Investigating prescribers' experiences of direct-acting oral anticoagulants for the management of nonvalvular atrial fibrillation.

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INVESTIGATING PRESCRIBERS' EXPERIENCES OF DIRECT-ACTING ORAL ANTICOAGULANTS FOR THE MANAGEMENT OF NONVALVULAR ATRIAL FIBRILLATION

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ABSTRACT

DOACs have relatively recently been licensed for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (AF) and have replaced warfarin as the first line agent of choice over warfarin. The aim of this research was to determine prescribers' views and experiences of the use of DOACs for the management of non-valvular AF.

The first phase was a PROSPERO registered systematic review of clinicians' views and experiences of DOACs for the management of non-valvular atrial fibrillation. Ten studies were identified; in those studies reporting clinician preference, DOACs were first choice over warfarin in naïve patients, based on perceptions of evidence of effectiveness equivalent or superior to warfarin and superior safety. Other advantageous factors were in those with an unstable International Normalized Ratio and likely to miss appointments. There were, however, concerns relating to management of over-anticoagulation and experiences of observed bleeding rates. In addition to the lack of studies, none of the studies had used theory in the development of the data collection tools or analysis indicating a gap in the literature

The second phase was a cross-sectional survey of prescriber's views, behaviours and experiences related to prescribing DOACs for the management of non-valvular AF. The survey was conducted in NHS Highland, inviting all medical and non-medical prescribers to participate. Items on potential influences on DOAC prescribing were based on the Theoretical Domains Framework (TDF). Principal component analysis (PCA) of the TDF items gave four components. Component scores for (i) role of professionals, their knowledge and skills and (ii) influences on prescribing were positive. There did, however, appear to be issues in switching from warfarin to DOACs or from one DOAC to another. Scores for (iii) consequences of prescribing and (iv) monitoring for safety and effectiveness were more neutral. There were low levels of agreement for statements relating to DOACs being more effective, safer and cost-eff ective than warfarin. There were similar responses around the complexity of bleeding management and detection of over and under-anticoagulation. Less experienced prescribers were statistically significantly more positive than more experienced prescribers in

terms of the consequences of prescribing ($p<0.05$). Content analysis of the responses to the open questions identified that the overwhelming perceived benefit was the absence of need for INR monitoring, with the main limitations being the lack of a suitable reversal agent and ability to monitor anticoagulation status.

Given the updated recommendations of Healthcare Improvement Scotland (HIS) to use edoxaban first line, the final phase was a cross-sectional survey of prescriber's views, behaviours and experiences related to prescribing edoxaban for the management of non-valvular AF. Responses were received from 103 prescribers in NHS Highland. While almost all respondents had been encouraged to implement this recommendation of prescribing edoxaban, less than one third had either switched patients from warfarin or other DOACs to edoxaban. The following three PCA components identified in the previous survey were applied to the TDF determinants: the role of professionals, their knowledge and skills; influences on prescribing; and consequences of prescribing. While component scores for the first two components were positive, the scores for consequences of prescribing were more neutral. Although a number of respondents described edoxaban (and other DOAC) related adverse drug reactions (ADRs), very few had submitted a Yellow Card report to the Medicines and Healthcare products Regulatory Agency (MHRA). Content analysis of the responses to the open questions identified benefits and limitations similar to the previous survey.

This doctoral research has generated original findings in terms of DOACs views, experiences and behaviours related to management of non-valvular AF. There is merit in reviewing the local and national guidelines, particularly in relation to switching and awareness of the evidence base. Attention should be paid to the literature on guideline implementation.

EXTERNAL OUTPUT

The doctoral research has resulted in the following outputs to date

Published peer reviewed papers

1. Stewart DC, Generalova D, Cunningham S, Leslie SJ, Rushworth GF, McIver L. Healthcare professional and patient views, behaviours and experiences surrounding novel oral anticoagulants (NOACs) for the management of non-valvular atrial fibrillation (AF): a systematic review protocol. PROSPERO 2016: CRD42016003840.
2. Generalova D, Cunningham S, Leslie SJ, Rushworth G, McIver L, Stewart D. Prescribers' views and experiences of using direct acting oral anticoagulants in the management of non-valvular atrial fibrillation: a survey in remote and rural Scotland. British Journal of Clinical Pharmacology. 2019; 85: 2414-2422.
3. Generalova D, Cunningham S, Leslie SJ, Rushworth G, McIver L, Stewart D. A systematic review of clinicians' views and experiences of direct-acting oral anticoagulants in the management of nonvalvular atrial fibrillation. British Journal of Clinical Pharmacology. 2018; 84, 2692-2703.
4. Generalova D, Cunningham S, Leslie SJ, Rushworth G, McIver L, Stewart D. Prescribers' experiences of direct acting oral anticoagulants for the management of non-valvular atrial fibrillation: a summative content analysis of data from a survey in remote and rural Scotland. Pharmacy Practice 2020. In press.

Peer reviewed conference abstracts

1. Generalova D, Cunninham S, Leslie S. J, Rushworth G, McLver L, Stewart D. A survey of prescribers in the Scottish Highlands on their perspectives of prescribing direct-acting oral anticoagulants (Oral presentation at the 47th International Symposium, European Society of Clinical Pharmacy, Belfast 2018).
2. Generalova D, Cunninham S, Leslie S. J, Rushworth G, McLver L, Stewart D. A systematic review of clinicians' views and experiences of direct-acting oral anticoagulants in the management of non-valvular atrial fibrillation (Poster presentation at the 47th International Symposium, European Society on Clinical Pharmacy, Belfast 2018).
3. Generalova D, Cunningham S, Leslie S. J, Rushworth G, McLver L, Stewart D. A survey of prescribers in the Scottish Highlands on their perspectives of the benefits and limitations of direct-acting oral anticoagulants (Oral presentation at the European Society of Clinical Pharmacy conference, Antwerp, March 2019).

ABBREVIATIONS

ABC	Age, biomarkers, clinical history
ADR	Adverse drug reaction
AF	Atrial Fibrillation
AMED	Allied and Complementary Medicine Database
ATRIA	Anticoagulation and risk factors in atrial fibrillation
CINAHL	Cumulative Index of Nursing and Allied Health Literature
$CHADS_2$	Congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism [doubled]
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age, [doubled], diabetes mellitus, prior stroke or TIA or thromboembolism[doubled], vascular disease, age, sex category
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPD	Continuing professional development
DARE	Database of Abstracts of Reviews of Effectiveness
DOACs	Direct-acting Oral Anticoagulants
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
ESC	European Society of cardiology
ERIC	European Research Infrastructure Consortium
GP	General Practitioner
HAS-BLED	Hypertension, abnormal renal/liver function, stroke, history of bleeding, liable INR, elderly, drug/alcohol, abuse
HRQol	Health-related quality of life
iDAPs	Interactive Drug Analysis Profiles
INR	International Normalized Ratio
IPA	International Pharmaceutical Abstracts
IQR	Interquartile range

ISI	International Sensitivity Index
JBI	Joanna Briggs Institute
KMO	Kaiser-Meyer-Olkin
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare Products Regulatory Agency Ministry of Health
HEMORR$_2$HAGES	Hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anaemia, genetic factors, excessive fall risk and stroke
HIS	Healthcare Improvement Scotland
NICE	National Institute for Health and Care Excellence
NHS	National Healthcare Service
NOACs	Novel Oral Anticoagulants
NSAIDs	Non-steroidal Anti Inflammatory Drugs
OAC	Oral Anticoagulation
OBRIT	Outcomes registry for better informed treatment of atrial fibrillation
PCA	Principal Component Analysis
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA- P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
PT	Prothrombin Time
RCT	Randomized Clinical trial
RIETE	Computerized registry of patients with venous Thromboembolism
RGU	Robert Gordon University
SIGN	Scottish Intercollegiate Guidelines Network
SPSS	Statistical Package for the Social Sciences

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TDF	Theoretical Domains Framework
UK	United Kingdom
USA	United States of America

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My PhD journey has been challenging at times, but filled with so many positive experiences. There are a number of people who have supported me throughout this journey and without their guidance, advice and kindness I would not have reached my destination.

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CHAPTER 1: GENERAL INTRODUCTION

This introductory chapter provides an overview of atrial fibrillation (AF), with particular emphasis on non-valvular AF, the diagnosis in the vast majority of patients and the subject of this doctoral research. The role of oral anticoagulants and the issues relating to the use of warfarin in the management of non-valvular AF is described. This is followed by the clinical pharmacology of a new class of oral anticoagulants, the direct-acting oral anticoagulants (DOACs), and the evidence base of efficacy, effectiveness and safety. The rationale for the doctoral research on prescribers' views and experiences of DOACs is given, along with the overall research aim and the aims of the different phases of research.

1.1 Research strategy terms

A systematic approach to the identification, retrieval and review of relevant literature was adopted throughout the doctoral research. The aims were to gain a thorough understanding of policies, guidelines, reviews and primary research related to DOAC prescribing in the management of non-valvular AF, and to maintain this throughout the research journey.

The search strategy focused on the following databases: Medline, Cumulative Index to Nursing and Allied Health Literature (CINHAL), International Pharmaceutical Abstracts and Google Scholar.

The search was conducted from Jan 2006 (two years prior to the launch of DOACs) until the completion of the research. Where possible, alerts were set up in the databases to enable continuous updating.

While the specific search terms, and application of Boolean operators, varied from database to database, the following provides an indication of the approach.

- Related to non-valvular AF; 'atrial fibrillation' OR 'non-valvular atrial fibrillation' OR 'non-valvular AF'
- Related to DOACs; 'direct acting oral anticoagulant*' OR 'novel oral anticoagulant*' OR 'DOAC*' OR 'NOAC*' OR 'dabigatran' OR ' rivaroxaban' OR 'edoxaban' OR 'warfarin*'
- Related to prescribing; 'prescrib*' OR 'guideline*' OR 'implementation'

- Related to health professionals; 'health professional*' OR 'healthcare professional*' OR 'doctor*' OR 'prescriber*' OR 'physician*' OR 'pharmacist*' OR 'nurse*'

These terms were applied as MESH headings (where possible), title, abstract or keywords. The search in Google Scholar was adapted due to the limitations of the search function.

1.2 Atrial fibrillation

1.2.1 Atrial fibrillation classification

AF is the most common sustained cardiac arrhythmia, defined as a 'supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial' (Camm et al., 2010, Kirchhof et al., 2016, January et al., 2014). In 2016, the European Society of Cardiology, in collaboration with the Task Force for the management of atrial fibrillation of the European Society of Cardiology, published updated guidelines. The guidelines were also developed with contributions from the European Heart Rhythm Association of the European Society of Cardiology and endorsed by the European Stroke Organisation. The classification of AF as described in the guidelines is given in Table 1.1.

Table 1.1. European Society of Cardiology classification of AF (Kirchhof et al., 2016)

Classification of AF	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal.
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing definition, not pursued in patients with permanent persistent AF'.

In 2014, the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society published their updated guidance for the management of AF, with classification largely similar to that of the European Society of Cardiology (Table 1.2).

Table 1.2.American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society classification of AF (January et al., 2014)

Classification of AF	Definition
Paroxysmal AF	Terminates spontaneously or with intervention within seven days of onset.
Persistent AF	Continuous and sustained for more than seven days.
Long-standing persistent AF	Continuous and sustained for more than 12 months.
Permanent AF	Patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.
Non-valvular AF	In the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair.

The key difference between these two classifications is the inclusion of non-valvular AF within the American guidelines. While the term 'non-valvular AF' is not listed within the classification of the ESC guidelines, it is explained that 'Traditionally, patients with AF have been dichotomized into 'valvular' and 'non-valvular' AF… we have decided to replace the historic term 'non-valvular' AF with reference to the specific underlying conditions.' However, given that 'non-valvular AF' is still widely used in the United Kingdom (UK) and is the term used in key UK guidelines (NICE, 2014), this term has been adopted for this doctoral research. The term 'non-valvular AF' represents the majority of patients with a diagnosis of AF.

1.2.2 Atrial fibrillation prevalence and clinical outcomes

The prevalence of AF varies depending on the population and cohort being studied, with prevalence varying with age, sex and ethnicity. AF has recently been referred to as a global epidemic, with worldwide prevalence estimated at up to 33.5 million, and is known to be increasing (Morin et al., 2016; Rahman et al., 2014). Prevalence is more clearly established in the western world, at around 1-2% of the adult population. Data consistently demonstrate prevalence increasing with age, being higher in males than females and higher in white individuals compared to black or Asian (Camm et al., 2010.

Martinez et al., 2015). Findings of a relatively recent systematic review illustrate that AF is present in 0.12–0.16% of those under 49 years of age, 3.7–4.2% in those aged 60–70 years and 10–17%in those aged 80 years and over (Zoni-Berisso et al., 2014).

Permanent AF occurs in approximately 50% of patients, and paroxysmal and persistent AF in 25% each (Zoni-Berisso et al., 2014), with non-valvular AF much more prevalent than valvular AF. Due to the significant reduction of rheumatic disease in western countries, the prevalence of valvular heart disease is very low with figures from the United States (US) of approximately 2.5% of those with AF. The prevalence of rheumatic heart disease is similar at an estimated 2-3% (Lung et al., 2011).

The aetiology and pathophysiology of AF are complex and beyond the scope of this doctoral research. Essentially, AF occurs when atrial structural abnormalities and/or atrial electrical abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Camm et al., 2010, Staerk et al., 2017). Many factors, modifiable and non-modifiable, can increase the risk of AF. Modifiable factors include: smoking, lack of exercise, excess alcohol intake, diabetes mellitus, heart failure, hypertension and hyperthyroidism. Non-modifiable risk factors include: increasing age, family history and valvular heart disease (Camm et al., 2010,Staerk et al., 2017).

The clinical outcomes of AF are potentially severe, as illustrated in Table 1.3.

Table 1.3. Clinical outcomes of AF (Camm et al., 2010, Staerk et al., 2017)

Clinical outcomes	Description
Death	Death rates may be doubled.
Stroke	Associated with increased risk of stroke and transient ischemic attack, up to 20-30% of strokes due to AF . Increased risk of long-term disability or death. Risk of stroke is variable and affected by other risk factors and AF management, can be in patients with a 'silent' and paroxysmal AF.
Cognitive decline and vascular dementia	AF is associated with an adjusted increased risk of cognitive impairment, dementia, Alzheimer's dementia, and vascular dementia in patients with and without a history of stroke.
Heart failure	Clinical outcome as well as a risk factor for AF.
Hospitalisation	10-40% patients with AF are hospitalized every year.
Quality of life	Patients quality of life is decreased independent of other cardiovascular diseases.

Symptoms of AF include heart palpitations, shortness of breath, weakness, dizziness, chest pain, confusion, lowered ability to exercise (Camm et al., 2010).

1.3 Management of AF

The goals in managing AF are to reduce symptoms and prevent complications listed in Table 1.3. The management of AF is described in national and international evidence-based guidelines (January et al., 2014, Camm et al., 2010, NICE, 2014, SIGN 129, 2013). Pharmacological approaches include the use of anticoagulants to reduce the risk of stroke, and antiarrhythmics to restore or maintain heart rhythm or to slow the heart rate in people who remain in AF. Non-pharmacological management includes electrical cardioversion, and catheter or surgical ablation. A pathway for AF treatment is given in Figure 1.1.

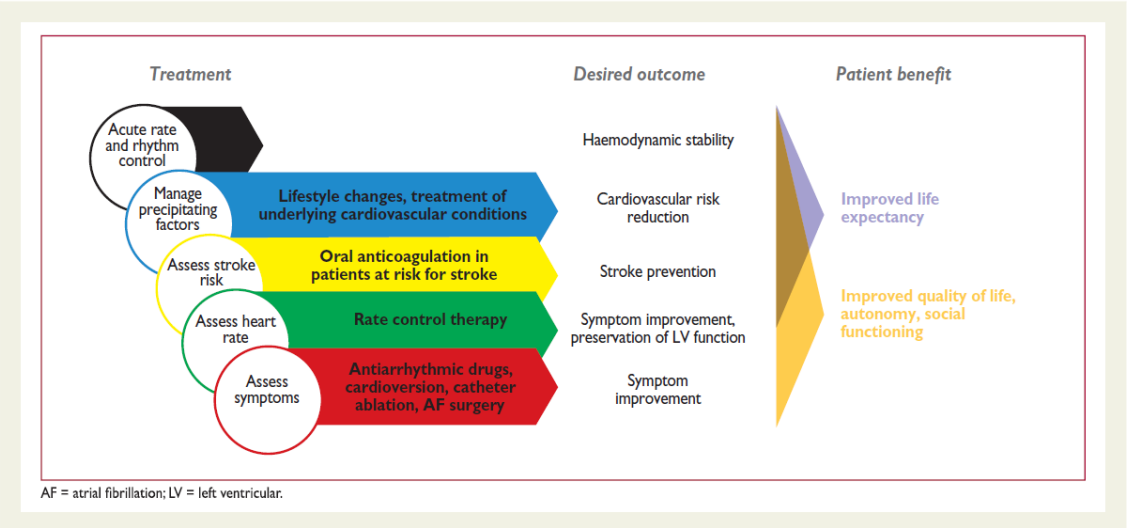


Figure 1.1. AF management pathway, as described in the European Society of Cardiology guidelines, 2016 (Krchhof et al., 2016)

Given that this doctoral research focuses on the use of oral anticoagulants in the management of non-valvular AF, detailed coverage of the mechanism of action and properties of anti-arrhythmic agents, electrical cardioversion, and catheter or surgical ablation is beyond the scope of this introduction.

From this point forward, the thesis focuses on non-valvular AF.

1.4 Use of oral anticoagulation in the management of non-valvular AF

As highlighted in Figure 1.2 oral anticoagulants feature heavily in the management of AF (valvular and non-valvular), with the main goal being to achieve anticoagulation thus preventing stroke while minimizing the risk of bleeding (January et al. 2014, Camm et al., 2010). The decision whether to commence an oral anticoagulant or not should be made in conjunction with the patient and with consideration of the risks of stroke and bleeding (Camm et al., 2010).

1.4.1 Stroke risk assessment

$CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism [doubled]) was initially introduced as a stroke risk predictor in patients and replaced by the updated CHA_2DS_2-VASc (congestive heart failure, hypertension, Age ≥75 years

[doubled], diabetes mellitus, prior stroke or TIA or thromboembolism [doubled], vascular disease, age 65 to 74 years, sex category) (Kirchohof, et al., 2016). CHA_2DS_2-VASc has a wider total score range (0-9) and includes a larger number of risk factors than $CHADS_2$. Table 1.4 describes the allocation of scores and the maximum possible scores for $CHADS_2$ and CHA_2DS_2-VASc

Table 1.4. Stroke risk assessment tools

	Score
$CHADS_2$	
Congestive heart failure	1
Hypertension	1
Age≥ 75 years	1
Diabetes	1
Stroke/TIA	2
Maximum possible score	6
CHA_2DS_2-VASc	
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Stoke/TIA	2
Vascular disease (MI, aortic plaque, peripheral artery disease)	1
Age 65-74 years	1
Sex (female)	1
Maximum possible score	9

The CHA_2DS_2-VASc score informs the decision whether or not to commence an oral anticoagulant, taking account of the risk benefit ratio. If the score is 1 and above for males and 2 and above for females then an oral anticoagulant is indicated (Kirchohof, et al., 2016).

1.4.2 Bleeding risk assessment

In addition to considering the risk of stroke prior to initiating an oral anticoagulant, clinicians should also consider the risk of bleeding. While bleeding risk is not necessarily a contraindication to anticoagulant use, the risk should be borne in mind. Of the different risk assessment tools, the most commonly used is HAS-BLED (hypertension, abnormal renal/liver function, stoke, history of bleeding, liable INR, elderly, drug/alcohol abuse [1 point allocated to each]). Other tools include OBRIT (outcomes registry for better

informed treatment of atrial fibrillation), ABC (age, biomarkers, clinical history), RIETE (computerized registry of patients with venous thromboembolism), HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anaemia, genetic factors, excessive fall risk and stroke) and ATRIA (anticoagulation and risk factors in atrial fibrillation) (January et al., 2014).

1.5 Warfarin in the management of non-valvular AF

1.5.1 Warfarin mechanism of action

For over 60 years warfarin has been the oral anticoagulant of choice for the management of non-valvular AF. Phenindione, the other coumarin anticoagulant is rarely used and reserved for those sensitive (allergic) to the effects of warfarin. Warfarin inhibits the activity of vitamin K dependent coagulation factors (II, VII, IX and X) of the coagulation cascade (Figure 1.2) through the inhibition of vitamin K epoxide reductase. This leads to the hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity (Lip et al., 2010; Jackson et al., 2014).

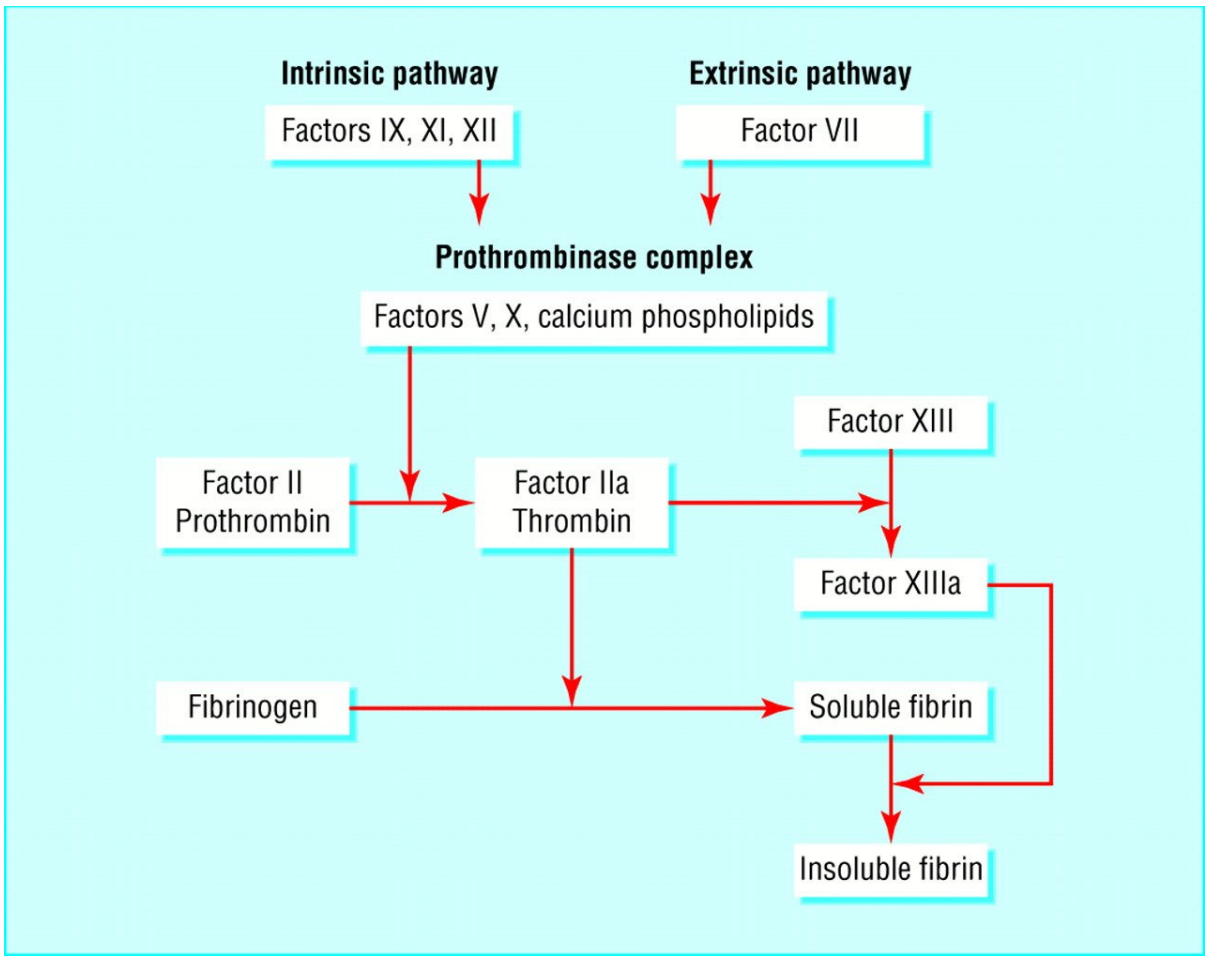


Figure 1.2. Simplified coagulation cascade. (Blann et al., 2002)

1.5.2 Warfarin pharmacokinetics

Warfarin is a mixture of two optically active isomers (the R and S forms) in almost equal proportions. It is completely absorbed from the gastrointestinal tract, has a long half-life and is very highly bound to plasma proteins (Table 1.5).

Table 1.5. Pharmacokinetic properties of warfarin (Xiong et al., 2015, Lip et *al.*, 2010)

Pharmacokinetic parameter	
Oral bioavailability	100%
Half-life	20-60 hours
Time to peak concentration	72-96 hours
Plasma protein bounding	Tightly bound to albumin 99%
Metabolism	Mixed function P450 oxidases (CYP2C9, CYP3A4, CYP1A2)
Renal clearance	Only very small amounts appear unchanged in urine

1.5.3 Warfarin disadvantages

There are major issues associated with the use of warfarin which compromise both effectiveness and safety.

1. Narrow therapeutic window

As warfarin has a non-linear pharmacokinetic profile and a very narrow therapeutic window, a small change in plasma concentration can have a marked effect on the likelihood of adverse effects, the most important of which is bleeding. It is therefore difficult to predict the dose for an individual patient which will maximise effectiveness while minimising these adverse effects.

2. Need for regular monitoring

Given these issues, regular monitoring of prothrombin time is required during initiation of therapy and on an ongoing basis. Prothrombin is an important procoagulant component of a coagulation pathway (factors VII, X, V, prothrombin, fibrinogen), as highlighted in Figure 1.3. The prothrombin time is expressed as the International Normalized Ratio (INR) which is the ratio of the patient's prothrombin time to control (patient prothrombin time/control prothrombin time)^{ISI}. The control prothrombin time is taken from the geometric mean of 20 or more healthy subjects, and the ISI is the International Sensitivity Index, which takes both the PT reagent and the

specific apparatus used into account (Porte et al., 2010). The pharmacokinetic profile also dictates that warfarin is given as a loading dose followed by a maintenance dose.

The relationship between the INR and effectiveness and likely bleeding is given in Figure 1.3, also demonstrating the narrow therapeutic window.

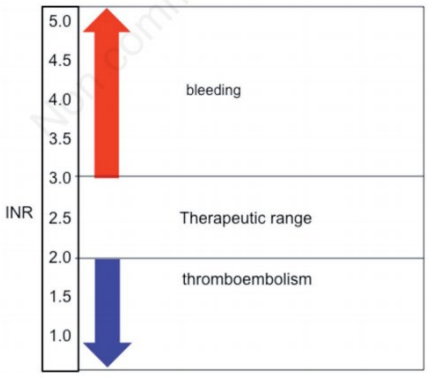


Figure 1.3. The relationship between INR, likely effectiveness and risk of bleeding (Masotti et al., 2013)

3. Potential for drug-drug interactions

One further complication in the use of warfarin is the potential for drug-drug interactions. As warfarin is metabolised by cytochrome P450 enzymes (CYP2C9, CYP3A4 and CYP1A2) there is potential for warfarin plasma concentrations to be significantly increased or decreased by enzyme inhibitors and inducers respectively. This could have consequences of altering effectiveness and the likelihood of adverse effects.

Key commonly prescribed enzyme inducers include carbamazepine and phenytoin.

Key commonly prescribed enzyme inhibitors include amiodarone, citalopram, erythromycin, fluconazole and omeprazole.

Other mechanisms of interactions include altering gastrointestinal absorption, protein binding displacement and excretion. Several interacting drugs may be obtained in the UK without a prescription (e.g. St John's Wort, omeprazole, cimetidine). While these drugs should not necessarily be avoided (and indeed

there is evidence for some co-prescription), they may require increased monitoring and vigilance (NHS Highland, 2018).

4. Potential for food-drug interactions

In addition to drug-drug interactions, there is potential for food-warfarin interactions. The most clinically important is in relation to foods high in vitamin K (e.g. broccoli, spinach, cabbage, brussel sprouts and lettuce) and changes in the consumption of these may lead to alterations in INR (Lip et al., 2010). Drinking alcohol to excess may also interfere with warfarin metabolism (Nutescu et al., 2006).

5. Genetic factors

Complex genetic factors can lead to affected individuals having a low tolerance to warfarin. This effect is due to polymorphism of in two main genes (CYP2C9 and VKORC1). Studies have confirmed variation in the prevalence of these different polymorphisms in different populations. It is estimated that these genetic factors, in addition to the non-genetic factors described above, account for up to 50% of warfarin dose variability. Several algorithms of patient characteristics to consider in relation to genetic factors have been developed by the Warfarin Pharmacogenetics Consortium (Johnson et al., 2011)

In summary, while there are very many systematic reviews highlighting the safe and effective use of warfarin in the management of non-valvular AF, it is far from ideal. Recent years have seen marked changes in the availability and prescription of oral anticoagulants worldwide with the introduction of a new class of agents, the Direct Acting Oral Anticoagulants, the subject of this doctoral research.

1.6 Direct Acting Oral Anticoagulants (DOACs)

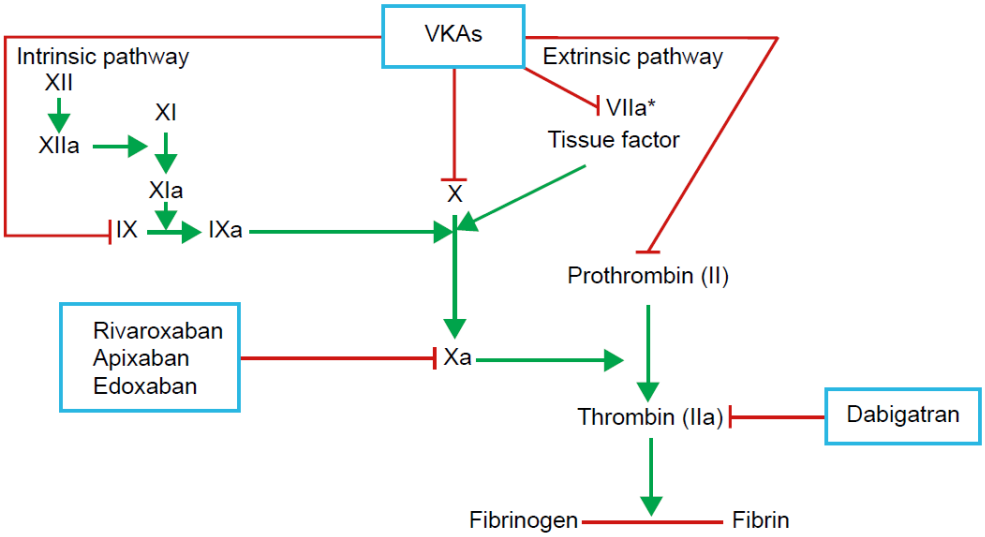
1.6.1 Name of drug class

The introduction of dabigatran to the UK market in 2008 was followed by rivaroxaban, apixaban and most recently edoxaban. While initially termed

'new' or 'novel' oral anticoagulants (NOACs), the International Society of Thrombosis and Haemostasis has suggested that 'direct-acting oral anticoagulant (DOAC)' be adopted universally (Barnes et al., 2015). This is more consistent with the pharmacotherapeutic classifications of direct thrombin inhibitors (dabigatran) or directed Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) (Gomez-Outes et al., 2015). The term DOAC will therefore be used throughout this thesis.

1.6.2 Mechanism of action of DOACs

Figure 1.4 illustrates the sites of action of DOACs on the coagulation cascade (Mejaj et al., 2015).



As DOACs directly inhibit either thrombin or activated factor X, they have a faster onset and offset of action compared to warfarin. In the UK, all four DOACs are licensed for stroke prevention in the management of non-valvular AF.

1.6.3 DOAC pharmacokinetics

In comparison to warfarin, DOACs have predictable pharmacokinetics. In general, they are rapidly absorbed following oral administration and have relatively short half-lives. A comparison of key pharmacokinetic properties of the available DOACs is given in Table 1.6.

Table 1.6. Pharmacokinetic properties of DOACs (adapted from Gomez-Outes et al., 2015)

Pharmacokinetic parameter	Dabigtatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability (%)	6	80-100	50	62
Time to maximum concentration (hrs)	0.5-2	2-4	3-4	1.5
Protein binding (%)	35	92-95	87	55
Half-life (h)	14-17	5-13	12	6-11
Metabolism	Glucuronidation	CYP3A4	CYP3A4/5	CYP3A4/5
Renal excretion (% of absorbed dose)	85 (80 unchanged)	73 (37 unchanged)	55 (44 unchanged)	56 (39 unchanged)
Pharmacokinetic parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Bioavailability (%)	6	80-100	50	62
Time to maximum concentration (hrs)	0.5-2	2-4	3-4	1.5
Protein binding (%)	35	92-95	87	55
Half-life (h)	14-17	5-13	12	6-11
Metabolism	Glucuronidation	CYP3A4	CYP3A4/5	CYP3A4/5
Renal excretion (% of absorbed dose)	85 (80 unchanged)	73 (37 unchanged)	55 (44 unchanged)	56 (39 unchanged)

1.6.4 Disadvantages of DOACs

In addition to predictable pharmacokinetics, the pharmacodynamic properties of DOACs are also predictable. Drug dosages are fixed (other than in those with hepatic or renal impairment) hence there is no need for monitoring anticoagulation status (Mosotti et al., 2013). Disadvantages of DOACs are described using the same headings as warfarin.

1. Therapeutic window

Unlike warfarin, DOACs have wide therapeutic windows hence the potential for adverse events is reduced. Reported adverse events include bleeding, abdominal pain, nausea, vomiting, dyspepsia and diarrhoea. Reversal of over-anticoagulation with DOACs is less straightforward than warfarin. Idarucizumab has only very recently been licensed for use in the UK and is indicated to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery (Pollack et al., 2015). No antidotes are currently available for the other three DOACs. Given that DOACs are relatively new to the market, post-surveillance monitoring and spontaneous reporting of all suspected adverse events is required (Mekaj et al., 2015).

2. Need for regular monitoring

As noted above, there is no requirement for monitoring anticoagulation status. Furthermore, the results of INR testing in patients prescribed DOACs are unreliable given the different modes of action on the coagulation cascade (Jackson et al., 2014).

3. Potential drug-drug interactions

The potential for clinically important interactions between DOACs and other drugs is greatly reduced in comparison to warfarin. Drug interactions can, however, occur during absorption, distribution and clearance. Pharmacokinetic interactions are medicated by the P-gp transporter protein and the cytochrome P450 enzymes, with inhibitors including clarithromycin and inducers including carbamazepine. Pharmacodynamic interactions include the risk of bleeding when given concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) (Hellwig et al., 2013).

4. Potential drug-food interactions

DOACs can be administrated before, during or after food, including vitamin-K containing products (Mekaj et al., 2015).

5. Genetic factors

The evidence base relating to polymorphism and DOACs is emerging, highlighted by the considerable inter-individual variations which have been detected. The first study on dabigatran polymorphism was published in 2011 and since then further polymorphisms for all DOACs hence been identified. The significance of these effects and implications for clinical practice are now being studied.
(Asic et al., 2018).

1.6.5. Evidence of effectiveness and safety

There is an extensive evidence base to support the adoption of DOACs into clinical practice. A search of Medline for was conducted for each of the years from 2008 to 2018, using the terms

> ['systematic review*' OR 'meta-analysis'] in the title
>
> AND
>
> ['direct oral anticoagulant*' OR 'new oral anticoagulant*' OR 'novel oral anticoagulant* OR 'dabigatran' OR 'rivaroxaban' OR 'edoxaban' OR 'apixaban'] in the title.

