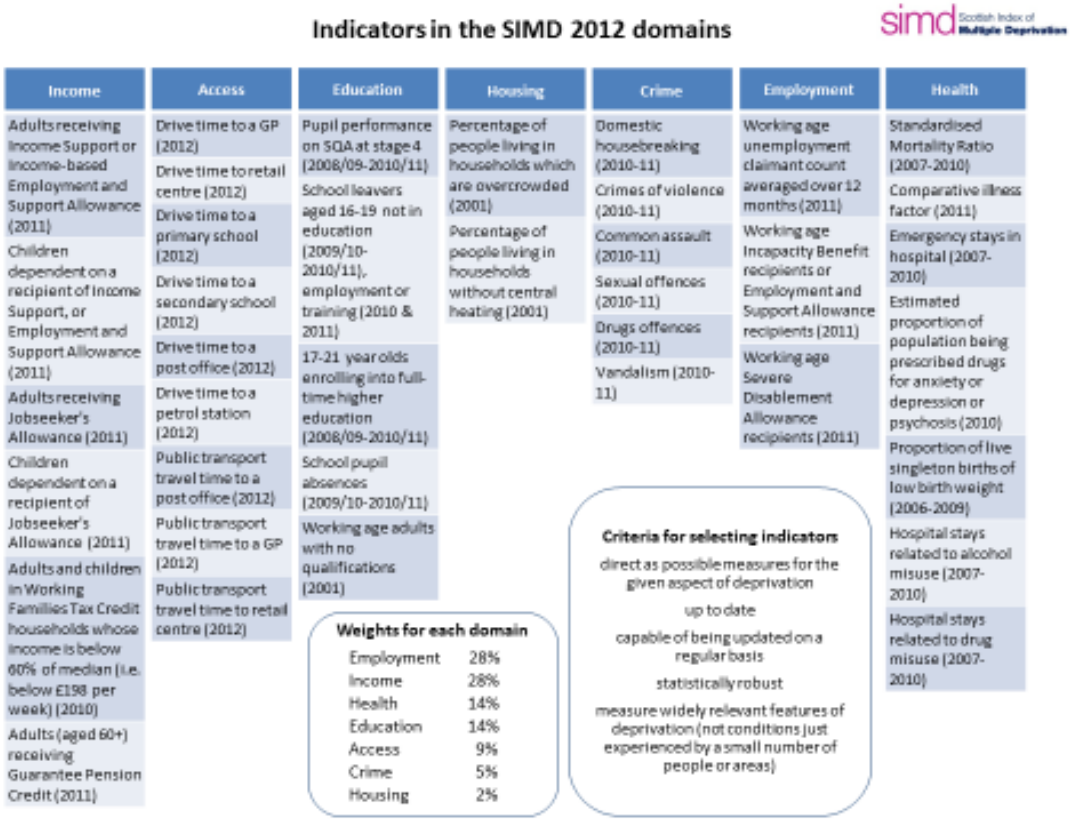

Figure A1: Indicators used for calculation of the Scottish Index of Multiple Deprivation (SIMD), 2012 edition. Source: (Scottish Government, 2014b)

Table A2: ICD-10 codes used for calculation of Charlson scores (Quan et al, 2005)

Charlson score (SMR00, SMR01)	
Myocardial infarction	I21, I22, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 – I42.9, I43, I50, P29.0
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45, G46, H34.0, I60 – I69
Dementia	F00 – F03, F05.1, G30, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40 – J47, J60 – J67, J68.4, J70.1, J70.3
Rheumatic disease	M05, M06, M31.5, M32 – M34, M35.1, M35.3, M36.0
Peptic ulcer disease	K25 – K28
Mild liver disease	B18, K70.0 – K70.3, K70.9, K71.3 – K71.5, K71.7, K73, K74, K76.0, K76.2 – K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	E10.2 – E10.5, E10.7, E11.2 – E11.5, E11.7, E12.2 – E12.5, E12.7, E13.2 – E13.5, E13.7, E14.2 – E14.5, E14.7
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0 – G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2 – N03.7, N05.2 – N05.7, N18, N19, N25.0, Z49.0 – Z49.2, Z94.0, Z99.2
Any malignancy except neoplasm of the skin	C00 – C26, C30 – C34, C37 – C41, C43, C45 – C58, C60 – C76, C81 – C85, C88, C90 – C97
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5 – K76.7
Metastatic solid tumour	C77 – C80
AIDS/HIV	B20 – B22, B24

AIDS – Acquired immunodeficiency syndrome; HIV – human immunodeficiency virus; ICD-10 – International Classification of Disease, 10th edition; SMR – Scottish Morbidity Records

Table A3: Adherence to DOAC treatment by sex and age group, overall and by drug – using two different methods

	All	Male	Female	p-value	<55	55-64	65-74	75-84	85 and older	p-value
DOAC overall										
Number patients	13,306	7,222	6,084		759	1,719	3,704	4,770	2,354	
Median number days follow-up (IQR) [1]	374 (199 – 624)	380 (202 – 640)	365 (198 – 603)		420 (223 – 654)	398 (209 - 666)	391.5 (211 – 646)	366 (197 – 617)	331.5 (182 – 566)	
Median number days' supply (IQR) [1]	336 (168 – 560)	336 (168 – 560)	336 (168 – 560)		280 (140 – 504)	336 (168 – 560)	364 (196 – 616)	336 (168 – 563)	284 (168 – 504)	
Median MRA (IQR) [2]	102.3 (90.1-112.5)	102.3 (88.7-112.1)	102.4 (91.4-112.8)	*>0.05*	96.0 (56.7-108.5)	102.3 (87.5-113.0)	103.7 (94.0-113.7)	102.4 (91.6-112.1)	100.8 (87.9-111.6)	*<0.001*
MRA > 80% (%) [2]	81.9	80.9	83.0	*0.002*	64.0	79.1	85.5	83.7	80.4	*<0.001*
Median number days follow-up (IQR) [3]	288 (127 – 532)	289 (127 – 543)	288 (127 – 523)		252 (109 – 510)	303 (139 – 546)	321 (146 – 566)	289 (126 – 539)	247 (112 – 459)	
Median number days' supply (IQR) [3]	280 (126 – 518)	280 (120 – 532)	280 (140 – 507)		224 (112 – 448)	280 (140 – 514)	310 (144 – 560)	280 (140 – 532)	252 (112 – 463)	
Median CR (IQR) [2]	102.3 (95.2-111.5)	101.7 (93.8-110.5)	103.2 (96.8-112.6)	*>0.05*	97.5 (84.0-106.2)	100.9 (91.8-108.7)	101.8 (95.7-109.8)	102.8 (96.3-112.0)	104.6 (97.4-116.5)	*0.003*
CR > 80% (%) [2]	90.5	89.5	91.7	*<0.001*	78.4	87.4	91.5	91.8	92.5	*<0.001*
Apixaban										
Number patients	5,518	2,929	2,589		347	745	1,488	2,006	932	
Median number days follow-up (IQR) [1]	288 (160 – 456)	287 (157 – 456)	290 (161 – 455)		297 (173 – 480)	290 (164 – 454)	301.5 (169 – 469)	281.5 (149 – 454)	280 (160 – 436)	
Median number days' supply (IQR) [1]	280 (157 – 425)	270 (142 – 420)	280 (168 – 448)		224 (112 – 364)	280 (162 – 420)	280 (168 – 448)	280 (154 – 440)	266 (146 – 415)	
Median MRA (IQR) [2]	103.3 (91.2-115.1)	103.2 (90.3-114.6)	103.4 (92.3-115.9)	*>0.05*	97.4 (66.5-112.4)	103.5 (88.7-115.3)	104.8 (94.6-116.7)	103.7 (93.6-115.0)	101.5 (88.7-114.3)	*0.009*
MRA > 80% (%) [2]	84.3	83.1	85.5	*0.017*	68.0	81.1	87.5	86.5	82.8	*<0.001*
Median number days follow-up (IQR) [3]	226 (106 – 392)	222 (104 – 390)	231 (110 – 393)		208 (90 – 357)	221 (108 – 396)	242.5 (118 – 413)	228 (104 – 392)	215.5 (101 – 371)	
Median number days' supply (IQR) [3]	224 (112 – 392)	224 (112 – 386)	231 (112 – 392)		172 (84 – 336)	224 (112 – 378)	228 (112 – 392)	224 (112 – 392)	224 (112 – 361)	
Median CR (IQR) [2]	102.8 (94.8-113.5)	101.9 (93.2-112.4)	103.7 (96.5-114.5)	*0.049*	97.5 (84.0-109.8)	100.9 (90.9-110.1)	102.3 (94.7-111.4)	103.5 (96.6-114.4)	105.7 (97.1-117.9)	*>0.05*
CR > 80% (%) [2]	91.1	90.0	92.4	*0.002*	80.1	87.9	91.5	93.0	93.1	*<0.001*

