

Medicines Management Programme

Oral anticoagulants for stroke prevention in non-valvular atrial fibrillation

Drugs in this review include:

- Warfarin
- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban



MEDICINES MANAGEMENT PROGRAMME

Approved by
Date approved
Date updated
Date updated

Prof. Michael Barry, Clinical Lead, MMP.
Version 1.0 June 2015
Version 1.1 September 2018
Version 1.2 March 2019

Executive Summary

The purpose of this review is to aid prescribers in the selection of an oral anticoagulant for stroke prevention in non-valvular atrial fibrillation. The drugs included in this review are: warfarin, apixaban, dabigatran, edoxaban and rivaroxaban.

The review evaluates evidence from clinical trials, meta-analyses, clinical guidelines and relevant drug information sources on oral anticoagulants. Key criteria included in the assessment are clinical efficacy and effectiveness, adverse effects, drug interactions, safety, patient factors including dosing, administration and storage considerations, cost, national prescribing trends and clinical guidelines.

Key findings from the review are summarised as follows:

- **Warfarin** is an appropriate first-line treatment option when the time in therapeutic range (TTR) is > 70%.
- **Apixaban** is the preferred **direct oral anticoagulant (DOAC)** for stroke prevention in non-valvular atrial fibrillation (NVAf) and may be considered for first-line treatment, particularly if there are tolerability issues and/or labile international normalised ratios (INRs) with warfarin.

Benefits of warfarin:

- Many years of experience using warfarin as an anticoagulant
- Warfarin has the lowest acquisition cost of any oral anticoagulant
- New therapies have not been shown to be superior to warfarin therapy with time in therapeutic range (TTR) >70%
- It is possible to monitor the efficacy of warfarin therapy through INR monitoring
- It is possible to reverse the effect of warfarin using Vitamin K and/or prothrombin complex concentrate (PCC)
- Long half-life ensures a level of underlying anticoagulant cover if a dose is missed

Benefits of apixaban:

- Apixaban appears to have an advantage in terms of safety and reduced bleeding , compared to warfarin and other DOACs
- Less drug and food interactions when compared with warfarin
- Monitoring of levels not necessary (as with all DOACs)
- Standard dosing (as with all DOACs)

DOAC summary:

- ✓ There is little difference in terms of efficacy for the four DOACs; apixaban, dabigatran, edoxaban and rivaroxaban.
- ✓ Apixaban and dabigatran 150 mg twice daily were superior to warfarin for the primary efficacy endpoint of stroke or systemic embolism
- ✓ The rates of ischaemic and haemorrhagic stroke were significantly lower with dabigatran 150 mg twice daily as compared to warfarin therapy
- ✓ Apixaban appears to have an advantage in terms of safety and reduced bleeding in pivotal clinical trials for the DOACs
- ✓ Major bleeding seems to be reduced with apixaban, dabigatran 110 mg twice daily and edoxaban (60 mg and 30 mg)
- ✓ Apixaban and rivaroxaban have favourable evidence in terms of administration including crushing, however rivaroxaban 15 mg and 20 mg doses must be taken with food to ensure appropriate absorption
- ✓ Rivaroxaban and edoxaban are licensed for once daily administration while apixaban and dabigatran are twice daily
- ✓ Dabigatran is currently the only DOAC with a licensed reversibility agent

This review represents the views of the Medicines Management Programme (MMP) and is intended as a guide only. Recommendations may not be appropriate in all circumstances and decisions to adopt specific recommendations should be made by the practitioner, taking into account the circumstances presented by individual patients and available resources. It is important that patients commenced on oral

anticoagulation therapy are provided with sufficient information on all available therapies.

Table of Contents

1. Background	1
1.1. Therapeutic Indications	2
1.2 Context for the OAC review	4
2. Aim	5
2.1 Definitions	6
3. Preferred Drug for anticoagulation in stroke prevention in NVAf	6
3.1 Considerations for Warfarin versus DOAC therapy	6
3.2 Preferred Anticoagulant for stroke prevention in NVAf	8
4. Consultation for DOAC therapies.....	8
5. Selection Criteria for DOAC review	9
5.1 Clinical Efficacy and Safety of DOACs versus warfarin.....	9
5.1.2 Patient selection in individual trials.....	19
5.1.3 Clinical trial parameters	26
5.1.4 Comparative efficacy and safety.....	33
5.1.5 Observational studies	40
5.2 Adverse Effects.....	42
5.3 Drug Interactions	45
5.4 Safety.....	50
5.5 Patient factors.....	53
5.5.1 Dosing.....	53
5.5.2 Administration	54
5.5.3 Storage considerations	56
5.5.4 Reversibility.....	56
5.6 Cost	58
5.6.1 Cost Summary	59
5.7 National Prescribing Trends	60
5.7.1 Data sources.....	60
5.7.2 Overall dispensing trends for OACs under the community drug schemes.	61
5.8 Clinical Guidance	67
6. Summary	74