This search identified 240 systematic reviews, largely relating to efficacy, effectiveness and safety. The increase in systematic reviews since the entry of DOACs to the market in 2008 is given in Figure 1.5. At the time of commencing this doctoral research, there was a major gap in relation to clinicians' views and experiences of prescribing DOACs for non-valvular AF. The one systematic review on this topic published in 2018 is from this thesis and described in Chapter 4 (Generalova et al., 2019). Further research on aspects of prescribers' views and experiences in prescribing DOACs is therefore warranted.

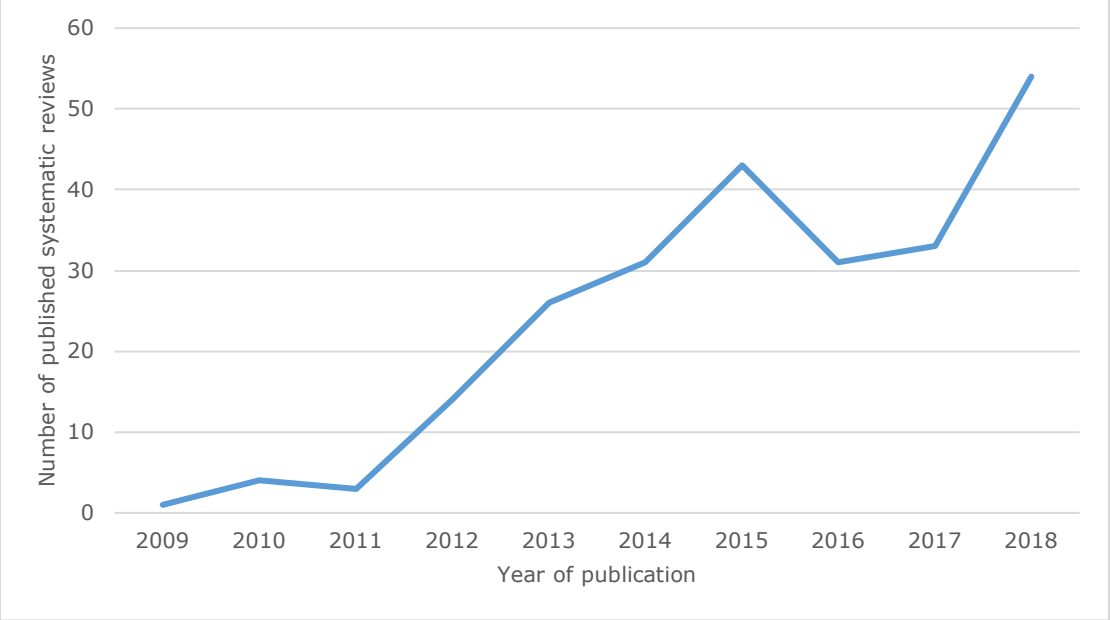


Figure 1.5. Graph of the number of published DOAC-related systematic reviews per year

1.7 Guidelines on the use of DOACs in the management of non-valvular AF

As a result of the evidence supporting the use of DOACs in the management of non-valvular AF, these have now been incorporated into local, national and international prescribing guidance and policy statements. The following sections describe international and national guidelines (UK and Scotland). Guidelines available in NHS Highland (the setting for the primary research, see later) are also described.

1.7.1 International guidelines

There are many examples of international guidelines on the use of DOACs generally and specifically relating to non-valvular AF. Key examples are those developed by the European Society of Cardiology (Camm et al., 2010), the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society (January et al., 2014), and the recently updated 2018 Practical Guide from the European Heart Rhythm Association (Steffel et al., 2018). Table 1.7 describes the key content of these guidelines highlighting the similarities. While only three DOACs are

recommended by the American College of Cardiology guidelines, these preceded the introduction of edoxaban. As the guidelines of the European Heart Rhythm Association specifically focus on DOACs, there are much more detailed in relation to all aspects of DOACs including switching, advice for patients and promoting clinician and patient adherence.

Table 1.7. Content of international guidelines in relation to the use of DOACs in non-valvular AF (January *et* al. 2014, Kirchhof et al., 2016, Steffel et al., 2018).

Key content of guideline	American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society	European Society of Cardiology	European Heart Rhythm Association
Year of publication	2014	2016	2018
Title	Guideline for the management of patients with AF	Guidelines for the management of AF	Practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with AF
Includes guidance on the selection of an oral anticoagulant (DOAC or warfarin)	Yes	Yes	Yes
DOAC recommended first choice in preference to warfarin	No	Yes	Yes
Specific DOACs recommended	Dabigatran, rivoroxaban, apixaban	Dabigatran, rivaroxaban, apixaban, edoxaban	Dabigatran, rivaroxaban apixaban, edoxaban
Guidance on commencing DOAC	Yes	Yes	Yes
Guidance on switching to/from warfarin	No guidance	No specific guidance but recommended switch from warfarin if time in therapeutic is not well controlled despite good adherence, or if patient preference without contra-indications	Yes, specific and detailed guidance on how to switch
Recommended patient involvement in decision to use DOAC	Yes	Yes	Yes

1.7.2 UK guidelines

The National institute for Health and Care Excellence (NICE), provides advice to improve health and social care in England and Wales (NICE, 2014). In 2014, NICE disseminated guidance on the management of AF which recommended dabigatran, rivaroxaban, apixaban or warfarin in those with non-valvular AF (NICE, 2014). As with the American College of Cardiology guidelines, NICE guidance preceded the introduction of edoxaban. This guidance has translated into practice, evidenced by a pharmacoepidemiological study of DOAC prescribing in primary care in the UK from 2009 to 2015. Data were extracted from the UK Clinical Practice Research Datalink. Results highlighted substantial increases in prescribing over the study period. The rate of new DOAC users increased, particularly from 2012 onwards with a 17-fold from 2012 to 2015. By 2015, DOACs had surpassed warfarin as the oral anticoagulants of choice, particularly for the management of AF (Loo et al., 2017).

1.7.3 Scottish guidelines

Healthcare Improvement Scotland (HIS) is the national healthcare improvement organisation for Scotland (HIS, 2012). The five key priorities are:

- Enabling people to make informed decisions about their care and treatment.
- Helping health and social care organisations to redesign and continuously improve services.
- Provide evidence and share knowledge that enables people to get the best out of the services they use and helps services improve.
- Provide quality assurance that gives people confidence in the services and supports providers to improve.
- Making the best use of resources, we aim to ensure every pound invested in our work adds value to the care people receive.

In 2017, HIS updated their guidance on the use of DOACs with the publication of 'A review of the clinical effectiveness of direct oral anticoagulants for the prevention of stroke and systemic embolism in adult patients with non-valvular AF' (HIS, 2017). Previous guidance has

recommended dabigatran, rivaroxaban and apixaban for patients not responding well to warfarin (HIS, 2012). The update noted a lack of direct comparisons between DOACs hence the recommendations were based entirely on indirect evidence from published network meta-analyses. Edoxaban is recommended as first line treatment with the other three DOACs being second line.

1.7.4 NHS Highland guidelines

The primary research described in Chapters 4 and 5 was conducted within the NHS Highland region of Scotland hence further emphasis is placed on the specific guidelines within that health board. The seventh edition of the NHS Highland formulary was published in January 2018. The formulary is described as '…limited list of medicines approved for local use in hospitals and primary care'. Choice is made on the basis of clinical effectiveness, cost-effectiveness, comparative safety and patient acceptability. Recommendations for oral anticoagulants in the management of non-valvular AF follow the national guidance of HIS (NHS Highland, 2018).

1.8 NHS Highlands

As described above, the primary research was conducted within the geographical area of NHS Highland. NHS Highland is largest geographical health board in the UK, covering approximately 32500 km^2 and 41% of the entire land mass of Scotland. This is significant given that the population is 320,000 people which is less than 10% of Scotland population. One quarter of the population live in 'urban areas' (defined as settlements ≥10000 people compared to 69.5% of the entire population of Scotland. Moreover 40.4% of population live in remote and rural areas (areas with a population of less than 3,000 people). Studies have demonstrated that for many people, access to hospitals, general medical practices and community pharmacies is limited (Stewart et al., 2017). Responsibility for the management of stroke prevention in patients with non-valvular AF is usually undertaken in primary care although patients can also be initiated on therapy in secondary care if they attend outpatient clinics or during admission. Figure 1.6 provides analysis of primary care prescribing of warfarin and DOACs indicating a downward trend in warfarin prescribing and an upward trend for DOACs.

While these data relate to prescribing for all indications, it is highly likely that the majority is for non-valvular AF.

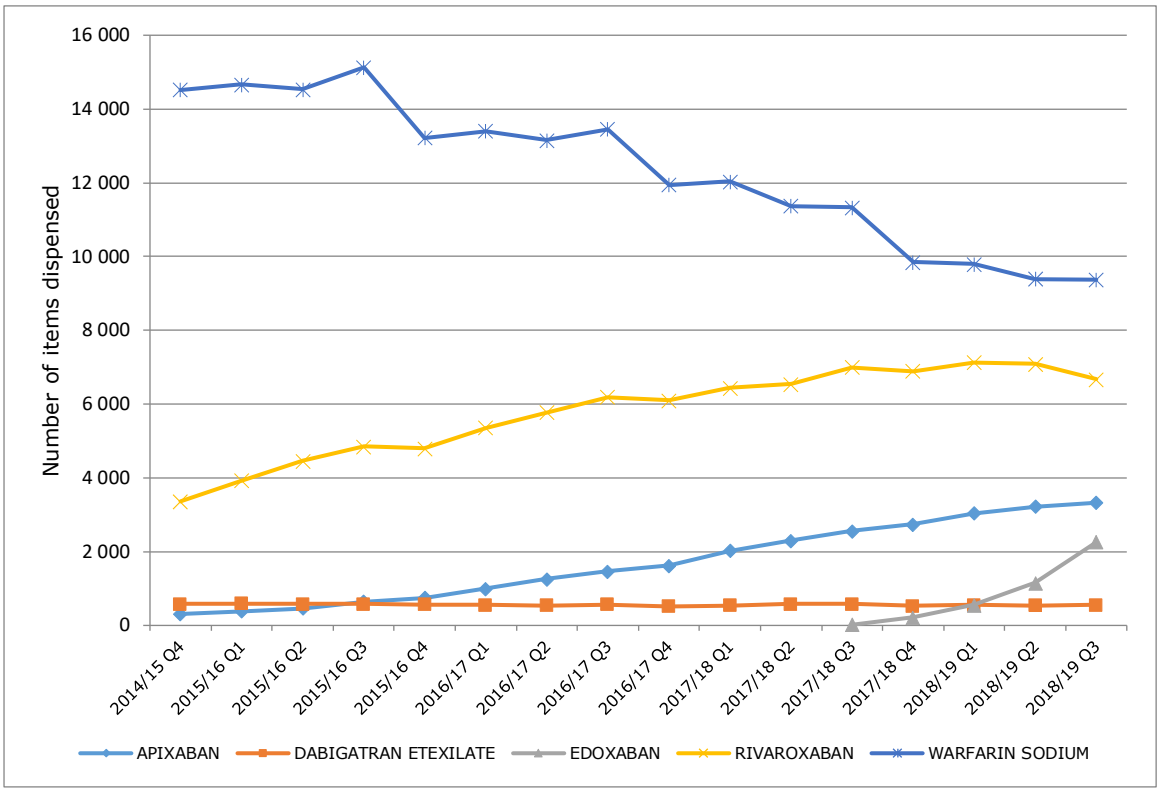


Figure 1.6. Number of items of warfarin and DOACs dispensed, NHS Highland

It is clear that DOACs are now first line for the management of non-valvular AF. There is a vast array of evidence from systematic reviews and meta-analyses of effectiveness, efficacy and safety and this evidence has translated into clinical guidelines and daily practice. However, there is a dearth of evidence on the views and experiences of prescribers. This information is critical as positive or negative views and experiences may impact prescribing behaviours. This doctoral research set out to provide robust and rigorous data on these aspects.

1.9 Aims and objectives of the doctoral research

The overall aim of this research was to determine clinicians' views and experiences of the use of DOACs for the management of non-valvular AF.

There are three phases of the doctoral research each with aims as described below.

Phase 1: To critically appraise, synthesise and present the available evidence of clinicians' views and experiences of the use of DOACs for the management of non-valvular AF.

In relation to DOACs for the management of non-valvular AF:

1. what are clinicians' views of the use of DOACs?
2. what are the influences on clinician's use of DOACs?
3. what are clinician's experiences, both positive and negative?

Phase 2: To determine prescribers' views, experiences and behaviours relating to prescribing DOACs for the management of non-valvular AF.

In relation to prescribers and DOACs, the research questions were:

1. how are DOACs initiated, prescribed and monitored?
2. which behavioural determinants impact behaviours around prescribing DOACs?
3. what are the perceived benefits and limitations of prescribing DOACs?
4. what are the positive and negative experiences of prescribing DOACs?
5. how could the appropriate use of DOACs in primary care be extended further?

Phase 3: To determine prescribers' views, experiences and behaviours relating to prescribing edoxaban for the management of non-valvular AF.

The detailed research objectives in relation to prescribing edoxaban for the management of non-valvular AF:

1. how is edoxaban initiated, prescribed and monitored?
2. which behavioural determinants potentially impact behaviours around prescribing edoxaban?
3. what are the perceived benefits and limitations of prescribing DOACs?
4. what are the positive and negative experiences of prescribing DOACs?

1.10. Chapter summary

This chapter has described the background literature on AF, non-valvular AF, stroke protection and the role and place of oral anticoagulants. It is clear that there is a need to research the perspectives of DOAC prescribers and this forms the basis of the doctoral research.

CHAPTER 2: RESEARCH METHODOLOGIES

This chapter provides justification of the research approaches employed, with consideration of the value in conducting systematic reviews and the use of quantitative and qualitative approaches. Research methodologies are outlined, with emphasis on the application of theories and theoretical frameworks. Issues of robustness, rigour and bias are described, along with approaches to enhance robustness and rigour whilst minimizing bias.

2.1 Research Philosophy

This section provides an overview of different philosophical approaches in conducting research, with justification for the approach selected and applied in this doctoral research.

The following figure of the 'research onion' highlights the interplay between philosophy, approaches and methodologies.

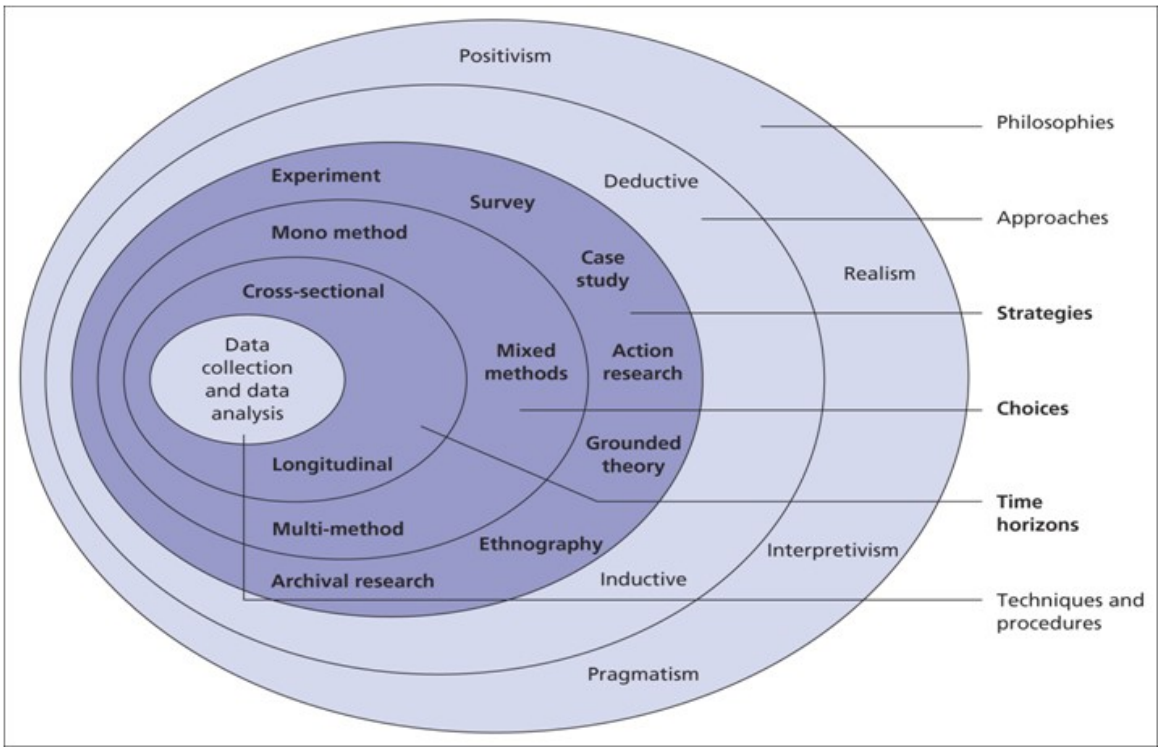


Figure 2.1. The research onion (Understanding the Research Onion)

While there are many different philosophical approaches, depending on the specific reference text, this figure gives positivism, realism, interpretivism

and pragmatism. Other sources extend this to include constructivism, hermeneutics, feminism, radicalised discourses, critical theory, Marxist models, cultural studies, queer theory etc. (Creswell, 2014). Positivism assumes that reality exists and can be measured; a deductive approach is taken starting with generation of a hypothesis which is tested using quantitative approaches. The methods and results are capable of being replicated by other researchers. The positivist approach has often been considered as the 'scientific' or 'traditional' approach, using experiments to study objective outcomes. The researcher collects data to allow conclusions of accepting or rejecting a null hypothesis (and hence accepting the alternative hypothesis (Creswell, 2014). The positivist philosophical approach therefore aligns with quantitative research methodologies.

At a certain level, realism and positivism share many similarities. Realism, however, attempts to distinguish between the 'real' world and the 'observable' world. While the 'observable' world is observed or as perceived by individuals (or groups, populations and societies), the 'real' world is real and not as observed. It there exists independently from human perceptions, theories, and constructions (Dean, 2006).

Interpretivism involves researchers using observations to interpret elements of study thus integrating human interest. Access to reality (given or socially constructed) is through social constructions such as language, consciousness, shared meanings, and instruments (Myers, 2008). Interpretivism therefore aligns with qualitative research methodologies and may involve generation of the theories which can then be tested using positivist approaches.

The pragmatic approach is considered to be a worldview of actions, situations and consequences in which researchers use all approaches available to understand the problem and answer specific research questions. This approach is frequently used in applied research, with many aligning it with mixed methods research. Researchers choose the methods, techniques and procedures of research which meet their needs and purposes (Creswell, 2014).

This doctoral research most closely aligns with the positivist stance. The systematic review presented in Chapter 3 was largely based on quantitative

studies which were therefore objective in nature. The cross-sectional surveys presented in Chapters 4 and 5 were, by definition, quantitative methodologies designed to answer specific research aims and objectives and involved many quantitative statistical approaches including testing of hypotheses and drawing conclusions based on probability values. While the analysis included a qualitative content analysis approach, this was not a pure qualitative methodology hence the data generated and the subsequent synthesis were limited.

The next layer of the research onion classifies research as deductive or inductive. Essentially, the deductive approach relates to testing theory or theoretical assumptions. The four stages of the deductive approach are: stating the existing theory; developing the hypothesis; collecting data; and analysing the data to draw conclusions relating to the hypothesis (Streefkerk, 2019). The deductive approach therefore aligns with a quantitative, positivist approach, although this term is also used in relation to approaches to qualitative data analysis in situations where data generation and analysis is driven by a theory or framework.

With an inductive approach, the focus is more on developing, rather than testing, a theory. The three stages are: observation; observing patterns; and developing theory (Streefkerk, 2019). Inductive approaches are generally used for analysing qualitative data involving condensing raw textual data into a brief, summary format. This is followed by establishing clear links to develop a framework of the underlying structure of experiences or processes (Thomas, 2006). An inductive approach was employed in this doctoral research in relation to the analysis of textual comments provided by questionnaire respondents.

2.2 RESEARCH DESIGN

The doctoral research was conducted in three specific phases, each aligned to the research aims and objectives outlined in Chapter 1, as follows

Phase 1

Aim	To critically appraise, synthesise and present the available evidence of views and experiences of healthcare professionals surrounding DOACs for the management of non-valvular AF
Design	Systematic review of the peer-reviewed literature

Phase 2

Aim	To determine prescribers' views and experiences relating to prescribing DOACs for the management of non-valvular AF
Design	Cross-sectional survey

Phase 3

Aim	To determine prescribers' views and experiences relating to prescribing edoxaban for the management of non-valvular AF
Design	Cross-sectional survey

2.3 SYSTEMATIC REVIEW OF THE PEER-REVIEWED LITERATURE

2.3.1 TYPOLOGY OF LITERATURE REVIEWS

There are very many different terms used to describe the various types of literature reviews. Table 2.1 describes some of the most commonly used terms.

Table 2.1. Typology of literature reviews (Grant M., et al., 2009)

Types of review	Description
Critical review	Review with emphasis on critical evaluation
Mapping review	Categorises literature, often used to commission primary research by identifying gaps in the literature
Narrative review	Traditional overview of the literature in a specific field
Rapid review	Review conducted rapidly, often only including very recently published literature; used in developing policy
Scoping review	Conducted to identify the volume of available research literature
State-of-the-art review	Review of recent literature in a specific field, with findings considered in the context of current approaches
Systematic review	Conducted to answer a very clear review question, with approach outlined in a detailed review protocol. May include meta-analysis to pool statistical data
Systematised review	A truncated version of a systematic review
Umbrella review	Pools evidence from several systematic reviews

Narrative literature reviews and systematic reviews are the two most frequently published within the healthcare literature. While narrative reviews are broad overviews within a research field, systematic reviews aim to answer specific review questions. For this doctoral research, a systematic review was the most appropriate to generate pooled data on health professionals' views and experiences of DOACs in the management of non-valvular AF.

Systematic reviews are considered to provide the very highest level of evidence (Burns et al., 2011), as described in Table 2.2.

Table 2.2. Descriptions of levels of evidence applied to therapeutic studies (SIGN, 2013)

Level	Type of evidence
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias. 1- Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal
3	Non-analytical studies, such as case reports and case series
4	Expert opinion

It should be noted that while the systematic review presented in Chapter 3 provided pooled and synthesised data, the studies were largely cross-sectional surveys hence the review itself provided a lower quality of evidence that a review of RCTs.

2.3.2 Conducting systematic reviews

Systematic reviews are conducted according to a protocol meeting defined criteria and standards. The PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) is a 17 items checklist categorised in three main sections of administrative information, introduction, and methods (Moher et al., 2015). The systematic review protocol was registered with the International Prospective Register of Ongoing Systematic Reviews (PROSPERO), an international database of all registered systematic reviews established by the Centre for Reviews and Dissemination, University of York (Stewart et al., 2016) .

2.4 Primary research approaches

2.4.1 Quantitative and qualitative research methodologies

Primary research methodologies in healthcare are classified as quantitative or qualitative (referred to as 'mono' method in the research onion in Figure 2.1). Mixed methods approaches describe the application of both quantitative and qualitative approaches (sequentially, in parallel or nested) to answer the same or related research questions. Multi-methods studies involve utilizing a number of approaches to answer distinct research questions.

While research phases 2 and 3 were essentially quantitative in nature (cross-sectional surveys), a more qualitative approach was also employed in the analysis of textual responses and summative content analysis). A comparison of quantitative and qualitative research approaches is given below describing how these differ with respect to the research aim, research questions, objectives, data collection and generation instruments, and data they produce (Rwegoshora, 2016).

As described earlier, quantitative approaches align with a positivist philosophy, assuming that reality exists and can be measured. Quantitative approaches rely on numerical data (i.e. outcome measures linked to specific research questions or objectives) which can be measured, with steps taken to assure the validity (accuracy) and reliability (consistency) of the data collection tools, methods and the data collected (Creswell, 2014). The common quantitative methodologies are experimental (randomised controlled trials) and non-experimental (cohort studies, case control studies and surveys). The research questions and objectives studied reflect the need to study outcomes based on careful observation and measurement of the objective reality. Depending on the nature of the specific research questions or objectives and methodology, the objective, measured, 'real' data may be used to determine prevalence, incidence, association or cause (taking into consideration issues of validity, reliability, bias, confounders etc.). Formal approaches to sample size calculation are employed, with researchers attempting to promote internal and external validity (generalizability) of the

data, results and conclusions (see later). (Bowling 2009, Creswell 2013, Johnson and Onwuegbuzie 2004).

Qualitative methodologies align with the interpretivism stance (although may also feature in realism and pragmatic approaches) and focus on the generation of rich data to allow in-depth description and understanding of phenomena, context, culture and the development of theory. While qualitative methodologies have traditionally been regarded as less scientific than quantitative approaches, their use and popularity in healthcare research has grown in more recent times. They are often used as part of mixed methods approaches (sequential, parallel, nested) to provide explanation of quantitative findings. While validity and reliability of quantitative research tools and data can be measured, tested and assured, quality assurance of qualitative research is much more challenging and cannot be measured or assured. Steps are taken to promote the trustworthiness of the data generation tools, methods and the data generated (see later). The main qualitative methodologies are narrative, phenomenology, grounded theory, ethnography and case studies. While quantitative research data are generally collected from larger sample sizes with the aspiration of internal and external validity, answering questions such as association, cause etc., this is not the case with qualitative research. Here, the approach generates detailed and rich description of the research topic from much smaller sample sizes. There is no intention of generalising the data, findings or conclusion beyond those studied. Approaches to data collection are varied, commonly involving interviews, focus groups, observation and documentary analysis. Data analysis approaches are markedly different compared to quantitative research, with no intention to test hypotheses. Indeed, qualitative research may results in the generation of theory which can then be used to develop hypotheses for future quantitative studies. The role of the researcher in quantitative research is one of data collector, with no influence on the data collected. In qualitative research, the research is a data generator hence the need for significant training, expertise and focus on research trustworthiness to reduce influence as much as possible (Bowling 2009, Creswell 2013, Johnson and Onwuegbuzie 2004).

Key quantitative and qualitative research methodologies are described and compared in Table 2.3.

Table 2.3. Description of commonly used quantitative and qualitative methodologies (Creswell 2013, Creswell 2014, Giorgi, 2012, Charmaz, 2006, Reeves, 2008, Yin, 2009).

Quantitative methodologies	**Qualitative methodologies**
Randomised controlled trials (RCT) in which participants are randomised into different groups to received treatments of intervention, comparator or placebo. Sample sizes are generally large and determined based on the power of the study to identify a clinically important difference.	Narrative relates to the spoken or written text describing a single event or a series of events from the perspectives of individuals, which are chronologically connected. Tends to include very small sample sizes.
Cohort studies of individuals identified and followed up to identify how exposure affects defined outcomes. Data from exposed and non-exposed cohorts are compared, aligned to specific hypotheses.	Phenomenology provides an understanding of the real-life experiences of the participants relating to a specific phenomenon or event. Often based on a specific theory or theoretical framework to capture and describe the essence of the experience.
Case-control studies in which two groups differing in outcome are compared based on a supposed causal attribute. Cases and controls are selected from the same source population, with the distribution of exposure between cases and controls expressed as an odds ratio.	Grounded theory aims to develop theory constructed from the data of individuals by making links between categories of data and postulating relationships. Involves analysing data through open coding, axial coding and selective coding.
Surveys are an approach to describe phenomena in real-life situations to determine meanings and frequencies of the phenomenon under investigation. Data are collected through a specific data collection questionnaire. The specific nature could be cross-sectionals or longitudinal.	Ethnography studies social interactions, behaviours and perceptions within groups, teams, organisations and communities. Aims to generate and an in-depth understanding of a particular culture.
	Case study explores a case (or multiple cases) through in-depth data generation involving multiple sources of information rich in context.

Following completion of the systematic review in phase 1, the next two phases were cross-sectional surveys to allow quantification of the views and experiences of prescribers of DOACs. A non-experimental, quantitative methodology was considered most appropriate to meet the specific aims and objectives, which were more objective in nature. While a qualitative or mixed methods approach would have generated in-depth data, the extent of free text comments received in response to the open questions were considered sufficient. These were analysed using a qualitative approach of summative content analysis. The next section describes cross-sectional studies in greater detail.

2.4.2 CROSS-SECTIONAL SURVEYS

A cross-sectional methodology is defined as a research design, which 'provides a quantitative or numeric description of trends, attitudes, or options of a population by studying a sample of that population' (Creswell, 2014). Surveys can be used to describe a study population, to investigate any associations between variables, trends and determine if associations are statistically significant. As described earlier, these align with the positivist philosophical stance. The research aim, questions or objectives are framed in an objective manner, using terms such as 'determine', 'quantify', correlate', 'associate' etc. Sample sizes are much larger than for qualitative research and are calculated *a priori*., with the form of calculation depending on the specific research questions or objectives. The sample is usually drawn from a larger population (sampling frame) unless the population is relatively small. Defined inclusion and exclusion criteria are stated. The data collection tool is the questionnaire which may be self-administered by the research participant having been sent by mail or increasingly via email or other electronic modes (internet, social media etc). The questionnaire may be administered by a researcher, particularly if the questions are difficult to understand, the subject sensitive or the study population unable to complete. Table 2.4 describes advantages and disadvantages of electronic compared to paper based questionnaires.

The questionnaire itself is developed according to the study research questions or objectives, reflecting the literature and grounded in any appropriate theory or theoretical framework (see later). The questionnaire is then pre-tested through a series of stages in terms of validity (e.g. face, content, construct, criterion) and reliability. This is then followed by piloting, which may be internal (i.e. using some of the future study participants) or external (i.e. using non-study participants but individuals similar to those described in the inclusion/ exclusion criteria).

Given the specific study research questions, a cross-sectional survey was considered appropriate, with an electronic delivery mode selected for several reasons including convenience, an easily defined study population with email addresses available to the research team, and cost.

Table 2.4. Advantages and disadvantages of electronic compared to paper based questionnaires (Bowling, 2014).

Advantages	**Disadvantages**
Greatly reduced costs in production and mailing	Some evidence of lower response rate
Less time taken in questionnaire administration	Need access to participant emails
Can have automatic data entry to analysis software	Limited if internet connection problems

Multiple approaches were used in an attempt to maximise the response rates (see Chapters 4 and 5). A systematic review by VanGeest et al. identified a number of evidence based approaches to maximizing questionnaire response rate. These included: design-based (e.g. personalized mails, design-friendly questionnaires); use of reminders; clear explanation of the potential benefits of the study; assurances of confidentiality and anonymity; and link to an academic institution (VanGeest et al., 2007).

Sample size and sampling require specific consideration for surveys. Sampling is essentially the process of selecting of a particular group of participants from the whole population or sampling frame. In quantitative

studies, a number of probability approaches to sampling are available, as described in Table 2.5.

Table 2.5 . Approaches to sampling in cross-sectional surveys (Lavrakas, 2008)

Types of sampling	**Definition**
Random	Selected from the population based on chance. Each individual in the population has an equal opportunity of being selected
Systematic	Similar to simple random sampling, but participants are chosen at specific intervals, e.g. every 20th
Stratified	Population is divided into homogenous subgroups, based on prior knowledge of the population (e.g. age, sex) before randomly sampling from each subgroup
Cluster	Similar to stratified in that population exist in certain pre-defined groups (e.g. medical practice) which are sampled

For the cross-sectional surveys reported in Chapters 4 and 5, the number of participants with experience of prescribing DOACs was unknown and could not be determined prior to the study hence there was no sampling and the entire populations surveyed.

The approach to data analysis in Chapters 4 and 5 was largely quantitative based on descriptive and inferential statistics. For the inferential statistics, several hypotheses were stated (null and alternative) and appropriate tests selected depending on the particular hypothesis, distribution of the data and number of dependent and independent variables.

Given the number and extent of textual responses to the small number of open questions, a content analysis approach was considered the most appropriate. Content analysis essentially involves several steps of data coding, comparison, and the identification and description of categories or themes (Cavanagh, 1997; Bowling, 2009). Hsiech et al. (2005) describes three forms and approaches of content analysis, namely conventional, directed and summative.

Conventional content analysis is generally considered to be observation driven, with codes identified during analysis and applied to the dataset. This is in contrast to conventional directed content analysis in which existing theory or prior research is used to develop the initial coding scheme prior to analysis. In summative content analysis, the approach is fundamentally different with the analysis focusing on single words (keywords) with analysis of the patterns leading to interpretation (Hsieh *et al*., 2005). This latter approach involves counting and classifying these keywords in analysis and for presentation of the findings. It should be noted that these keywords are 'counted' rather than 'quantified' signaling that this is not a quantitative approach and that the counts are to allow interpretation rather than representing percentages of a specific population. Given that the textual data were generated in response to a small number of open ended statements in the questionnaire providing opportunity for further comment, a summative content analysis approach was considered most appropriate. There was no intention to either use theory or derive theory from the findings, more just to describe the responses hence a narrative synthesis was employed. As Heieh et al. state, summative content analysis approaches are 'limited by their inattention to the broader meanings present in the data' (Hsieh *et al*., 2005).

2.5 Use of theory in research

Theory is increasingly being used in quantitative, qualitative and mixed methods research. A theory is defined as 'a set of interrelated constructs (variables), definitions and propositions that presents a systematic view of phenomena by specifying relations among variables, with the purpose of explaining natural phenomena' (Kerlinger, 1979). Using theory in research increases the quality in several ways

- Allows the researchers to justify the research rationale from a theoretical as well as pragmatic perspective
- Encourages the researchers to state the research aim, questions, objectives, hypotheses etc. within a similar body of research

- Facilitates the development of research tools (questionnaires, interview schedules), which are comprehensive, considering a wide range of factors, issues etc.
- Facilitates the development of comprehensive coding frameworks for qualitative research
- Allows the researchers to consider data interpretation in a more theoretical and comprehensive manner
- Allows the researchers to contribute to the development of the theory (Bradbury-Jones et al., 2014)

For the systematic review, theory was used in the quality assessment and data extraction stages and aided the identification of gaps in the literature. Theory was also used in the development of the cross-sectional survey questionnaires and in data analysis and interpretation.

2.5.1 Theoretical Domains Framework

Given that the focus of the research was the experiences resulting from prescribing DOACs (i.e. the practice or behaviour), behavioural theories were selected as being most relevant (Creswell, 2014). The Theoretical Domains Framework (TDF) is not a theory but rather a framework of theories of behaviour and behaviour change. TDF was developed by a group of psychological theorists, health service researchers and health psychologists (Michie et al. 2005). The aim of TDF is to '…simplify and integrate a plethora of behaviour change theories and make theory more accessible to, and usable by, other disciplines'. TDF was derived from 33 psychological theories and 128 theoretical constructs. These constructs are organised into overarching domains (groups of related theoretical constructs); initially there were 12 domains of TDF and this has now been extended to 14, as described in Table 2.6.

Table 2.6. The Theoretical Domain Framework (adapted from Cane, O'Connor and Michie 2012)

Domain	Examples
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/Professional Role and Identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Beliefs about Capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	The confidence that things will happen for the best or that desired goals will be attained
Beliefs about Consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, Attention and Decision Processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
Environmental Context and Resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioural Regulation	Anything aimed at managing or changing objectively observed or measured actions

TDF was used in the development of questionnaire items to allow comprehensive consideration of the positive and negative influences in prescribing, as described in Chapters 4 and 5.

2.6 ROBUSTNESS AND RIGOUR IN RESEARCH

2.6.1 ROBUSTNESS IN QUANTITATIVE RESEARCH

Internal validity, external validity and reliability are the criteria to consider in achieving the goal of robustness in quantitative research. Essentially, validity is 'the accuracy and truth of the data being produced in terms of the concepts being investigated' (Heale et al., 2015). Internal validity relates to the confidence placed in the research processes together with data collected while external validity (generalisability) is the extent to which the findings can be extrapolated to other populations, settings etc. (Hasson and Keeney, 2011). While there are a number of different approaches to determining validity (e.g. face, content, construct, criterion, concurrent, predictive etc.) those employed in the cross-sectional surveys were largely face and content. Face validity is the extent to which a questionnaire covers the concepts it purports to measure in terms of transparency or relevance. Content validity considers the extent to which a questionnaire represents all facets of a given construct (Hasson F., Bolarinwa 2015, Holloway 2014).