	All	Male	Female	p-value	<55	55-64	65-74	75-84	85 and older	p-value
Dabigatran										
Number patients	986	626	360		84	178	318	275	131	
Median number days follow-up (IQR) [1]	882 (549 – 1178)	885 (552 – 1199)	877.5 (546 – 1162)		909 (678 – 1133)	970 (674 – 1234)	897.5 (556 – 1212)	831 (547 – 1141)	672 (323 – 1047)	
Median number days' supply (IQR) [1]	542.5 (196 – 900)	523.5 (180 – 879)	598 (240 – 927)		264 (120 – 719)	523 (180 – 893)	601.5 (287 – 988)	570 (240 – 948)	375 (180 – 690)	
Median MRA (IQR) [2]	90.3 (41.4-103.3)	87.5 (34.7-103.0)	96.5 (46.1-105.1)	*>0.05*	40.4 (12.9-92.0)	71.4 (28.2-101.9)	96.6 (54.6-104.7)	96.2 (51.6-104.0)	86.8 (52.2-101.2)	*<0.001*
MRA > 80% (%) [2]	56.5	54.2	60.6	*>0.05*	31.0	43.3	64.8	65.1	52.7	*<0.001*
Median number days follow-up (IQR) [3]	515.5 (158 – 918)	494 (153 – 909)	546.5 (190 – 928)		387.5 (100 – 780)	507.5 (151 – 923)	594 (241 – 985)	550 (187 – 916)	343 (141 – 679)	
Median number days' supply (IQR) [3]	507 (150 – 840)	477 (147 – 840)	540 (180 – 870)		206 (90 – 667)	463 (150 – 840)	568 (237 – 930)	540 (180 – 899)	338.5 (150 – 660)	
Median CR (IQR) [2]	100.2 (91.6-107.7)	99.4 (89.6-107.3)	101.3 (95.3-108.2)	*>0.05*	95.5 (79.0-105.8)	99.0 (85.0-107.8)	100.5 (93.2-107.7)	101.1 (94.8-108.6)	101.4 (93.4-107.8)	*>0.05*
CR > 80% (%) [2]	85.1	82.7	89.2	*0.008*	69.0	78.1	86.2	90.9	90.1	*<0.001*
Rivaroxaban										
Number patients	6,661	3,602	3,059		316	783	1,859	2,434	1,269	
Median number days follow-up (IQR) [1]	430 (227 – 694)	433.5 (231 – 706)	427 (226 – 681)		468.5 (265 – 715)	458 (245 – 719)	442 (234 – 717)	442 (231 – 702)	360 (195 – 622)	
Median number days' supply (IQR) [1]	364 (196 – 616)	364 (196 – 644)	341 (181 – 616)		329 (168 – 616)	392 (196 – 658)	392 (224 – 672)	364 (196 – 616)	308 (168 – 560)	
Median MRA (IQR) [2]	102.0 (89.6-110.9)	102.2 (88.9-110.9)	101.8 (90.1-110.9)	*>0.05*	97.4 (59.6-107.6)	102.6 (90.7-111.6)	103.6 (93.6-112.4)	101.5 (89.6-109.9)	100.7 (87.5-110.5)	*<0.001*
MRA > 80% (%) [2]	80.9	80.7	81.2	*>0.05*	66.1	81.5	84.1	81.1	79.3	*<0.001*
Median number days follow-up (IQR) [3]	321 (139 – 596)	329 (142 – 604)	314 (135 – 579)		302 (118 – 598)	360 (166 – 631)	346 (158 – 627)	325.5 (140 – 609)	272 (113 – 520)	
Median number days' supply (IQR) [3]	315 (140 – 588)	336 (140 – 588)	308 (140 – 560)		280 (112 – 560)	336 (168 – 616)	336 (168 – 616)	336 (149 – 588)	280 (112 – 518)	
Median CR (IQR) [2]	102.4 (96.6-110.9)	101.8 (95.3-109.8)	103.0 (97.8-112.0)	*>0.05*	98.8 (88.9-105.7)	101.2 (94.0-107.7)	101.9 (96.8-109.1)	102.7 (96.9-111.1)	104.3 (98.5-115.7)	*>0.05*
CR > 80% (%) [2]	91.8	91.3	92.5	*>0.05*	81.3	90.4	92.8	92.2	93.1	*<0.001*

CR – compliance rate; DOAC – direct oral anticoagulant; IQR – interquartile range; MRA – medication refill adherence
[1] Index date to study end date; [2] Includes all patients with at least two prescriptions during the study period; [3] Index date up to, but not including last recorded prescription.

Table A4: Crude persistence with DOAC treatment by sex and age group, overall and by drug – based on three different versions of discontinuation

	All	Male	Female	p-value	<55	55-64	65-74	75-84	85 and older	p-value
DOAC overall										
Number patients	14,811	8,063	6,748		858	1,889	4,113	5,291	2,660	
Persistence rate (%) [1]	58.6	58.3	58.9	*>0.05*	46.9	58.7	62.7	58.7	55.6	*<0.001*
Persistence rate (%) [2]	69.5	68.4	70.8	*0.001*	53.8	67.7	73.2	70.7	67.6	*<0.001*
Persistence rate (%) [3]	77.7	77.9	77.3	*>0.05*	66.8	80.6	83.0	78.0	70.8	*<0.001*
Apixaban										
Number patients	6,273	3,353	2,920		405	832	1,715	2,251	1,070	
Persistence rate (%) [1]	65.5	66.0	65.0	*>0.05*	53.3	69.2	69.2	66.1	60.1	*<0.001*
Persistence rate (%) [2]	75.1	74.7	75.6	*>0.05*	59.8	75.4	77.8	77.0	72.3	*<0.001*
Persistence rate (%) [3]	80.7	81.1	80.2	*>0.05*	69.6	84.5	85.1	81.7	72.9	*<0.001*
Dabigatran										
Number patients	1,129	706	423		100	200	348	324	157	
Persistence rate (%) [1]	26.1	24.1	29.6	*>0.05*	11.0	20.0	30.7	28.4	28.7	*<0.001*
Persistence rate (%) [2]	36.7	34.4	40.4	*0.050*	18.0	27.0	44.0	40.4	36.9	*<0.01*
Persistence rate (%) [3]	49.1	47.7	51.3	*>0.05*	32.0	42.0	58.3	50.9	44.6	*<0.001*
Rivaroxaban										
Number patients	7,409	4,004	3,405		353	857	2,050	2,716	1,433	
Persistence rate (%) [1]	55.4	55.7	55.1	*>0.05*	47.3	55.1	60.3	54.0	53.4	*<0.001*
Persistence rate (%) [2]	66.7	66.2	67.3	*>0.05*	54.1	66.4	71.0	65.9	65.2	*<0.001*
Persistence rate (%) [3]	74.5	75.6	73.2	*0.017*	66.0	79.8	80.0	73.2	67.8	*<0.001*