Reliability is the extent to which results are consistent over time. While there are several approaches to determining reliability of the tool (e.g. test-retest reliability) (Chahal et al., 2014), these could not be applied due to the online nature of the cross-sectional surveys. Internal consistency was determined (see later).

2.6.2 Rigour in qualitative research

In qualitative research, the concepts of validity and reliability are less relevant, with more attention given to the trustworthiness of the research processes, data, findings and conclusions. Trustworthiness is described as four components, as described in Table 2.7.

Table 2.7. Components of research trustworthiness applied to qualitative research (Tobin and Begly, 2004)

Trustworthiness	Description
Credibility	Credibility is similar to internal validity, asking whether the findings are a true reflection of reality. Promoted by: using well-established methodologies and methods; providing detailed description of the phenomenon studied; encouraging participant honesty; and meeting with team members frequently for debriefing sessions and peer review
Dependability	Similar to reliability, described as the extent to which similar findings would be obtained if the study were repeated with the same methods etc.
Transferability	Similar to external validity. Achieved by providing detailed information to enable readers to consider the applicability of the study to their own setting
Confirmability	Concerned with establishing that the data and interpretation of the findings are derived from the research and not figments of the inquirer's imagination

As a qualitative approach was only employed in the analysis of textual data, many of these concepts were not relevant, as described in later chapters.

2.6.3 Bias as a threat to validity, reliability and trustworthiness

Bias occurs when 'systematic error is introduced into sampling or testing by selecting or encouraging one outcome or answer over others' (Bowling, 2014). The specific types of research bias and the approaches employed to minimise these when conducting and reporting the cross-sectional surveys are described in Table 2.8.

Table 2.8 Research biases and approaches to minimize (Bowling, 2009)

Bias	Description	Approach to minimise
Selection (sampling) bias	Sample is not representative of the population interest	All prescribers were invited to participate, with no selection (sampling)
Acquiescence response bias	Respondents more likely to respond positively	Range of question styles used, including negatively worded items
Response bias	Respondents provides non-honest and inaccurate answers	Clear statements of the purpose of the study, potential uses of the data and assurance of anonymity and confidentiality
Non-respondent bias	Those responding have very different views and experiences to those not responding	Various approaches to maximise the response rate
Social Desirability bias	The tendency to give a socially desirable answer even if it is not true	Clear statements of the purpose of the study, potential uses of the data and assurance of anonymity and confidentiality
Missing data	Incorrect interpretation as a result of excessive missing data	Various approaches to encourage completion of all items
Reporting, publication bias	Tendency to not report or publish negative findings	Clear dissemination strategy for conference abstracts and peer-reviewed papers

2.7 Ethical considerations in doctoral research

2.7.1 Concepts of ethical research

The four fundamental concepts in ethical research are autonomy, non-maleficence, beneficence, and justice.

Autonomy in research relates to respecting thought, intention, and action when making decisions, with decision making processes free of extreme

persuasion or coercion. Decisions to participate should be made of the basis of being fully informed. In the cross-sectional surveys in this doctoral research, all governance approvals were in place prior to any field work commencing, full study information was provided to potential participants who could elect whether or not to participate and could withdraw from the study at any time. While signed, informed consent was not collected, completion and submission of the questionnaire was taken as an indication of informed consent, as part of standard practice (Owonikoko, 2013)..

Non-maleficence relates to the study causing no harm. While this cannot be guaranteed in all studies (e.g. RCTs of new or existing drug treatments), participation in a cross-sectional study is unlikely to cause harm, perhaps other than by breach of confidentiality.

Beneficence relates to the study having the intention of doing 'good' thus promoting well-being. The governance reviews for this doctoral research involved assessment of risk and benefit. While there was unlikely benefit to the individual participant, the results had the potential to impact patient care and professional practice in the longer term.

Justice in research relates to all participants being treated fairly. In these studies, all participants were subjected to exactly the same processes, namely completion of an electronic questionnaire.

2.7.2 Research Governance

Research governance describes the system of administration and supervision through which research is managed, subjects and staff are protected, and accountability is assured (Shaw et al., 2005). It relates to the regulations, principles and standards of good practice that ensure high quality research.

All research conducted in Robert Gordon University must be conducted within the framework of the university research governance policy (Robert Gordon University, 2014). According to this policy, research governance 'defines and communicates clear quality standards concerning ethics (encompassing

approval, consent, data protection and consumer involvement); scientific quality; the performance of research; safety and finance'.

This encompasses defining and communicating clear quality standards concerning

- ethics (encompassing approval, consent, data protection and consumer involvement)
- scientific quality
- the performance of research
- safety
- finance.

There are mechanisms to achieve these standards and associated monitoring of quality and assessing adherence to these standards. By adhering to this policy, researchers will improve research quality, protect research subjects and researchers and achieve public confidence in evidence.

These standards were adhered to throughout this doctoral research by

- ensuring that all governance approvals (ethics and research and development) were in place prior to any data collection
- detailed research protocols were developed and approved for each phase
- the doctoral student was trained in all processes and supervised by an experienced team
- detailed, auditable records were maintained
- participant consent was obtained (by virtue of completing questionnaires)
- data were anonymised and protected throughout
- participant and researcher safety were paramount
- the research was costed prior to commencement and finance continuously monitored.

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2.8 SUMMARY

This chapter has presented many underlying methodological concepts which were applied in all phases of the research. The specific research methods are described in detail in Chapters 3, 4 and 5.

CHAPTER 3 - Clinicians' views and experiences of direct-acting oral anticoagulants in the management of non-valvular atrial fibrillation: a systematic review

3.1 INTRODUCTION

This chapter provides the aim, method, results and discussion of a PROSPERO (International Prospective Register of Systematic Reviews) registered systematic review of clinicians' views and experiences of the use of DOACs for the management of non-valvular AF.

As highlighted in Chapter 1, while there are very many systematic reviews reporting efficacy, safety and cost effectiveness of DOACs in general and specifically relating to the management of non-valvular AF, none have focused on clinician's perspectives. A preliminary search of the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports, the Cochrane Library the Centre for Reviews and Dissemination and PROSPERO revealed that there was no registered systematic review protocol in this area. Furthermore, a search of Medline indicated a number of published studies hence the potential for conducting a systematic review.

3.2 AIM OF THE REVIEW

The aim of the systematic review was to critically appraise, synthesise and present the available evidence of clinicians' views and experiences of the use of DOACs for the management of non-valvular AF.

3.2.1 Review questions

In relation to DOACs for the management of non-valvular AF

1. What are clinicians' views of the use of DOACs?
2. What are the influences on clinician's use of DOACs?
3. What are clinician's experiences, both positive and negative?

3.3 METHOD

A systematic review protocol was created according to the standards of PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols), a checklist of 17 numbered items (26 sub-items) that should be described, at minimum, in protocols of systematic reviews. PRISMA-P was developed and published in 2015 by an international collaboration with expertise in systematic review methodology, protocol registry development, and reporting guideline development (Moher et al., 2015). PRIMSA-P items are categorised into three main sections:

- administrative information (e.g. title, registration, authors)
- introduction (e.g. rationale, aim), and
- methods (e.g. eligibility criteria, information sources, search strategy) (Moher et al, 2015).

The systematic review protocol was registered in PROSPERO in February 2016 (Stewart et al., 2016). PROSPERO, which is based at the Centre for Reviews and Dissemination, University of York, UK, is an international database of registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome (Stewart et al., 2016). For registration in PROSPERO, the protocol is submitted with key information about the design and conduct of the review, in line with the PRISMA-P statements.

3.3.1 Inclusion criteria

The inclusion criteria for the review were described in terms of the PICO acronym as follows.

<u>Population</u>

The review included clinicians, most likely doctors, nurses and pharmacists, as these were the key professions involved in prescribing, dispensing and administration of DOACs.

Interventions/Phenomenon of interest

The review focused on studies involving DOACs as a drug class or any of the individual DOACs (i.e. dabigatran, rivaroxaban, apixaban, edoxaban).

Comparators

There were no comparators for this review as there was no intention to compare the views and experiences across different groups of clinicians.

Outcomes

The review included studies which reported health professionals' views, experiences and behaviours in relation to the prescribing and use of DOACs.

Types of studies

The review included primary research studies which employed qualitative, quantitative or mixed methodologies. Views and experiences may be researched using qualitative methodologies such as narrative, phenomenology, grounded theory, case studies and discourse analysis (Creswell 2014). In terms of quantitative methodologies, cross sectional sectional surveys may use closed questions, such as Likert type scales, to quantify views and experiences (Barua 2013).

3.3.2 Search strategy

A three-step search strategy was conducted as follows:

1. An initial scoping search of Medline and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) was undertaken, using search terms of ['doctor*' OR 'nurse*' OR 'pharmacist*'] AND ['novel oral anticoagulant*' OR 'dabigatran' OR 'rivaroxaban' OR 'apixaban' OR 'edoxaban'] AND ['view*' OR 'experience*']

2. Using the keywords and main title and abstract words/phrases identified, searches of all databases were undertaken. The search string was applied with results and exceptions recorded.

3. The reference lists of all identified papers were reviewed to identify additional studies.

The following bibliographic databases were used for this search: Medline, CINAHL, International pharmaceutical abstracts (IPA), Psycharticles, Cochrane Database of Systematic Reviews. Details of each database are given in Table 3.1.

Table 3.1 Databases selected for the systematic review.

Database	**Characteristic**
Medline	Medical Literature Analysis and Retrieval System Online, or MEDLARS Online is a bibliographic database of life sciences and biomedical information. It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care. It contains over 14 million records (US National Library Of Medicine).
CINAHL	Cumulative Index to Nursing and Allied Health Literature (CINAHL) is a database of nursing, allied health articles, includes pharmacy, biomedicine and 17 allied health disciplines. Full articles and abstracts can be found. CINAHL also can provides books, conference abstracts, clinical trials results, nursing dissertations (EBSCO Health)
IPA	Database mostly includes articles in pharmacy (pharmacy practice) and other health related disciplines). Pharmacy and cosmetic journals are included. Masters and doctoral thesis of School of Pharmacy students can be searched. The American Society of Health-System Pharmacists (ASHP) developed the IPA, with the first abstract published in 1964 (Fishman et al., 1996).
Embase	A database for health care disciplines. It is possible to find rare case reports and find articles, which have not found by using Medline (Woods *et al*., 1998).
Scopus	A database of abstracts and citations of peer-reviewed documents: journals, books, conference abstracts in different disciplines, such as medicine, science, social sciences, etc.
Psycarticles	Psycatricles is the American Psychological Association (APA) database which provides full text articles from 50 journals, some of which are official American Psychological Association, Canadian Psychological Association journals and APA specialty journals as well as book chapters (Piotrowski et al., 2003).
Cochrane Database of Systematic Reviews	Database of published systematic reviews in healthcare disciplines. Cochrane reviews are peer-reviewed, with each assessed by a Cochrane Review Group (Cochrane Library).
Joanna Briggs Institute (JBI) Database of Systematic Reviews	The online journal for published systematic reviews and systematic review protocols which have adhered to JBI requirements. Both qualitative and quantitative reviews can be published (Joanna Briggs Institute, 2011)
Database of Abstracts of Reviews of Effectiveness (DARE)	The DARE database of the Centre for Reviews and Dissemination, provides summaries of quality assessed systematic reviews (Petticrew et al., 1999).

The final search terms (title, abstract, text, keyword) were: (clinician* OR doctor* OR surgeon* OR general practitioner* OR family doctor* OR physician* OR pharmacist* OR nurse* OR health professional* OR healthcare Professional* OR health carer* OR practitioner* OR prescriber* OR healthcare provider*) AND (new oral anticoagulant* OR novel oral anticoagulant* OR direct oral anticoagulant* OR non-vitamin K oral anticoagulant* OR dabigatran OR rivaroxaban* OR apixaban OR edoxaban) AND (experience* OR use* OR utility* OR evaluation* OR audit* OR behav* OR knowledge OR satisfaction OR skill* OR practice* OR practise* OR belief* OR attitude* OR view* OR opinion* OR perspective*). The reference lists of all identified papers were reviewed to identify additional studies. A random sample of 10% of titles, abstracts and full papers were screened by an independent researcher to confirm reliability of the screening process.

The search comprised peer reviewed studies published in English from January 2006 (launch of DOACs) to the search date of July 2017, to include studies conducted post launch of DOACs. Abstracts, conference proceedings and letters etc. were excluded.

3.3.3 Quality assessment

All studies identified during database searching were assessed for relevance by two independent reviewers in terms of the review protocol (aim, questions, inclusion criteria) based on information contained within the study title, abstract and full paper. A third reviewer was consulted if consensus could not be reached.

For quality assessment of the quantitative studies, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies was applied (see Appendix 3.1). STROBE is an international, collaboration of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and reporting of observational studies. The aim of STROBE is to improve the reporting of observational studies within the peer reviewed literature. STROBE checklists were developed in 2004 and contain 22 items with focus

on the study title, abstract, introduction, methods, results, and discussion sections of articles (von Elm et al., 2014).

STROBE is a reporting checklist which is being used increasingly by journals as part of the peer review process. For quality assessment in this systematic review, the STROBE checklist was adapted to focus on those 15 items most relevant to potential study bias, as follows:

1. Study aim/objectives
2. Methods
3. Setting
4. Participants
5. Variables
6. Data sources/measurement
7. Bias
8. Study size
9. Quantitative variables
10. Statistical methods
11. Results
12. Participants
13. Descriptive data
14. Outcome data
15. Main results

Each study was quality assessed independently by two reviewers, classifying each of the 13 items as 'yes' (present and satisfactory), 'no' (present but unsatisfactory) or 'partly', along with detailed justification. A third reviewer was used in instances of non-agreement.

For quality assessment of any qualitative studies, the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist was applied (Appendix 3.2). COREQ was developed and published in 2007, following a comprehensive search of many different databases (e.g. Medline, Cochrane, CINHAL) to identify reporting checklists for qualitative studies. Twenty-two different checklists were identified and grouped into three domains of 32

items. The domains are: research team and reflexivity; study design; and data analysis and reporting. (Tong et al., 2007).

As with STROBE, COREQ is a reporting checklist hence for the purposes of this review, an adapted 19-item checklist with focus on aspects of bias, was used as follows:

1. Study aim/objectives
2. Interviewer /facilitator
3. Interviewer characteristics
4. Methodological orientation and Theory
5. Sampling
6. Method of approach
7. Sample size
8. Non-participation
9. Setting of data collection
10. Description of sample
11. Interview guide
12. Audio/visual recording
13. Fields notes
14. Data saturation
15. Number of data coders
16. Description of the coding tree
17. Deviation of themes
18. Quotations presented
19. Data and findings consistent

Each study was quality assessed independently by two reviewers, classifying each of the 18 items as 'yes' (present and satisfactory), 'no' (present but unsatisfactory) or 'partly', along with detailed justification. A third reviewer was used in instances of non-agreement.

3.3.4 Data extraction

Quantitative and qualitative data were extracted independently by two reviewers from papers included in the review using a standardised data extraction tool (Appendix 3.3). The data extracted included specific details of significance to the objective and specific review questions. Data extracted were:

- Authors and year of publication
- Aim
- Country/setting
- Design
- Participants
- Theory applied
- Number of participants (response rate)
- Key findings

3.3.5 Data synthesis

The approach to data synthesis in a systematic review depends upon the nature of the data (quantitative of qualitative), the number of studies, the outcome measures and the quality of the data.

In systematic review of quantitative studies and data, the ideal approach is a meta-analysis. This is a statistical technique with the results from each study pooled thereby increasing power compared to the single studies. For meta-analysis to be valid, study populations and outcome measures need to be homogeneous. This is tested in two ways; the methodological information provided in the studies and specific computations during analysis. The results of meta-analysis are given graphically in a forest plot and by odds ratios (Akobeng, 2005). In this systematic review, quantitative studies were extremely heterogeneous in terms of study aims, populations, data collection approaches and outcome measures hence a meta-analysis approach was rejected and the results presented in simple narrative form.

The most common approach to pooling of qualitative data and synthesis in conducting systematic reviews is meta-aggregative synthesis (Munn et al., 2014). This involves aggregation of the findings (e.g. themes) provided by the authors of the specific studies into one overarching framework. It does not involve extracting and synthesising data from the individual study datasets (Hannes et al., 2012). While it had been intended that qualitative research would be pooled with aggregation or synthesis of findings to generate a set of statements that represented that aggregation, only one qualitative study was identified.

3.4 RESULTS

3.4.1 Searching

The PRISMA flowchart is given in Figure 3.1 Removal of duplicates and screening of the titles reduced the number of papers from 979 to 394. Screening of the abstracts reduced this number to 195 and a further 186 removed following screening of the full papers. Reasons for exclusion of full papers included: review articles (systematic and narrative, n=41); editorials and opinion papers (n=36); no data relating to DOACs (n=36); clinician reports of patient registries or databases (n=38); and primary research data on patients' views and experiences only (n=35). Nine papers were retained for quality assessment plus one further paper identified from screening the reference lists of the nine papers. Of the ten papers, nine were quantitative (cross-sectional survey based methodology) and one qualitative (semi-structured interview method, no methodology stated).

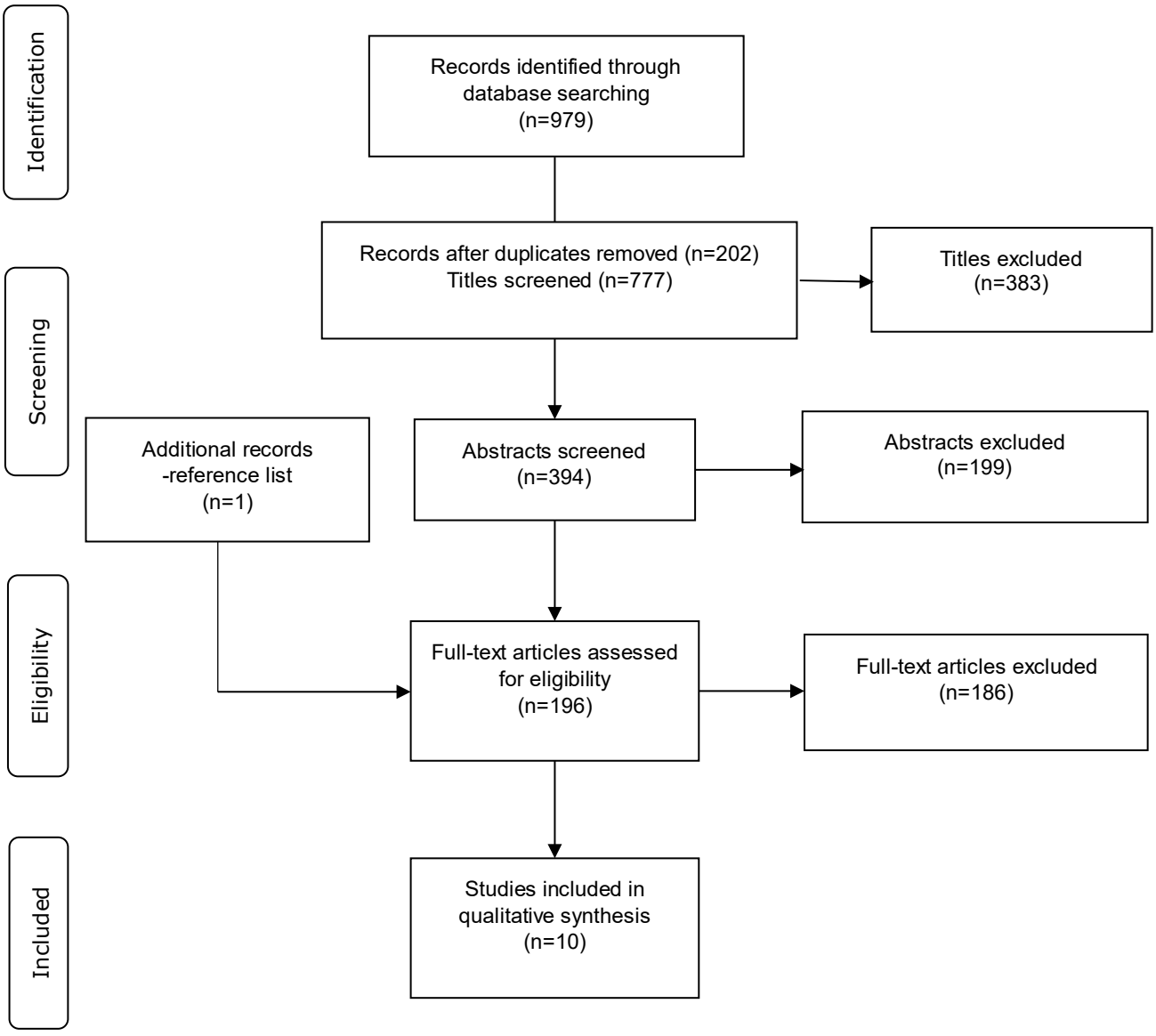

Figure 3.1. PRISMA Chart (Preferred Reporting Items of Systematic reviews and Meta-Analyses) for systematic review of DOACs

3.4.2 Quality assessment

The quality assessments are given in Tables 3.2 and 3.3 for the quantitative studies and the one qualitative study respectively.

For the quantitative studies, key areas of strength were the clarity of statement of study aims and description of participants, settings and outcome measures. Fewer studies (Faraoni et al., 2013, Sauter et al., 2016) provided detailed information on sampling strategies, and justification of sample size was only provided in two studies (Huang et al., 2013, Faraoni et al., 2014). There was also a lack of detailed provided on the approaches to recruitment. Similarly, very few (Huang et al., 2013, Sauter et al., 2016, Faraoni et al., 2013) described any approach to questionnaire development, item selection and pre-testing. Notably theory was not used to support development of questionnaire domains and items in any of the studies reviewed.

While the one qualitative study involved semi-structured interviews, the study methodology (e.g. phenomenology, grounded theory) was not stated. Key areas of strength were aspects of research trustworthiness (e.g. double coding of interview transcripts and representing the participants' voices through illustrative quotes). Areas of weakness were: the lack of consideration of the researcher perspective, no theory to underpin the development of the interview schedule or coding framework, and the limited sample size of seven which reduced the potential of obtaining data saturation.

All studies were, however, considered to be of sufficient quality to be included within the data extraction phase.

Table 3.2 Quality assessment of the nine cross-sectional studies using adapted STROBE criteria

STROBE criteria		Huang et al., 2013	Lip et al., 2013	Wutzler et al., 2014	Faraoni, et al., 2014	Potpara et al., 2014	Larsen et al., 2015	Andrade et al., 2016	Olaiya et al., 2016	Sauter et al., 2016
Aim	State specific aim/ objectives	Yes	Partly	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods										
Setting	Describe the setting, locations, and relevant dates	Yes	Partly	Yes	Yes	Partly	Partly	Partly	Partly	Partly
Participants	Give the eligibility criteria, and the sources and methods of participant selection	Partly	Partly	Partly	Partly	No	No	Partly	Partly	Partly
Variables	Clearly define all outcomes	Partly	Partly	Partly	Partly	Partly	Partly	Yes	Yes	Partly
Data sources	For each variable of interest, give sources of data and details of methods of assessment	Yes	Partly	Partly	Partly	Partly	Partly	Partly	Yes	Partly
Bias	Describe any efforts to address potential sources of bias	Partly	No	No	No	No	No	Partly	Partly	No
Study size	Explain how the study size was arrived at	Partly	Partly	No	Yes	Partly	Partly	Partly	Partly	No
Quantitative variables	Explain how quantitative variables were	Yes	Partly	No	Yes	Partly	Partly	Yes	Yes	Partly

	handled in the analyses									
Statistical methods	(*a*) Describe all statistical methods	Partly	Partly	No	Yes	Partly	Partly	Partly	Partly	No
	(*b*) Describe any methods used to examine subgroups and interactions	Partly	N/A	No	Yes	N/A	N/A	No	Partly	N/A
Participants	(a) Report numbers of individuals at each stage of study	Yes	N/A	Partly	Yes	Yes	Yes	Partly	Partly	Yes
	(b) Give reasons for non-participation at each stage	N/A	No	No	Partly	No	No	N/A	N/A	N/A
Descriptive data	(a) Give characteristics of study participants	Yes	No	Partly	Yes	Partly	Partly	Partly	Partly	Yes
	(b) Indicate number of participants with missing data for each variable of interest	N/A	No	No	Partly	No	No	No	Yes	Yes
Outcome data	Report numbers of outcome events or summary measures	Yes	Yes	Partly	Yes	Partly	Partly	Yes	Yes	Yes

Table 3.3 Quality assessment of the qualitative study using adapted COREQ criteria

Criteria		Kirley et al., 2016
Aim	State specific aim/objectives	Yes
Personal Characteristics	(a) Interviewer/facilitator. Which author/s conducted the interview or focus group?	Yes
	(b) Interviewer characteristics. What characteristics were reported about the interviewer/facilitator?	No
Methodological orientation and Theory	What methodological orientation was stated to underpin the study?	No
Sampling	How were participants selected?	Yes
Method of approach	How were participants approached?	No
Sample size	How many participants were in the study?	Yes
Non-participation	How many people refused to participate or dropped out? Reasons?	No
Setting of data collection	Where were the data collected?	No
Description of sample	What are the important characteristics of the sample?	Partly
Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Partial
Audio/visual recording	Did the research use audio or visual recording to collect the data?	Yes
Field notes	Were field notes made during and/or after the interview or focus group?	No
Data saturation	Was data saturation discussed?	Partly
Number of data coders	How many data coders coded the data?	Yes
Description of the coding tree	Did authors provide a description of the coding tree?	No
Derivation of themes	Were themes identified in advance or derived from the data?	Yes
Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified?	Yes
Data and findings consistent	Was there consistency between the data presented and the findings?	Yes

3.4.3 Data extraction

Data extraction of these ten studies is given in Tables 3.4 and 3.5.

All nine studies were of a cross-sectional survey methodology conducted largely in Europe (n=7) and North America (n=3), with one study reporting data from Europe and North America. DOACs as a group were the focus of eight studies with one specifically related to dabigatran. Populations studied were described as: GPs (n=4), centres of research networks (n=3), cardiologists (n=3), general internists (n=2), hospital doctors (n=1), members of associations (n=1) and non-medical prescribers (n=1), with many of the studies reporting data from more than one group. None of the studies referred to any theories (e.g. psychological, organisational) considered as part of data collection tool development. The number of respondents ranged from 38 to 450 with response rates of 9% to 35.9%. Only three studies quoted a response rate.

The one qualitative study reported data from seven physicians in the USA. There was no description of any theory used in the stages of data generation, analysis or interpretation.

Table 3.4 Data extraction of the nine quantitative studies

Authors /years	Aim(s)	Country/ setting (if stated)	Design	Participants	Theory applied	Number of participants (response rate)	Key findings
Huang et al., 2013	To identify factors that influence doctors' decisions to prescribe dabigatran. To compare levels of comfort with prescribing dabigatran between healthcare professionals.	USA (California)	Cross-sectional survey	Cardiologists and general internists	No	65/181 (35.9%) responses; 13 cardiologists, 51 general internists (one not stated).	In warfarin naive patients, the main influences were: affordability for patient; renal function; and CHADS2 score. For those prescribed warfarin, were: unstable INR; affordability for patient; missed appointments. Cardiologists preferred to prescribe dabigatran more often compared to general internists who were less comfortable prescribing cardiologists.
Lip et al., 2013	To assess European clinical practice in relation to the use of oral anticoagulants for stroke prevention in AF with particular focus on DOACs as a management strategy.	European countries	Cross-sectional survey	Participating centres of the Electro-physiology Research Network	No	No overall response rate given. Responses from 45 centres, 66.7% were university hospitals, 22.2% private hospitals, 11.1% others.	There were clear practice differences evident, and also the need for greater adherence to the guidelines, especially since guideline adherent management results in better outcomes. Reassuring information on current practice in Europe for the use of DOACs for stroke prevention in AF was evident, although VKA use remained dominant in some clinical scenarios.

Faraoni et al., 2014	To assess: physicians' level of knowledge about perioperative management of patients treated with NOACs; current practices; and perspectives needed to improve the management of patients treated with NOACs.	Europe and USA	Cross–sectional survey	All members of Society of Cardiovascular Anesthesi-ologists and European Association of Cardiothoracic Anaesthesi-ologists	No	450/5262 (9%) but only 117 completed all sections of the questionnaire.	29% stated no guidelines on DOAC reversal used in their institution while 28% used local guidelines, 35% national and 14% international guidelines. 46% stated that no agreement had been reached in their institution on the use of guidelines and 18% believed that no guidelines had been established due to the lack evidence. 97% thought guidelines were needed to improve management generally and particularly for monitoring (69%) and reversal (73%).
Potpara et al.,2014	To assess the European practice of treatment of patients with non-valvular AF presenting with an Acute Coronary Syndrome.	European countries	Cross-sectional survey	European Heart Rhythm Association electrophysiol ogy research network participating centres	No	No overall response rate given. Responses from 47 centres, 85.4% university hospitals. Cardiac surgery available in 82.9%.	Key findings were two important areas of uncertainty regarding: the optimal composition and duration of antithrombotic therapy with multiple drugs; and the optimal regimen(s) of DOACs.
Wutzler et al., 2014	To access physicians' acceptance and appreciation of the DOACs in a real-life community setting.	Germany	Cross-sectional survey	Cardiologists and general practitioners	No	227 response from physicians.	45.4% considered DOACs and VKAs to be equally safe and 82.8% to be equally effective. Bleeding complications following the use of DOACs were observed by 39.6%.

Larsen et al., 2015	To assess the clinical practice in relation to the use of OAC therapy for patients with AF in Europe, in different clinical situations.	Multiple countries in Europe. University hospitals, private hospitals, other sites	Cross-sectional survey	Participating centres of the Electro-physiology Research Network	No	No overall response rate given. Responses from 38 centres, 65.8% were university hospitals, 21.0% private hospitals, 13.2% others.	33.3% stated that DOACs were their preferred treatments. 48.5% considered DOACs to be equally effective compared to VKAs. 12% preferred using DOACs for dual antiplatelet therapy in AF patients undergoing percutaneous coronary intervention.
Andrade et al., 2016	To determine the attitudes, values, preferences, and experience of physicians prescribing OAC therapy for non-valvular AF.	Canada	Cross-sectional survey	GPs, cardiologists, internal medicine specialists	No	178 physicians were randomly selected and responded.	Preferences regarding OAC therapy largely focused on characteristics related to safety and efficacy. Physicians stated preferred anticoagulant was apixaban (61%), however, 49% of physicians spontaneously stated rivaroxaban as their preferred agent (vs 25% apixaban).
Olaiya et al., 2016	To determine healthcare professionals' level of awareness of the DOACs and to examine their understanding of the effects of DOACs on a hypothetical patient.	Scotland	Cross-sectional survey	Hospital doctors, GPs, non-medical independent prescribers (nurses and pharmacists)	No	143 practising clinicians and non-medical prescribers responded to the questionnaire.	There were significant differences in awareness of DOACs. 88%, 80% and 50%, respectively, recognised rivaroxaban, dabigatran, and apixaban to be DOACs. When provided with a routine clinical situation, only 13.5%, 17.5% and 16.8% respondents respectively recognised that the hypothetical patient was anticoagulated, and only 55–58% recognised that it was unsafe to proceed with an invasive procedure.

Sauter *et al.*, 2016	To investigate physicians' preferences of DOACs, prevalence and choice of DOACs, clinical follow up including follow up blood testing and bleeding complications.	Switzerland	Cross-sectional survey	GPs attending a GP emergency medicine congress	No	53 GPs participated in our survey (response rate 40.8%).	Participants treated 32.7% (±19) of their patients requiring oral anticoagulation with DOACs. New patients who had started oral anticoagulation received DOACs from 92.5% but most would not switch patients from warfarin to DOACs. In the preceding 2 years, GPs had seen 1.9 (±2.87) bleeding complications in patients with DOACs.

Table 3.5 Data extraction of the one qualitative study

Authors/years	Aim	Country	Design	Participants	Theory applied	Key findings
Kirley et al. 2016	A qualitative study of physicians' decision-making processes regarding anticoagulation management in AF, with a specific focus on the role of NOACs.	USA	Semi-structured interviews	A total of seven physicians, three family physicians, one internist, two cardiologists, one cardiologist sub-specialising in electro-physiology.	No	Four themes emerged: the likelihood of prescribing DOACs depended upon their willingness to try new medications and experience; they typically balanced the benefits and risks of anticoagulation in AF patient; patient convenience and preferences, as well as physician convenience, were important; and concerns regarding out-of-pocket cost of DOACs deterred many from prescribing.

3.4.4 Data synthesis

The heterogeneity of the quantitative studies in terms of study aims and specific domains and items within the questionnaires limited the approach to data synthesis. Given that there was only one qualitative study, meta-synthesis of the qualitative findings was not possible. Table 3.6 gives the synthesis of the findings from the nine quantitative studies, highlighting the lack of homogeneity in the specific elements studied in each. While only one quantitative study reported factors influencing DOAC use (Huang et al., 2013), this was also the aim of the one qualitative study (Kirley at al., 2016). The quantitative study highlighted the top three factors determining eligibility for dabigatran in warfarin naïve patients as: cost to the patient (reported by 25% of respondents); non-compromised renal function (21%); and CHADS2 score (18%). For patients on warfarin, these were: having an unstable INR (37%); patient affordability (9%); and missed appointments (17%) (Huang et al., 2013). Some of these also emerged in the qualitative study in terms of risks to the patient, patient convenience and cost, with additional themes of the clinician willingness to try new agents and their experience of these agents (Kirley et al., 2016).

Six studies reported data on clinician preference for DOACs compared to warfarin (Huang et al., 2013, Lip et al., 2013, Wutzler et al., 2014, Larsen et al., 2015, Andrade et al., 2016, Sauter et al., 2016). In a study of 65 cardiologists and general internists, cardiologists were significantly more comfortable than general internists in prescribing DOACs over warfarin, as were those who had prescribed DOACs in more than ten patients (Wutzler et al., 2014). While DOACs were not the main focus of a study of 45 research network centres, there were differences across centres in the use of DOACs first line (Lip et al., 2013). Data from a further study of 38 of these centres identified that 33.3% of respondents preferred DOACs to warfarin, with 48.5% considering them to be equally safe (Larsen et al., 2015). Similar safety data were reported in a study of 227 cardiologists and GPs, with over 80% considering DOACs as effective as warfarin (Wutzler et al., 2014). Rivaroxaban was selected as first line oral anticoagulant by 178 physicians, with only 12% opting for warfarin (Andrade et al., 2016).

DOACs were also selected first line by 70% of 53 GPs attending a medical congress (Sauter et al., 2016). Key reasons reported in these studies for DOAC preference were the perceptions of evidence of effectiveness equivalent or superior to warfarin and superior safety. While DOACs were largely considered more appropriate in warfarin naïve patients, there was less support for switching patients established on warfarin.

DOAC associated bleeding was a key issue, being observed in patients of 40% (n=90) of cardiologists and GPs (Wutzler et al., 2014). In the preceding two years, 53 GPs had seen 1.9 ± 2.87 (range 0–14) bleeding complications in patients prescribed DOACs, of which 0.5 ± 0.95 (range 0–5) were referred to hospital (Sauter et al., 2016). Two studies reported the need for guidelines to support the use of DOACs in the management of AF, with respondents welcoming specific guidance on the management of DOAC induced bleeding (Lip et al., 2013, Wutzler et al., 2014).