DOAC – direct oral anticoagulant

[1] Based on discontinuation, calculated using the refill-gap method, admissible gap 28 days.
[2] Based on discontinuation, calculated using the refill-gap method, admissible gap 28, and taking into account previous oversupply.
[3] Based on discontinuation, calculated based only on patients with no subsequent prescriptions recorded during the study period after discontinuation.

Table A5: Persistence with DOAC treatment over time by sex and age group, overall and by drug – using two different methods

	All	Male	Female	p-value	<55	55-64	65-74	75-84	85 and older	p-value
DOAC overall										
Patients with at least 6 months follow-up time	10,793	5,870	4,923		656	1,417	3,043	3,827	1,850	
Persistence rate after 6 months – refill-gap method (%)	76.6	75.9	77.5	*>0.05*	59.8	74.0	79.5	78.5	76.2	*<0.001*
Persistence rate after 6 months – anniversary method (%)	85.6	85.6	85.7	*>0.05*	73.0	85.4	88.1	86.6	84.1	*<0.001*
Patients with at least 12 months follow-up time	7,075	3,907	3,168		451	960	2,063	2,502	1,099	
Persistence rate after 12 months – refill-gap method (%)	66.2	65.1	67.6	*0.029*	45.0	63.6	70.1	68.3	65.2	*<0.001*
Persistence rate after 12 months – anniversary method (%)	80.6	80.0	81.3	*>0.05*	60.8	78.9	84.5	82.6	78.3	*<0.001*
Patients with at least 18 months follow-up time	4,383	2,465	1,918		286	591	1,294	1,570	642	
Persistence rate after 18 months – refill-gap method (%)	59.7	58.6	61.1	*>0.05*	36.7	53.5	65.4	61.1	60.4	*<0.001*
Persistence rate after 18 months – anniversary method (%)	78.2	77.8	78.8	*>0.05*	58.4	73.6	82.8	80.6	76.3	*<0.001*
Patients with at least 24 months follow-up time	2,516	1,443	1,073		170	377	755	891	323	
Persistence rate after 24 months – refill-gap method (%)	52.9	51.0	55.5	*0.030*	27.6	47.7	59.7	55.7	48.6	*<0.001*
Persistence rate after 24 months – anniversary method (%)	75.6	74.6	76.9	*>0.05*	54.1	71.9	80.9	78.8	69.7	*<0.001*
Patients with at least 30 months follow-up time	1,342	794	548		95	223	427	452	145	

Persistence rate after 30 months – refill-gap method (%)	47.0	43.8	51.6	*0.006*	21.1	41.3	52.2	49.8	49.0	*<0.001*
Persistence rate after 30 months – anniversary method (%)	72.7	69.6	77.0	*0.004*	45.3	69.1	78.2	76.1	69.0	*<0.001*
Patients with at least 36 months follow-up time	679	410	269		43	121	229	218	68	
Persistence rate after 36 months – refill-gap method (%)	40.1	35.1	47.6	*0.002*	9.3	32.2	46.3	42.7	44.1	*<0.001*
Persistence rate after 36 months – anniversary method (%)	69.7	65.9	75.5	*0.010*	32.6	65.3	73.8	73.9	73.5	*<0.001*
Apixaban										
Patients with at least 6 months follow-up time	4,026	2,122	1,904		271	537	1,118	1,426	674	
Persistence rate after 6 months – refill-gap method (%)	79.1	78.1	80.3	*>0.05*	61.3	76.2	81.2	81.8	79.7	*<0.001*
Persistence rate after 6 months – anniversary method (%)	88.3	87.9	88.7	*>0.05*	73.4	89.2	89.5	89.7	88.6	*<0.001*
Patients with at least 12 months follow-up time	2,128	1,127	1,001		149	284	614	747	334	
Persistence rate after 12 months – refill-gap method (%)	68.9	66.4	71.7	*0.009*	44.3	66.9	71.3	73.0	68.0	*<0.001*
Persistence rate after 12 months – anniversary method (%)	83.6	82.3	85.1	*>0.05*	61.7	83.5	87.0	86.9	80.2	*<0.001*
Patients with at least 18 months follow-up time	908	478	430		67	110	263	330	138	
Persistence rate after 18 months – refill-gap method (%)	61.7	60.5	63.0	*>0.05*	37.3	51.8	62.7	68.2	63.8	*<0.001*
Persistence rate after 18 months – anniversary method (%)	81.3	80.3	82.3	*>0.05*	61.2	76.4	84.0	86.1	78.3	*<0.001*

Patients with at least 24 months follow-up time	277	143	134		19	37	75	103	43	
Persistence rate after 24 months – refill-gap method (%)	60.3	60.8	59.7	*>0.05*	47.4	48.6	65.3	69.9	44.2	*0.012*
Persistence rate after 24 months – anniversary method (%)	80.9	83.9	77.6	*>0.05*	73.7	78.4	84.0	87.4	65.1	*0.027*
Patients with at least 30 months follow-up time	42	22	20		5	8	15	11	3	
Persistence rate after 30 months – refill-gap method (%)	61.9	54.5	70.0	*>0.05*	40.0	62.5	73.3	54.5	66.7	*>0.05*
Persistence rate after 30 months – anniversary method (%)	81.0	72.7	90.0	*>0.05*	40.0	87.5	100.0	72.7	66.7	*0.039*
Dabigatran										
Patients with at least 6 months follow-up time	1,047	657	390		97	190	330	298	132	
Persistence rate after 6 months – refill-gap method (%)	57.3	56.0	59.5	*>0.05*	36.1	50.5	62.7	60.1	62.9	*<0.001*
Persistence rate after 6 months – anniversary method (%)	69.1	67.7	71.3	*>0.05*	51.5	67.9	73.9	69.1	71.2	*<0.001*
Patients with at least 12 months follow-up time	956	598	358		93	176	309	273	105	
Persistence rate after 12 months – refill-gap method (%)	45.8	43.8	49.2	*>0.05*	25.8	39.8	50.8	49.1	50.5	*<0.001*
Persistence rate after 12 months – anniversary method (%)	61.8	60.2	64.5	*>0.05*	38.7	56.8	68.0	64.8	64.8	*<0.001*
Patients with at least 18 months follow-up time	830	523	307		84	159	265	238	84	
Persistence rate after 18 months – refill-gap method (%)	40.1	36.7	45.9	*0.011*	20.2	31.4	46.8	43.3	46.4	*<0.001*

Persistence rate after 18 months – anniversary method (%)	57.5	55.3	61.2	*>0.05*	35.7	50.3	64.9	61.3	58.3	*<0.001*
Patients with at least 24 months follow-up time	678	426	252		69	144	210	193	62	
Persistence rate after 24 months – refill-gap method (%)	33.6	31.9	36.5	*>0.05*	10.1	28.5	41.9	36.3	35.5	*<0.001*
Persistence rate after 24 months – anniversary method (%)	53.8	52.8	55.2	*>0.05*	29.0	50.0	63.3	56.5	48.4	*<0.001*
Patients with at least 30 months follow-up time	516	332	184		48	114	170	137	47	
Persistence rate after 30 months – refill-gap method (%)	28.7	26.2	33.2	*>0.05*	6.3	19.3	35.3	34.3	34.0	*<0.001*
Persistence rate after 30 months – anniversary method (%)	49.4	47.0	53.8	*>0.05*	25.0	43.0	57.1	56.2	42.6	*<0.001*
Patients with at least 36 months follow-up time	338	220	118		30	74	113	91	30	
Persistence rate after 36 months – refill-gap method (%)	23.4	20.9	28.0	*>0.05*	0.0	14.9	34.5	23.1	26.7	*<0.001*
Persistence rate after 36 months – anniversary method (%)	46.4	44.5	50.0	*>0.05*	20.0	39.2	54.9	51.6	43.3	*0.006*
Rivaroxaban										
Patients with at least 6 months follow-up time	5,720	3,091	2,629		288	690	1,595	2,103	1,044	
Persistence rate after 6 months – refill-gap method (%)	75.9	76.2	75.6	*>0.05*	65.3	75.8	79.1	75.8	74.2	*<0.001*
Persistence rate after 6 months – anniversary method (%)	83.8	84.8	82.6	*0.028*	77.1	84.5	86.7	83.5	81.1	*<0.001*
Patients with at least 12 months follow-up time	3,991	2,182	1,809		209	500	1,140	1,482	660	

Persistence rate after 12 months – refill-gap method (%)	66.1	66.8	65.3	*>0.05*	52.2	66.6	70.8	65.5	63.8	*<0.001*
Persistence rate after 12 months – anniversary method (%)	78.6	79.4	77.7	*>0.05*	64.6	79.0	82.5	78.5	76.4	*<0.001*
Patients with at least 18 months follow-up time	2,645	1,464	1,181		135	322	766	1,002	420	
Persistence rate after 18 months – refill-gap method (%)	61.1	61.8	60.3	*>0.05*	44.4	60.9	67.9	59.0	59.5	*<0.001*
Persistence rate after 18 months – anniversary method (%)	77.2	78.0	76.3	*>0.05*	64.4	76.7	81.2	76.9	75.2	*<0.001*
Patients with at least 24 months follow-up time	1,561	874	687		82	196	470	595	218	
Persistence rate after 24 months – refill-gap method (%)	55.3	54.8	55.9	*>0.05*	34.1	57.7	61.3	54.6	50.0	*<0.001*
Persistence rate after 24 months – anniversary method (%)	76.0	75.9	76.3	*>0.05*	59.8	79.1	78.7	76.8	71.6	*0.002*
Patients with at least 30 months follow-up time	784	440	344		42	101	242	304	95	
Persistence rate after 30 months – refill-gap method (%)	52.0	49.8	54.9	*>0.05*	28.6	55.4	56.2	52.0	48.4	*0.018*
Persistence rate after 30 months – anniversary method (%)	76.0	74.5	77.9	*>0.05*	57.1	82.2	77.7	77.0	70.5	*0.015*
Patients with at least 36 months follow-up time	341	190	151		13	47	116	127	38	
Persistence rate after 36 months – refill-gap method (%)	49.0	44.7	54.3	*>0.05*	23.1	51.1	50.0	49.6	50.0	*>0.05*
Persistence rate after 36 months – anniversary method (%)	75.1	73.7	76.8	*>0.05*	46.2	83.0	73.3	76.4	76.3	*>0.05*

DOAC – direct oral anticoagulant

Table A6: Sensitivity analyses – length of admissible gap

	DOAC	Apixaban	Dabigatran	Rivaroxaban	p
Admissible gap: 14 days					
Discontinuation rate (%) [1]	61.8	55.6	88.0	64.1	<0.001
Discontinuation rate (%) [2]	42.8	38.2	74.0	44.5	<0.001
Cessation rate (%) [3]	29.8	27.8	54.2	32.3	<0.001
Persistence rate after 6 months (%) [4]	82.9	85.3	66.3	81.2	<0.001
Persistence rate after 12 months (%) [4]	77.8	80.4	58.6	76.3	<0.001
Persistence rate after 18 months (%) [4]	75.8	78.3	55.3	75.1	<0.001
Persistence rate after 24 months (%) [4]	73.3	77.6	51.8	74.0	<0.001
Persistence rate after 30 months (%) [4]	70.6	78.6	48.3	73.5	<0.001
Persistence rate after 36 months (%) [4]	67.5	n/a	44.7	73.0	<0.001
Admissible gap: 56 days					
Discontinuation rate (%) [1]	23.4	17.0	57.4	27.2	<0.001
Discontinuation rate (%) [2]	20.2	14.5	53.4	23.5	<0.001
Cessation rate (%) [3]	15.6	11.6	46.0	19.4	<0.001
Persistence rate after 6 months (%) [4]	88.7	91.3	74.5	86.7	<0.001
Persistence rate after 12 months (%) [4]	82.6	86.3	64.4	80.3	<0.001
Persistence rate after 18 months (%) [4]	80.5	84.3	59.8	79.3	<0.001
Persistence rate after 24 months (%) [4]	77.4	84.1	55.5	78.0	<0.001
Persistence rate after 30 months (%) [4]	75.1	88.1	51.7	78.1	<0.001
Persistence rate after 36 months (%) [4]	71.3	n/a	47.6	76.5	<0.001

Admissible gap: 84 days					
Discontinuation rate (%) [1]	17.4	11.8	50.5	20.7	<0.001
Discontinuation rate (%) [2]	16.1	10.7	48.4	19.3	<0.001
Cessation rate (%) [3]	13.1	9.2	44.2	16.6	<0.001
Persistence rate after 6 months (%) [4]	91.1	93.0	78.6	89.8	<0.001
Persistence rate after 12 months (%) [4]	83.9	87.9	66.0	81.5	<0.001
Persistence rate after 18 months (%) [4]	81.4	85.1	61.4	80.2	<0.001
Persistence rate after 24 months (%) [4]	78.2	84.1	56.8	78.8	<0.001
Persistence rate after 30 months (%) [4]	76.0	88.1	52.7	79.1	<0.001
Persistence rate after 36 months (%) [4]	71.9	n/a	48.2	77.1	<0.001

DOAC – direct oral anticoagulant

1] Refill-gap method
[2] Refill-gap method, taking into account previous oversupply
[3] Includes only patients with no subsequent prescriptions recorded during the study period.
[4] Anniversary method.