Table 3.6 Synthesis of the key findings from the nine quantitative studies

	Huang et al., 2013	Lip et al., 2013	Wutzler et al., 2014	Faraoni, et al., 2014	Potpara et al., 2014	Larsen et al., 2015	Andrade et al., 2016	Olaiya et al., 2016	Sauter et al., 2016
Factors influencing DOAC use	Cost, renal function, CHADS2 score, unstable INR, patient attendance	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Easier dosing, fewer blood tests, follow-up and bleeding events
Preference over warfarin	Cardiologists preferred more than others Cardiologists more confident	Clear practice differences, warfarin remained dominant	Majority considered equally effective, half equally safe	Not reported	Not reported	Third preferred DOACs, half considered equally safe	Over half selected apixiban	Not reported	New patients started DOACs, less likely to change stabilised on warfarin
Comments on guidelines	Not reported	Need for greater adherence to AF guidelines in general	Not reported	Need for guidelines on use of DOACs and reversal specifically	Not reported	Not reported	Not reported	Not reported	Not reported
Issues in use of DOACs	Not reported	Not reported	Almost 40% had observed bleeding complication	Not reported	Need for evidence on optimal regimens	Not reported	Not reported	Not reported	Poor clinician recognition of specific DOACs as anti-coagulants

3.5 DISCUSSION

3.5.1 Statement of key findings

This systematic review has highlighted that relatively few studies have reported clinician perspectives; nine cross-sectional surveys and one qualitative study were included in the review, with marked heterogeneity in the specific outcomes reported. In those studies reporting preference, DOACs were first choice over warfarin in naïve patients based on perceptions of evidence of effectiveness equivalent or superior to warfarin and superior safety. Other advantageous factors were in those with an unstable INR and likely to miss appointments. There were, however, concerns relating to their experiences of observed bleeding rates.

3.5.2 Strengths and weaknesses

One key strength of this systematic review was conducted according to best practice and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) standards (Moher et al., 2009). However, the generalisability or transferability of review findings to other countries or cultures may be limited given that all were conducted in either Europe or the USA. None of the quantitative studies had response rates over 40%, increasing the likelihood of response bias thus threatening internal validity. Furthermore, to date, only one qualitative study and no mixed-methods studies have been reported. As noted earlier, the approach to synthesis was limited by the nature of the data.

3.5.3 Interpretation

This is the first systematic review which has focused on clinicians' perspectives of DOACs which is rather surprising given the vast number of systematic reviews and meta-analyses of effectiveness and safety. While each of the studies was generally of good quality, reporting could be enhanced by referring to design specific checklists which are now hosted on the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) website. In particular, none of the studies reporting influences on prescribing options were grounded in theories of behaviour. Frameworks such as the

Theoretical Domains Framework, which is derived from 33 psychological theories and 128 theoretical constructs, which are organised into 14 overarching domains, would provide a more comprehensive approach thus facilitating development of behaviour change interventions if required (Michie et al., 2005).

Despite the limited number of studies, review findings have highlighted a number of issues which merit further consideration given current prescribing levels and likely future increases (Loo et al., 2017). Positive factors influencing selection of a DOAC over warfarin, such as patient convenience, reduced risk and stability of INR reflect DOAC clinical pharmacological properties relating to mechanism of action eliminating the need for INR testing (Gomez-Outes et al., 2015). There appeared to be awareness of the evidence base of DOAC effectiveness and safety, although also a stated need for practice guidelines, particularly to support management of over-anticoagulation and anticoagulant reversal. Given that idarucizumab is now licensed for use and is indicated to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery (Pollack et al., 2015), it is likely that these issues will resolve in the near future.

The findings of our systematic review provide some evidence of the need to support decision-making and management of those patients already established on warfarin and how to transfer safely to DOACs if appropriate. The recently updated 2018 European Heart Rhythm Association Practical Guide on the use of DOACs in non-valvular AF provides much needed protocols for tapering, stopping and switching from DOACs to warfarin and vice versa (Steffel et al., 2018).

Views of patients should also be central to decision-making around choice of oral anticoagulants. A systematic review of patients' values and preferences for DOACs versus warfarin generated heterogeneous findings, highlighting the need for focusing on patients' individual values and preferences (Loewen et al., 2017). A further systematic review reported that stroke risk reduction and a moderate increase in the risk of bleeding were the most important attributes for patients when deciding between DOACs and warfarin (Wilke et al., 2017). The need to focus on the patient perspective is increasingly

highlighted within local, national and international guidelines (NICE 2014, Camm et al., 2010, January et al., 2014, Steffel et al., 2018).

Forty percent of respondents in one study included in this systematic review reported observed bleeding complications in those prescribed DOACs (Wutzler et al., 2014). While the incidence and severity of bleeding were not reported, several systematic reviews have concluded that the risk of major bleeding is generally equivalent to or less than that with warfarin, there is a need for further high quality studies (Burr et al., 2017, Deitelzweig et al., 2017, Miller et al., 2017). There is therefore a need for intensive patient monitoring and reporting of events to national and international pharmacovigilance schemes.

Given the limited evidence base, there is a need for more robust and rigorous research which systematically explores experiences, views and behaviours of clinicians, with the overall aim of optimising appropriate use of DOACs. Mixed quantitative-qualitative approaches are recommended to allow, specifically an explanatory, sequential mixed methods design characterised by the collection and analysis of quantitative data followed by generation and analysis of qualitative data. The qualitative findings will generate in-depth and rich data to assist in exploring, explaining and interpreting the statistically based results of the quantitative element.

3.5.4 Conclusion

This systematic review has identified a limited evidence base of clinicians' views and experiences and a need for further research. While DOACs were first choice over warfarin in naïve patients based and perceptions being advantageous in those with an unstable INR and likely to miss appointments, there is a need to support prescribing and specifically the management of over-anticoagulation.

3.5.5 Further research phases

This systematic review has identified the lack of robust and rigorous research focusing on the perspectives of clinicians. Furthermore, there has been a notable absence of the use of theory in the development of data collection and generation tools, and the analysis of findings. The primary research of

this doctoral research seeks to fill these gaps, as reported in the following chapters.

CHAPTER 4 A cross-sectional survey of prescribers in NHS Highland

4.1 INTRODUCTION

As noted in the previous chapter, there is a lack of high quality research on the views and experiences of clinicians prescribing DOACs in the management of non-valvular AF. The systematic review reported in Chapter 3 provided a synthesis of the findings from only ten studies, nine cross-sectional surveys and one qualitative study. This chapter presents the method, results and discussion of a cross-sectional survey of prescribers views, experiences and behaviours relating to prescribing DOACs for the management of non-valvular AF.

4.2 RESEARCH AIM

The aim of this phase of research was to determine prescribers' behaviours, views and experiences and relating to prescribing DOACs for the management of non-valvular AF.

4.2.1 Research questions

In relation to prescribers and DOACs, the research questions were:

1. how are DOACs initiated, prescribed and monitored?
2. which behavioural determinants are potentially influential in prescribing DOACs?
3. what are the perceived benefits and limitations of prescribing DOACs?
4. what are the positive and negative experiences of prescribing DOACs?
5. how could the appropriate use of DOACs in primary care be extended further?

4.3 RESEARCH METHOD

4.3.1 Research design

A positivist, quantitative approach was employed with a cross-sectional survey methodology, as described in Chapter 2.

4.3.2 Research Governance

Prior to conducting any fieldwork, approval was obtained from:

- the ethical review panel of the School of Pharmacy and Life Sciences, Robert Gordon University (Appendix 4.1)
- NHS Highland Research & Development committee (Appendix 4.2)

There was no requirement to obtain NHS ethics approval.

4.3.3 Setting

The research was conducted across primary and secondary care in NHS Highland, as described in Chapter 1.

4.3.4 Inclusion and exclusion criteria

All prescribers practising within NHS Highland were invited to participate. This included all medical prescribers of all grades and non-medical prescribers (nurse independent prescribers and pharmacist supplementary and independent prescribers). Full-time, part-time and sessional prescribers were included. There were no exclusion criteria.

4.3.5 Sampling

The entire population of prescribers practising within NHS Highland was included, without sampling. A sample size of 377 was required for a precision of 5% with 95% confidence intervals (Qualtrics, 2019). There were around 270 general practitioners (GPs) registered within NHS Highland at the time of the study, with an estimated equivalent numbers of hospital based prescribers/non-medical prescribers. A response rate of around 50% would therefore generate sufficient data.

4.3.6 Method of data collection

Given that all prescribers within NHS Highland could be contacted via email, an online approach to data collection was adopted. Table 4.1 gives a comparison of the advantages and disadvantages of online versus postal distribution of questionnaires.

Table 4.1. Comparison of online versus postal distribution of questionnaires (McKenzie-McHarg et al., 2005; Sahlvist et al., 2011)

Mode of questionnaire distribution	Advantages	Disadvantages
Online	• lower cost • less time from creation to sending • may increase response rate • ease of sending reminders • no need for manual data entry	• may be Internet connection issues • need access to email addresses • recruitment bias with those without email access • less of an evidence base to maximising response rates
Postal	• good evidence base around maximising response rates • easier to personalise	• higher cost • time consuming process from creation to sending • requires manual data entry

4.3.7 Questionnaire development

A draft questionnaire were developed according to the specific research questions of views, experiences and behaviours. Notably, the systematic review presented in Chapter 3 identified very little literature on which the questionnaire could be based. As described in Chapter 2, TDF was selected as the most relevant theoretical framework on which to base questionnaire items relating to behavioural determinants. The questionnaire was presented in four distinct sections and comprised open, closed and Likert type items.

The first section gathered data relating to respondents' personal and practice demographics and characteristics. One question was included to characterise respondents using Rogers' 'Diffusion of Innovations' typology of innovators, early adopters, early majority, late majority and laggards, based on receptivity to change (Rogers 2010).

The second section attempted to gauge current practice in terms of initiating, continuing, altering and deprescribing of warfarin and DOACs. While the options of 'weekly', 'monthly', 'annually' and 'never' may have been difficult for respondents to be completely certain, and hence the data potentially lack

validity, it did allow identification of those who never prescribed (or would never prescribe) any oral anticoagulants. Items relating to specific knowledge of the NHS Highland guidelines (NHS Highland, 2017) were also included.

The third section was the largest of the questionnaire and focused on behavioural determinants (i.e. influences) of prescribing. As described in Chapter 2, TDF was used as a basis for the development of these items. The Determinants of Implementation Behavior Questionnaire (Huijg et al., 2014) was used as a basis for the development of individual items, adapted as relevant to prescribing of DOACs. These items were presented as 5-point Likert scales (strongly agree to strongly disagree).

The final section contained open questions on aspects of: benefits and limitations of DOACs; examples of positive and negative experiences of using DOACs; NHS guidelines; CPD undertaken or needed; and comments relating to extending the appropriate use of DOACs within NHS Highland.

Following review by the research supervisory team, the draft questionnaires was tested for face and content validity (Humphrey, et al., 2013), as described in Chapter 2. Six leading researchers and practitioners were selected from the professional networks of the supervisors and invited by email to comment on the questionnaire in relation to the aims and objectives. The six comprised: a health psychologist; a general practitioner, a consultant medical physician; two senior pharmacist prescribers; and the lead for pharmacist prescribing at NHS Education for Scotland. Comments were emailed to the principal supervisor for review by the doctoral student and supervisory team. Comments were generally very supportive, with revisions suggested to the wording of specific questions. The main comment was to include additional questions on the initiation, continuation, monitoring, discontinuation of DOACs and warfarin, and switching between the two.

Following modification of the questionnaire, the next stage was to undertaken ‘think aloud testing’, which involves a small number of individuals voicing their interpretation of the items and their responses. This allows the researchers to determine that the items are likely to be interpreted as

planned (Smith et al, 2013). This was undertaken with one medical and one non-medical prescriber based outwith NHS Highland.

The pilot version of the questionnaire was formatted in Snap 10 Professional® (software for web and email questionnaire design, publication, data entry and analysis) by an e-technologist at RGU. Piloting was undertaken for several reasons:

i. to estimate likely survey the response rates

ii. to test that questionnaire items are completed as intended (Bowden et al, 2002)

iii. to determine the extent of completion of the open-ended questions (Simon et al, 2003; Bowden et al, 2002).

The pilot was performed on a sample of 30 prescribers outwith NHS Highland, identified from the professional networks of the supervisors. Thirteen responses were received (response rate of 43.3%), review of which identified that no further changes to the questionnaire were required.

4.3.8 Data collection

The final questionnaire also included an information leaflet, which was prepared according to the standardised format required by NHS ethics committees in the UK (Appendix 4.3). The final questionnaire can be found in Appendix 4.4. Providing full information of the aims of the study, potential benefits and assuring anonymity and confidentiality has been shown to increase response rates. The following evidence based measures were also adopted to maximise the survey response rate: professional design; use of reminders; and incentives (invitation to be included in a draw for £50 of shopping vouchers) (Cottrell et al., 2015).

The questionnaires were sent in January 2016 by a member of staff in NHS Highland with access to the database of prescribers' emails. The email text was developed by the research team and contained the link to the information leaflet and questionnaire. Two reminder emails were sent at approximately two-weekly intervals.

4.3.9 Quality in research: maximizing validity and reliability

The following measures were adopted in an attempt to increase validity and reliability and hence the robustness of the study:

i. questionnaire items were developed from the results of the systematic review in Chapter 3, the published literature around DOACs in general, TDF and the NHS guidelines, all of which enhanced criterion validity, as described in Chapter 2
ii. the draft questionnaire was reviewed for face and content validity by key, targeted experts
iii. a pilot study was performed to ensure the questionnaire quality
iv. statistical testing was performed to established internal consistency (reliability) of any scales

A number of approaches were taken in an attempt to reduce various forms of bias (Wyrick et al.,2011), (Clifford et al., 2015), (Suárez-Alvarez et al., 2018), (Whelan et al., 2008):

i. the invitation email was sent to all prescribers within NHS Highland thus eliminating any recruitment bias
ii. evidence based measures were adopted to increase response rate thus reducing any response bias
iii. the questions were worded in such a way as to reduce social desirability and attention bias
iv. questionnaire items were mainly Likert scales and close-ended questions to minimise acquiescence response set bias
v. questionnaires responses were anonymous to minimise evaluation apprehension

4.3.10 Data analysis

The questionnaire generated anonymised emails of online submissions to the e-technologist at RGU. These were imported into Snap 10 Professional® before direct export to SPSS (SPSS Inc., Cary, NC version 21.0). As described earlier, the number of prescribers for whom prescribing of anticoagulants would be relevant was unknown hence a response rate could

not be given. Respondent demographics were presented as descriptive statistics (e.g. frequencies, percentages, mean (standard deviation), median (interquartile range)).
Results for the specific research questions were analysed as follows.

RQ1. how are DOACs initiated, prescribed and monitored?

- descriptive statistics

RQ2. which behavioural determinants are potentially influential in prescribing DOACs?

- descriptive statistics of responses to Likert scale items

Relevant questionnaire items were subjected to exploratory factor analysis (principal component analysis (PCA) with varimax rotation), to identify a smaller number of components of interrelated variables. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and the Bartlett's Test of Sphericity were used to assess the suitability of the sample for PCA (Worthington and Whittaker 2006).

The number of components to be retained was decided based on:

- the Kaiser criterion (aiming for Eigenvalues ≥ than 1)
- the scree plot, aiming for the point at which the 'elbow' flattended
- meaningfulness of component items in relation to TDF (Costello and Osborne 2005, Hayton et al. 2004).

Analysis included items that were not freestanding, cross-loading or decreasing the scale's internal consistency, and that displayed acceptable communalities, with factor pattern/structure coefficients above 0.4 (Costello and Osborne, 2005, Fabrigar et al. 1999, Hogarty et al. 2005, Sharma 1996).

Following PCA, internal consistency was determined by calculation of the Cronbach's alpha for each component, with negatively worded items being reverse scored (DeVellis 2003). Cronbach's alpha gives an indication of the average correlation among all of the items within the component scale. Values range from 0 to 1, with higher values indicating greater reliability (ref,

SPSS-survival- manual, version 12). Nunnally (1978) suggests a minimum level of 0.7 for the component scale to be considered reliable.

If shown to be reliable, total component scores were obtained by assigning scores of 1 (strongly disagree) to 5 (strongly agree) to each of the Likert statement responses, with negatively worded items being reverse scored. The median and IQR scores of each reliable component were determined and compared to the mid-point of the component.

Non-parametric statistics were used to determine any significant differences between the following and the scores for each component:

- health profession
- setting
- years of experience as a health professional
- years of experience as a prescriber
- Rogers' 'Diffusion of Innovations' typology

Mann-Whitney U-test was used for two groups and Kruskall Wallis for more than two groups. p-values ≤0.05 were considered to be statistically significant.

RQ3-5

- what are the perceived benefits and limitations of prescribing DOACs?
- what are the positive and negative experiences of prescribing DOACs?
- how could the appropriate use of DOACs in primary care be extended further?

Textual responses to the open questions were analysed using a summative content analysis approach involving the counting of keywords and content, (Hsieh et al., 2005) as previously described.

4.4 RESULTS

4.4.1 Demographics

One hundred and fifty-four responses were received, 120 (77.9%) from doctors (76 general practitioners), 18 (11.7%) from nurse prescribers and 10 (6.4%) from pharmacist prescribers, (6 did not state their profession). The mean age of the respondents was 43.3 years (standard deviation 11.9 years). Respondents were experienced as health professionals, with just over half (n=84, 54.5%) having twenty of more years of experience as health professionals. Slightly less (n=61, 39.6%) had twenty of more years of experience as prescribers. Around one quarter (n=34, 22.1%) rated themselves as 'innovators' and 25 (16.2%) as 'early adopters'. None of the respondents rated themselves as 'laggards'. The demographic characteristics of the respondents are given in Table 4.2. Several prescribers within NHS Highland contacted members of the research team stating that the survey was not relevant to their fields of practice (e.g. psychiatry, dermatology etc.) hence a response rate could not be calculated. While the number of respondents was less than that planned (see section 4.3.5), it was still sufficient for the analysis undertaken.

Table 4.2. Respondent demographics (N=154)

Characteristic	Percentage	Frequency, n
Profession		
Doctor	77.9	120
Nurse prescriber	11.7	18
Pharmacist prescriber	6.5	10
Missing	3.9	6
Sex		
Male	42.9	66
Female	57.1	88
Academic qualifications		
PhD	0.6	1
MD	4.5	7
MSc	13.0	20
Postgraduate Diploma	31.2	48
Postgraduate Certificate	18.2	28
MBChB (or equivalent)	70.8	109
MPharm	2.6	4
BSc	24.0	37
Practice setting		
Secondary care	32.5	50
Primary care	64.9	100
Other	3.6	4
Years worked as health professional		
≤5	7.1	11
6-10	12.3	19
11-15	9.7	15
16-20	14.9	23
20-25	18.2	28
26-30	14.3	22
>30	22.1	34
Missing	1.3	2
Years worked as prescriber		
≤5	16.2	25
6-10	17.5	27
11-15	13.0	20
16-20	11.7	18
20-25	12.3	19
26-30	12.3	19
>30	14.9	23
Missing	1.9	3
Responses in relation to changing professional practice		
- I resist new ways of working	0	0
- I am cautious in relation to new ways of working; I tend to change once most of my peers have done so	9.7	15
- I think for some time before adopting new ways of working	51.9	80
- I serve as a role model for others in relation to new ways of working	16.2	25
- I am innovative with new ways of working	22.1	34

4.4.2 Current practice with warfarin and DOACs

Current practice relating to the prescribing of warfarin and DOACs in given in Table 4.3. The most common behaviours were continuing prescribing warfarin if initiated by others (n=110, 71.4% weekly or monthly) and continuing DOACs if initiated by others (n=112, 72.8% weekly or monthly). Sixty-six respondents (42.9%) initiated DOACs either weekly or monthly.

Table 4.3: Approximate frequency of anticoagulant prescribing behaviours (N=154)

Prescribing behaviour	Weekly % (n)	Monthly % (n)	Annually % (n)	Never % (n)	Missing % (n)
Initiate warfarin	0.6 (1)	29.2 (45)	35.7 (55)	34.4 (53)	0
Continue prescribing warfarin if initiated by others	40.9 (63)	30.5 (47)	8.4 (13)	20.1 (31)	0
Discontinue warfarin	1.3 (2)	25.3 (39)	50 (77)	23.4 (36)	0
Initiate DOACs	3.9 (6)	39.0 (60)	29.2 (45)	26.6 (41)	1.3 (2)
Switch individual patients from warfarin to DOACs	0.6 (1)	18.2 (28)	40.9 (63)	38.3 (59)	1.9 (3)
Switch individual patients from DOACs to warfarin	0	5.2 (8)	31.2 (48)	63.6 (98)	0
Continue DOACs if initiated by others	32.5 (50)	40.3 (62)	10.4 (16)	16.9 (26)	0
Discontinue DOACs	1.3 (2)	22.7 (35)	44.2 (68)	31.2 (48)	0.6 (1)

Sixteen respondents (10.4%) never prescribed warfarin or DOACs under any circumstances and had no plans to prescribe in the future, hence were removed from any further analysis. These sixteen were seven nurses, five doctors, 2 physiotherapists, one pharmacist and one podiatrist.

4.4.3 Responses to items based on NHS Highlands Guidelines

Responses to items based on selected statements within the NHS Highlands Guidelines (NHS, 2018) are given in Table 4.4, with the correct response underlined.

Table 4.4: Responses to questions within the NHS Highlands Guidelines (N=138)

Questionnaire Item	True % (n)	False % (n)	Don't know % (n)	Missing % (n)
DOACs should be considered in patients whose INR is outside the INR window more than 60% of the time (as estimated by appropriate software which provides time in treatment range (TTR) data)	71.7 (99)	7.2 (10)	19.6 (27)	1.4 (2)
DOACs should be considered first line in patients likely or known to be non-adherent	39.9 (55)	34.8 (48)	23.2 (32)	2.2 (3)
Dabigatran is the first choice DOAC	8.0 (11)	65.9 (91)	23.9 (33)	2.2 (3)
Apixaban is the second choice DOAC	9.4 (13)	55.1 (76)	33.3 (46)	2.2 (3)
Rivaroxaban dose should be altered in the elderly, irrespective of renal function	15.2 (21)	57.2 (79)	24.6 (34)	2.9 (4)
Patient must be able to swallow capsule whole before prescribing dabigatran	47.8 (66)	2.9 (4)	48.6 (67)	0.7 (1)

Almost three quarters of respondents (n=99, 71.9%) were aware of initiation of dabigratran in relation to TTR and the INR window. However, around one fifth or greater answered 'don't know' to each of the statements, with the highest (n=67, 48.6%) being in relation to administration of dabigatran.

4.4.4 Behavioral determinants

The responses to items the TDF of behavioural determinants are given in Tables 4.5-4.16.

Table 4.5. Response to items in the domain of knowledge (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have sufficient knowledge of the guidelines to allow me to prescribe DOACs appropriately	8.0 (11)	62.3 (86)	10.9 (15)	10.1 (14)	4.3 (6)	4.3 (6)
I have sufficient knowledge of the clinical pharmacology of DOACs to allow me to prescribe these safely and effectively	8.0 (11)	58.7 (81)	15.2 (21)	11.6 (16)	2.2 (3)	4.3 (6)
I have sufficient knowledge of the evidence base of DOACs to allow me to prescribe these safely and effectively	8.0 (11)	58.0 (80)	13.0 (18)	13.8 (19)	2.9 (4)	4.3 (6)
I have sufficient knowledge of how to initiate the prescribing of DOACs	10.1 (14)	65.9 (91)	6.5 (9)	10.9 (15)	1.4 (2)	5.1 (7)
I have sufficient knowledge of how to monitor the effectiveness and toxicity of DOACs	6.5 (9)	48.6 (67)	23.9 (33)	14.5 (20)	2.2 (3)	4.3 (6)
I have sufficient knowledge of when and how to switch patients from warfarin to DOACs	6.5 (9)	46.4 (64)	16.7 (23)	20.3 (28)	5.1 (7)	5.1 (7)
I have sufficient knowledge of when and how to switch patients from DOACs to warfarin	6.5 (9)	36.2 (50)	23.9 (33)	23.9 (33)	4.3 (6)	5.1 (7)
I have sufficient knowledge of how to manage adverse reactions of DOACs	5.8 (8)	40.6 (56)	26.1 (36)	20.3 (28)	2.9 (4)	4.3 (6)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

While responses to most statements were positive, those relating to monitoring DOACs for effectiveness and toxicity (n=76, 55.1% strongly agree/ agree), managing ADRs (n=64, 46.4% strongly agree/ agree) and switching patients from warfarin to DOACs (n=73, 52.9% strongly agree/ agree) were more neutral. The statement with the lowest level of agreement

was that relating to switching patients from DOACs to warfarin (n=59, 42.7% strongly agree/ agree).

Table 4.6 Response to items in the domain of professional role and identity (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
It is part of my role to initiate the prescribing of DOACs	17.4 (24)	52.2 (72)	5.1 (7)	14.5 (20)	5.1 (7)	5.8 (8)
It is part of my role to initiate the prescribing of warfarin	19.6 (27)	53.6 (74)	2.9 (4)	15.2 (21)	5.1 (7)	3.6 (5)
I should only prescribe DOACs when they have been initiated by others	0.7 (1)	13.0 (18)	5.1 (7)	49.3 (68)	28.3 (39)	3.6 (5)
Only specialists should initiate the prescribing of DOACs	0.7 (1)	8.7 (12)	10.1 (14)	54.3 (75)	25.4 (35)	0.7 (1)
It is part of my role to switch patients from warfarin to DOACs	10.9 (15)	60.1 (83)	8.0 (11)	8.7 (12)	5.1 (7)	7.2 (10)
It is part of my role to switch patients from DOACs to warfarin	12.3 (17)	52.9 (73)	11.6 (16)	10.9 (15)	5.1 (7)	7.2 (10)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The majority of respondents were in agreement that the various prescribing actions relating to oral anticoagulants were part of their role and not restricted to specialists. For example, while almost three quarters of respondents (n=96, 69.6% agreed/ strongly agreed) that it was part of their role to initiate the prescribing of DOACs, over three quarters (n=110, 79.7%) disagreed/ strongly disagreed that only specialists should commence DOACs.

Table 4.7. Response to items in the domain of belief of capabilities (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I am confident in my ability to initiate the prescribing of DOACs	13.0 (18)	48.6 (67)	13.0 (18)	15.9 (22)	5.8 (8)	3.6 (5)
I am confident in my ability to initiate the prescribing of warfarin	20.3 (28)	59.4 (82)	4.3 (6)	8.7 (12)	3.6 (5)	3.6 (5)
I am confident in switching patients from warfarin to DOACs	9.4 (13)	44.2 (61)	14.5 (20)	20.3 (28)	5.8 (8)	5.8 (8)
I am confident in switching patients from DOACs to warfarin	10.9 (15)	29.7 (41)	25.4 (35)	23.9 (33)	5.1 (7)	5.1 (7)
I am confident in my ability to prescribe DOACs when they have been initiated by others	23.9 (33)	62.3 (86)	2.9 (4)	5.1 (7)	1.4 (2)	4.3 (6)
I am competent in initiating the prescribing of DOACs	16.7 (23)	50.0 (69)	14.5 (20)	9.4 (13)	3.6 (5)	5.8 (8)
I am competent in initiating the prescribing of warfarin	22.5 (31)	54.3 (75)	5.8 (8)	8.0 (11)	2.9 (4)	6.5 (9)
I am competent in continuing the prescribing of DOACs initiated by others	21.0 (29)	65.9 (91)	3.6 (5)	2.2 (3)	0.7 (1)	6.5 (9)
I am competent in switching patients from warfarin to DOACs	13.0 (18)	47.1 (65)	21.0 (29)	9.4 (13)	3.6 (5)	5.8 (8)
I am competent in switching patients from DOACs to warfarin	11.6 (16)	37.0 (51)	28.3 (39)	14.5 (20)	3.6 (5)	5.1 (7)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Respondents were in overwhelming agreement that they were both confident and competent in various prescribing activities relating to initiating oral anticoagulants. The lowest levels of agreement were in relation to switching from warfarin to DOACs (n=74, 53.6% agreed/ strongly agreed confident; n=83, 60.1% agreed/ strongly agreed competent) and lower for switching DOACs to warfarin (n=56, 40.6% agreed/ strongly agreed confident; n=67, 48.6% agreed/ strongly agreed competent).

Table 4.8. Response to items in the domain of optimism (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
Implementing the guidelines on prescribing DOACs will be better for patients	16.7 (23)	60.1 (83)	18.8 (26)	2.2 (3)	0	2.2 (3)
Implementing the guidelines on prescribing DOACs will be better for me	16.7 (23)	60.9 (84)	15.9 (22)	2.2 (3)	1.4 (2)	2.9 (4)
Implementing the guidelines on prescribing DOACs will be better for my NHS organisation	16.7 (23)	55.8 (77)	23.2 (32)	2.9 (4)	0.7 (1)	0.7 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The majority of respondents were optimistic around the use of the NHS Highland guidelines on DOACs and benefits for patients (n=106, 76.8% agreed/ strongly agreed), themselves (n=107, 77.6% agreed/ strongly agreed) and the organisation (n=100, 72.5%).

Table 4.9. Response to items in the domain of beliefs of consequences (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more effectively	7.2 (10)	21.0 (29)	34.8 (48)	32.6 (45)	2.2 (3)	2.2 (3)
If I prescribe DOACs rather than warfarin, I believe that patients will have less adverse effect	5.8 (8)	14.5 (20)	45.7 (63)	29.7 (41)	2.2 (3)	2.2 (3)
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more cost effectively	2.9 (4)	13.8 (19)	47.8 (66)	29.0 (40)	4.3 (6)	2.2 (3)
If I do not prescribe DOACs according to the guidelines, patients may come to harm	6.5 (9)	50.0 (69)	19.6 (27)	18.8 (26)	2.2 (3)	2.9 (4)
If I switch patients stabilized on warfarin to DOACs, I believe that patient care may be compromised	0.7 (1)	18.8 (26)	32.6 (45)	42.8 (59)	2.9 (4)	2.2 (3)
If I prescribe DOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging	10.1 (14)	54.3 (75)	16.7 (23)	15.2 (21)	0.7 (1)	2.9 (4)
I believe that If I prescribe DOACs rather than warfarin, over-anticoagulation will not be easily detected	5.8 (8)	37.0 (51)	29.7 (41)	21.7 (30)	0	5.8 (8)
I believe that If I prescribe DOACs rather than warfarin, under-anticoagulation will not be easily detected	7.2 (10)	36.2 (50)	31.2 (43)	21.0 (29)	0.7 (1)	3.6 (5)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Respondents, in general, were rather ambivalent about the consequences of prescribing DOACs in relation to outcomes of effectiveness (n=39, 28.2% agreed/ strongly agreed), safety (n=28, 20.3% agreed/ strongly agreed) and cost-effectiveness (n=23, 16.7%) in comparison to treatment with warfarin. There appeared to be some concern over switching patients stabilised on warfarin to DOACs, with 27 respondents (19.5%) agreeing/ strongly agreeing that patient care might be compromised. Almost two thirds of respondents (n=89, 64.4%) agreed/ strongly agreed that the management of severe

bleeding would be more challenging in those prescribed DOACs. Just under half agreed/ strongly agreed that over-anticoagulation (n=59, 42.8%) and under-anticoagulation (n=60, 43.4%) would not be easily be detected.

Table 4.10 Response to items in the domain of reinforcement (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
Cost is a deterrent to my prescribing of DOACs	3.6 (5)	25.4 (35)	7.2 (10)	47.8 (66)	8.0 (11)	8.0 (11)
The views of my colleagues are a deterrent to my prescribing of DOACs	0.7 (1)	18.1 (25)	8.7 (12)	52.9 (73)	13.0 (18)	6.5 (9)
Potentially increased scrutiny of my prescribing by the health board is a deterrent to my prescribing of DOAC	2.9 (4)	16.7 (23)	8.7 (12)	50.7 (70)	13.8 (19)	7.2 (10)
Potentially reduced workload in patient monitoring influences my prescribing of DOACs rather than warfarin	5.1 (7)	34.8 (48)	7.2 (10)	39.1 (54)	5.8 (8)	8.0 (11)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Just over half of respondents (n=77, 55.8%) disagreed/ strongly disagreed that cost was a deterrent to prescribing DOACs, with even more disagreeing/ strongly disagreeing in relation to colleague views (n=91, 65.9%) and health board scrutiny (n=89, 64.5%). However, 55 respondents (39.8%) agreed/ strongly agreed that reduced workload in monitoring of INR was a positive influence on DOAC prescribing.

Table 4.11: Response to items in the domain of goals (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have clear goals for prescribing DOACs according to the guidelines	7.2 (10)	49.3 (68)	21.0 (29)	15.2 (21)	1.4 (2)	5.8 (8)
I have clear goals relating to my continuing professional development around DOACs	5.8 (8)	44.2 (61)	22.5 (31)	18.8 (26)	2.9 (4)	5.8 (8)
Prescribing DOACs according to the guidelines is high priority for me	11.6 (16)	47.8 (66)	16.7 (23)	16.7 (23)	0.7 (1)	6.5 (9)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

In relation to goals, more than half of respondents agreed/ strongly agreed that they had clear goals to prescribe DOACs according to the NHS guidelines (n=78, 56.5%) and that prescribing according to the guidelines was a high priority (n=82, 59.4%). However, as illustrated in Table 4.12, just under half (n=58, 42.1%) agreed/ strongly agreed that the guidelines the guidelines were easy to interpret and one quarter (n=36, 26.0%) that it was difficult to decide whether to prescribe DOACs or warfarin.

Table 4.12. Response to items in the domain of memory, attention and decision processes (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I find the guidelines on DOACs easy to interpret	5.1 (7)	37.0 (51)	34.8 (48)	15.2 (21)	1.4 (2)	6.5 (9)
I find it difficult to decide whether to prescribe DOACs or warfarin	1.4 (2)	24.6 (34)	9.4 (13)	49.3 (68)	6.5 (9)	8.7 (12)
Others have to remind me to prescribe DOACs according to the guidelines	0.7 (1)	6.5 (9)	5.1 (7)	62.3 (86)	12.3 (17)	13.0 (18)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Table 4.13 Response items in the domain of environmental context and resources (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
Prescribing DOACs is compatible with my daily practice	13.0 (18)	59.4 (82)	7.2 (10)	8.0 (11)	1.4 (2)	10.9 (15)
I have sufficient time to prescribe DOACs	12.3 (17)	59.4 (82)	7.2 (10)	4.3 (6)	1.4 (2)	15.2 (21)
My drug budget is sufficient to allow me to prescribe DOACs	3.6 (5)	23.2 (32)	34.8 (48)	8.0 (11)	2.2 (3)	28.3 (39)
My prescribing systems enable me to prescribe DOACs	13.0 (18)	68.8 (95)	5.1 (7)	2.2 (3)	0	10.9 (15)
I have sufficient support from specialists to enable me to prescribe DOACs safely and effectively	8.7 (12)	60.1 (83)	11.6 (16)	7.2 (10)	0	12.3 (17)
The lack of need for monitoring influences my prescribing of DOACs	10.9 (15)	41.3 (57)	8.7 (12)	24.6 (34)	2.2 (3)	12.3 (17)
The rurality of my practice influences my prescribing of DOACs	9.4 (13)	29.7 (41)	3.6 (5)	26.1 (36)	2.2 (3)	29.0 (40)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Of note, less than one third of respondents (n=37, 26.8%) agreed/ strongly agreed that their drug budget was sufficient for prescribing DOACs. The absence of need for INR monitoring when prescribing DOACs was an influence of prescribing for just over half (n=72, 52.2%), with rurality being an influence for more than one third (n=54, 39.3%).