Appendix III: Sample R code

Ever / never analysis

 # identify patients switching drugs and exclude if taking different drugs simultaneously

```
# patients more than one DOAC
switchID <- unique(base$ID[base$number_diff_DOAC != 1])

# subset discontinuation: patients more than one DOAC
discont.switch <- subset(discont2.drug, ID %in% switchID)

# patients more than one DOAC but no discontinuation (exclude)
switchID2 <- unique(discont.switch$ID[discont.switch$event2 == 0])

# patients with more than one DOAC and discontinuation
switchID3 <- unique(discont.switch$ID[discont.switch$event2 == 1])
check.disc1 <- subset(DOAC.util, ID %in% switchID3)

# manually check whether drug switching back and forth with the same drug has occurred
check.disc2 <- subset(DOAC.util, ID %in% c(...))
switchID4 <- unique(check.disc2$ID)

# patients switching drug back and forth - might be misidentified in discontinuation b/c of subsequent prescriptions
check.disc3 <- subset(discont2.drug, ID %in% switchID4)
check.disc3 <- check.disc3[order(check.disc3$ID),]

# manually check whether switching coincides with discontinuation
discont.switch2 <- subset(discont2.drug, ID %in% c(...))
switchID5 <- unique(discont.switch2$ID)

# patients more than one DOAC but disconinuantion misidentified (exclude)
excludeID <- union(switchID2, switchID5)
```

 # patients with follow_up time > 0; select covariates fixed at baseline

```
base_sub <- base[! base$ID %in% excludeID,]
base_sub$mult.DOAC <- 0
base_sub$mult.DOAC[base_sub$number_diff_DOAC > 1] <- 1

index <- subset(base_sub, follow_up > 0, select=c(ID, first_date, end_date, follow_up, mult.DOAC))
index_ID <- unique(index$ID)

covars <- subset(base, ID %in% index_ID, select=c(ID, first_item, pat_sex, pat_age_prescr, age_cat, pat_HB_PIS, pat_ur_PIS, simd5_PIS, CHADS_VASc, HAS_BLED, charlson, SSRI.use, cancer, polypharm))
```

 # censor follow-up time for discontinuation (admissible gap between prescriptions 28 days, adjusted for oversupply) including switching (if switching identified as discontinuation)

```
discont <- subset(discont2.drug, ID %in% index_ID, select=c(ID, event2, supply_end,
time.disc2))
discont <- rename(discont, c("event2" = "discontinued", "supply_end" = "end_supply",
        "time.disc2" = "follow_up.cens_all"))

index <- merge(index, discont, c("ID"))
index$end_date.cens_all <- index$end_date
index$end_date.cens_all[index$discontinued == 1] <- index$end_supply[index$discontinued
== 1]
index$end_date.cens_sw <- index$end_date
index$end_date.cens_sw[index$mult.DOAC == 1] <- index$end_supply[index$mult.DOAC
== 1]
index$follow_up.cens_sw <- as.numeric(index$end_date.cens_sw - index$first_date)

base2 <- merge(index, covars, c("ID"))
```

 # identify endpoints

health conditions other than death

```
smr.outcomes <- subset(smr.study, smr.study$ID %in% index_ID, select=c(ID, diag_date,
ICD.1, ICD.2, ICD.3, ICD.4, ICD.5, ICD.6, CIS_MARKER))

smr.outcomes$all_stroke.ident <- 0
for (i in 3:8) {smr.outcomes$all_stroke.ident[substring(smr.outcomes[,i], 1, 3) %in% c("I60",
"I61", "I63", "I64")] <- 1}
smr.outcomes$isc_stroke.ident <- 0
for (i in 3:8) {smr.outcomes$isc_stroke.ident[substring(smr.outcomes[,i], 1, 3) %in% c("I63",
"I64")] <- 1}
smr.outcomes$TIA.ident <- 0
for (i in 3:8) {smr.outcomes$TIA.ident[substring(smr.outcomes[,i], 1, 3) == "G45"] <- 1}
smr.outcomes$SE.ident <- 0
for (i in 3:8) {smr.outcomes$SE.ident[substring(smr.outcomes[,i], 1, 3) == "I74"] <- 1}
smr.outcomes$PE.ident <- 0
for (i in 3:8) {smr.outcomes$PE.ident[substring(smr.outcomes[,i], 1, 3) == "I26"] <- 1}
smr.outcomes$MI.ident <- 0
for (i in 3:8) {smr.outcomes$MI.ident[substring(smr.outcomes[,i], 1, 3) %in% c("I21", "I22")]
<- 1}
smr.outcomes$comp_eff1.ident <- 0
for (i in 3:8) {smr.outcomes$comp_eff1.ident[substring(smr.outcomes[,i], 1, 3) %in%
        c("I63", "I64", "I74")] <- 1}
smr.outcomes$comp_eff2.ident <- 0
for (i in 3:8) {smr.outcomes$comp_eff2.ident[substring(smr.outcomes[,i], 1, 3) %in% c("G45",
"I60", "I61", "I63", "I64", "I74")] <- 1}
smr.outcomes$haem_stroke.ident <- 0
for (i in 3:8) {smr.outcomes$haem_stroke.ident[substring(smr.outcomes[,i], 1, 3) %in%
        c("I60", "I61")] <- 1}
smr.outcomes$ICH.ident <- 0
for (i in 3:8) {smr.outcomes$ICH.ident[substring(smr.outcomes[,i], 1, 3) == "I61"] <- 1}
smr.outcomes$SAH.ident <- 0
for (i in 3:8) {smr.outcomes$SAH.ident[substring(smr.outcomes[,i], 1, 3) == "I60"] <- 1}
smr.outcomes$GI_bleed.ident <- 0
```

```
for (i in 3:8) {smr.outcomes$GI_bleed.ident[substring(smr.outcomes[,i], 1, 4) %in% c("K250",
"K252", "K254", "K256", "K260", "K262", "K264", "K266", "K270", "K272", "K274", "K276",
"K280", "K282", "K284", "K286", "K290", "K625", "K920", "K921", "K922")] <- 1}
smr.outcomes$other_bleed.ident <- 0
for (i in 3:8) {smr.outcomes$other_bleed.ident[substring(smr.outcomes[,i], 1, 3) %in%
          c("D62", "I62", "N02", "R04", "R31", "R58") | substring(smr.outcomes[,i], 1, 4) %in%
c("H113", "H356", "H431", "J942", "N950")] <- 1}
smr.outcomes$all_bleed.ident <- 0
for (i in 3:8) {smr.outcomes$all_bleed.ident[substring(smr.outcomes[,i], 1, 3) %in% c("D62",
"I60", "I61", "I62", "N02", "R04", "R31", "R58") | substring(smr.outcomes[,i], 1, 4) %in%
c("H113", "H356", "H431", "J942", "K250", "K252", "K254", "K256", "K260", "K262", "K264",
"K266", "K270", "K272", "K274", "K276", "K280", "K282", "K284", "K286", "K290", "K625",
"K920", "K921", "K922", "N950")] <- 1}
smr.outcomes$other_ADR.ident <- 0
for (i in 3:8) {smr.outcomes$other_ADR.ident[substring(smr.outcomes[,i], 1, 4) %in%
c("T455", "T887", "Y442")] <- 1}

outcomes_SMR <- merge(index, smr.outcomes, c("ID"))


### cause of death

nrs.outcomes <- subset(NRS, NRS$ID %in% index_ID, select=c(ID, pat_dod,
main_cause_death, ocause_death1, ocause_death2, ocause_death3, ocause_death4,
ocause_death5, ocause_death6, ocause_death7, ocause_death8, ocause_death9,
ocause_death10))

nrs.outcomes$all_death.ident <- 1
nrs.outcomes$CVD_death.ident <- 0
for (i in 3:13) {nrs.outcomes$CVD_death.ident[substring(nrs.outcomes[,i], 1, 3) %in% c("I11",
"I13", "I20", "I21", "I22", "I23", "I24", "I25", "I26", "I46", "I47", "I49", "I50", "I60", "I61", "I62",
"I63", "I64", "I67", "I73", "I74")] <- 1}

outcomes_NRS <- merge(index, nrs.outcomes, c("ID"))


# select outcomes

out_SMR <- subset(outcomes_SMR, diag_date > first_date & diag_date <=
end_date.cens_all, select=c(ID,  first_date, diag_date, all_stroke.ident, isc_stroke.ident,
TIA.ident, SE.ident, PE.ident, MI.ident,    comp_eff1.ident, comp_eff2.ident,
haem_stroke.ident, ICH.ident, SAH.ident, GI_bleed.ident, other_bleed.ident, all_bleed.ident,
other_ADR.ident, CIS_MARKER))
sub1 <- subset(out_SMR, is.na(out_SMR$CIS_MARKER))
sub2 <- subset(out_SMR, complete.cases(out_SMR$CIS_MARKER))
sub2 <- sub2[! duplicated(sub2[,c("ID", "first_date", "all_stroke.ident", "isc_stroke.ident",
"TIA.ident", "SE.ident", "PE.ident", "MI.ident", "comp_eff1.ident", "comp_eff2.ident",
"haem_stroke.ident", "ICH.ident", "SAH.ident", "GI_bleed.ident", "other_bleed.ident",
"all_bleed.ident", "other_ADR.ident", "CIS_MARKER")]),]
out_SMR <- rbind(sub1, sub2)
out_SMR <- out_SMR[order(out_SMR$ID, out_SMR$diag_date),]

out_NRS <- subset(outcomes_NRS, pat_dod > first_date & pat_dod <= end_date.cens_all)
```

 # first event, time to event

```
iscs <- subset(out_SMR, isc_stroke.ident == 1, select=c(ID, diag_date, isc_stroke.ident))
iscs <- iscs[order(iscs$ID, iscs$diag_date),]
iscs <- iscs[! duplicated(iscs$ID),]
iscs <- merge(base2, iscs, c("ID"), all=TRUE)
iscs$isc_stroke.ident[is.na(iscs$isc_stroke.ident)] <- 0
iscs$time.isc.stroke <- as.numeric(iscs$diag_date - iscs$first_date)
iscs$time.isc.stroke[is.na(iscs$time.isc.stroke)] <-
iscs$follow_up.cens_all[is.na(iscs$time.isc.stroke)]

CVDd <- subset(out_NRS, CVD_death.ident == 1, select=c(ID, pat_dod, CVD_death.ident))
CVDd <- merge(base2, CVDd, c("ID"), all=TRUE)
CVDd$CVD_death.ident[is.na(CVDd$CVD_death.ident)] <- 0
CVDd$time.CVD.death <- as.numeric(CVDd$pat_dod - CVDd$first_date)
CVDd$time.CVD.death[is.na(CVDd$time.CVD.death)] <-
CVDd$follow_up.cens_all[is.na(CVDd    time.CVD.death)]

MI <- subset(out_SMR, MI.ident == 1, select=c(ID, diag_date, MI.ident))
MI <- MI[order(MI$ID, MI$diag_date),]
MI <- MI[! duplicated(MI$ID),]
MI <- merge(base2, MI, c("ID"), all=TRUE)
MI$MI.ident[is.na(MI$MI.ident)] <- 0
MI$time.MI <- as.numeric(MI$diag_date - MI$first_date)
MI$time.MI[is.na(MI$time.MI)] <- MI$follow_up.cens_all[is.na(MI$time.MI)]

allb <- subset(out_SMR, all_bleed.ident == 1, select=c(ID, diag_date, all_bleed.ident))
allb <- allb[order(allb$ID, allb$diag_date),]
allb <- allb[! duplicated(allb$ID),]
allb <- merge(base2, allb, c("ID"), all=TRUE)
allb$all_bleed.ident[is.na(allb$all_bleed.ident)] <- 0
allb$time.all.bleed <- as.numeric(allb$diag_date - allb$first_date)
allb$time.all.bleed[is.na(allb$time.all.bleed)] <-
allb$follow_up.cens_all[is.na(allb$time.all.bleed)]
```

 # crude IR of outcomes by drug

```
py1.iscs <- pyears(Surv(time.isc.stroke, isc_stroke.ident) ~ first_item, data=iscs)
summary(py1.iscs)
py1.CVDd <- pyears(Surv(time.CVD.death, CVD_death.ident) ~ first_item, data=CVDd)
summary(py1.CVDd)
py1.MI <- pyears(Surv(time.MI, MI.ident) ~ first_item, data=MI)
summary(py1.MI)
py1.allb <- pyears(Surv(time.all.bleed, all_bleed.ident) ~ first_item, data=allb)
summary(py1.allb)
```

 # Cox proportional hazard - reference: rivaroxaban

```
### ischaemic stroke
iscs$first_item <- relevel(iscs$first_item, "RIVAROXABAN")
cox1.iscs <- coxph(Surv(time.isc.stroke, isc_stroke.ident) ~ first_item, data=iscs)
summary(cox1.iscs)
anova(cox1.iscs)
```

```
# iscs$first_item <- relevel(iscs$first_item, "DABIGATRAN ETEXILATE")
# iscs$first_item <- relevel(iscs$first_item, "APIXABAN")
cox1.iscs2 <- coxph(Surv(time.isc.stroke, isc_stroke.ident) ~ first_item + pat_sex +
pat_age_prescr + pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson +
HAS_BLED + polypharm, data=iscs)
summary(cox1.iscs2)
anova(cox1.iscs2)
cox.zph(cox1.iscs2)

### CVD death
CVDd$first_item <- relevel(CVDd$first_item, "RIVAROXABAN")
cox1.CVDd <- coxph(Surv(time.CVD.death, CVD_death.ident) ~ first_item, data=CVDd)
summary(cox1.CVDd)
anova(cox1.CVDd)

# CVDd$first_item <- relevel(CVDd$first_item, "DABIGATRAN ETEXILATE")
# CVDd$first_item <- relevel(CVDd$first_item, "APIXABAN")
cox1.CVDd2 <- coxph(Surv(time.CVD.death, CVD_death.ident) ~ first_item + pat_sex +
pat_age_prescr +          pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson
+ HAS_BLED + polypharm,       data=CVDd)
summary(cox1.CVDd2)
anova(cox1.CVDd2)
cox.zph(cox1.CVDd2)

### myocardial infarction
MI$first_item <- relevel(MI$first_item, "RIVAROXABAN")
cox1.MI <- coxph(Surv(time.MI, MI.ident) ~ first_item, data=MI)
summary(cox1.MI)
anova(cox1.MI)

# MI$first_item <- relevel(MI$first_item, "DABIGATRAN ETEXILATE")
# MI$first_item <- relevel(MI$first_item, "APIXABAN")
cox1.MI2 <- coxph(Surv(time.MI, MI.ident) ~ first_item + pat_sex + pat_age_prescr +
pat_HB_PIS +   pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson + HAS_BLED +
polypharm, data=MI)
summary(cox1.MI2)
anova(cox1.MI2)
cox.zph(cox1.MI2)

### all bleeds
allb$first_item <- relevel(allb$first_item, "RIVAROXABAN")
cox1.allb <- coxph(Surv(time.all.bleed, all_bleed.ident) ~ first_item, data=allb)
summary(cox1.allb)
anova(cox1.allb)

# allb$first_item <- relevel(allb$first_item, "DABIGATRAN ETEXILATE")
# allb$first_item <- relevel(allb$first_item, "APIXABAN")
cox1.allb2 <- coxph(Surv(time.all.bleed, all_bleed.ident) ~ first_item + pat_sex +
pat_age_prescr +          pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson
+ HAS_BLED + polypharm,       data=allb)
summary(cox1.allb2)
anova(cox1.allb2)
cox.zph(cox1.allb2)
```