Table 4.14. Response to items in the domain of social influences (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
Professionals who are important to me prescribe DOACs	10.1 (14)	58.7 (81)	15.9 (22)	6.5 (9)	0	8.7 (12)
Members of the multidisciplinary team prescribe DOACs	5.1 (7)	39.1 (54)	18.8 (26)	22.5 (31)	2.2 (3)	12.3 (17)
My prescribing of DOAC is discouraged by my peers	0.7 (1)	3.6 (5)	8.0 (11)	63.8 (88)	16.7 (23)	7.2 (10)
My prescribing of DOAC is discouraged by my multidisciplinary team	0.7 (1)	2.2 (3)	7.2 (10)	60.1 (83)	15.9 (22)	13.8 (19)
My prescribing of DOAC is discouraged by my organisation	0.7 (1)	9.4 (13)	15.9 (22)	56.5 (78)	10.1 (14)	7.2 (10)
My prescribing of DOAC is discouraged by specialists	0.7 (1)	0	12.3 (17)	65.2 (90)	15.3 (21)	6.5 (9)
Patients put me under pressure to prescribe DOACs	0	7.2 (10)	2.9 (4)	61.6 (85)	19.6 (27)	8.7 (12)
Patients put me under pressure to prescribe DOACs in situations where they are not indicated	0	5.1 (7)	5.8 (8)	57.2 (79)	22.5 (31)	9.4 (13)
Family members and carers of patients put me under pressure to prescribe DOACs in situations where they are not indicated	0	2.9 (4)	4.3 (6)	59.4 (82)	23.9 (33)	9.4 (13)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Notably, very few respondents agreed that patients, family members or carers exerted any pressure for prescribing DOACs (n=10, 7.2%; n=7, 5.1%; n=4, 2.9% respectively) and no respondents strongly agreed with these statements. There were, however, influences from key professionals (n=95, 68.8%) and the multidisciplinary team (n=61, 44.2%). The vast majority disagreed/ strongly disagreed that prescribing was discouraged by their peers (n=111, 80.5%), their organisation (n=92, 66.6%) and specialists (n=111, 80.5%).

Table 4.15. Response to items in the domain of emotions (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I feel comfortable when initiating the prescribing of DOACs	12.3 (17)	52.2 (72)	5.8 (8)	13.8 (19)	2.9 (4)	13.0 (18)
I feel comfortable when switching patients from warfarin to DOACs	11.6 (16)	44.2 (61)	10.1 (14)	16.7 (23)	2.9 (4)	14.5 (20)
I feel comfortable when prescribing DOACs which have been initiated by others	15.2 (21)	68.1 (94)	6.5 (9)	2.2 (3)	1.4 (2)	6.5 (9)
I get professional satisfaction when initiating the prescribing of DOACs	2.2 (3)	25.4 (35)	26.8 (37)	16.7 (23)	5.1 (7)	23.9 (33)
I get professional satisfaction when switching patients from warfarin to DOACs	1.4 (2)	23.2 (32)	26.8 (37)	18.8 (26)	5.1 (7)	24.6 (34)
I get professional satisfaction when switching patients from DOACs to warfarin	0	13.0 (18)	28.3 (39)	26.8 (37)	5.1 (7)	26.8 (37)
I get professional satisfaction when prescribing DOACs which have been initiated by others	0.7 (1)	23.9 (33)	27.5 (38)	23.2 (32)	6.5 (9)	18.1 (25)
I feel anxious when initiating the prescribing of DOACs	0.7 (1)	16.7 (23)	5.1 (7)	50.7 (70)	11.6 (16)	15.2 (21)
I feel anxious when switching patients from warfarin to DOACs	0.7 (1)	17.4 (24)	9.4 (13)	38.4 (53)	10.9 (15)	23.2 (32)
I feel anxious when switching patients from DOACs to warfarin	1.4 (2)	17.4 (24)	11.6 (16)	34.1 (47)	9.4 (13)	26.1 (36)
I feel anxious when prescribing DOACs which have been initiated by others	0	9.4 (13)	5.8 (8)	60.1 (83)	13.8 (19)	10.9 (15)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

In terms of emotions, there appeared to be very little issues around comfort when prescribing DOACs, either when initiating (n=74, 65.5% agreeing/ strongly agreeing) or continuing prescribing initiated by others (n=115, 83.3% agreeing/ strongly agreeing). Slightly fewer were comfortable when switching from warfarin to DOACs (n=67, 55.8% agreeing/ strongly agreeing). The levels of agreement for being anxious when initiating,

continuing or changing were much less with the highest being when switching from DOACs to warfarin (n=26, 18.8%).

Table 4.16. Response to items in the domain of behavioural regulation (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have ways of monitoring the quality of my prescribing of DOACs	2.2 (3)	21.7 (30)	19.6 (27)	35.5 (49)	5.1 (7)	15.9 (22)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Less than one quarter or respondents (n=33, 23.9%) agreed/ strongly agreed that they had ways of monitoring the quality of DOAC prescribing.

4.4.5 Principal component analysis

As described earlier, PCA is a statistical approach to identify a smaller number of components of interrelated variables which can then be used as outcome measures for further statistical analysis. Given the number of questionnaire responses, it was necessary to reduce the number of items to include in PCA. Those items which referred to 'prescribing' of DOACs in general were retained and those which referred to sub-actions of prescribing (e.g. initiating, switching, discontinuing) were excluded. While this may have some limitations (see discussion), it was considered that the more general 'prescribing' would also encompass the sub-actions. Table 4.17 lists the 33 items which were retained for PCA.

Table 4.17. Questionnaire items retained for PCA

Questionnaire items
I have sufficient knowledge of the guidelines to allow me to prescribe DOACs appropriately
I have sufficient knowledge of the clinical pharmacology of DOACs to allow me to prescribe these safely and effectively
I have sufficient knowledge of the evidence base of DOACs to allow me to prescribe these safely and effectively
I have sufficient knowledge of how to initiate the prescribing of DOACs
I have sufficient knowledge of how to monitor the effectiveness and toxicity of DOACs
I have sufficient knowledge of how to manage adverse reactions of DOACs
It is part of my role to initiate the prescribing of DOACs
I should only prescribe DOACs when they have been initiated by others
Only specialists should initiate the prescribing of DOACs
I am confident in my ability to initiate the prescribing of DOACs
I am competent in initiating the prescribing of DOACs
Implementing the guidelines on prescribing DOACs will be better for patients
Implementing the guidelines on prescribing DOACs will be better for my NHS organisation
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more effectively
If I prescribe DOACs rather than warfarin, I believe that patients will have less adverse effect
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more cost effectively
If I prescribe DOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging
I believe that If I prescribe DOACs rather than warfarin, over-anticoagulation will not be easily detected
I believe that If I prescribe DOACs rather than warfarin, under-anticoagulation will not be easily detected
Cost is a deterrent to my prescribing of DOACs
Potentially increased scrutiny of my prescribing by the health board is a deterrent to my prescribing of DOACs
Potentially reduced workload in patient monitoring influences my prescribing of DOACs rather than warfarin
I find the guidelines on DOACs easy to interpret
I find it difficult to decide whether to prescribe DOACs or warfarin
Others have to remind me to prescribe DOACs according to the guidelines
I have sufficient support from specialists to enable me to prescribe DOACs safely and effectively
The lack of need for monitoring influences my prescribing of DOACs
The rurality of my practice influences my prescribing of DOACs
My prescribing of NOAC is discouraged by my peers
My prescribing of DOAC is discouraged by my organisation
My prescribing of DOAC is discouraged by specialists
Patients put me under pressure to prescribe DOACs
I feel anxious when initiating the prescribing of DOACs

When all 33 items were subjected to PCA, the Kaiser–Meyer–Olkin measure of sampling adequacy (0.721) and Bartlett's test of sphericity (significance <0.001) confirmed the factorability of the items. Many of the the correlation matrix scores were greater than 0.3.

The number of components to be retained was determined by observation of the scree plot, the Eigenvalues and cumulative percentage variance. The Scree plot is given in Figure 4.1. Ideally, the number of components is identified at the 'elbow' point where the curve starts to flatten. In Figure 4.1, this could be at any point between 4 and 11 components.

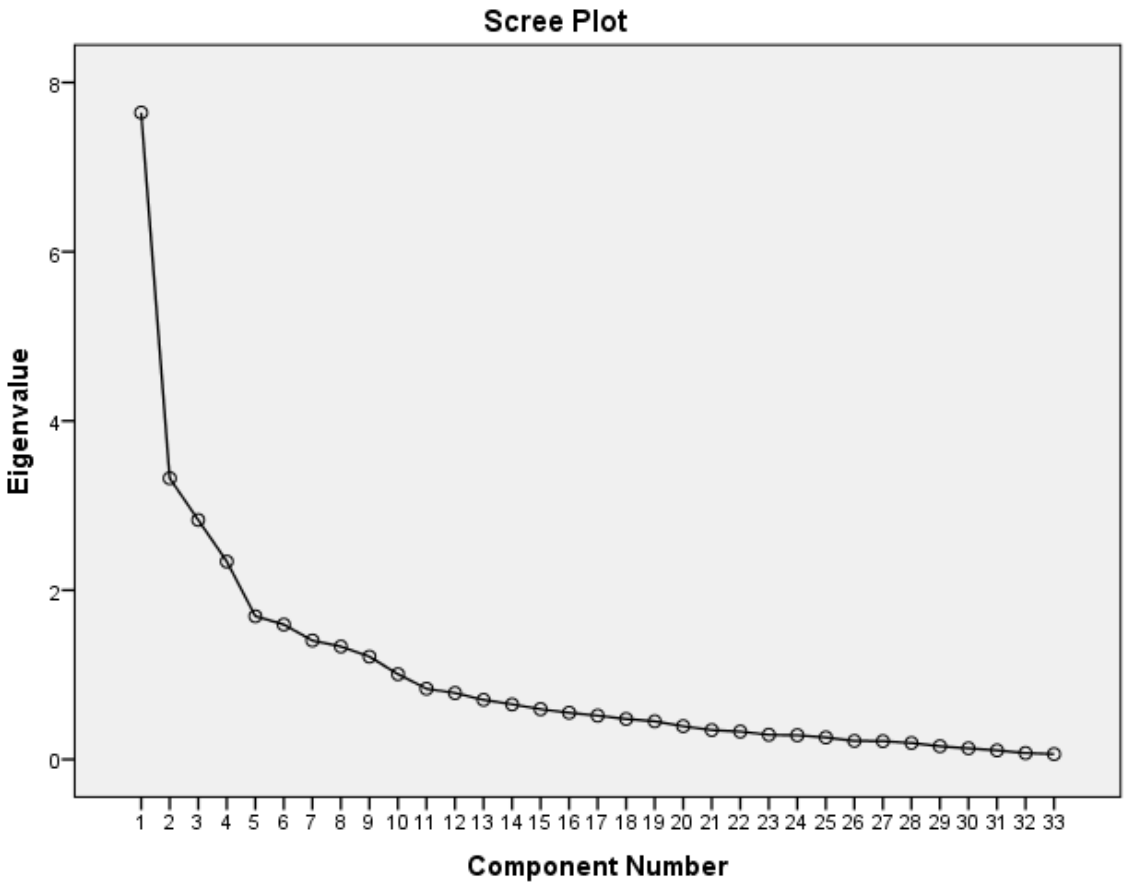

Figure 4.1. Scree plot generated from PCA of 33 items

Table 4.18 gives those components with Eigenvalues greater than 1 and their associated number of items per component.

Table 4.18. Components, Eigenvalues and number of items loaded following Varimax rotation

Component number	Number of items	Eigenvalues
1	16	7.644
2	10	3.322
3	11	2.829
4	4	2.339
5	6	1.692
6	8	1.593
7	4	1.405
8	2	1.334
9	4	1.214
10	3	1.007

While those components with Eigenvalues over 1 could be retained, six of these had low numbers of items loading (≤6). The remaining four components had a cumulate percentage variance of 48.9% which was adequate hence a four component solution was retained. Table 4.19 gives the pattern matrix loadings for all 33 items onto the four components.

Table 4.19. Loading of questionnaire items onto each of the four components

Questionnaire items	1	2	3	4
I have sufficient knowledge of the guidelines to allow me to prescribe DOACs appropriately	0.698			
I have sufficient knowledge of the clinical pharmacology of DOACs to allow me to prescribe these safely and effectively	0.823			
I have sufficient knowledge of the evidence base of DOACs to allow me to prescribe these safely and effectively	0.840			
I have sufficient knowledge of how to initiate the prescribing of DOACs	0.877			
I have sufficient knowledge of how to monitor the effectiveness and toxicity of DOACs	0.787			
I have sufficient knowledge of how to manage adverse reactions of DOACs	0.715			
It is part of my role to initiate the prescribing of DOACs	0.718			
I should only prescribe DOACs when they have been initiated by others	-0.616			
Only specialists should initiate the prescribing of DOACs	-0.429			
I am confident in my ability to initiate the prescribing of DOACs	0.869			
I am competent in initiating the prescribing of DOACs	0.772			
Implementing the guidelines on prescribing DOACs will be better for patients			0.601	
Implementing the guidelines on prescribing DOACs will be better for my NHS organisation			0.449	-0.378
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more effectively			0.694	
If I prescribe DOACs rather than warfarin, I believe that patients will have less adverse effect			0.645	
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more cost effectively			0.685	
If I prescribe DOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging				0.549
I believe that If I prescribe DOACs rather than warfarin, over-anticoagulation will not be easily detected				0.729
I believe that If I prescribe DOACs rather than warfarin, under-anticoagulation will not be easily detected				0.683
Cost is a deterrent to my prescribing of DOACs		0.451		
Potentially increased scrutiny of my prescribing by the health board is a deterrent to my prescribing of DOACs		0.689		
Potentially reduced workload in patient monitoring influences my prescribing of DOACs rather than warfarin			0.604	0.334
I find the guidelines on DOACs easy to interpret	0.306			
I find it difficult to decide whether to prescribe DOACs or warfarin	-0.460			
Others have to remind me to prescribe DOACs according to the guidelines	-0.449			
I have sufficient support from specialists to enable me to prescribe DOACs safely and effectively	0.316			
The lack of need for monitoring influences my prescribing of DOACs			0.362	0.563
The rurality of my practice influences my prescribing of DOACs				0.377
My prescribing of NOAC is discouraged by my peers		0.851		
My prescribing of DOAC is discouraged by my organisation		0.781		
My prescribing of DOAC is discouraged by specialists		0.818		
Patients put me under pressure to prescribe DOACs*				
I feel anxious when initiating the prescribing of DOACs	-0.573			

*this item did not load onto any of the four components

Tables 4.20-4.23 list the items within each component and the TDF domain as per the original questionnaire.

Table 4.20. Component 1, items related to 'the role of professionals and their knowledge and skills' (n=16)

Statements	TDF domain
I have sufficient knowledge of the guidelines to allow me to prescribe DOACs appropriately	Knowledge
I have sufficient knowledge of the clinical pharmacology of DOACs to allow me to prescribe these safely and effectively	Knowledge
I have sufficient knowledge of the evidence base of DOACs to allow me to prescribe these safely and effectively	Knowledge
I have sufficient knowledge of how to initiate the prescribing of DOACs	Knowledge
I have sufficient knowledge of how to monitor the effectiveness and toxicity of DOACs	Knowledge
I have sufficient knowledge of how to manage adverse reactions of DOACs	Knowledge
It is part of my role to initiate the prescribing of DOACs	Professional role and identity
I should only prescribe DOACs when they have been initiated by others	Professional role and identity
Only specialists should initiate the prescribing of DOACs	Professional role and identity
I am confident in my ability to initiate the prescribing of DOACs	Beliefs of capabilities
I am competent in initiating the prescribing of DOACs	Beliefs of capabilities
I find the guidelines on DOACs easy to interpret	Memory, attention and decision process
I find it difficult to decide whether to prescribe DOACs or warfarin	Memory, attention and decision process
Others have to remind me to prescribe DOACs according to the guidelines	Memory, attention and decision process
I have sufficient support from specialists to enable me to prescribe DOACs safely and effectively	Environmental context and resources
I feel anxious when initiating the prescribing of DOACs	Emotions

Sixteen items loaded onto component 1 and these originated largely from TDF domains of knowledge, professional role, beliefs of capabilities and decision process. This component was therefore labelled 'the role of professionals and their knowledge and skills'.

Table 4.21. Component 2, items related to 'influences on prescribing' (n=5)

Statement	TDF domain
Cost is a deterrent to my prescribing of DOACs	Reinforcement
Potentially increased scrutiny of my prescribing by the health board is a deterrent to my prescribing of DOACs	Reinforcement
My prescribing of DOACs is discouraged by my peers	Social influences
My prescribing of DOACs is discouraged by my organisation	Social influences
My prescribing of DOACs is discouraged by specialists	Social influences

Five items loaded onto component 2 and these all originated from the TDF domain of social influences and reinforcement. This component was therefore labelled 'influences on prescribing'.

Table 4.22. Component 3, items related to 'consequences of prescribing' (n=6)

Statement	Original TDF
Implementing the guidelines on prescribing DOACs will be better for patients	Optimism
Implementing the guidelines on prescribing DOACs will be better for my NHS organisation	Optimism
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more effectively	Beliefs of consequences
If I prescribe DOACs rather than warfarin, I believe that patients will have less adverse effect	Beliefs of consequences
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more cost effectively	Beliefs of consequences
Potentially reduced workload in patient monitoring influences my prescribing of DOACs rather than warfarin	Beliefs of consequences

Six items loaded onto component 3 and these all originated from the TDF domains of beliefs of consequences and optimism. This component was therefore labelled 'consequences of prescribing'.

Table 4.23. Component 4, items related to 'monitoring for safety and effectiveness' (n=5)

Statement	TDF domain
If I prescribe DOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging	Beliefs of consequences
I believe that If I prescribe DOACs rather than warfarin, over-anticoagulation will not be easily detected	Beliefs of consequences
I believe that If I prescribe DOACs rather than warfarin, under-anticoagulation will not be easily detected	Beliefs of consequences
The lack of need for monitoring influences my prescribing of DOACs	Environmental context and resources
The rurality of my practice influences my prescribing of DOACs	Environmental context and resources

Five items loaded onto component 4 and these all originated from the TDF domains of beliefs of consequences and environmental context and resources. This component was labelled 'monitoring for safety and effectiveness.

Internal reliability

Internal consistency values (Cronbach's alpha) were calculated for each of the four components, aiming for values over 0.7, with all negatively worded items reversed.

Tables 4.24-4.27 give the item responses and Cronbach's alpha values for each component, along with median and IQR values.

Table 4.24. Component 1, responses to items related to 'the role of professionals and their knowledge and skills' (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have sufficient knowledge of the guidelines to allow me to prescribe DOACs appropriately	8.0 (11)	62.3 (86)	10.9 (15)	10.1 (14)	4.3 (6)	4.3 (6)
I have sufficient knowledge of the clinical pharmacology of DOACs to allow me to prescribe these safely and effectively	8.0 (11)	58.7 (81)	15.2 (21)	11.6 (16)	2.2 (3)	4.3 (6)
I have sufficient knowledge of the evidence base of DOACs to allow me to prescribe these safely and effectively	8.0 (11)	58.0 (80)	13.0 (18)	13.8 (19)	2.9 (4)	4.3 (6)
I have sufficient knowledge of how to initiate the prescribing of DOACs	10.1 (14)	65.9 (91)	6.5 (9)	10.9 (15)	1.4 (2)	5.1 (7)
I have sufficient knowledge of how to monitor the effectiveness and toxicity of DOACs	6.5 (9)	48.6 (67)	23.9 (33)	14.5 (20)	2.2 (3)	4.3 (6)
I have sufficient knowledge of how to manage adverse reactions of DOACs	5.8 (8)	40.6 (56)	26.1 (36)	20.3 (28)	2.9 (4)	4.3 (6)
It is part of my role to initiate the prescribing of DOACs	17.4 (24)	52.2 (72)	5.1 (7)	14.5 (20)	5.1 (7)	5.8 (8)
*I should only prescribe DOACs when they have been initiated by others	0.7 (1)	13.0 (18)	5.1 (7)	49.3 (68)	28.3 (39)	3.6 (5)
*Only specialists should initiate the prescribing of DOACs	0.7 (1)	8.7 (12)	10.1 (14)	54.3 (75)	25.4 (35)	0.7 (1)
I am confident in my ability to initiate the prescribing of DOACs	13.0 (18)	48.6 (67)	13.0 (18)	15.9 (22)	5.8 (8)	3.6 (5)
I am competent in initiating the prescribing of DOACs	16.7 (23)	50.0 (69)	14.5 (20)	9.4 (13)	3.6 (5)	5.8 (8)
I find the guidelines on DOACs easy to interpret	5.1 (7)	37 (51)	34.8 (48)	15.2 (21)	1.4 (2)	6.5 (9)
*I find it difficult to decide whether to prescribe DOACs or warfarin	1.4 (2)	24.6 (34)	9.4 (13)	49.3 (68)	6.5 (9)	8.7 (12)
*Others have to remind me to prescribe DOACs according to the guidelines	0.7 (1)	6.5 (9)	5.1 (7)	62.3 (86)	12.3 (17)	13 (18)
I have sufficient support from specialists to enable me to prescribe DOACs safely and effectively	8.7 (12)	60.1 (83)	11.6 (16)	7.2 (10)	0	12.3 (17)
*I feel anxious when initiating the prescribing of DOACs	0.7 (1)	16.7 (23)	5.1 (7)	50.7 (70)	11.6 (16)	15.3 (21)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing; * reverse scored)

The Cronbach's alpha value at 0.904 is in excess of 0.7 therefore the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree (negatively worded items reverse scored) gives the minimum possible value for the scale of 16 (representing most negative responses) and the maximum possible value for the scale of 80 (representing most positive responses) and a midscale point of 48.

With a median value of 61 and IQR of 54-64 (minimum 36, maximum 79), respondents generally gave positive responses.

Table 4.25. Component 2, items related to 'influences on prescribing' (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
*Cost is a deterrent to my prescribing of DOACs	3.6 (5)	25.4 (35)	7.2 (10)	47.8 (66)	8.0 (11)	8.0 (11)
*Potentially increased scrutiny of my prescribing by the health board is a deterrent to my prescribing of DOACs	2.9 (4)	16.7 (23)	8.7 (12)	50.7 (70)	13.8 (19)	7.2 (10)
*My prescribing of DOAC is discouraged by my peers	0.7 (1)	3.6 (5)	8.0 (11)	63.9 (88)	16.7 (23)	7.2 (10)
*My prescribing of DOAC is discouraged by my organisation	0.7 (1)	9.4 (13)	15.9 (22)	56.5 (78)	10.1 (14)	7.2 (10)
*My prescribing of DOAC is discouraged by specialists	0.7 (1)	0	12.3 (17)	65.2 (90)	15.2 (21)	6.5 (9)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing; * reverse scored)

The Cronbach's alpha value at 0.802 is in excess of 0.7 hence the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree (negatively worded items reverse scored) gives the minimum possible value for the scale of 5 (representing most negative responses) and the maximum possible value for the scale of 25 (representing most positive responses) and a midscale point of 15.

With a median value of 19 and IQR of 17-20 (minimum 8, maximum 25), respondents generally gave positive responses.

Table 4.26. Component 3, responses to items related to 'consequences of prescribing' (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	S % (n)	M % (n)
Implementing the guidelines on prescribing DOACs will be better for patients	16.7 (165)	60.1 (83)	18.8 (26)	2.2 (3)	0	2.2 (3)
Implementing the guidelines on prescribing DOACs will be better for my NHS organisation	16.7 (23)	55.8 (77)	23.2 (32)	2.9 (4)	0.7 (1)	0.7 (1)
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more effectively	7.2 (10)	21.0 (29)	34.8 (48)	32.6 (45)	2.2 (3)	2.2 (3)
If I prescribe DOACs rather than warfarin, I believe that patients will have less adverse effect	5.8 (8)	14.5 (20)	45.7 (63)	29.7 (41)	2.2 (3)	2.2 (3)
If I prescribe DOACs rather than warfarin, I believe that patients will be treated more cost effectively	2.9 (4)	13.8 (19)	47.8 (66)	29.0 (40)	4.3 (6)	2.2 (3)
Potentially reduced workload in patient monitoring influences my prescribing of DOACs rather than warfarin	5.1 (7)	34.8 (48)	7.2 (10)	39.1 (54)	5.8 (8)	8.0 (11)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The Cronbach's alpha value at 0.714 is in excess of 0.7 hence the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree gives the minimum possible value for the scale of 6 (representing most negative responses) and the maximum possible value for the scale of 30 (representing most positive responses) and a midscale point of 18.

With a median value of 19 and IQR of 17-21.25 (minimum 12, maximum 30) respondents generally gave more neutral responses. Fifty-three respondents (38.4%) scored the midscale point of 18 or less.

Table 4.27. Component 4, responses to items related to 'monitoring for safety and effectiveness' (N=138)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
If I prescribe DOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging	10.1 (14)	54.3 (75)	16.7 (23)	15.2 (21)	0.7 (1)	2.9 (4)
I believe that If I prescribe DOACs rather than warfarin, over-anticoagulation will not be easily detected	5.8 (8)	37.0 (51)	29.7 (41)	21.7 (30)	0	5.8 (8)
I believe that If I prescribe DOACs rather than warfarin, under-anticoagulation will not be easily detected	7.2 (10)	36.2 (50)	31.2 (43)	21.0 (29)	0.7 (1)	3.6 (5)
The lack of need for monitoring influences my prescribing of DOACs	10.9 (15)	41.3 (57)	8.7 (12)	24.6 (34)	2.2 (3)	12.3 (17)
The rurality of my practice influences my prescribing of DOACs	9.4 (13)	29.7 (41)	3.6 (5)	26.1 (36)	2.2 (3)	29 (40)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The Cronbach's alpha value at 0.612 is lower than 0.7 hence the scale may lack reliability. Scoring 1 for strongly disagree to 5 for strongly agree gives the minimum possible value for the scale of 5 (representing most negative responses) and the maximum possible value for the scale of 25 (representing most positive responses) and a midscale point of 15.

With a median value of 17 and IQR of 14-19 (minimum 9, maximum 25), respondents gave more neutral responses. Thirty-eight respondents (27.5%) of respondents scored the midscale point of 15 or less.

4.4.6 Exploring relationships between demographic variables and component scores

Independent Samples Mann-Whitney U tests (two variables) Kruska Wallis tests (more than two variables) were used to compare the component scores across key demographic variables:

- the null hypotheses were that there were no differences in scores
- the alternative hypotheses were that there were differences in scores

Note that the study may not have been sufficiently powered to detect important differences hence the findings should be interpreted with caution.

Health professions

Comparison of scores for each component and the different health professions is given in Table 4.28. Given the number of pharmacist and nurse prescribers, these were combined as non-medical prescribers.

Table 4.28. Comparison of component scores for doctors and non-medical prescribers (nurses and pharmacists) (N=138)

Component	Profession	Median	IQR	P-value	Decision
'the role of professionals and their knowledge and skills'	Doctor	61	54-64	0.496	Retain the null hypothesis; there is no difference
	Non-medical prescriber	58	57-58		
'influences on prescribing'	Doctor	19.5	17.5-20	0.306	Retain the null hypothesis; there is no difference
	Non-medical prescriber	18	14-20		
'consequences of prescribing'	Doctor	19	17-21.5	0.601	Retain the null hypothesis; there is no difference
	Non-medical prescriber	19.5	18-21		
'monitoring for safety and effectiveness'	Doctor	17	15-19	0.254	Retain the null hypothesis; there is no difference
	Non-medical prescriber	14	12-20		

No significant differences were identified for any of the four components.

Setting

Comparison of scores for each component and the different settings of primary and secondary care is given in Table 4.29.

Table 4.29. Comparison of component scores across primary and secondary care setting (N=138)

Component	Setting	Median	IQR	P-value	Decision
'the role of professionals and their knowledge and skills'	Primary care	62	56-64	0.033	Reject the null hypothesis; there is a statistically significant difference
	Secondary care	58	49-62		
'influences on prescribing'	Primary care	19	16-20	0.033	Reject the null hypothesis; there is a statistically significant difference
	Secondary care	20	18-20.5		
'consequences of prescribing'	Primary care	19	17-21	0.078	Retain the null hypothesis; there is no difference
	Secondary care	20	18-23		
'monitoring for safety and effectiveness'	Primary care	17	15-19	0.732	Retain the null hypothesis; there is no difference
	Secondary care	16	14-20		

While statistically significant differences were found in terms of 'the role of professionals and their knowledge and skills' and 'influences on prescribing', all scores were generally high and above the midpoint of 48 ('the role of professionals and their knowledge and skills') and 15 ('influences on prescribing'). Those in primary care were more positive around items on their professional role and knowledge and skills while those in secondary care were more positive around items on influences on prescribing.

Years registered as a health professional

Comparison of scores for each component and the number of years each respondent had been registered as a health professional is given in Table 4.30.

Table 4.30. Comparison of component scores and years registered as a health professional (N=138)

Component	Years registered	Median	IQR	P-value	Decision
'the role of professionals and their knowledge and skills'	≤5	52	51-54	0.011	Reject the null hypothesis; there is a statistically significant difference
	6-10	63	53.5-64		
	11-15	56	51-59		
	16-20	62	55-63		
	21-25	60	56-64		
	26-30	64	58-69		
	≥30	62	58-71		
'influences on prescribing'	≤5	20	20-21	0.537	Retain the null hypothesis; there is no difference
	6-10	20	17-20		
	11-15	18.5	17.5-20		
	16-20	19	17.5-20		
	21-25	19	18-20		
	26-30	20	16-20		
	≥30	18	16-21		
'consequences of prescribing'	≤5	21	18-24	0.243	Retain the null hypothesis; there is no difference
	6-10	21	19-24		
	11-15	19	17-20		
	16-20	19	18-20		
	21-25	18	17-21		
	26-30	18	16-22		
	≥30	19	18-21		
'monitoring for safety and effectiveness'	≤5	15	14-17	0.264	Retain the null hypothesis; there is no difference
	6-10	18.5	14-20		
	11-15	16	14-16		
	16-20	17	16-19		
	21-25	16	14-19		
	26-30	18	16-20		
	≥30	17.5	15.5-19.5		

While a statistically significant difference was found in terms of 'the role of professionals and their knowledge and skills', all scores were generally high and above the midpoint of 48. Those with the least experience scored significantly lower than the others.

Years registered as a as prescriber

Comparison of scores for each component and the number of years each respondent had been registered as a prescriber is given in Table 4.31.

Table 4.31. Comparison of component scores and years registered as a prescriber (N=138)

Component	Years registered	Median	IQR	P-value	Decision
'the role of professionals and their knowledge and skills'	≤5	52	49-58	<0.001	Reject the null hypothesis; there is a statistically significant difference
	6-10	63	55-64		
	11-15	52	51-56		
	16-20	63	60-64		
	21-25	59.5	54-63		
	26-30	64	63-65		
	≥30	61	57-72		
'influences on prescribing'	≤5	20	18-20	0.823	Retain the null hypothesis; there is no difference
	6-10	20	17-20		
	11-15	18	17-20		
	16-20	19	17-20		
	21-25	19	18-20		
	26-30	20	16-20		
	≥30	18	16-21		
'consequences of prescribing'	≤5	21	18-23	0.017	Reject the null hypothesis; there is a statistically significant difference
	6-10	21	19-24		
	11-15	19	17.5-21.5		
	16-20	19	16-20		
	21-25	18	17-20		
	26-30	18	16-20		
	≥30	19	16-20		
'monitoring for safety and effectiveness'	≤5	15	14-18	0.041	Reject the null hypothesis; there is a statistically significant difference
	6-10	19	14-20		
	11-15	15	13-16		
	16-20	16.5	16-19		
	21-25	16	14-18		
	26-30	18	16-19.5		
	≥30	18.5	16-20		

While a statistically significant difference was found in terms of 'the role of professionals and their knowledge and skills', all scores were generally high and above the midpoint of 48. Those with the least experience as prescribers scored significantly lower than those with most experience. Overall, the scores for 'consequences of prescribing' and 'monitoring for safety and effectiveness' were more neutral. Those with least experience as prescribers

scored more positively in around the 'consequences of prescribing' but less positively for 'monitoring effectiveness and safety'.

4.4.7 Analysis of textual responses to open questions

This section provides findings generated from the content analysis of the responses to the open questions of: perceived benefits and limitations of prescribing DOACs; positive and negative experiences of prescribing DOACs; and how the appropriate use of DOACs in primary care be further extended. These are presented using a narrative synthesis approach with brief labelling of respondents to protect anonymity.

Perceived benefits and limitations

Ninety-nine respondents (71.7%) provided responses. The overwhelming benefit, cited by 47 respondents was the absence of need for INR monitoring,

> *"we have been overwhelmed with the need to do regular blood monitoring of patients in recent years. This includes warfarin and DMARDS. No additional resources have been made available in spite of a 300% increase in blood tests we are doing for all types of monitoring. Therefore anything which reduces this, such as the use of DOACs instead of warfarin helps us to survive"*
>
> [general practitioner, 26-30yrs prescriber]

The absence of need for monitoring was often mentioned in the context of other benefits such as particular patient groups,

> *"no need for monitoring, especially practical in elderly/housebound"*
>
> [general practitioner, years not stated]
>
> *"good for rural practice and younger patients who can reliably take tablets every day"*
>
> [general practitioner, years not started]

and overall cost,

"no need to monitor therefore cost effective".

[general practitioner, 21-25 yrs prescriber]

Thirteen respondents commented on the likelihood of better adherence,

"patients understand why they take these drugs and often state how it is much easier to take than warfarin especially with the interactions of diet and alcohol".

[nurse, <5 yrs prescriber]

Eleven respondents noted benefits in terms of the evidence base,

"overall the evidence is that DOACs are at least as good as warfarin for preventing stoke and have a lower incidence of fatal bleeding".

[cardiologist, years not started]

Ten respondents commented on the more favourable dosing regimens compared to warfarin,

"…and a single daily dose, not changing like warfarin".

[general practitioner, >5 yrs. prescriber]

A similar number remarked on the benefits in those with labile INRs,

"less likely to get out of therapeutic range…suitable for patients with fluctuating INR". [anaesthetist, >30 yrs. prescriber]

Less commonly cited benefits were: better use of GP time, especially in remote areas; reduced frequency of ADRs; and easier patient management.

The key limitation, cited by 31 respondents, was the lack of a suitable reversal agent,

> *"significant concerns regarding how to reverse anticoagulation in patient who then sustain injury/ head trauma"*
>
> [secondary care doctor, years not started]

> *"anxious about the lack of an easily available reversal agent"*
>
> [general practitioner, years not started]

> *"no antidote yet for rivaroxaban or apixaban"*
>
> [consultant, >30 yrs prescriber]

The high cost of DOACs compared to warfarin was considered a limitation by 17 respondents,

> *"I'd prescribe it more for patients with AF if health board not breathing down my neck about cost"*
>
> [general practitioner, 16-20 yrs prescriber]

One respondent commented that whilst the drug costs were higher, there were savings when considering other associated costs,

> *"costly but saves on nurse/lab/doctor time to dose warfarin"*
>
> [general practitioner, 16-20 yrs prescriber]

Ten respondents were concerned by the lack of ability to monitor anticoagulation status,

> *"the main negative is the lack of longer term follow up to ensure patients CONTINUE to take the drug as prescribed regularly and on time"*. [consultant, 21-25 yrs prescriber]

One respondent noted that this was a particular concern in their area of practice,

"When injecting a joint I prefer to know a patient is on Warfarin as I can just check their INR. If they are on DOAC they have to stop their medication the previous day, I then have to book them in early in the morning and then they take their next dose mid-day. This reduces patient choice as to when I can see them".

[physiotherapist, <5 yrs prescriber]

Eight respondents noted their concerns over the lack of long term evidence of benefit,

"concerned that long term benefits may not be as great as expected, i.e. problems of this group of drugs will show after they have been used for more years especially in elderly patients"

[general practitioner, >30 yrs prescriber]

"I have concerns about the widespread adoption of these drugs and suspect the risks of warfarin are over estimated from old studies not based on efficient, well run, safe monitor in primary care"

and adverse effects,

"I think we do need robust evidence of the risks across the population over the next few years".

Less commonly cited limitations were around perceptions of increased prevalence of adverse effects and dose adjustment in renal impairment.

Positive experiences

Seventy-two respondents (52.2%) provided descriptions of their positive experiences of DOACs. As with the benefits of DOACs, the main positive experiences surrounded the absence of need to monitor INR, cited by 38 respondents,

"90 year old on warfarin for AF for 20 years. Became unable to drive and a lot of strain on family for weekly INR with no capacity in single handed GP to visit frequently".

[general practitioner, years not started]

"a gentleman who had stopped his warfarin due to the difficulties of coming in to get his INR checked as he was away a lot. Changed to DOAC". [general practitioner, 21-25 yrs prescriber]

"patient working abroad was able to continue work because INR monitoring was no longer required"

[general practitioner, 21-25 yrs, prescriber]

Several respondents described similar experiences which were considered particularly relevant to those living in remote areas,

"Initiating anti-coagulation in patient who lives miles away, avoiding blood tests, living over 30 miles from GP surgery".

[general practitioner, 26-30 yrs prescriber]

Nineteen respondents gave descriptions of positive feedback from patients,

"Feedback from patients has been positive - they no longer have to frequently attend the surgery, they can go on holiday more easily, they can be more relaxed with the choice of diet"

[general practitioner, 26-30 yrs prescriber]

"Quality of life improved by not having to come to the practice for his INR bloods and not having to alter dosage"

[general practitioner, years not started]

In some situations, patients had declined warfarin but were willing to commence DOACs,

"another patient would not accept warfarin but did DOAC".

[general practitioner, years not started]

Seven respondents commented on enhanced management of those with previously labile INRs,

"a patient whose INR was impossible to keep in therapeutic range was able to get proper treatment".

[general practitioner, 16-20 yrs prescriber]

Less commonly cited experiences were around better patient management and more rapid, effective anticoagulation.

Negative patient experiences

Descriptions of negative patient experiences were provided by 64 respondents (46.4%), with an additional 19 (13.8%) stating that they had no negative experiences to report.

The key negative experience was around adverse events of bleeding, described by 24 respondents,

"patient admitted with severe upper GI bleed while on prophylactic dose after hip replacement",

[consultant, 21-25 yrs prescriber]

"brisk bleed requiring admission (epistaxis) on switching from warfarin. Specialist initiated and within guideline",

[general practitioner, 26-30 yrs prescriber]

"a patient developed a large knee effusion (no trauma) which was heavily bloodstained. I stopped his DOAC".

[general practitioner, >30 yrs prescriber]

Two of these respondents reported that bleeding had led to death of the patient,

"death of a patient from an intracranial bleed on rivaroxaban".

[general practitioner, years not started]

An additional five respondents commented on issues related to bleeds,

"emergency admission for surgery - prolonged operation due to increased (but not unmanageable) bleeding".

[consultant, years not started]

Thirteen respondents commented on their experiences of non-bleeding adverse events of varying severity and with diverse consequences,

> *"patient developed side effect from DOACs (severe nausea) and returned to warfarin"*. [general practitioner, years not started]

> *"terrible oesophagitis with dabigatran"*

> [general practitioner, >30 yrs prescriber]

Three respondents described issues relating to the consequences of rapid anticoagulation on discontinuing DOACs,

> *"we have had 3 patients who have had strokes shortly after discontinuing DOACS"*. [general practitioner, >30 yrs prescriber]

Less commonly cited negative experiences included issues relating to inadequate monitoring of patients prior to commencing DOACs,

> *"colleagues not monitoring renal function and LFTs so overdosed DOAC and patient admitted"*. [general practitioner, >30 yrs prescriber]

Several described issues related to clinician lack of recognition of the names of DOACs as anticoagulants,

> *"DOAC not stopped despite bleeding as not noted as a blood thinner in same way as warfarin".* [consultant, 21-25 yrs prescriber]

> *"Prescription of dabigatran when enoxaparin hadn't been stopped"*

> [consultant, years not stated]

and patient anxiety,

> *"patients are often wary to start treatment with a DOAC as they are aware of the lack of antidote"*.

> [pharmacist, < 5yrs prescriber]

Comments on NHS Highland guidelines

Seventy-four respondents (53.6%) provided comments in relation to the NHS Highland guidelines. Forty respondents considered these to be accessible, clear and easy to follow,

"easily accessible in NHS Highland formulary",

[general practitioner, years not started]

"guidelines in formulary good. Cardiologists always happy to help if patients not quite fitting n guidelines but I felt merited it",

[general practitioner, years not started]

"NHS highland guidance is excellent and clear for this".

[general practitioner, years not started]

Thirteen respondents commented that they were not aware of the guidelines or had not read them,

"unfamiliarity with them - both for myself and colleagues. People more familiar with warfarin therefore more comfortable",

[general practitioner, years not started]

"…but I will look them up now". [nurse, years not started]

Seven respondents raised concerns over significant differences between guidelines from different sources and also product marketing authorisations,

"don't know that apixaban should be third line, Greater Glasgow and Clyde now has it first line. The guidelines specify renal function as eGFR but the license for all these drugs is CrCl. This can be substantially different. Have had to insert a calculator on Vision to work this out and have had to make sure nurses are updating height and weight etc". [pharmacist, years not started]

Similarly, five respondents commented that the guidelines were out of date,

"Highland guidance appears to be out of date although it could be formulary is too old" [general practitioner, years not started]

Continuing professional development (CPD)

Thirty-seven respondents (26.8%) described a range of CPD activities undertaken relating to DOACs, most commonly symposia, meetings and reading journals,

"attended anticoagulation symposium this year in Stirling on the subject". [nurse, years not started]

"cardiology Heart of the Matter events very useful refresher and update". [general practitioner, > 30 yrs. prescriber]

"I read several journal articles on DOACs in AF when they were first coming into use which I found useful".

[general practitioner, years not started]

Forty respondents (29.0%) remarked on CPD they were planning or would like to see provided. Eleven commented on their own needs to read the NHS guidelines,

"I need to look at the guidelines and the suggested learning module".

[general practitioner, years not started]

Nine respondents suggested further face-to-face events,

"face-to-face to allow questions and answers would be immensely valuable". [nurse, years not started]

with some suggesting specific topics,

"I think a simple update from a pharmacist on interactions, prescribing considerations e.g. dose alterations in renal function, taking with meals etc. would be useful. I am also unfamiliar with if and when monitoring is indicated". [cardiologist, years not started]

One described the need for development of the entire multidisciplinary team, even those not prescribing DOACs,

"I also feel monitoring INRs and dosing widely done by HCAs [healthcare assistants] *and nurses with no understanding of warfarin and DOACs etc is dangerous and there should be an online module that*

everyone involved in INR testing/warfarin monitoring should have to undertake at least once".

Extending the appropriate use of DOACs

Forty-eight respondents (34.8%) provided comments on extending the appropriate use of DOACs. CPD related activities were described by 11 respondents,

> *"further training of safety aspect - a lot of misinformation still being given to patients".* [general practitioner, years not started]

Several of these respondents commented more appropriate use would be derived through increased experience,

> *"need more confidence in using which comes with experience and training. More training will likely lead to more use and eventually more confidence'*. [general practitioner, years not started]

Seven respondents suggested reviewing all patients prescribed anticoagulants for consideration of DOACs,

> *"consideration of switching to DOAC when attending anticoagulation clinic - patients tend to stay on meds long term not always with good reason or proper review".*
>
> [general practitioner, 16-20 yrs prescriber]

Seven respondents remarked on the need to review the NHS Highland guidelines. One of these respondents considered the guideline to be restrictive,

> *"prescribing freedom for prescribers i.e. no restrictive guideline or fear of budgets etc. if they were able to just consider what would be best for the patient in front of them"*. [nurse, < 5yrs prescriber]

Four respondents, however, commented on the need to be cautious in extending the use of DOACs, particularly the need for longer term evidence of safety,

> *"I'd need to hear convincing arguments about why we should - I'm concerned that the potential harms of widespread use are not yet apparent".* [general practitioner, >30 yrs prescriber]

> *"We generally avoid, where possible, starting our patients on any new drugs in our practice until ten years post licensing, although there are situations when we might start new drugs. This is because often problems are not immediately apparent at the time of licensing or in the first few years afterwards, or worse, withheld by drug companies".*

> [general practitioner, >30 yrs prescriber]

4.5 DISCUSSION

4.5.1 Main findings

This survey captured data from mostly experienced medical and nonmedical prescribers across different settings. PCA of the TDF determinants gave 4 components: the role of professionals, their knowledge and skills; influences on prescribing; consequences of prescribing; and monitoring for safety and effectiveness. While component scores for the role of professionals, their knowledge and skills, and influences on prescribing were positive, those for the other 2 components were more neutral. There were low levels of agreement for statements relating to more effective, safer and cost-effective treatment when prescribing DOACs rather than warfarin. There were similar responses around the complexity of bleeding management and detection of over and under-anticoagulation. The lack of need for INR monitoring was, however, identified as a positive aspect of DOAC use.

4.5.2 Strength and weaknesses

This study adds to the limited evidence base on prescribers' perspectives of DOAC use for nonvalvular AF, as identified in a recently published systematic

review (Generalova et al, 2018). Furthermore, this is the first study which based questionnaire items on a theoretical framework thus increasing the likely construct and criterion validity. There are, however, several limitations to the study hence the findings should be interpreted with caution. Although a response rate could not be determined, the number of responses, particularly from secondary care, appears low. As a self-reported study, it may be subject to biases such as social desirability and acquiescence biases. Furthermore, the study was conducted in 1 remote and rural geographical area of Scotland thus the results and conclusions may lack external validity. While the analysis of the open comments add some explanation, this was not a mixed-methods study and hence the summative content analysis does not represent qualitative methodology. Furthermore, the summative content analysis was descriptive and not intended to generate any theory during synthesis.

4.5.3 Interpretation of findings

This study is both relevant and timely given the increase in DOAC prescribing (Loo et al, 2017), and being the first-line recommendation for non-AF management in national and international guidelines (NICE, 2014, January et al, 2014, Kirchhof et al, 2016, Steffel et al 2018). The consequences of prescribing and monitoring for safety and effectiveness had neutral scores. While there was general agreement that implementing DOAC guidelines would be good for patients and organisations, there was markedly less agreement that patients prescribed DOACs in preference to warfarin would be treated more effectively, safely and cost-effectively. At first glance, these findings appear contradictory but it may be that prescribers consider guidelines beneficial to patient care but are less aware of the specific evidence from which the guidelines are derived. Notably, less experienced prescribers were statistically significantly more positive in their responses, which could be as a result of more recent university and practice-based education and training on DOACs or having less real world experience to question the results of even large randomised controlled trials. The majority of respondents in a survey of German physicians considered DOACs equally effective as warfarin and almost half equally safe (Wutzler et al., 2014).

In terms of monitoring for safety and effectiveness, few respondents disagreed that DOAC related bleeding would be more challenging to manage than warfarin. These concerns were also identified in previous surveys of European research network centres and German physicians (Lip et al., 2013, Wutzler et al., 2014). Given that idarucizumab is now licensed for use and is indicated to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery (Pollack et al., 2015) and that reversal agents for other DOACs are being developed (Arbit et al., 2016) , it is likely that these concerns will be abated. Many respondents believed that DOAC-related over and under-anticoagulation could not easily be detected. Again, less experienced prescribers were statistically significantly more positive in their responses. Analysis of the open comments also identified this as a potential issue in relation to non adherence. The specific site of action of DOACs on the coagulation cascade, together with the predictable pharmacokinetic and pharmacodynamic properties and fixed drug dosages (other than renal impairment) eliminate the need and usefulness of INR monitoring (Gómez-Outes et al., 2015). The scores for the role of professionals, their knowledge and skills, and influences on prescribing were much more positive. Responses indicated self-reported knowledge of aspects of DOAC guidelines, evidence base and clinical pharmacology. They were aware of how to initiate and monitor DOACs, responding that this was part of their role, and that they were generally competent and confident. While there were mixed responses on deciding between DOACs and warfarin, local and national guidelines have since been updated with DOACs as first line. For influences on prescribing, the most negative responses were in relation to cost and scrutiny by the health board. Systematic reviews of the cost-effectiveness of DOACs compared to warfarin have recommended that, while further real-world data are required

DOACs are more cost-effective than warfarin despite the higher acquisition costs (Jegathisawaran et al., 2017, Pinyol et al., 2016). The specific findings of the more neutral components and statements with negative responses should be considered to optimise DOAC prescribing for nonvalvular AF. In 2017, Healthcare Improvement Scotland updated their guidance on the use of DOACs in nonvalvular AF with the publication of a rapid review of clinical

effectiveness (HIS, 2017). The lack of direct comparisons between DOACs was noted hence the recommendations were based entirely on indirect evidence from published network meta-analyses. Edoxaban is now recommended as first-line treatment for nonvalvular AF with the other 3 DOACs being second line. The local guidelines in NHS Highland, along with other health boards in Scotland, have been adapted accordingly.
As well as raising awareness of the updated guidance, attention should be paid to specific aspects including the evidence base of effectiveness, safety and cost effectiveness, management of bleeding, issues of over- and under-anticoagulation.

Content analysis of the textual comments captured in this survey complement the quantitative data. Not having to monitor INR was the most cited benefit, particularly for prescribers and patients in remote and rural settings, followed by potentially improved patient adherence. These benefits were reflected in descriptions of positive experiences and patient feedback. The main limitations were the lack of reversal agents, cost and inability to monitor anticoagulation status. Many described experiences of adverse effects including fatal and non-fatal bleeding, and upper GI disturbances.

This study adds to the limited evidence base of prescribers' experiences of DOACs, and is timely given that DOACs are now recommended first line for those with non-valvular AF (NICE, 2014, January et al., 2014, Kirchhof et al., 2016, Steffel et al., 2018, Loo et al., 2017). However, given that data were collected in one remote and rural area of Scotland, the results may lack generalisability and transferability to other settings. Furthermore, the data were collected using a crosssectional survey methodology rather than through a qualitative approach (e.g. interviews and focus groups) which limited the depth of enquiry. As the findings represent perceptions of benefits and limitations, the analysis was not informed by any theoretical framework.

Studies of healthcare provision in remote and rural areas have identified access as an issue, particularly in older populations and those with higher healthcare utility (Prior et al., 2010, Haggerty et al., 2014, Wong at el., 2009, Manthorpe J et al., 2008, King et al., 2009, Rushworth et al., 2018). While many positive perceptions of DOACs identified in this study may be generic to all settings, these are particularly relevant in such areas. The specific site of

action of DOACs on the coagulation cascade, predictable pharmacokinetic and pharmacodynamic properties and fixed dosages eliminate the need and usefulness of INR monitoring (Gomez-Outes et al., 2015). Not having to monitor was perceived as a major benefit, and was highlighted in descriptions of patient positive experiences. However, lack of monitoring was also perceived a limitation, specifically the lack of ability to closely monitor coagulation status. These are original findings, not having been reported in the systematic review of clinicians' experiences, nor any systematic reviews of patients' experiences (Generalova et al., 2018, Loewen et al., 2017, Wilke et al., 2017).

Adverse reactions, most notably bleeding related, were described by many respondents. It is, however, worth noting that evidence so far indicates that DOACs are associated with clinically important reductions in the frequency of major bleeding, including life-threatening bleeding events and, especially, intracranial bleeding, when compared with patients receiving warfarin(January et al., 2014, Kirchhof at al., 2016, Steffel et al., 2018). In the UK, DOACs are labelled 'black triangle drugs' meriting reporting of all adverse reactions (irrespective of severity) to the Medicines and Healthcare products Regulatory Agency (MHRA). Given that under-reporting is a major limitation of pharmacovigilance processes, further research on DOAC reporting is warranted. There were also descriptions of adverse events attributed to rapid reversal of anticoagulation following DOAC discontinuation prior to surgical intervention, as noted by others (Gonzalez-Gonzalez et al., 2013, Levy et al., 2016). Guidelines on the management of patients prescribed DOACs requiring elective and emergency procedures are emerging (Gomez-Outes et al., 2015). Concerns of managing DOAC related bleeding may also diminish with the licensing of idarucizumab to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery (Pollack et al., 2017). Andexanet alfa, a class-specific antidote for the factor Xa inhibitors, is now available and other DOAC reversal agents are in development (Arbit et al., 2016).

Different views were given in relation to DOAC cost, with some describing cost as a limitation while others believed costs reduced given the additional resources incurred in warfarin monitoring. Systematic reviews and meta-

analyses of the cost-effectiveness of DOACs versus warfarin have recommended that, while further real world data are required, DOACs are more cost-effective despite higher prescribing costs (Jegathisawaran et al., 2017, Pinyol et al., 2016).

There was a range of views around the widespread adoption of DOACs with some supporting the evidence base of effectiveness, cost-effectiveness and safety while others were more cautious due to the lack of real-life, longterm evidence. This finding has been identified for many newly launched agents; in a recent study of the adoption of cardiovascular drugs in the United States, physicians were found to be generally conservative, with a minority adopting dabigatran, aliskiren or pitavastatin in the first 15 months of market launch market (Anderson et al., 2018).

4.5.4 Conclusion

This study has demonstrated that prescriber respondents in NHS Highland perceive themselves to be knowledgeable, confident and competent in the use of DOACs for nonvalvular AF. There was, however, markedly less awareness of the evidence base of the effectiveness, safety and cost-effectiveness of DOACs. There were issues around the management of DOAC related bleeding and the identification of over- and under-anticoagulation. Further emphasis of these aspects is required during continuing professional development, and implementation and evaluation of guidelines.

4.6 Reflections and future directions

Given that the guidance issued nationally in Scotland recommends edoxaban first line (HIS, 2017), and that this recommendation has been adopted in NHS Highland (NHS Highland, 2018) there is merit in conducting research relating to edoxaban prescribing in the management of non-valvular AF and how this change has been implemented. This research is reported in Chapter 5.

CHAPTER 5 A cross-sectional survey of prescribers in NHS Highland: determining views and experiences relating to prescribing edoxaban for the management of non-valvular AF

5.1 INTRODUCTION

As noted in Chapter 4, there is a need to focus on edoxaban given its primary role in national and local guidelines. This chapter presents the method, results and discussion of a cross-sectional survey of prescribers' behaviours, views and experiences relating to prescribing edoxaban for the management of non-valvular AF.

5.2 RESEARCH AIM

The aim of this phase of research was to determine prescribers' behaviours, views and experiences relating to prescribing edoxaban for the management of non-valvular AF.

5.2.1 Research questions

In relation to prescribers and edoxaban, the research questions were:

1. how is edoxaban initiated, prescribed and monitored?
2. which behavioural determinants potentially impact behaviours around prescribing edoxaban?
3. what are the perceived benefits and limitations of prescribing DOACs?
4. what are the positive and negative experiences of prescribing DOACs?

5.3 RESEARCH METHOD

The research methodology and method was replicated as described in Chapter 4 with the following exceptions.

i. Questionnaire items focused on edoxaban, rather than DOACs as a group
ii. Increased emphasis was placed on aspects of pharmacovigilance given the issues highlighted in the previous chapter
iii. The initial emailing of the questionnaire took place in April 2019

iv. Given that the behavioural determinant items were very similar, the PCA components identified from the previous survey were used in analysis. Also note that the number of respondents was insufficient to undertake PCA

v. The number of responses precluded any inferential analysis

The final questionnaire can be found in Appendix 5.1

5.4 RESULTS

5.4.1 Demographics

One hundred and three responses were received, 96 (93.2%) from doctors (67 general practitioners), six (5.8%) from pharmacist prescribers and one (1.6%) from a nurse prescriber. As explained in Chapter 4, a response rate could not be calculated. The mean age of the respondents was 45.3 years (standard deviation 11.9 years). Respondents were experienced as health professionals, with just under half (n=48, 46.6%) having twenty of more years of experience as health professionals. Slightly less (n=46, 44.7%) had twenty or more years of experience as prescribers. The demographic characteristics of the respondents are given in Table 5.1.

Table 5.1. Respondent demographics (N=103)

Characteristic	Percentage	Frequency, n
Profession		
Doctor	93.2	96
Pharmacist prescriber	5.8	6
Nurse	1.0	1
Sex		
Male	49.5	51
Female	48.5	50
Prefer not to answer	1.9	2
Academic qualifications		
PhD	1.0	1
MD	5.8	6
MSc	8.7	9
Postgraduate Diploma	22.3	23
Postgraduate Certificate	12.6	13
MBChB (or equivalent)	31.1	32
MPharm	3.9	4
BSc	9.7	10
Practice setting		
Primary care	63.1	65
Secondary care	27.2	28
Other	1.0	1
Missing	8.7	9
Years worked as health professional		
≤5	1.9	2
5-10	7.8	8
11-15	16.5	17
16-20	25.2	26
21-25	14.6	15
26-30	11.7	12
>30	20.4	21
Missing	1.9	2
Years worked as prescriber		
≤5	6.8	7
6-10	7.8	8
11-15	14.6	15
16-20	24.3	25
21-25	14.6	15
26-30	12.6	13
>30	17.5	18
Missing	1.9	2

5.4.2 Current practice with edoxaban

Current practice relating to the prescribing of edoxaban, and in relation to other DOACs in given in Table 5.2

Table 5.2. Approximate frequency of edoxaban prescribing behaviours (N=103)

Prescribing behaviour	Weekly % (n)	Monthly % (n)	Annually % (n)	Never % (n)	Missing % (n)
Initiate edoxaban	1.0 (1)	39.8 (41)	28.2 (29)	30.1 (31)	1.0 (1)
Switch patients from warfarin to edoxaban	0	22.3 (23)	42.7 (44)	34.0 (35)	1.0 (1)
Switch patients from other DOACs to edoxaban	0	16.5 (17)	28.2 (29)	54.4 (56)	1.0 (1)

Twenty-nine respondents never prescribed edoxaban and were not likely to do so in the near future hence were excluded from further analysis. These 29 respondents were psychiatrists, anaesthetists, anaesthetic specialists, renal specialists, orthopaedic/trauma/emergency medicine specialists and GPs.

Of the 74 respondents prescribing edoxaban, the majority (n=64, 86.5%) reported being aware that edoxaban was the first line recommendation within the NHS guidelines. Almost all respondents (n=61, 88.9%) had been encouraged to implement this recommendation. Only around one third (n=26, 35.1%) had switched all appropriate patients from warfarin to edoxaban, with slightly more (n=30, 40.5%) having switched all appropriate patients from other DOACs to edoxaban.

Seven respondents (9.5%) reported that patients had experienced adverse drug reactions to edoxaban. Of these, two respondents (28.6%) had submitted a Yellow Card report to the Medicines and Healthcare products Regulatory Agency (MHRA). Twenty-seven respondents (36.5%) reported that patients had experienced adverse drug reactions to other DOACs, five (18.5%) of whom had submitted a Yellow Card report to the MHRA.

5.4.3 Behavioral determinants

The responses to items the TDF of behavioural determinants are given in Tables 5.3-5.10.

Table 5.3. Response to items in the domain of knowledge (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have sufficient knowledge of the guidelines to allow me to prescribe edoxaban safely and effectively	14.9 (11)	71.6 (53)	8.1 (6)	4.1 (3)	1.4 (1)	0
I have sufficient knowledge of the clinical pharmacology of edoxaban to allow me to prescribe safely and effectively	10.8 (8)	64.9 (48)	16.2 (12)	6.8 (5)	1.4 (1)	0
I have sufficient knowledge of the evidence base of edoxaban to allow me to prescribe safely and effectively	8.1 (6)	66.2 (49)	13.5 (10)	9.5 (7)	1.4 (1)	1.4 (1)
I have sufficient knowledge of how to initiate edoxaban	12.2 (9)	64.1 (57)	8.1 (6)	2.7 (2)	0	0
I have sufficient knowledge of how to monitor the effectiveness and toxicity of edoxaban	1.4 (1)	56.8 (42)	25.7 (19)	12.2 (9)	0	4.1 (3)
I have sufficient knowledge of when and how to switch patients from warfarin to edoxaban	6.8 (5)	58.1 (43)	23.0 (17)	9.5 (7)	1.4 (1)	1.4 (1)
I have sufficient knowledge of when and how to switch patients from other DOACs to edoxaban	1.4 (1)	47.3 (35)	32.4 (24)	14.9 (11)	1.4 (1)	2.7 (2)
I have sufficient knowledge of how to manage adverse reactions of edoxaban	1.4 (1)	56.8 (42)	25.7 (19)	16.2 (12)	0	0

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

While responses to most statements were positive, there was less agreement relating to knowledge around switching patients from warfarin to edoxaban (n=48, 64.9% strongly agree/ agree), switching patients from other DOACs to edoxaban (n=36, 48.7% strongly agree/ agree) and monitoring adverse reactions of edoxaban (n=43, 58.2% strongly agree/ agree).

Table 5.4 Response to items in the domain of professional role and identity (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
It is part of my role to initiate edoxaban	9.5 (7)	66.2 (49)	14.9 (11)	5.4 (4)	2.7 (2)	1.4 (1)
I should only prescribe edoxaban when initiated by others	2.7 (2)	4.1 (3)	9.5 (7)	62.2 (46)	20.3 (15)	1.4 (1)
Only specialists should initiate edoxaban	1.4 (1)	2.7 (2)	12.2 (9)	60.8 (45)	21.6 (16)	1.4 (1)
It is part of my role to switch patients from other DOACs to edoxaban where indicated	2.7 (2)	63.5 (47)	24.3 (18)	8.1 (6)	0	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The majority of respondents were in agreement that the various prescribing actions relating to edoxaban were part of their role and not restricted to specialists. Three quarters of respondents (n=56, 75.7% agreed/ strongly agreed) that it was part of their role to initiate edoxaban, with slightly less (n = 49, 66.2% agreed/strongly agreed) that it was their role to switch patients from other DOACs to edoxaban, where indicated.

Table 5.5. Response to items in the domain of belief of capabilities (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I am confident in my ability to initiate edoxaban	14.9 (11)	64.9 (48)	16.2 (12)	4.1 (3)	0	0
I am confident in switching patients from warfarin to edoxaban	9.5 (7)	56.8 (42)	25.7 (19)	8.1 (6)	0	0
I am confident in switching patients from other DOACs to edoxaban	6.8 (5)	55.4 (41)	28.4 (21)	8.1 (6)	0	1.4 (1)
I am competent in initiating edoxaban	13.5 (10)	70.3 (52)	12.2 (9)	1.4 (1)	0	2.7 (2)
I am competent in switching patients from warfarin to edoxaban	10.8 (8)	60.8 (45)	24.3 (18)	2.7 (2)	0	1.4 (1)
I am competent in switching patients from other DOACs to edoxaban	9.5 (7)	62.2 (46)	25.7 (19)	2.7 (2)	0	0

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Respondents were in agreement that they were both confident and competent in various prescribing activities relating to initiating edoxaban, switching patients from warfarin to edoxaban and switching patients from other DOACs to edoxaban. The lowest levels of agreement were in relation to being confident in switching from other DOACs to edoxaban (n=46, 62.2% agreed/ strongly agreed) and for being confident in switching from warfarin to edoxaban (n=49, 66.3% agreed/ strongly agreed).

Table 5.6. Response to items in the domain of optimism (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
Implementing the guidelines on prescribing edoxaban will be better for patients	1.4 (1)	50.0 (37)	36.5 (27)	8.1 (6)	0	4.1 (3)
Implementing the guidelines on prescribing edoxaban will be better for my NHS organisation	5.4 (4)	63.5 (47)	24.3 (18)	2.7 (2)	2.7 (2)	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The majority of respondents were optimistic around the use of the NHS Highland guidelines on edoxaban and benefits for patients (n=38, 51.4% agreed/ strongly agreed), and the organisation (n=51, 68.9%).

Table 5.7. Response to items in the domain of beliefs of conseque**nces** (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more effectively	6.8 (5)	48.6 (36)	37.8 (28)	5.4 (4)	0	1.4 (1)
If I prescribe edoxaban rather than warfarin, I believe that patients will have less adverse effects	6.8 (5)	35.1 (26)	47.3 (35)	8.1 (6)	0	2.7 (2)
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more cost effectively	5.4 (4)	40.5 (30)	40.5 (30)	9.5 (7)	1.4 (1)	2.7 (2)
If I prescribe edoxaban rather than other DOACs, I believe that patients will be treated more effectively	0	20.3 (15)	56.8 (42)	18.9 (14)	2.7 (2)	1.4 (1)
If I prescribe edoxaban rather than other DOACs, I believe that patients will have less adverse effects	0	13.5 (10)	66.2 (49)	16.2 (12)	2.7 (2)	1.4 (1)
If I prescribe edoxaban rather than other DOACs , I believe that patients will be treated more cost effectively	5.4 (4)	52.7 (39)	32.4 (24)	4.1 (3)	1.4 (1)	4.1 (3)
If I switch patients on other DOACs to edoxaban, I believe that patient care may be compromised	1.4 (1)	10.8 (8)	29.7 (22)	50.0 (37)	5.4 (4)	2.7 (2)
If I prescribe edoxaban rather than other DOACs, I believe that my management of severe bleeding will be more challenging	0	4.1 (3)	47.3 (35)	43.2 (32)	4.1 (3)	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Respondents, in general, were rather ambivalent about the consequences of prescribing edoxaban in relation to outcomes of effectiveness (n=41, 55.4% agreed/ strongly agreed), safety (n= 31, 41.9% agreed/ strongly agreed) and cost-effectiveness (n=34, 45.9%) in comparison to treatment with

warfarin. There was much less agreement around the consequences of prescribing edoxaban rather than other DOACs in terms of effectiveness (n=15, 20.3% agreed) and safety (n=10, 13.5% agreed). However, there was more agreement relating to cost-effectiveness (n=43, 57.1% agreed/ strongly agreed). There was uncertainty around compromising patient care by switching patients on other DOACs to edoxaban (n=31, 41.9% unsure/ agreed/ strongly agreed), and that management of severe bleeding will be more challenging when prescribing edoxaban rather than other DOACs (n = 38, 51.4% unsure/ agreed).

Table 5.8. Response to items in the domain of memory, attention and decision processes (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I find the guidelines on edoxaban easy to interpret	5.4 (4)	64.9 (48)	21.6 (16)	4.1 (3)	0	5.4 (3)
I find it difficult to decide whether to prescribe edoxaban, rivaroxaban, dabigatran or apixaban	2.7 (2)	17.6 (13)	18.9 (14)	54.1 (40)	4.1 (3)	2.7 (2)
Others have to remind me to prescribe edoxaban according to the guidelines	0	10.8 (8)	14.9 (11)	60.8 (45)	9.5 (7)	4.1 (3)
Unless contra-indicated, I intend to prescribe edoxaban for all new patients with non-valvular AF	9.5 (7)	64.9 (48)	16.2 (12)	6.8 (5)	0	2.7 (2)
I have sufficient support from specialists to enable me to prescribe edoxaban safely and effectively	8.1 (6)	58.1 (43)	27.0 (20)	2.7 (2)	2.7 (2)	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The responses from more than one third of respondents indicated difficulty in selecting a DOAC (n=29, 39.2% unsure/ agree/ strongly agree). Two thirds of respondents agreed/ strongly agreed that they had sufficient support from specialists to enable me to prescribe edoxaban safely and effectively (n=49, 64.2%).

Table 5.9. Response to items in the domain of social influences (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
My prescribing of edoxaban is discouraged by my peers	1.4 (1)	0	17.6 (13)	64.9 (48)	14.9 (11)	1.4 (1)
My prescribing of edoxaban is discouraged by my organisation	0	0	10.8 (8)	70.3 (52)	14.9 (11)	4.1 (3)
My prescribing of edoxaban is discouraged by specialists	0	0	13.5 (10)	73.0 (54)	12.2 (9)	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

Responses within this domain were positive with few agreeing that prescribing of edoxaban was discouraged by their peers, specialists or their organisation).

Table 5.10. Response to items in the domain of emotions (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I feel anxious when initiating edoxaban	0	6.8 (5)	16.2 (12)	63.5 (47)	10.8 (8)	2.7 (2)
I feel anxious when switching patients from warfarin to edoxaban	0	9.5 (7)	21.6 (16)	58.1 (43)	8.1 (6)	2.7 (2)
I feel anxious when switching patients from edoxaban to other DOACs	0	8.1 (6)	24.3 (18)	58.1 (43)	6.8 (5)	2.7 (2)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

In terms of emotions, there appeared to be few issues around prescriber anxiety when either initiative edoxaban or switching patients from either warfarin or other DOACs to edoxaban.

5.4.4 Principal component analysis

As described earlier, PCA is a statistical approach to identify a smaller number of components of interrelated variables which can then be used as outcome measures for further statistical analysis. Given the number of responses to the edoxaban questionnaire, it was not possible to undertake PCA. With 33 questionnaire TDF items, this would have required a minimum of 33 x 5 = 165 response. However, as the TDF items were largely the same as those used in the survey reported in Chapter 4, the edoxaban TDF items were organised into the same components. These are described in Tables 5.11-5.14.

Table 5.11. Component 1, items related to 'the role of professionals and their knowledge and skills' (n=16)

Statements	TDF domain
I have sufficient knowledge of the guidelines to allow me to prescribe edoxaban safely and effectively	Knowledge
I have sufficient knowledge of the clinical pharmacology of edoxaban to allow me to prescribe safely and effectively	Knowledge
I have sufficient knowledge of the evidence base of edoxaban to allow me to prescribe safely and effectively	Knowledge
I have sufficient knowledge of how to initiate edoxaban	Knowledge
I have sufficient knowledge of how to monitor the effectiveness and toxicity of edoxaban	Knowledge
I have sufficient knowledge of how to manage adverse reactions of edoxaban	Knowledge
It is part of my role to initiate edoxaban	Professional role and identity
I should only prescribe edoxaban when initiated by others	Professional role and identity
Only specialists should initiate edoxaban	Professional role and identity
I am confident in my ability to initiate edoxaban	Beliefs of capabilities
I am competent in initiating edoxaban	Beliefs of capabilities
I find the guidelines on edoxaban easy to interpret	Memory, attention and decision process
I find it difficult to decide whether to prescribe edoxaban, rivaroxaban, dabigatran and apixaban	Memory, attention and decision process
Others have to remind me to prescribe edoxaban according to the guidelines	Memory, attention and decision process
I have sufficient support from specialists to enable me to prescribe edoxaban safely and effectively	Environmental context and resources
I feel anxious when initiating edoxaban	Emotions

Table 5.12. Component 2, items related to 'influences on prescribing' (n=3)

Statement	TDF domain
	Social influences
My prescribing of edoxaban is discouraged by my organisation	Social influences
My prescribing of edoxaban is discouraged by my peers	Social influences

Table 5.13. Component 3, items related to 'consequences of prescribing' (n=5)

Statement	Original TDF
Implementing the guidelines on prescribing edoxaban will be better for patients	Optimism
Implementing the guidelines on prescribing edoxaban will be better for my NHS organization	Optimism
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more effectively	Beliefs of consequences
If I prescribe edoxaban rather than warfarin, I believe that patients will have less adverse effects	Beliefs of consequences
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more cost effectively	Beliefs of consequences

Table 5.14. Component 4, items related to 'monitoring for safety and effectiveness' (n=1)

Statement	TDF domain
If I prescribe edoxaban rather than other DOACs, I believe that my management of severe bleeding will be more challenging	Beliefs of consequences

Given that there is only one item within this component, this will not feature in any further analysis.

Internal consistency values (Cronbach's alpha) were calculated for the three remaining components, aiming for values greater than 0.7, with all negatively worded items reversed.

Tables 5.15-5.17 give the item responses and Cronbach's alpha values for each component, along with median and IQR values.