Dose-response analysis

 # cumulative exposure

subset DOAC prescriptions - exclude patients using more than one DOAC

```
base3 <- subset(base2, mult.DOAC == 0)

index_ID <- unique(base3$ID)
index <- subset(base3, ID %in% index_ID, select=c(ID, first_date, end_date, follow_up))

DOACs <- subset(DOAC.util, ID %in% index_ID, select=c(ID, item_name, item_dose,
date_prescr, days_supply))
DOACs <- DOACs[order(DOACs$ID, DOACs$date_prescr),]
DOACs$prescr_no <- unlist(tapply(DOACs$ID, DOACs$ID, function(x) seq(1, length(x),1)))
DOACs <- merge(DOACs, index, c("ID"), all=TRUE)
```

calculate cumulative exposure and create categorical variable

```
DOACs <- transform(DOACs, cumul.exp=ave(days_supply, ID, FUN = function(x)
cumsum(c(0, head(x, -1)))))
exp_labels <- c("0-3 months", "3-6 months", "6-9 months", "9-12 months", "12-18 months",
        "18-24 months" ,">24 months")
DOACs$exp_level <- as.factor(cut(DOACs$cumul.exp, breaks = c(0, 92, 184, 275, 366, 549,
732, 1768), right = FALSE, labels = exp_labels))
exp_labels2 <- c("0-6 months", "6-12 months", "12-18 months", ">18 months")
DOACs$exp_level2 <- as.factor(cut(DOACs$cumul.exp, breaks = c(0, 184, 366, 549, 1768),
        right = FALSE, labels = exp_labels2))
exp_labels3 <- c("0-3 months", "3-6 months", "6-12 months", "12-18 months", ">18 months")
DOACs$exp_level3 <- as.factor(cut(DOACs$cumul.exp, breaks = c(0, 92, 184, 366, 549,
1768), right = FALSE, labels = exp_labels3))
```

select prescription when exposure levels change and adjust start time for previous oversupply

```
DOACs <- DOACs[order(DOACs$ID, DOACs$date_prescr),]

DOACs2 <- DOACs[!duplicated(DOACs[c(1, 11)]),]
DOACs2$start <- as.numeric(DOACs2$date_prescr - DOACs2$first_date)
DOACs2$start[DOACs2$exp_level == "3-6 months" & DOACs2$start < 92] <- 92
DOACs2$start[DOACs2$exp_level == "6-9 months" & DOACs2$start < 184] <- 184
DOACs2$start[DOACs2$exp_level == "9-12 months" & DOACs2$start < 275] <- 275
DOACs2$start[DOACs2$exp_level == "12-18 months" & DOACs2$start < 366] <- 366
DOACs2$start[DOACs2$exp_level == "18-24 months" & DOACs2$start < 549] <- 549
DOACs2$start[DOACs2$exp_level == ">24 months" & DOACs2$start < 731] <- 731

DOACs3 <- DOACs[!duplicated(DOACs[c(1, 12)]),]
DOACs3$start <- as.numeric(DOACs3$date_prescr - DOACs3$first_date)
DOACs3$start[DOACs3$exp_level2 == "6-12 months" & DOACs3$start < 184] <- 184
DOACs3$start[DOACs3$exp_level2 == "12-18 months" & DOACs3$start < 366] <- 366
DOACs3$start[DOACs3$exp_level2 == ">18 months" & DOACs3$start < 549] <- 549
DOACs3$exp_level <- NULL
DOACs3 <- rename(DOACs3, c("exp_level2" = "exp_level"))

DOACs4 <- DOACs[!duplicated(DOACs[c(1, 13)]),]
DOACs4$start <- as.numeric(DOACs4$date_prescr - DOACs4$first_date)
```

```
DOACs4$start[DOACs4$exp_level == "3-6 months" & DOACs4$start < 92] <- 92
DOACs4$start[DOACs4$exp_level2 == "6-12 months" & DOACs4$start < 184] <- 184
DOACs4$start[DOACs4$exp_level2 == "12-18 months" & DOACs4$start < 366] <- 366
DOACs4$start[DOACs4$exp_level2 == ">18 months" & DOACs4$start < 549] <- 549
DOACs4$exp_level <- NULL
DOACs4 <- rename(DOACs4, c("exp_level3" = "exp_level"))
```

 # select outcomes

excluding patients using more than one DOAC

```
out_SMR <- subset(outcomes_SMR, ID %in% index_ID)
out_SMR <- subset(out_SMR, diag_date > first_date & diag_date <= end_date, select=c(ID,
first_date,          diag_date, all_stroke.ident, isc_stroke.ident, TIA.ident, SE.ident, PE.ident,
MI.ident,            comp_eff1.ident, comp_eff2.ident, haem_stroke.ident, ICH.ident, SAH.ident,
GI_bleed.ident,  other_bleed.ident, all_bleed.ident, other_ADR.ident, CIS_MARKER))
sub1 <- subset(out_SMR, is.na(out_SMR$CIS_MARKER))
sub2 <- subset(out_SMR, complete.cases(out_SMR$CIS_MARKER))
sub2 <- sub2[! duplicated(sub2[,c("ID", "first_date", "all_stroke.ident", "isc_stroke.ident",
"TIA.ident",        "SE.ident", "PE.ident", "MI.ident", "comp_eff1.ident", "comp_eff2.ident",
"haem_stroke.ident",      "ICH.ident", "SAH.ident", "GI_bleed.ident", "other_bleed.ident",
"all_bleed.ident",           "other_ADR.ident", "CIS_MARKER")]),]
out_SMR <- rbind(sub1, sub2)
out_SMR <- out_SMR[order(out_SMR$ID, out_SMR$diag_date),]

out_NRS <- subset(outcomes_NRS, ID %in% index_ID)
out_NRS <- subset(out_NRS, pat_dod > first_date & pat_dod <= end_date)
```