Table 5.15. Component 1, responses to items related to 'the role of professionals and their knowledge and skills' (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
I have sufficient knowledge of the guidelines to allow me to prescribe edoxaban safely and effectively	14.9 (11)	71.6 (53)	8.1 (6)	4.1 (3)	1.4 (1)	0
I have sufficient knowledge of the clinical pharmacology of edoxaban to allow me to prescribe safely and effectively	10.8 (8)	64.9 (48)	16.2 (12)	6.8 (5)	1.4 (1)	0
I have sufficient knowledge of the evidence base of edoxaban to allow me to prescribe safely and effectively	8.1 (6)	66.2 (49)	13.5 (10)	9.5 (7)	1.4 (1)	1.4 (1)
I have sufficient knowledge of how to initiate edoxaban	12.2 (9)	64.1 (57)	8.1 (6)	2.7 (2)	0	0
I have sufficient knowledge of how to monitor the effectiveness and toxicity of edoxaban	1.4 (1)	56.8 (42)	25.7 (19)	12.2 (9)	0	4.1 (3)
I have sufficient knowledge of how to manage adverse reactions of edoxaban	1.4 (1)	56.8 (42)	25.7 (19)	16.2 (12)	0	0
It is part of my role to initiate edoxaban	9.5 (7)	66.2 (49)	14.9 (11)	5.4 (4)	2.7 (2)	1.4 (1)
*I should only prescribe edoxaban when initiated by others	2.7 (2)	4.1 (3)	9.5 (7)	62.2 (46)	20.3 (15)	1.4 (1)
Only specialists should initiate edoxaban	1.4 (1)	2.7 (2)	12.2 (9)	60.8 (45)	21.6 (16)	1.4 (1)
I am confident in my ability to initiate edoxaban	14.9 (11)	64.9 (48)	16.2 (12)	4.1 (3)	0	0
I am competent in initiating edoxaban	13.5 (10)	70.3 (52)	12.2 (9)	1.4 (1)	0	2.7 (2)
I find the guidelines on edoxaban easy to interpret	5.4 (4)	64.9 (48)	21.6 (16)	4.1 (3)	0	4.1 (3)
*I find it difficult to decide whether to prescribe edoxaban, rivaroxaban, dabigatran and apixaban	2.7 (2)	17.6 (13)	18.9 (14)	54.1 (40)	4.1 (3)	2.7 (2)
*Others have to remind me to prescribe edoxaban according to the guidelines	0	10.8 (8)	14.9 (11)	60.8 (45)	9.5 (7)	4.1 (3)
I have sufficient support from specialists to enable me to prescribe edoxaban safely and effectively	8.1 (6)	58.1 (43)	27.0 (20)	2.7 (2)	2.7 (2)	1.4 (1)

*I feel anxious when initiating edoxaban	0	6.8 (5)	16.2 (12)	63.5 (47)	10.8 (8)	2.7 (2)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing; * reverse scored)

The Cronbach's alpha value at 0.874 is greater than 0.7 therefore the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree (negatively worded items reverse scored) gives the minimum possible value for the scale of 16 (representing most negative responses) and the maximum possible value for the scale of 80 (representing most positive responses) and a midscale point of 48.

With a median value of 61 and IQR of 58-64 (minimum 38, maximum 76), respondents generally gave positive responses.

Table 5.16. Component 2, items related to 'influences on prescribing' (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	SD % (n)	M % (n)
*My prescribing of edoxaban is discouraged by my peers	1.4 (1)	0	17.6 (13)	64.9 (48)	14.9 (11)	1.4 (1)
*My prescribing of edoxaban is discouraged by my organization	0	0	10.8 (8)	70.3 (52)	14.9 (11)	4.1 (3)
*My prescribing of edoxaban is discouraged by specialists	0	0	13.5 (10)	73.0 (54)	12.2 (9)	1.4 (1)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing; * reverse scored)

The Cronbach's alpha value at 0.852 is greater than 0.7 therefore the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree (negatively worded items reverse scored) gives the minimum possible value for the scale of 3 (representing most negative responses) and the maximum possible value for the scale of 15 (representing most positive responses) and a midscale point of 9.

With a median value of 12 and IQR of 12-12 (minimum 9, maximum 15), respondents generally gave positive responses.

Table 5.17. Component 3, responses to items related to 'consequences of prescribing' (N=74)

Statements	SA % (n)	A % (n)	U % (n)	D % (n)	S % (n)	M % (n)
Implementing the guidelines on prescribing edoxaban will be better for patients	1.4 (1)	50.0 (37)	36.5 (27)	8.1 (6)	0	4.1 (3)
Implementing the guidelines on prescribing edoxaban will be better for my NHS organisation	5.4 (4)	63.5 (47)	24.3 (18)	2.7 (2)	2.7 (2)	2.7 (2)
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more effectively	6.8 (5)	48.6 (36)	37.8 (28)	5.4 (4)	0	1.4 (1)
If I prescribe edoxaban rather than warfarin, I believe that patients will have less adverse effects	6.8 (5)	35.1 (26)	47.3 (35)	8.1 (6)	0	2.7 (2)
If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more cost effectively	5.4 (4)	40.5 (30)	40.5 (30)	9.5 (7)	1.4 (1)	2.7 (7)

(SA, strongly agree; A, agree; U, unsure; D, disagree; SD, strongly disagree; M, missing)

The Cronbach's alpha value at 0.733 is greater than 0.7 therefore the scale is considered to be reliable. Scoring 1 for strongly disagree to 5 for strongly agree (negatively worded items reverse scored) gives the minimum possible value for the scale of 5 (representing most negative responses) and the maximum possible value for the scale of 25 (representing most positive responses) and a midscale point of 15.

With a median value of 17 and IQR of 16-19.75 (minimum 9, maximum 24), respondents generally gave neutral responses.

Given the number of responses, sub-analysis to rest for differences in scores (e.g. health professionals, years of experience etc.) could not be conducted.

5.4.5 Analysis of textual responses to open questions

As in Chapter 4, this section provides findings generated from the content analysis of the responses to the open questions of: oral anticoagulant of choice for new patients with non-valvular AF; perceived benefits and limitations of implementing of guidelines on edoxaban; and patient adverse reactions to either edoxaban or other DOACs.

Oral anticoagulant of choice for new patients with non-valvular AF

All respondents provided comments, with three quarters (n=56, 75.7%) opting for the guideline recommendation of edoxaban, and a minority for rivaroxaban (n=9, 12.2%), apixaban (n=4, 5.4%), warfarin (n=4, 5.4%), and one respondent stating 'NOAC'.

Justification was largely in the form of edoxaban being recommended within the guidelines (n=36),

> *"Because it is the current formulary choice".*
>
> [general practitioner, 26-30 yrs prescriber]

The selection of five respondents was based on familiarity,

> *"Familiar with this".* [general practitioner, 26-30 yrs. prescriber]
>
> *"I can remember the dosing and interactions".*
>
> [general practitioner, 26-30 yrs. prescriber]

Four respondents based choice on adverse event profile,

> *"Less bleeds for same stroke prevention as rivaroxaban"*.
>
> [general prescriber, 16-20 yrs prescriber]

Several noted issues relating to edoxaban in those with compromised renal function as justification for selecting rivaroxaban,

"We have had several incidences of patients being discharged from Raigmore on the wrong dose of edoxaban for renal function or weight".

[general practitioner, 5-10 yrs prescriber]

Other less commonly cited justification included advice from specialists, cost, adherence and drug-drug interactions.

Benefits relating to implementing of guidelines on edoxaban

Thirty-one respondents (41.9%) provided comments in relation to benefits. The main benefit, cited by nine respondents, was the lack of INR monitoring,

"Patients do not require monitoring of INR and this has meant increased availability of nurse appointments".

[general practitioner, 21-25 yrs prescriber]

Eight respondents cited cost implications,

"... cost benefit mainly".

[general practitioner, 16-20 yrs prescriber]

Less commonly cited benefits were related to immediate anticoagulation, easier dosing, being 'better' for patients and health professionals, and safety.

Limitations relating to implementing of guidelines on edoxaban

Twenty-four responses (32.4%) were provided, describing a range of aspects of edoxaban prescribing.

Four respondents described issues relating to patients' concerns, particularly around switching from one anticoagulant to another,

"Hassle for doctors and patients switching medicines that are long-standing and patients happy with the old way",

[general practitioner, 16-20 yrs prescriber]

"Patients anxious about switching to new medicine as many have been on warfarin for long time".

[general practitioner, 21-25 yrs prescriber]

Four respondents remarked on issues around dosing in patients with renal insufficiency,

"…dosage reductions required in renal impairment".

[pharmacist, 5-10 yrs prescribers]

Three respondents noted issues relating to easy access of information on the NHS guidelines,

"Difficult to access any NHS Highland guidelines when working as a locum as requires access to NHS intranet. GPs cannot access this from outwith a practice (unless they purchase an IT key system)".

[general practitioner, >30 yrs prescriber]

Three cited concerns around the evidence base to support the use of edoxaban compared to other DOACs,

"Less good outcomes compared to other DOACS and higher risk of bleeding". [general practitioner, 26-30 yrs prescriber]

Less comply cited limitations were the time and hassle of switching and not being able to monitor coagulation status.

Patient adverse events on receiving edoxaban or other DOACs

Twenty-four respondents (32.4%) provided descriptions of adverse events, most commonly bleeding which was cited by 22 respondents. Three of these respondents described cases of cerebral haemorrhage and intracranial haemorrhage and two others stated *"major"* bleeds. Several noted that while patients had experienced bleeding, they believed that this would have happened irrespective of the anticoagulant,

"Occasional bleeding as they would have had were they on warfarin",

[general practitioner, 26-30 yrs prescriber]

"Nose bleeds but would have happened whichever type of anticoagulant". [general practitioner, 16-20 yrs prescriber]

Less commonly cited adverse events were rash, arthralgia and gastrointestinal problems

Other comments on prescribing edoxaban and other DOACs.

Eight respondents (10.8%) provided responses in relation to "any other comments". These included DOACs being easier for patients, and being resistant to change to edoxaban as familiar with other DOACs.

One respondent commented on the need to ensure consistent information in all sources,

"Update NHS highland shared clinical guidelines to reflect formulary".

[general practitioner, 16-20 yrs prescriber]

Others noted specific issues in relation to providing guidance in specific situations,

"Formulary guidelines need to take account of adults potentially being on DOAC and give a guide on what to do (e.g. contraindications) especially with guidelines that initiate heparin/ Fondaparinux. Better guidance needed on what to do if adults present needing emergency surgery e.g. appendicitis or hip fracture. In my view access to Factor Xa test is an essential going forward to help deal with these situations and others, e.g. adults with CVA where unclear if has taken the DOAC or not can have a big impact on emergency treatment decisions, e.g. around lysis". [consultant, 21-25 yrs prescriber]

"Perhaps a risk-based approach could be used by some specialists. Apixaban for patients with high risk of events (bleeding or stroke). Apixaban has the lowest HR for major bleeding, except unlicensed edoxaban half-dose which has questionable efficacy",

[cardiologist, 16-20 yrs prescriber]

5.5 DISCUSSION

5.5.1 Main findings

This survey captured data from mostly experienced medical and nonmedical prescribers across different settings. While almost all respondents had been encouraged to implement this recommendation of prescribing edoxaban, less than one third had either switched patients from warfarin or other DOACs to edoxaban. The following three PCA components identified in the previous survey were applied to the TDF determinants 4: the role of professionals, their knowledge and skills; influences on prescribing; and consequences of prescribing. While component scores for the first two components were positive, the scores for consequences of prescribing were more neutral. Although a number of respondents described edoxaban (and other DOAC) related ADRs, very few had submitted a Yellow Card report to the MHRA.

5.5.2 Strength and weaknesses

Many of the study strengths and weaknesses are as described for the survey reported in Chapter 4 hence these are not repeated here. One further strength is the focus on edoxaban which is therefore highly relevant given the policy and practice direction in Scotland and NHS Highland. The main additional weakness surrounds the number or response. As explained in Chapter 4, a response rate cannot be determined but the number of responses for the edoxaban survey is markedly lower across all professional groups than that for the DOACs survey. While a number of factors may have influenced this reduced uptake, there may be questionnaire fatigue. Furthermore, while the theoretical base of the questionnaire items may enhance content and construct validity, this resulted in a rather long questionnaire. One consequence of the relatively low number of responses was that it was not statistically valid to conduct PCA which requires a minimum number of responses for five times (or even time times) the number of questionnaire items. The decision was taken to use the PCA components generated from Chapter 4. While this may be reasonable given that the items were largely the same, it may lead to some issues around the

validity of the findings, interpretation and conclusions. The low number of responses, both generally and across specific sub-populations, precluded any inferential analysis.

5.5.3 Interpretation of findings

This study is both relevant and timely. As noted earlier, DOAC prescribing in the UK has significantly increased in recent years (Loo et al, 2017). In a more recent publication, Sheth et al. (2019) studied the association of stroke and bleed events in nonvalvular AF patients with DOACs in NHS England between 2013 and 2016. The results on DOAC prescribing demonstrated an increase in the number of anticoagulation prescriptions, with the mean proportion of DOAC prescriptions increasing from 4.4% to 21.4% from 2013 to 2016, giving an average increase in the proportion of DOAC prescriptions by 122% per annum. The focus on edoxaban is particularly important given its first line recommendation for non-valvular AF nationally and locally. Guidance for Scotland produced by HIS in 2017 and updated in 2018 based on a rapid review of the literature identified little differences in clinical efficacy between the different DOACs. Given the significant differences in cost, edoxaban was recommended as the first line DOAC (NICE, 2015). This recommendation was adopted in NHS Highland in the regional drug formulary (NHS, Highland 2018). In the study reported in this chapter, the majority of respondents (86.5%) were aware that edoxaban was the first line recommendation. Similarly, the majority (75.5%) stated that edoxaban was their first choice DOAC, largely for reasons of this being the formulary recommendation and familiarity in prescribing.

While the majority of respondents (88.9%) had been encouraged to implement the national and local recommendation of edoxaban being first line recommendation, fewer (35.1%) had switched all appropriate patients from warfarin to edoxaban, with slightly more (n=30, 40.5%) having switched all appropriate patients from other DOACs to edoxaban. There could be several explanations for these data on switching. Caution in prescribing new agents due to the lack of real-life, long-term evidence has been identified for many newly launched agents. A recent study reported the

adoption of cardiovascular drugs by a cohort of primary care physicians and cardiologists in the United States. Those sampled regularly prescribed anticoagulants, antihypertensives and statins. The physicians were found to be generally conservative, with a minority adopting dabigatran, aliskiren or pitavastatin in the first 15 months of market launch market (Anderson et al., 2018).

There may also be issues of lack of knowledge, confidence and competence in relation to switching. While responses to most knowledge statements were positive, there was less agreement relating to knowledge around switching patients from warfarin to edoxaban (64.9% strongly agree/ agree) and switching patients from other DOACs to edoxaban (48.7% strongly agree/ agree). Similarly, for statements relating to belief of capabilities, the lowest levels of agreement were in relation to being confident in switching from other DOACs to edoxaban (62.2% agreed/ strongly agreed), and for being confident in switching from warfarin to edoxaban (66.3% agreed/ strongly agreed) confident. Furthermore, respondents were rather ambivalent about the consequences of prescribing edoxaban in relation to outcomes of effectiveness (55.4% agreed/ strongly agreed), safety (41.9% agreed/ strongly agreed) and cost-effectiveness (45.9%) in comparison to treatment with warfarin. There was much less agreement around the consequences of prescribing edoxaban rather than other DOACs in terms of effectiveness (20.3% agreed) and safety (n=10, 13.5% agreed). There was uncertainty around compromising patient care by switching patients on other DOACs to edoxaban (41.9% unsure/ agreed/ strongly agreed). These findings are similar to those presented in Chapter 4 in terms of responses to items on DOACs in general.

There is also a notable lack of guidance on several of the key international guidelines described in Chapter 1.

The 2014 American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society provide no guidance on switching from warfarin to DOACs of switching DOACs. The 2016 European Society of Cardiology provide little specific guidance on switching from warfarin to DOACs of switching DOACs. It is stated within the guidelines

that should a patient suffer a stroke or TIA whilst taking an anticoagulant, switching to another anticoagulant should be considered. In addition, there is the recommendation of switching from warfarin to a DOAC when a high time in therapeutic range cannot be sustained (Kirchhof et al., 2016). However, the 2018 European Heart Rhythm Association guidance provides detailed information on switching from warfarin to DOAC, and vice versa, and how to switch from one DOAC to another. In switching from warfarin, it is recommended that the DOAC can immediately be initiated once the INR is <2.0, delaying immediately or delaying till the next day if between 2.0 and 2.5, and rechecking in one to three days if greater than 2.5. In switching between DOACs, an alternative can be initiated when the next dose of the DOAC is due, except in situations where higher than therapeutic plasma concentrations are expected (e.g. in a patient with impaired renal function). In such situations, a longer interval in between DOACs is recommended (Barrett et al., 2017).

In Scotland, neither the national guidance on DOACs published in 2018 nor the local guidelines provide any detail on how to switch patients for either warfarin or other DOACs to edoxaban (NHS Highland, 2018). It is clear from the results of this study that such guidance is warranted, and the European Heart Rhythm Association guidance could form the basis of such recommendations.

A small number of studies have also reported data relating to switching from warfarin to DOACs or from one DOAC to another. Of the studies in the systematic review in Chapter 3, Andrade et al. reported some data on switching. In a study of 175 physicians in Canada, prior use of warfarin was reported in 55% of apixaban, 83% of dabigatran, and 48% of rivaroxaban patients respectively. The main reason to switch the anticoagulation therapy was the physician's recommendation in just over half of the respondents (Andrade et al., 2016). No data were reported on physicians views and experiences of switching.

Hale et al (2016) aimed to test the hypothesis that warfarin-treated patients with AF who elected to change therapy would be younger and with fewer

comorbidities as compared to those patients who chose to remain on warfarin (Hale et al., 2016). Data of demographics and comorbid conditions, stroke and bleeding risk scores, and reasons for switching were abstracted for 3873 patients. Patients who switched from warfarin to a DOAC had similar baseline characteristics, risk scores, and insurance status but differed in baseline creatinine clearance. The most common reasons for switching were patient related ease of use concerns as opposed to clinical reasons. A minority of patients that switched to a DOAC switched back to warfarin by the end of the study period (Hale et al., 2016).

Baker et al. (2019) examined switching and discontinuation rates for the three most frequently initiated DOACs in non-valvular AF patients in the US. Data of over forty thousand patients were extracted from a prescription claims database. During the follow-up period, the drug switching rates of patients treated with apixaban, rivaroxaban, and dabigatran were 3.6%, 6.3%, and 11.1%, respectively. After controlling for differences in patient characteristics, patients treated with rivaroxaban and dabigatran had a significantly greater likelihood for drug switching than patients treated with apixaban. No data were provided on the reasons for switching or the experiences of prescribers and patients.

A small study in Ireland aimed to identify the reasons for patients switching from a DOAC to (or back to) warfarin. Data were prospectively collected from a four year period in a warfarin dose adjustment clinic. Of the 40 patients identified as having switched from a DOAC to warfarin, the most common reasons for switching were bleeding, re thrombosis and renal deterioration. Other reasons included medication interactions and adverse events. The authors concluded that switching from a DOAC to warfarin was seldom deemed necessary by clinicians.

In those situations where a switch in treatment is planned, patients must be part of the decision-making process. The need for this is outlined in many evidence-based guidelines and statements and is central to the guidance issued by NICE in 2009 entitled, ‘Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence’. Patient involvement in relation to decisions around anticoagulants as part of non-

valvular AF management is also highlighted in the local, national and international documents previously described (NICE, 2009,).

As described earlier, the PCA components identified from the analysis of the data in Chapter 4 were adopted in Chapter 5, namely 'the role of professionals and their knowledge and skills', 'influences on prescribing' and 'consequences of prescribing'. While this may have introduced limitations, it permit easy comparison of results. In general, the results of the two chapters are similar, with positive response for the first two components and more neutral responses for the third component. Notably, there was less agreement for edoxaban being more effective, safer and cost-effective compared to other DOACs (levels of agreement 20.3%, 13.5%, 57.1%) than compared to warfarin (levels of agreement 55.2%, 41.9%, 45.9%). The findings in relation to other DOACs in terms of effectiveness and safety are not too surprising given that the guidance from HIS states that results for efficacy and safety were generally similar, with some differences between particular DOACs and doses. For example, 'the effects of apixaban 5mg, edoxaban 60mg and dabigatran 150mg on stroke and systemic embolism prevention were similar' (HIS, 2017). The higher percentage of respondents in agreement around cost-effectiveness also reflects the national selection of edoxaban largely based on cost. The results of agreement in relation to effectiveness, safety and cost-effectiveness in relation to warfarin were largely the same as for Chapter 4 and perhaps for the same reasons. Notably, the benefits and limitations in the open comments were also similar to those described by the respondents in Chapter 4.

The questionnaire in Chapter 5 had greater focus on issues of ADRs and reporting of ADRs compared to the questionnaire in Chapter 4. In the UK, DOACs are labelled 'black triangle drugs' meriting reporting of all adverse reactions (irrespective of severity) to the Medicines and Healthcare products Regulatory Agency [30] via the 'Yellow Card Scheme'. Many respondents in Chapters 4 and 5 described DOAC related ADRs, and ADRs to edoxaban specifically were captured in Chapter 5. Despite these being black triangle drugs, few prescribers had submitted Yellow Card reports. Notably, there are no published papers describing analysis of DOAC ADR reports submitted to the MHRA.

Under-reporting of ADRs is a significant limitation to the Yellow Card Scheme and all other spontaneous reporting schemes. Hazell et al. (2006) reported a systematic review to estimate the extent of under-reporting of ADRs to spontaneous reporting systems and to investigate whether there were differences between different types of ADRs. The 37 studies identified from 12 countries used a wide variety of surveillance methods, generating 43 numerical estimates of under-reporting. The median under-reporting rate across the 37 studies was 94% (interquartile range 82–98%). Five of the ten primary care based provided evidence of a higher median under-reporting rate for all ADRs compared with more serious or severe ADRs (95% and 80%, respectively). It is therefore evident that black triangle status made no difference to ADR reporting. While it should be borne in mind that this systematic review was published in 2006, other more recent studies have demonstrated that under-reporting remains a significant issue. A later systematic review by Lopez-Gonzalez et al. (2009) reported the reasons for under-reporting, synthesised from 45 studies. Key reasons were: lack of confidence in identifying ADRs; not being confident that the drug was the cause of the ADR; ignorance that only severe ADRs should be reported; belief that the ADR was already well known; lack of knowledge of the reporting system; difficulty of reporting; and lack of time. A further systematic review by Varallo et al. (2014) also reported reasons for under-reporting pooled from 29 studies. The main reasons were ignorance, insecurity and indifference (lack of time, lack of interest to register ADRs).

5.5.4 Conclusion

This study has demonstrated that prescribers in NHS Highland have knowledge, confidence and competence how to prescribe edoxaban for management of nonvalvular AF. There was lack of knowledge, confidence and competence in relation to switching edoxaban and other DOACs. There was less agreement for edoxaban being more effective, safer and cost-effective compared to other DOACs. There were less agreement about the consequences of prescribing edoxaban in relation to outcomes of effectiveness, safety and cost-effectiveness. However, low percentage of

prescribers have registered ADRs of edoxaban and other DOACs and very few have submitted the Yellow card to the MHRA.

CHAPTER 6: DISCUSSION

6.1 AIMS AND KEY FINDINGS

The overall aim of this research was to determine clinicians' views and experiences of the use of DOACs for the management of non-valvular AF. The doctoral research was conducted in three phases, the key findings of which are briefly revisited for completion. Prior to conducting the primary research, a systematic review of published literature on clinicians' views and experiences of the use of DOACs for the management of non-valvular AF was undertaken. From the very limited number of relevant papers, there were limited findings of perceptions of evidence of effectiveness equivalent or superior to warfarin and superior safety, the lack of need for INR testing. The systematic review highlighted the lack of theory informed research which reinforced the initial ideas for the primary research. This was based on a positivist approach comprising two consecutive cross-sectional surveys, both of which were grounded in behavioural theories and conducted in NHS Highlands. The first focused on DOACs in general with key findings that responses to items on consequences of prescribing and monitoring for safety and effectiveness were rather neutral. Summative content analysis of free text responses identified key themes of benefit of not having to monitor INR, potentially improved patient adherence and the evidence base. Limitations were around the lack of a reversal agent, higher medication costs, not being able to monitor coagulation status and adverse effects. Given the policy recommendation in Scotland to use edoxaban first line, this was the focus of the second cross-sectional survey. Again, the main finding was that responses for consequences of prescribing were more neutral. One additional aspect not explored in detail in the first survey related to ADRs. Although a number of respondents described edoxaban (and other DOACs) related ADRs, very few had submitted a Yellow Card report to the MHRA.

6.2 CRITICAL COMMENTARY ON THE DOCTORAL RESEARCH

This section provides critical commentary on the research design, synthesis of findings from the three research phases and contextualization of the research within the international literature.

6.2.1. Research design justification

The doctoral research was designed using a multiple methods approach of systematic review followed by primary research. As with many research studies, a number of methodological approaches could be employed mapped to the specific aims and research questions/ objectives. While all literature reviews should be undertaken systematically, the first phase was a systematic review of the peer reviewed, published literature to answer specific review questions following a protocol led approach (Stewart et al., 2016, Moher et al., 2015), and conducted and reported according to specific, accepted criteria (Liberati et al., 2009). A scoping systematic review could have been conducted as an alternative to a systematic review. This would have captured a broader range of studies with greater variation in study designs, and is more appropriate to summarise and describe literature in a specific field. Given the vast number of available systematic reviews on aspects of DOACs (as highlighted in Chapter 1), it was considered that a systematic review with specific questions was more appropriate. In addition to answering the specific review questions, the systematic review also highlighted gaps in the current literature and the limitations of the current literature which reinforced the planned primary study research design.

6.2.2 Research philosophy, methodology and methods justification and reflection

As noted in Chapters 2, the research onion highlights the interplay between philosophy, approaches and methodologies. Systematic reviews follow defined methodological pathways, with the philosophical stance being dictated by the specific review questions and the nature of studies, designs and outcomes captured. In this systematic review, all but one of the studies was cross-sectional, with quantitative outcome measures hence were positivist in nature. The diverse range of specific outcomes, and lack of application of any consistent outcome measures between studies, greatly limited the synthesis which was restricted to being narrative. As more studies are published with greater homogeneity, then a more meta-analysis type synthesis may be possible. It was noticeable that the systematic review

captured only one qualitative study. Again, as more studies are published with an interpretivism based philosophical stance, then a meta-synthesis approach can be taken.

Given the lack of theory driven cross-sectional surveys, this methodological approach was selected for phases 2 and 3, aligned to the more quantitative research aims and objectives hence a positivist philosophical approach. TDF was selected as a theoretical framework capturing 33 behaviour change theories and their associated constructs. The questionnaire provided opportunity for free text comment and extensive comments were provided by the respondents. While a mixed methods, explanatory sequential approach of cross-sectional survey followed by qualitative research could have been undertaken, it was considered by the research team that this would have added little to the analysis of summative content analysis. On reflection, a truly qualitative phase would have allowed greater exploration of the survey findings than was afforded through the open comments. This would have provided opportunity to probe findings and allow more extensive synthesis linking the context and mechanism to the analysis.

Despite this limitation, there are key strengths to this doctoral research. As noted earlier, the systematic review allowed clear identification of the gap in the literature and was itself conducted according to best practice. This robust approach provides assurance of the validity and reliability of the findings. The questionnaire were grounded in TDF which is being extensively used in healthcare research to allow identification of potential behavioural determinants acting as facilitators (positive effects) or barriers (negative effects). The findings can then for the targets for any behaviour change interventions. While there was no specific measure of prescribing behaviour in this doctoral research, the findings allow reflection on particular potentially positive and negative influences on DOAC prescribing. Given the established nature of TDF and that it is derived from established theories, this added elements of content, construct and criterion validity to the studies. There were also measures to attempt to confirm the face and content validity of the questionnaires themselves. In terms of validity, the key limitation of the cross-sectional surveys relates to external validity (generalisability). The surveys were restricted to one atypical geographical area of Scotland hence

the findings may not be representative of the larger population of prescribing in Scotland and beyond. While this is accepted as a limitation, the atypical remote and rural nature of NHS Highland in itself is worthy of investigation. The results of the surveys have to be interpreted cautiously given the many potential biases which are inherent in this research methodology which may affect the validity of any findings. Key biases are response (provide non-honest, inaccurate answers), non-respondent (respondents have different views to non-respondents), social desirability (tendency to give socially desirable responses) and acquiescence response (more likely to respond positively). While a number of measures described in Chapter 2 were taken to minimize these, they can never be completely eliminated.

In addition to issues of validity, reliability should be considered. As noted earlier, the online delivery of the questionnaire precluded any test-retest reliability hence only internal reliability calculations were undertaken.

Further strengths of the cross-sectional surveys lie in the analytical approach of the quantitative data. PCA is an established statistical approach which was undertaken according to best practice. The limitations of the inferential analysis in terms of potential issues with sample size and power are highlighted in earlier chapters.

While a content analysis approach of open comments does not satisfy the definition and description of qualitative research, attempts were made to enhance trustworthiness in analysis and data interpretation. These included considerations of credibility (well established methods, frequent research team meetings and discussion of data), dependability (attention to processes), transferability (description of setting and participants) and confirmability (reflecting the participants' voices).

Reflecting on the philosophical and methodological approaches of the doctoral research, the systematic review was entirely appropriate and would be repeated if starting the research at this point in time. In terms of the survey approach, on reflection and if starting at this point in time, a mixed-methods methodology (sequential explanatory) would be selected encompassing positivist and interpretivism based philosophical stances. The cross-sectional surveys would be sampled across Scotland with sample size calculated to

allow comparisons (e.g. for different geographical regions). The questionnaires would still be grounded in TDF with an attempt to link behavioural determinants to DOAC prescribing behaviours. These changes have impacts in terms of feasibility and resources hence these issues would have required in-depth review prior to commencing the research.

6.3 SYNTHESIS OF THE FINDINGS OF ALL RESEARCH PHASES

This section provides synthesis of the findings of all three research phases while avoiding repetition of the discussions in Chapters 3-5. As noted, the systematic review highlighted a paucity of relevant research studies with generally poor methodologies and methods and limited collection of specific data related to clinicians' views and experiences of research. It is therefore difficult to synthesise these results in terms of the survey results; rather they simply highlight the need for the robust, theory informed cross-sectional surveys. In addition, the aims of the two surveys were very similar with the first focusing on DOACs in general and the second specifically on edoxaban. This similarity was also reflected in the two questionnaires which were also very similar hence the synthesis is limited to being more comparison of the differences observed in the findings. Furthermore, the lower number of responses for the edoxaban precluded PCA being undertaken and the four PCA components for the first survey used in the second. Interestingly, and perhaps not unsurprising, the PCA findings for both survey were similar with the scores for the components of (i) role of professionals, their knowledge and skills and (ii) influences on prescribing being positive. Those for (iii) consequences of prescribing and (iv) monitoring for safety and effectiveness were more neutral, with statistically significantly more positive scores of health lower scores for consequences of prescribing from less experienced prescribers. In both surveys there were generally low levels of agreement for statements relating to DOACs and edoxaban being more effective, safer and cost-effective than warfarin. There were similar responses around the complexity of bleeding management and detection of over and under-anticoagulation. The lack of need for INR monitoring was, however, identified as a positive aspect of DOAC and edoxaban use. The themes identified in the summative content analysis were also remarkably similar with benefits in

themes of not having to monitor INR, potentially improved patient adherence and the evidence base. Limitation were in themes of the lack of a reversal agent, higher medication costs, not being able to monitor coagulation status and adverse effects. These findings and their implications are discussed at length in Chapters 4 and 5. It is also worth noting that since completing this doctoral research, no additional studies on clinicians' or prescribers' views and experiences of DOACs (as a group or individual agents) have been published.

The remainder of this section focuses on interpretation of the findings. Note that no new findings of the doctoral research are presented; the studies and any supporting data are derived from the peer reviewed literature and publicly available sources.

TDF provided a theoretical framework for the development of the questionnaire items. The rationale for applying TDF to this study was to provide comprehensive coverage of the potential factors (including positive and negative views) which may have influenced DOAC prescribing. Given that TDF is an integrative framework of behaviour change theories, it could be used to inform the development of interventions to improve DOAC prescribing. However, in this doctoral research, no data were collected to indicate that prescribing was suboptimal and outwith national and local guidance.

While respondents reported being knowledgeable, confident and competent in initiating and monitoring DOACs, responses were less positive in relation to switching. This included switching from warfarin to DOACs (including edoxaban) and also switching between DOACs. This is relevant given the national and local policy statements. There were also less positive responses in relation to aspects of the evidence of DOACs in terms of their effectiveness, safety and cost-effectiveness, and also monitoring and management of over and under anticoagulation. There is therefore a need to focus on these aspects in future prescribing guidelines, as described in previous chapters. Specific attention should also be placed on the implementation of these guidelines into practice.

A literature search was conducted to identify evidence to support guideline implementation. The search was conducted in Medline, CINAHL and International pharmaceutical abstracts (IPA) databases to identify systematic reviews published in English from 2000 to April 2020. Search terms were guideline* (title) AND systematic review* (title) AND implement* (abstract). While many of the systematic reviews identified were for specific drug groups (e.g. antidepressants, heart failure treatments etc.), Table 6.1 gives those which were more general in nature and scope. It is clear from the findings of these reviews that there is no robust evidence on effective guideline implementation strategies. In the seminal review in this field, Grimshaw et al. (2004) reviewed the evidence from 235 studies concluding that studies were of varied and generally poor quality and that a number of different approaches should be undertaken simultaneously to optimise effectiveness. In a further piece of work published in 2010, the same group (Davies et al., 2010) reviewed these 235 studies in terms of the application of theory (e.g. behaviour change theory, implementation theory) as part of guideline intervention. They noted that a minority of studies used theory and often with little or no justification for the choice of theory. It is worth noting that the studies included in this review preceded the development of TDF as a framework of behaviour change theories. It should also be borne in mind that TDF was included in this doctoral research to provide comprehensive coverage of potential influences on prescribing behaviours and not behaviours around guideline implementation. The results relating to TDF cannot therefore be used as part of intervention development to enhance guideline implementation.

Translating these findings to NHS Highland and Scotland in terms of the implementation of DOAC guidelines, a number of multifaceted implementation strategies should be employed including: interactive education and training activities; high quality printed materials; user friendly checklists and tools; clinical reminder systems; use of reminders; audit and feedback; local opinion leaders.

Table 6.1 Data extraction for systematic reviews relating to guidelines implementation

Authors (year of publication)	Review aim	Databases	Search terms	Years of search	Number of papers included in the review	Key findings
Fischer et al. (2016)	To describe and categorize the most important barriers to guideline implementation	PubMed	(guideline*OR guidance* OR clinical protocol*) AND (strateg* OR barrier*) AND implement* AND (compliance OR accept* OR conform* OR approv* OR adherence)	Database inception - 2015	69	The following aspects were central elements of successful strategies for guideline implementation: dissemination, education and training, social interaction, decision support systems and standing orders
Gagliardi et al. (2015)	To examine trends in guideline implementation by topic over a 10-year period and to explore whether and how strategies may be suitable for addressing differing barriers	Medline and Embase	The search strategy was purposefully broad to be as inclusive as possible. Guideline topics included arthritis, colorectal cancer, diabetes and heart failure.	2004 - 2013	32	Education for professionals or patients and print material were the most commonly employed strategies for translating guidelines to practice. Mapping of strategies onto the published taxonomy identified gaps in guideline implementation that represented opportunities for future research and expanded the taxonomy
Medves et al. (2010)	To synthesise the literature relevant to	AMED, CINAHL, Cochrane	'Guidelines', 'protocol',	1994 to 2007	88	Multiple approaches using teams of healthcare providers were reported to have statistically significant results in

	guideline dissemination and implementation strategies for healthcare teams and team-based practice.	Database, Embase, ERIC, Healthstar, Medline, PsycINFO	'standard', 'clinical pathway			knowledge, practice and or outcomes. Team-based healthcare helps to endure that patients receive optimum assistance to manage complex health problems. Authors described complex healthcare requiring increasingly complex approaches to ensure evidence-based guidelines were utilised into practice, including using multiple dissemination and implementation strategies.
Davies et al. (2010)	A systematic review of use of theory in rigorous evaluations of guideline dissemination and implementation studies	Medline, Embase, Cochrane Database	Gold standard search strategy developed from hand searches of key journals	between 1976 and 1998	235	Fifty-three were judged to have employed theories, 42 of which used only one theory. Twenty-five different theories were used. There was poor justification of use of theory in implementation research. Greater use of explicit theory to understand barriers, design interventions, and explore mediating pathways and moderators is needed to advance the science of implementation research.
Prior et al. (2008)	To establish the effectiveness of clinical guideline implementation strategies (based on evidence derived from systematic reviews)	Medline, AMED, CINAHL, Academic Search Elite, Cochrane	[(guidelines-based OR guidelines) AND care] OR [clinical AND (guidelines OR algorithm)] OR care pathways OR management protocol. (implementation OR uptake). (systematic OR review) (effectiveness	1987–2007	33 systematic reviews	Implementation strategies were varied, rarely comparable, with variable outcomes. Effective implementation strategies included multifaceted interventions, interactive education and clinical reminder systems. Didactic education and passive dissemination strategies were ineffective. Cost-effectiveness studies were rare.

Grimshaw et al. (2004)	To undertake a systematic review of the effectiveness and costs of different guideline development, dissemination and implementation strategies. To estimate the resource implications of these strategies. To develop a framework for deciding when it is efficient to develop and introduce clinical guidelines.	Medline, Healthstar, Cochrane, Embase	Gold standard search strategy developed from hand searches of key journals	Inception - 1998	235	There is an imperfect evidence base to support decisions about which guideline dissemination and implementation strategies are likely to be efficient under different circumstances. Decision makers need to use considerable judgement about how. This should include consideration of the lmited resources they have to maximise population benefits.

While many of the survey respondents in Chapters 4 and 5 described negative patient experiences with DOACs, it appears that very few Yellow Card reports had been submitted to the MHRA.

The MHRA website provides freely available information on ADR reports submitted via the Yellow Card Scheme. Interactive Drug Analysis Profiles (iDAPs) are provided for all licensed drugs for reports of suspected ADRs have been received (iDAPs, MHRA). Each iDAP contains data for all spontaneous suspected ADR reports submitted by healthcare professionals and patients. At April 2020, key data for each of the four DOACs were as follows:

- Dabigatran, first report submitted in 2008; total number of reports = 1977; total number of ADRs = 4253 (many reports described more than one ADR); total number of serious ADRs = 1523; total number of fatal ADRs = 165.
- Rivaroxaban, first report submitted in 2009; the total number of reports = 6594; total number of ADRs = 13570; total number of serious ADRs = 4930; total number of fatal ADRs = 420.
- Apixaban, first report submitted in 2009; the total number of reports = 4084; total number of ADRs = 8231; total number of serious ADRs = 3041; total number of fatal ADRs = 282.
- Edoxaban, first report submitted in 2016; the total number of reports = 648; total number of ADRs = 1158; total number of serious ADRs = 429; total number of fatal ADRs = 29.

Table 6.2 provides the number of ADRs for each of the four DOACs per year.

Table 6.2 Number of ADRs (non-serious, serious, fatal) submitted to the MHRA

Year	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
2008	2			
2009	101	117	1	
2010	115	168	0	
2011	133	147	1	
2012	315	192	14	
2013	406	510	53	
2014	252	766	213	
2015	200	1165	507	
2016	151	1195	665	18
2017	142	957	831	74
2018	77	735	840	169
2019	68	537	792	287
2020	15	105	167	100

Table 6.3 provides the number of fatal ADRs for each of the four DOACs.

Table 6.3 Number of fatal ADRs (non-serious, serious, fatal) submitted to the MHRA

Reaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Cardiac disorders	17	23	16	0
Gastrointestinal disorders	38	57	42	5
General disorders and administration site conditions	25	30	24	3
Nervous system disorders	39	216	144	13
Respiratory, thoracic and mediastinal disorders	10	18	5	2
Vascular disorders	8	23	19	1
Other	28	53	34	5

As discussed in Chapters 4 and 5, DOACs are black triangle hence all ADRs, irrespective of severity, should be reported to the MHRA. The number of reports described for edoxaban in Chapter 5 and the data in Table 6.2 indicate likely under-reporting. Indeed, data for DOAC prescribing in NHS Highland in Chapter 1 (Figure 1.6) indicates in excess of ten thousand dispensing episodes in quarter 3 of 2018/ 2019. Further work is therefore required to increase ADR reporting for all drugs but particularly those labelled as black triangle.

A very recent systematic review by Li et al. (2020) aimed to assess the impact of various strategies to improve ADR reporting published in the last decade and compare this with the strategies identified in a previous systematic review. Papers published between 2010 and 2019 were identified from a search of Medline and Embase databases. Study designs included were: quasi-experimental and time series studies; randomised/non-randomised controlled studies; and cluster-randomised controlled studies. A total of 13 publications were included in the review, the majority of which were conducted in Europe. Most studies examined the effectiveness of a single form of intervention to improve ADR reporting, the most common of which was educational (presentations, lectures etc.). Of note, single interventions studies produced a seven-fold increase in reporting rate compared to nine-fold for multifaceted strategies. The most effective intervention centred on the use of electronic reporting tools to improve ADR reporting, with an increase in reporting rate of thirteen-fold. The authors of the review highlighted the general poor quality of the studies included in the review which was implications for the interpretation of the findings. Further limitations included the absence of behavioural theory and behaviour change theory in intervention development and the absence of studies investigating the sustainability of interventions.
It appears that further research is required to develop, implement and sustain approaches to optimise ADR reporting in general and specifically for DOACs.

While this doctoral research focused on the perspectives of prescribers, the perspectives of patients are clearly highly important. As with the perspectives of prescribers, there have been relatively few studies on patients compared to the vast number of studies of effectiveness, safety and cost-effectiveness. In 2019, Afzal et al. published a systematic review which aimed to analyse the impact of patient-reported outcomes in patients on direct oral anticoagulant treatment, prescribed for any indication (for example, venous thromboembolism treatment or atrial fibrillation) using controlled trials and real-world observational studies. Outcomes of interest were those related to health-related quality of life (HRQoL), satisfaction, adherence and compliance. Included studies were published in English between September 2018 and October 2018 identified from search of

PubMed, CINAHL, Medline and Embase. Twenty-one articles were retrieved, six controlled trials and 15 observational studies, the majority of which were conducted in Europe and the US. In those studies researching HRQoL, scores were similar in those patients prescribed DOACs or warfarin. The majority of those studies measuring patient satisfaction (using self-reported scales) described enhanced satisfaction in those prescribed DOACs compared to those prescribed warfarin with significantly lower burden and increased perceived benefit scores. Studies of patient-reported adherence (largely using the 8-point Morisky Medication Adherence Scale tool) gave similar results for those prescribed DOACs or warfarin.

6.4 ORIGINALITY OF THE RESEARCH

These three phases of research have generated original findings which extend eth knowledge of the views of prescribers in relation to the use of DOACs for non-valvular AF. As noted throughout, while there is an extensive evidence based of the efficacy, effectiveness, safety and cost-effectiveness of DOACs in non-valvular AF, little attention has been placed on the perspectives of those prescribing DOACs and managing patients.

The phase one systematic review protocol was registered with PROSPERO and the systematic review itself published in the British Journal of Clinical Pharmacology. This is the first published systematic review focusing on the perspectives of clinicians.

The systematic review identified the gap in the literature given that only ten primary studies on the views and experiences of clinicians had been published. All studies had limitations, particularly the lack of any theoretical framework. The studies in the following two phases aimed to add to the evidence and were theoretically informed surveys conducted in the remote and rural setting of NHS Highland. The questionnaires were based upon the TDF to provide comprehensive coverage of potential determinants of DOAC prescribing. The findings of the first survey on DOACs formed the basis of a publication in the British Journal of Clinical Pharmacology and, at the time of submitting the

doctoral thesis, a paper describing the second survey focusing on edoxaban was under review. Taken together, the systematic review and the two surveys provide a comprehensive and linked study of prescribers' views and experiences of DOACs in the management of non-valvular AF.

Study strengths and weaknesses are described in each chapter. One further strength is that the studies are linked, with each being based on the findings of the previous study. In addition, the surveys reflect changing practice in Scotland from the initial HIS recommendations on the use of DOACs to the later recommendation on the use of edoxaban.

6.5 FURTHER RESEARCH

In addition to a focus on guideline implementation, as discussed earlier, to key areas for further research surround switching patients from warfarin to DOACs or from one DOAC to another, and issues of ADR reporting.

6.5.1 Study 1

The aim of the first study is to explore the views and experiences of prescribers and patients on switching from warfarin to DOACs or from one DOAC to another. This is important given the specific results on switching (i.e. knowledge, confidence and competence) highlighted in the surveys reported in Chapters 5 and 6. A qualitative, constructivist approach is more appropriate than a quantitative positivist approach to provide rich data and in depth understanding. Semi-structured interviews would be conducted with samples of prescribers with experience of switching and their patients, with sampling and recruitment continued to the point of saturation in both groups. Sampling would be purposive to include a range of prescribers (medical and non-medical, remote and rural, experienced and less experienced) and patients (different age ranges, remote and rural). Analysis would be thematic using a framework approach. The findings would provide in depth understanding of how switching was planned, effected, the positive and negative aspects and would inform further DOAC guideline developments on how to switch.

6.5.2 Study 2

Given the prevalence of DOAC prescribing, and the likely future increases, further work is required to promote submission of ADR reports to the MHRA. The second study aims to determine the impact of interventions on ADR reports relating to DOACs. There are two approaches to developing the intervention. The first would be based on the findings of the recent systematic review by Li et al. (2020). As described earlier in this chapter, multifaceted strategies were more effective than single strategies, with the use of electronic reporting tools appearing particularly effective. The second approach would be to conduct primary research on the determinants of the behaviour of not reporting ADRs. TDF could be used in a mixed methods study to determine and explore these determinants and then interventions developed based on these specific findings. The limitation of this approach is that it would take much longer to develop and implement the intervention.

Baseline data would be collected on the number and types of ADRs reported over a defined period of time. After implementing the intervention, targeting health professionals and patients, a post-intervention period of data collection would be conducted and the results pre and post-intervention compared.

6.6 IMPACT OF RESEARCH

Research impact is defined as being a situation in which, "…the knowledge generated by our research contributes to, benefits and influences society, culture, our environment and the economy" (What is research impact, University of York). This research has potential to impact at several different levels, as described below. It should, however, be noted that the research described in this thesis is observational and not based on any interventions.

6.6.1 Academic impact

Conducting this research has impacted the doctoral student, the members of the supervisory and advisory teams and the university. Presentation of the findings at international conferences (European Society of Clinical Pharmacy) and publication in peer-reviewed journals (British Journal of Clinical Pharmacology) has added to the knowledge and evidence base around the use of DOACs in clinical practice. Throughout the doctoral research attempts have been made to highlight gaps in the evidence base and potential for further research.

6.6.2 The healthcare organisation

The findings have potential to impact healthcare organisations within Scotland and beyond. Reflection on the results of the systematic review allows greater consideration of the findings of influences on DOAC prescribing. Similarly, reflection on the findings of the two surveys will allow health organisations to consider specific aspects of how to support those prescribing DOACs, specifically in relation to switching. There is need to consider issues of switching in further versions of any local, national or international guidelines. Furthermore, there is a need for organisations to highlight the specific evidence base for the effectiveness, cost-effectiveness and safety of DOACs. Healthcare organisations need to support ADR reporting by health professionals and patients.

6.6.3 Health professionals

Many of the impacts relating to health organisations also apply at the level of health professionals. In addition, reflection on the findings of the systematic review and the two surveys will allow further consideration of the facilitators and barriers relating to DOAC prescribing in comparison to their peers. They will also be able to review the positive and negative patient experiences.

6.6.4 Patients

While noting that patients were not included as participants in the doctoral research, they could be impacted as described for healthcare organisations and health professionals.

6.7 CONCLUSION

This doctoral research has generated original findings in relation to prescribers' views and experiences of DOACs in the management of patients with non-valvular AF. The specific conclusions are as follows

- The systematic review identified a limited evidence base of prescribers' views and experiences and a need for further research.
- Findings of the systematic review identified that DOACs were first choice over warfarin in naïve patients based and perceptions being advantageous in those with an unstable INR and likely to miss appointments.
- The two surveys identified positive and negative views and experiences of prescribing DOACs.
- Prescriber respondents in NHS Highland perceived themselves to be knowledgeable, confident and competent in the use of DOACs for nonvalvular AF.
- There was, however, markedly less awareness of the evidence base of the effectiveness, safety and cost-effectiveness of DOACs. There were issues around the management of DOAC related bleeding and the identification of over- and under-anticoagulation.
- In relation to edoxaban, a minority of respondents had either switched patients from warfarin or other DOACs to edoxaban.
- Very few prescribers had submitted a Yellow Card report to the MHRA.

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APPENDICES

Appendix 3.1 Critical appraisal tool

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Decision		Comment
			Yes	No	
Objectives	1	State specific objectives, including any pre specified hypotheses			
Methods					
Setting	2	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			
	3	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants			
Variables	4	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable			
Data sources/ measurement	5*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	6	Describe any efforts to address potential sources of bias			
Study size	7	Explain how the study size was arrived at			

Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why			
Statistical methods	9	(*a*) Describe all statistical methods, including those used to control for confounding			
		(*b*) Describe any methods used to examine subgroups and interactions			
		(*c*) Explain how missing data were addressed			
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy			

Results

Participants	10*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed			
		(b) Give reasons for non-participation at each stage			
		(c) Consider use of a flow diagram			
Descriptive data	11*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders			
		(b) Indicate number of participants with missing data for each variable of interest			

Outcome data	12*	*Cross-sectional study*—Report numbers of outcome events or summary measures			
Main results	13	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included			

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 3.2 Clinical appraisal tool

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

	Item No	Recommendation	Decision		Comment
			Yes	No	
Domain 1: Research team and reflexivity					
Personal Characteristics	1	Interviewer/facilitator Which author/s conducted the interview or focus group?			
	2	Interviewer characteristics What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic			
Domain 2: study design					
Theoretical framework					
Methodological orientation and Theory	3	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis			
Participant selection					
Sampling	4	How were participants selected? e.g. purposive, convenience, consecutive, snowball			
Method of approach	5	How were participants approached? e.g. face-to-face, telephone, mail, email			
Sample size	6	How many participants were in the study?			
Non-participation	7	How many people refused to participate or dropped out? Reasons?			
Setting					

Setting of data collection	8	Where was the data collected? e.g. home, clinic, workplace			
Description of sample	9	What are the important characteristics of the sample? e.g. demographic data, date			
Data collection					
Interview guide	10	Were questions, prompts, guides provided by the authors? Was it pilot tested?			
Audio/visual recording	11	Did the research use audio or visual recording to collect the data?			
Field notes	12	Were field notes made during and/or after the interview or focus group?			
Data saturation	13	Was data saturation discussed?			

Domain 3: analysis and findings

Data analysis					
Number of data coders	14	How many data coders coded the data?			
Description of the coding tree	15	Did authors provide a description of the coding tree?			
Derivation of themes	16				
		Were themes identified in advance or derived from the data?			
Reporting					
Quotations presented	17	Were participant quotations presented to illustrate the themes / findings? Was eachquotation identified? e.g. participant number			

Data and findings consistent	18	Was there consistency between the data presented and the findings?		

Appendix 3.3 Data Extraction Tool

Authors/ years	Aim	Country/ setting	Design	Participants	Theory applied	Number of participants (response rate)	Key findings
			.				

Appendix 4.1: The ethical review panel of the School of Pharmacy and Life Sciences at Robert Gordon University- Phase 2 & 3

School of Pharmacy and Life Sciences Research Ethics Committee

7 October 2015

Research Project Title	A cross-sectional survey of prescribers in NHS Highland: determining views, experiences and behaviours relating to prescribing novel oral anticoagulants (NOACs) for the management of non- valvular atrial fibrillation

Dear Daria

The School Research Ethics Committee has assessed your application and the overall decision is that there are no ethical issues with your project.

I can now confirm that you are able to proceed with your research and any further ethics applications.

Should there be any amendments to this project during the research we would advise you to consult with the convener of the ethics committee as to whether a further ethical review would be required.

We wish you success with your project.

Regards

Convener of the School Ethics Review Panel

Appendix 4.2 NHS Highland Research & Development committee statement

Professor Angus Watson

Research & Development Director

NHS Highland Research & Development Office Room S101

Centre for Health Science Old Perth Road Inverness

IV2 3JH

Tel: 01463 255822

Fax: 01463 255838

E-mail: angus.watson@nhs.net

06/1/15

NHS Highland R&D ID: **1158**

NRSPCCID:NA

Prof S Leslie
Consultant Cardiologist
Cardivascular Dept
Raigmore Hospital
Inverness

Dear Prof Leslie,

Management Approval for Non Commercial Research

I am pleased to tell you that you now have Management Approval for the research project entitled: 'A cross-sectional survey of prescribers in NHS Highland: determining views, experiences and behaviours relating to prescribing novel oral anticoagulants (NOACs) for the management of non- valvular atrial fibrillation'. **[Protocol V1 16/11/15].** I acknowledge that:

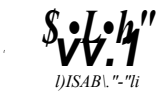
- The project is sponsored by Robert Gordon University.
- The project does not require external funding.
- The project does not require Research Ethics approval.

- The project is Site-Specific Assessment exempt.

The following conditions apply:

- The responsibility for monitoring and auditing this project lies with the Robert Gordon University.
- This study will be subject to ongoing monitoring for Research Governance purposes and may be audited to ensure compliance with the Research Governance Framework for Health and Community Care in Scotland (2006, 2nd Edition),

\ Aeo(/ however prior written notice of audit will be given.



Headquarters:

NHS Highland, Assynt House, Beechwood Park, Inverness, IV2 3HG

Chairman: Mr Garry Coutts
Chief Executive: Elaine Mead

Highland NHS Board is the common name of Highland Health Board

Appendix 4.3 Information leaflet

RESEARCH TEAM

PhD student, Daria Generalova Professor Stephen Leslie Mrs Laura McIver

Professor Derek Stewart Mr Gordon Rushworth

Dr Scott Cunningham

PARTICIPANT INFORMATION LEAFLET

A cross-sectional survey of prescribers in NHS Highland: determining views and experiences relating to prescribing edoxaban for the management of non-valvular atrial fibrillation

Dear prescriber

You are being invited to take part in a research study about your views and experiences relating to

prescribing edoxaban for the management of non-valvular atrial fibrillation (AF). Thank you for taking

the time to read the following information carefully. It is important that you understand why the research

is being done and what it will involve. Please ask if there is anything that is not clear or if you would like

more information. Take your time to decide whether or not you wish to take part.

What is the purpose of the study?

A recent review published by Healthcare Improvement Scotland (HIS) of clinical effectiveness of Direct Acting Oral Anticoagulants (DOACs) for the prevention of stroke and pulmonary embolism in adult patients with non-valvular AF recommends edoxaban as first line therapy. This recommendation has been adopted within NHS Highland. We

are interested in your views and experiences with edoxaban and implementing this recommendation in practice.

Why have I been chosen?

This invitation has been sent to all prescribers (doctors, nurse independent prescribers and pharmacist independent/supplementary prescribers) within NHS Highland.

Do I have to take part?

No. Participation in this study is voluntary so you may withdraw at any time.

What will happen to me if I take part?

If you decide to take part, you should complete and submit the following questionnaire. This should

take no more than 30 minutes to complete the questionnaire. At the end of the questionnaire, you

will be given the option of entering a prize draw for £50 of shopping vouchers.

What are the possible benefits of taking part?

While the research will be of no direct benefit to you, the findings will help us to understand better the prescribers' views and experiences and hence, as such, may inform further developments.

Will my contribution to this study be kept confidential?

Yes. The questionnaire is completely anonymous and we cannot link the details you give for the entering

the prize draw with your questionnaire responses.

What will happen to the results of the research study?

We can send you a short report of the findings on request. The full findings of the study will be

presented locally, at national and international conferences, and submitted for publication in a peer

reviewed journal.

Who is organising and funding the research?

This project is being conducted as part of the PhD programme of Daria Generalova, a student at Robert

Gordon University, in collaboration with NHS Highland and Healthcare Improvement Scotland.

There is no external funding for this work.

Who has reviewed the study?

The aims and intentions of the study have been reviewed by academic experts and approved by the

ethical review panel of the School of Pharmacy and Life Sciences at Robert Gordon University. The study

is exempt from NHS ethical review but has been approved by the Research, Development and

Innovation Department of NHS Highland.

What next?

If you decide to take part in the research, please complete and submit the questionnaire.

On behalf of the research team, thank you for your time and consideration in reading this information sheet.

If you have further questions about this study please contact the PhD principal supervisor, or one of the individuals named above. Best wishes

Professor Derek Stewart

Telephone: 01224 262432 Email: d.stewart@rgu.ac.uk

Appendix 4.4 A cross-sectional survey of prescribers in NHS Highland: Determining views, experiences and behaviours relating to prescribing novel oral anticoagulants for the management of non-valvular atrial fibrillation.

Section A - some questions about you and yourpractice

What is your profession?:

- ○ *Doctor*
- ○ *Nurse*
- ○ *Pharmacist*

What is your job title?

What is your specialty, if any?

Which of the following academic qualifications do you have?

- ☐ *PhD*
- ☐ *MSc*
- ☐ *Postgraduate Diploma*
- ☐ *Postgraduate Certificate*
- ☐ *MBChB*
- ☐ *BSc*
- ☐ *MPharm*

What is your main practice setting?

- ☐ *primary care*
- ☐ *secondary care*
- ☐ *community pharmacy*
- ☐ *care home*
- ☐ *other (please state)*

What is the postcode or address of your main practice setting?

How many years have you worked as a health professional?

○ *≤5* ○ *5-10* ○ *11-15* ○ *16-20* ○ *21-25* ○ *26-30* ○ *≥30*

How many years have you worked as a prescriber?

○ *≤5* ○ *5-10* ○ *11-15* ○ *16-20* ○ *21-25* ○ *26-30* ○ *≥30*

What is your age?

What is your gender?

○ *Male*

○ *Female*

In relation to changes to your professional practice, choose one phrase which best describes your approach

- *I resist new ways of working*
- *I am cautious in relation to new ways of working; I tend to change once most of my peers have done so*
- *I think for some time before adopting new ways of working*
- *I serve as a role model for others in relation to new ways of working*

I am innovative with new ways of working

Section B - some questions about your current practice with warfarin and NOACs

Approximately how frequently do you initiate warfarin?

weeklv	monthlv	annuallv	never

Approximately how frequently do you continue prescribing warfarin if initiated by another?

weeklv	monthlv	annuallv	never

Approximately how frequently do you discontinue warfarin?

weeklv	monthlv	annuallv	never

Approximately how frequently do you initiate NOACs?

weeklv	monthlv	annuallv	never

If 'never' do you plan to do this in the future?

yes	no	not sure

Approximately how frequently do you switch individual patients from warfarin to NOACs

weeklv	monthlv	annuallv	never

Approximately how frequently do you switch individual patients from NOACs to warfarin?

○	○	○	○
weeklv	*monthlv*	*annuallv*	*never*

If 'never' do you plan to do this in the future?

○	○	○
yes	*no*	*not sure*

Approximately how frequently do you continue NOACs if initiated by another?

weeklv	monthlv	annuallv	never

If 'never' do you plan to do this in the future?

yes	no	not sure

Approximately how frequently do you discontinue NOACs?

weeklv	monthlv	annuallv	never

If 'never' do you plan to do this in the future?

yes	no	not sure

Section C - some attitudinal questions about NOACs

The guidelines referred to in all questions are the NHS Highland guidelines on the management of non-valvular AF

I have sufficient knowledge of the guidelines to allow me to prescribe NOACs appropriately

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of the clinical pharmacology of NOACs to allow me to prescribe these safely and effectively

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of the evidence base of NOACs to allow me to prescribe these safely and effectively

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of how to initiate the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of how to monitor the effectiveness and toxicity of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of when and how to switch patients from warfarin to NOACs

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

It is part of my role to initiate the prescribing of NOACs warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient knowledge of how to manage adverse reactions of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

It is part of my role to initiate the prescribing of warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I should only prescribe NOACs when they have been initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Only specialists should initiate the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

It is part of my role to initiate the prescribing of NOACs

It is part of my role to switch patients from warfarin to NOACs where indicated

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

It is part of my role to switch patients from NOACs to warfarin where indicated

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

I am confident in my ability to initiate the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am confident in my ability to initiate the prescribing of warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am confident in switching patients from warfarin to NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am confident in switching patients from NOACs to warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am confident in my ability to prescribe NOACs when they have been initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am competent in initiating the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am competent in initiating the prescribing of warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am confident in my ability to initiate the prescribing of NOACs

I am competent in continuing the prescribing of NOACs initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I am competent in switching patients from warfarin to NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
☐	☐	☐	☐	☐	☐

I am competent in switching patients from NOACs to warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
☐	☐	☐	☐	☐	☐

Please add any comments you wish to make

I am competent in switching patients from NOACs to warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Implementing the guidelines on prescribing NOACs will be better for patients

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Implementing the guidelines on prescribing NOACs will be better for me

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Implementing the guidelines on prescribing NOACs will be better for my NHS organisation

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

If I prescribe NOACs rather than warfarin, I believe that patients will be treated more effectively

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I prescribe NOACs rather than warfarin, I believe that patients will have less adverse effects

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I prescribe NOACs rather than warfarin, I believe that patients will be treated more cost effectively

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I do not prescribe NOACs according to the guidelines, I believe that patients may come to harm

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I switch patients stabilized on warfarin to NOACs, I believe that patient care may be compromised

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I prescribe NOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

If I prescribe NOACs rather than warfarin, I believe that patients will be treated

If I prescribe NOACs rather than warfarin, I believe that my management of severe bleeding will be more challenging

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

I believe that If I prescribe NOACs rather than warfarin, over-anticoagulation will not be easily detected

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I believe that If I prescribe NOACs rather than warfarin, under-anticoagulation will not be easily detected

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

Cost is a deterrent to my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

The views of my colleagues are a deterrent to my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Potentially increased scrutiny of my prescribing by the healthboard is a deterrent to my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Potentially reduced workload in patient monitoring influences my prescribing of NOACs rather than warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

I have clear goals for prescribing NOACs according to the guidelines

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have clear goals relating to my continuing professional development around NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Prescribing NOACs according to the guidelines is high priority for me

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

I find the guidelines on NOACs easy to interpret

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I find it difficult to decide whether to prescribe NOACs or warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Others have to remind me to prescribe NOACs according to the guidelines

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

Prescribing NOACs is compatible with my daily practice

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient time to prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My drug budget is sufficient to allow me to prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My prescribing systems enable me to prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I have sufficient support from specialists to enable me to prescribe NOACs safely and effectively

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

The lack of need for monitoring influences my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

The rurality of my practice influences my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Prescribing NOACs is compatible with my daily practice

Please add any comments you wish to make

Professionals who are important to me prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Members of the multidisciplinary team prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My prescribing of NOAC is discouraged by my peers

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My prescribing of NOAC is discouraged by my multidisciplinary team

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My prescribing of NOAC is discouraged by my organisation

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

My prescribing of NOAC is discouraged by specialists

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Patients put me under pressure to prescribe NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Professionals who are important to me prescribe NOACs

Patients put me under pressure to prescribe NOACs in situations where they are not indicated

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

Family members and carers of patients put me under pressure to prescribe NOACs in situations where they are not indicated

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

I feel comfortable when initiating the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I feel comfortable when switching patients from warfarin to NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I feel comfortable when prescribing NOACs which have been initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I get professional satisfaction when initiating the prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I get professional satisfaction when switching patients from warfarin to NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I get professional satisfaction when switching patients from NOACs to warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I get professional satisfaction when prescribing NOACs which have been initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I feel comfortable when initiating the prescribing of NOACs

I feel anxious when initiating the prescribing of NOACs

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

I feel anxious when switching patients from warfarin to NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I feel anxious when switching patients from NOACs to warfarin

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

I feel anxious when prescribing NOACs which have been initiated by others

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

I have ways of monitoring the quality of my prescribing of NOACs

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

Please add any comments you wish to make

Please answer the following in relation to the NHS guidelines on the use of NOACs in non-valvular AF. For each question, answer as TRUE, FALSE, DON'T KNOW

NOACs should be considered in patients whose INR is outside the INR window more than 60% of the time (as estimated by appropriate software which provides time in treatment range (TTR) data)

True	False	Don't Know

NOACs should be considered first line in patients likely or known to be non- adherent

True	False	Don't Know

Dabigatran is the first choice NOAC

True	False	Don't Know

Apixaban is the second choice NOAC

True	False	Don't Know

Rivaroxaban dose should be altered in the elderly, irrespective of renal function

True	False	Don't Know

Patient must be able to swallow capsule whole before prescribing dabigatran

True	False	Don't Know

True	False	Don't Know

Section D: some other questions

Please give your views on benefits and limitations of prescribing NOACs.

Please describe ONE positive patient experience you have encountered in prescribing NOACs.

Please describe ONE negative patient experience you have encountered in prescribing NOACs.

Please give any views you have on the guidelines (e.g. accessibility, ease of use etc)

If you have undertaken any training or other form of continuing professional development relating to NOACS please describe briefly the format, content and usefulness

Please describe any additional training or other form of continuing professional development relating to NOACS you feel you need

How could the appropriate use of NOACs in primary care be extended further?

Please add any other comments you think are relevant.

Thank you for your time

If you would like to be entered into the prize draw for £50 of shopping vouchers, please give your name and contact details. These will not be used to match your questionnaire responses.

Full name

Email address

Again, on behalf of the research team, thank you for your time.

Professor Derek Stewart

Telephone: 01224 262432
Email: d.stewart@rgu.ac.uk

Appendix 5.1 A cross-sectional survey of prescribers in NHS Highland: determining views and experiences relating to prescribing edoxaban for the management on non- valvular atrial fibrillation

1. **What is your profession?**

- *Doctor*
- *Nurse*
- *Pharmacist*

2. **What is your job title?**

3. **What is your specialty, if any?**

4. **Which of the following academic qualifications do you have?**

- *PhD*
- *MSc*
- *Postgraduate Diploma*
- *Postgraduate Certificate*
- *MBChB*

If you selected Other, please specify:

5. **What is your main practice setting?**

- *primary care*
- *secondary care*
- *community pharmacy*
- *care home*
- *other (please state)*

6. **How many years have you worked as a health professional?**

<5	5-10	11-15	16-20	21-25	26-30	>30

7. **How many years have you worked as a prescriber?**

<5	5-10	11-15	16-20	21-25	26-30	>30

8. What is your age?

9.What is your gender?

- *Male*
- *Female*
- Rather not indicate

10. Approximately how frequently do you initiate edoxaban?

weekly	*monthly*	*annually*	*never*

10a. If "never" do you plan to do this in the future?

Yes	No

11. Approximately how frequently do you switch individual patients from warfarin to edoxaban?

weekly	*monthly*	*annually*	*never*

11a. If "never" do you plan to do this in the future?

Yes	No

12. Approximately how frequently do you switch patients from other DOACs to edoxaban?

Weekly	Monthly	Annually	Never

12a. If “never" do you plan to do this in the future?

Yes	No	Not sure

13. Which is your oral anticoagulant of choice for new patients with non-valvular AF?

13a. What are the reasons for this choice?

14. Are you aware of the NHS Highland guidelines which recommend edoxaban as first line treatment in non-valvular AF?

Yes	No

14a. If "yes" do you support this recommendation?

14b. Please give any comments on the NHS Highland guidelines.

15.Have you been encouraged to implement this recommendation?

Yes	No

15a. If "yes" please give us some details of who and how.

16. Have you switched, where relevant, all patients from warfarin to edoxaban?

Yes	No

16a. If not, please give any comments about future plans and intentions.

17 .Have you switched, where relevant, all patients from other DOACs to edoxaban?

Yes	No

17a. If not, please give any comments about future plans and intentions.

18 I have sufficient knowledge of the guidelines to allow me to prescribe edoxaban safely and effectively.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

19.I have sufficient knowledge of the clinical pharmacology of edoxaban to allow me to prescribe safely and effectively.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

20.Have sufficient knowledge of the evidence base of edoxaban to allow me to prescribe safely

and effectively.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

21.I have sufficient knowledge of how to initiate edoxaban

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

22. I have sufficient knowledge of how to monitor the effectiveness and toxicity of edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

23. I have sufficient knowledge of when and how to switch patients from warfarin to edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

24. I have sufficient knowledge of when and how to switch patients from other DOACs to edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

25. I have sufficient knowledge of how to manage adverse reactions of edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

26. It is part of my role to initiate edoxaban

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

27. I should only prescribe edoxaban when initiated by others.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

28. Only specialists should initiate edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

29. It is part of my role to switch patients from other DOACs to edoxaban where indicated.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

30. I am confident in my ability to initiate edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

31. I am confident in switching patients from warfarin to edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

32. I am confident in switching patients from other DOACs to edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

33. I am competent in initiating edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

34. I am competent in switching patients from warfarin to edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

35. I am competent in switching patients from other DOACs to edoxaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

36. Please add any comments you wish to make.

37. Implementing the guidelines on prescribing edoxaban will be better for patients.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

38. Implementing the guidelines on prescribing edoxaban will be better for my NHS organisation.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

39. If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more effectively

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

40. If I prescribe edoxaban rather than warfarin, I believe that patients will have less adverse effects.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

41. If I prescribe edoxaban rather than warfarin, I believe that patients will be treated more cost effectively.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

42. If I prescribe edoxaban rather than other DOACs, I believe that patients will be treated more effectively

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

43. If I prescribe edoxaban rather than other DOACs, I believe that patients will have less adverse

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

44. If I prescribe edoxaban rather than other DOACs, I believe that patients will be treated more cost effectively.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

45. If I switch patients on other DOACs to edoxaban, I believe that patient care may be compromised.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

46. If I prescribe edoxaban rather than other DOACs, I believe that my management of severe bleeding will be more challengi

47. I find the guidelines on edoxaban easy to interpret.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

48. I find it difficult to decide whether to prescribe edoxaban, rivaroxaban, dabigatran and apixaban.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

49. Others have to remind me to prescribe edoxaban according to the guidelines.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

50. Unless contraindicated, I intend to prescribe edoxaban for all new patients with non-valvular AF

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

51. I have sufficient support from specialists to enable me to prescribe edoxaban safely and effectively.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

52. My prescribing of edoxaban is discouraged by my peers.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

53. My prescribing of edoxaban is discouraged by my organisation.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applicable*

54. My prescribing of edoxaban is discouraged by specialists.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

55. I feel anxious when initiating edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

56. I feel anxious when switching patients from warfarin to edoxaban.

strongly agree	agree	unsure	disagree	strongly disagree	not applicable
○	○	○	○	○	○

57. I feel anxious when switching patients from edoxaban to other DOACs.

○	○	○	○	○	○
strongly agree	*agree*	*unsure*	*disagree*	*strongly disagree*	*not applic able*

58. Please add any comments you wish to make.

59 Please describe any benefits you consider relating to the implementation of the guidelines on edoxaban.

60.Please describe any limitations you consider relating to the implementation of the guidelines on edoxaban.

61 Have any of your patients experienced adverse reactions with edoxaban?

No	Yes

61a If "yes", please describe the most impactful.

61 b Was a yellow card completed?

No	Yes

62. Have any of your patients experienced adverse reactions with other DOACs?

No	Yes

62a. If "yes" please describe the most impactful.

62 b Was a yellow card completed?

No	Yes

63. Please add any other comments on prescribing edoxaban or other DOACs for the management of non-valvular AF.