 # prepare datasets for each outcome category individually

excluding patients using more than one DOAC

```
base4 <- subset(base3, select=c(ID, first_item, first_date, follow_up, pat_sex,
pat_age_prescr, pat_HB_PIS,    pat_ur_PIS, simd5_PIS, CHADS_VASc, HAS_BLED,
charlson, polypharm))
```

first event, time to event

```
iscs <- subset(out_SMR, isc_stroke.ident == 1, select=c(ID, diag_date, isc_stroke.ident))
iscs <- iscs[order(iscs$ID, iscs$diag_date),]
iscs <- iscs[! duplicated(iscs$ID),]
iscs <- merge(base4, iscs, c("ID"), all=TRUE)
iscs$isc_stroke.ident[is.na(iscs$isc_stroke.ident)] <- 0
iscs$time.isc.stroke <- as.numeric(iscs$diag_date - iscs$first_date)
iscs$time.isc.stroke[is.na(iscs$time.isc.stroke)] <- iscs$follow_up[is.na(iscs$time.isc.stroke)]

MI <- subset(out_SMR, MI.ident == 1, select=c(ID, diag_date, MI.ident))
MI <- MI[order(MI$ID, MI$diag_date),]
MI <- MI[! duplicated(MI$ID),]
MI <- merge(base4, MI, c("ID"), all=TRUE)
MI$MI.ident[is.na(MI$MI.ident)] <- 0
MI$time.MI <- as.numeric(MI$diag_date - MI$first_date)
MI$time.MI[is.na(MI$time.MI)] <- MI$follow_up[is.na(MI$time.MI)]
```

```
CVDd <- subset(out_NRS, CVD_death.ident == 1, select=c(ID, pat_dod, CVD_death.ident))
CVDd <- merge(base4, CVDd, c("ID"), all=TRUE)
CVDd$CVD_death.ident[is.na(CVDd$CVD_death.ident)] <- 0
CVDd$time.CVD.death <- as.numeric(CVDd$pat_dod - CVDd$first_date)
CVDd$time.CVD.death[is.na(CVDd$time.CVD.death)] <-
CVDd$follow_up[is.na(CVDd$time.CVD.death)]

allb <- subset(out_SMR, all_bleed.ident == 1, select=c(ID, diag_date, all_bleed.ident))
allb <- allb[order(allb$ID, allb$diag_date),]
allb <- allb[! duplicated(allb$ID),]
allb <- merge(base4, allb, c("ID"), all=TRUE)
allb$all_bleed.ident[is.na(allb$all_bleed.ident)] <- 0
allb$time.all.bleed <- as.numeric(allb$diag_date - allb$first_date)
allb$time.all.bleed[is.na(allb$time.all.bleed)] <- allb$follow_up[is.na(allb$time.all.bleed)]
```

 # drug exposure

```
exp <- subset(DOACs4, select=c(ID, item_name, item_dose, exp_level, start))

iscs.t <- tmerge(iscs, iscs, id=ID, iscs=event(time.isc.stroke, isc_stroke.ident))
iscs.t <- tmerge(iscs.t, exp, id=ID, exp_level=tdc(start, exp_level))

MI.t <- tmerge(MI, MI, id=ID, MI=event(time.MI, MI.ident))
MI.t <- tmerge(MI.t, exp, id=ID, exp_level=tdc(start, exp_level))

allb.t <- tmerge(allb, allb, id=ID, allb=event(time.all.bleed, all_bleed.ident))
allb.t <- tmerge(allb.t, exp, id=ID, exp_level=tdc(start, exp_level))
```

 # Cox proportional hazard - reference: rivaroxaban, exp > 18 months

```
### ischaemic stroke
cox2.iscs <- coxph(Surv(tstart, tstop, iscs) ~ exp_level:first_item, data=iscs.t)
summary(cox2.iscs)
anova(cox2.iscs)

cox2.iscs2 <- coxph(Surv(tstart, tstop, iscs) ~ exp_level:first_item + pat_sex +
pat_age_prescr + pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson +
HAS_BLED + polypharm, data=iscs.t)
summary(cox2.iscs2)
anova(cox2.iscs2)
cox.zph(cox2.iscs2)

### myocardial infarction
cox2.MI <- coxph(Surv(tstart, tstop, MI) ~ exp_level:first_item, data=MI.t)
summary(cox2.MI)
anova(cox2.MI)

cox2.MI2 <- coxph(Surv(tstart, tstop, MI) ~ exp_level:first_item + pat_sex + pat_age_prescr
+ pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson + HAS_BLED +
polypharm, data=MI.t)
summary(cox2.MI2)
anova(cox2.MI2)
cox.zph(cox2.MI2)
```

```
### cardivascular death
cox2.CVDd <- coxph(Surv(tstart, tstop, CVDd) ~ exp_level:first_item, data=CVDd.t)
summary(cox2.CVDd)
anova(cox2.CVDd)

cox2.CVDd2 <- coxph(Surv(tstart, tstop, CVDd) ~ exp_level:first_item + pat_sex +
pat_age_prescr + pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson +
HAS_BLED + polypharm, data=CVDd.t)
summary(cox2.CVDd2)
anova(cox2.CVDd2)
cox.zph(cox2.CVDd2)

### all bleeds
cox2.allb <- coxph(Surv(tstart, tstop, allb) ~ exp_level:first_item, data=allb.t)
summary(cox2.allb)
anova(cox2.allb)

cox2.allb2 <- coxph(Surv(tstart, tstop, allb) ~ exp_level:first_item + pat_sex +
pat_age_prescr + pat_HB_PIS + pat_ur_PIS + simd5_PIS + CHADS_VASc + charlson +
HAS_BLED + polypharm, data=allb.t)
summary(cox2.allb2)
anova(cox2.allb2)
cox.zph(cox2.allb2)


# graphs

### set up for use with DOACs4

z.c <- summary(cox2.allb2)$coefficients
z.c <- z.c[31:45,]                          # to select only exp:first_item in adjusted model
z.c[15,] <- c(0,1,0,0,1)

z.lower.limit <- -5
z.upper.limit <- 2
z.exponential <- TRUE
z.ylab="log HR"

z.exp <- rep(c(1:5),3)
z.drug <- rep(c("AP","DA","RI"),rep(5,3))
z.exp <- z.exp - 0.2*(z.drug=="AP")
z.exp <- z.exp + 0.2*(z.drug=="RI")
z.lcl <- z.c[,"coef"] - 1.96*z.c[,"se(coef)"]
z.ucl <- z.c[,"coef"] + 1.96*z.c[,"se(coef)"]
z.cf <- z.c[,"coef"]
z.cf[z.cf<z.lower.limit] <- z.lower.limit
z.lcl[z.lcl<z.lower.limit] <- z.lower.limit
z.ucl[z.ucl<z.lower.limit] <- z.lower.limit
z.cf[z.cf>z.upper.limit] <- z.upper.limit
z.lcl[z.lcl>z.upper.limit] <- z.upper.limit
z.ucl[z.ucl>z.upper.limit] <- z.upper.limit
if (z.exponential) {
z.cf <- exp(z.cf)
z.lcl <- exp(z.lcl)
z.ucl <- exp(z.ucl)
z.ylab <- "HR"
z.lower.limit <- exp(z.lower.limit)
```

```
z.upper.limit <- exp(z.upper.limit)
}


z.col <- list(AP="black", DA="red", RI="green")

dev.new()
plot(z.exp,z.c[,"coef"],xlab="drug exposure",ylab=z.ylab, ylim=c(z.lower.limit,z.upper.limit),
type="n",axes=F)
axis(2)
axis(1,at=1:5,label=c("0-3 months", "3-6 months", "6-12 months", "12-18 months", "over 18
months"))
box()
for (z.dd in c("AP","DA","RI")) {
z.sel <- z.drug==z.dd
z.e <- z.exp[z.sel]
z.cf.sel <- z.cf[z.sel]
z.u <- z.ucl[z.sel]
z.l <- z.lcl[z.sel]
lines(z.e, z.cf.sel, col= z.col[[z.dd]],lwd=2)
for (z.i in 1:length(z.e)) segments(z.e[z.i],z.l[z.i],z.e[z.i],z.u[z.i],col=z.col[[z.dd]],lty=2)
}
legend("topright",legend=c("apixaban","dabigatran","rivaroxaban"),lty=1,lwd=2,col=as.charac
ter(z.col))
abline(h=1.0, col="black")
```