7. Conclusion.....	75
References	88
Bibliography	88
Appendix 1: Pivotal clinical trials for stroke prevention in non-valvular atrial fibrillation for NOACs	90
Appendix 2: Anticoagulation Prescribing Tips -Warfarin and DOACs.....	99
Appendix 3: Preferred DOAC for stroke prevention in AF Prescribing Tips	100

Tables

Table 1: Changing DOAC vs Warfarin Landscape December 2013-October 2018	5
Table 2: Pivotal clinical trials for stroke prevention in NVAF	10
Table 3: Efficacy and safety endpoints for pivotal trials for stroke prevention in NVAF	11
Table 4: Outcomes from the pivotal clinical trials for stroke prevention in AF.....	12
Table 5: ENGAGE AF-TIMI treatment groups.....	16
Table 6: Age categories in AF clinical trials	19
Table 7: Proportion of patients in CHADS2 score categories	23
Table 8: Time in Therapeutic Range (TTR) for warfarin arm in pivotal AF clinical trials	27
Table 9: Breakdown of doses in pivotal trials	30
Table 10: Common adverse effects of DOAC therapies	43
Table 11: Discontinuation of study drug in clinical trials.....	44
Table 12: Pharmacokinetic profile of DOACs.....	46
Table 13: Apixaban drug interactions	48
Table 14: Dabigatran drug interactions	49
Table 15: Edoxaban drug interactions	49
Table 16: Rivaroxaban drug interactions	50
Table 17: Administration with food	54
Table 18: Information on crushing medication	55
Table 19: Cost of OAC therapies per daily dose based on reimbursed price	58
Table 20: Prescribing frequency of OACs dispensed in 2017 under Community Drugs Schemes	64
Table 21: Reimbursed ingredient cost of OACs dispensed in 2017 under Community Drugs Schemes.....	65
Table 22: Clinical Guidelines/Recommendations	69

Figures

Figure 1: Number of patients in receipt of each oral anticoagulant. GMS, DP and LTI scheme data, January 2013- October 2018 inclusive	61
Figure 2: Distribution of oral anticoagulation patient numbers January 2013	62
Figure 3: Distribution of oral anticoagulation patient numbers October 2018	63
Figure 4: Total expenditure on oral anticoagulants on GMS, DP and LTI schemes January 2013	66
Figure 5: Total expenditure on oral anticoagulants on GMS, DP and LTI schemes October 2018	66
Figure 6: Oral anticoagulant expenditure January 2013-October 2018.....	67

List of abbreviations

AF	Atrial fibrillation
AHA/ACC/HRS	American Heart Association/American College of Cardiology/Heart Rhythm Society
AHA/ASA	American Heart Association/American Stroke Association
aPTT	Activated partial thromboplastin time
ARD	Absolute risk difference
ARISTOTLE	Apixaban for the Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation
BD	Twice daily
CHMP	Committee for Medicinal Products for Human Use
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CRNM	Clinically relevant or non-major (bleeding)
cTTR	Centre average time in therapeutic range
CSANZ	Cardiac society of Australia and New Zealand
CV	Cardiovascular
CYP450	Cytochrome P450
DDD	Defined daily dose
DOAC	Direct oral anticoagulant (See NOAC below)
DP	Drug Payment
DVT	Deep vein thrombosis
ENGAGE AF-TIMI 48	Effective anticoagulation with factor Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyltransferase

GI	Gastrointestinal
GMS	General Medical Service
GP	General Practitioner
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
IMB	Irish Medicines Board
IMSN	Irish Medication Safety Network
INR	International normalised ratio
IPHA	Irish Pharmaceutical Healthcare Association
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
iTTR	Individual time in therapeutic range
LMWH	Low molecular weight heparin
MHRA	Medicines and Healthcare products Regulatory Authority
MI	Myocardial infarction
mITT	Modified intention to treat
MMP	Medicines Management Programme
NCPE	National Centre for Pharmacoeconomics
NHFA	National Heart Foundation Australia
NICE	National Institute for Health and Care Excellence
NOAC	Non-vitamin K oral anticoagulant (see DOAC above)
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
OD	Once daily
PCC	Prothrombin complex concentrate
PCRS	Primary Care Reimbursement Service
PE	Pulmonary embolism
P-gp	P-glycoprotein
PPI	Proton pump inhibitor
PT	Prothrombin time

RCT	Randomised controlled trial
RE-LY	Randomised Evaluation of Long-term Anticoagulant therapy
ROCKET-AF	Rivaroxaban once daily oral direct factor Xa inhibition compared with Vitamin K antagonism for prevention of stroke and embolism trial in Atrial Fibrillation
SEE	Systemic embolic event
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SNRI	Serotonin-Noradrenaline Reuptake Inhibitors
SSE	Stroke and systemic embolism
SSRI	Selective serotonin reuptake inhibitors
TTR	Time in therapeutic range
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. Background

Oral anticoagulants (OACs) are indicated for a number of thromboembolic conditions, including stroke prevention in non-valvular atrial fibrillation (NVAF) and the prevention and treatment of venous thromboembolism (VTE).¹ Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide occurring in approximately 1-2% of the general population.² AF is a disease of increasing age and it is estimated that 4-7% of those aged 65-74 years have the condition, rising to 14-19% in those aged over 85 years.²

VTE is responsible for the death of more than 500,000 people in Europe each year and is the third leading cause of death from cardiovascular causes after myocardial infarction and stroke.¹ For many years vitamin K antagonists (usually warfarin) were the only OACs available. Warfarin is indicated for prophylaxis of systemic embolisation in patients with rheumatic heart disease and AF. It is also indicated for prophylaxis of venous thrombosis and pulmonary embolism (PE) and for use in the treatment of these conditions to prevent their extension.^{3,4}

Warfarin has been licensed for use as an anticoagulant since 1954 and there were over 30,000 patients on warfarin treatment on the GMS and DP schemes when the original review of the Primary Care Reimbursement Service (PCRS) database was carried out (October 2014). However with the availability of newer agents the numbers seen on warfarin therapy has decreased steadily, with figures falling from approximately 34,700 in January 2013 to 16,500 in October 2018.⁵

Treatment with warfarin requires regular monitoring of the international normalised ratio (INR) to ensure the patient's level of anticoagulation is maintained within a safe range (usually 2-3). The dosing regimen for all indications is based around individual dose adjustment to maintain patients within their therapeutic range for the maximal possible time (percentage time in therapeutic range - TTR).¹

In order to ascertain appropriate rates of INR control with warfarin, clinicians review past results and calculate the amount of time the INR results were within their defined range (TTR) with optimal therapy considered when the TTR is > 70%.^{6,7}

The direct oral anticoagulants (DOACs) first became available throughout the European Union in 2008 for the licensed indication of thromboprophylaxis post orthopaedic surgery. In subsequent years the licensed indications have been expanded to include stroke prevention in NVAF and treatment of VTE i.e. deep vein thrombosis (DVT) and PE. Dabigatran etexilate, a direct thrombin inhibitor, was licensed in 2011 for stroke prevention in NVAF followed by the first factor Xa inhibitor, rivaroxaban later that year. The licence for stroke prevention in NVAF for the factor Xa inhibitor, apixaban, was granted in 2013. Edoxaban, a factor Xa inhibitor, was licensed for stroke prevention in NVAF in 2015.

Patients commencing oral anticoagulation therapy should be given full information with regard to all anticoagulant options prior to the prescribing of a particular agent.⁸ The National Institute for Health and Care Excellence (NICE) in the United Kingdom have published a patient decision aid to inform patients prior to anticoagulation choice.⁹

1.1. Therapeutic Indications

Warfarin can be used for the following therapeutic indications:

- Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation
- Prophylaxis and treatment of venous thrombosis and pulmonary embolism
- Prophylaxis after insertion of prosthetic heart valves
- Transient cerebral ischaemic attacks¹⁰

Warfarin is currently available in Ireland as Warfant[®] and Warfarin Teva[®] which are licensed for the first two indications.^{3,4}

Apixaban, dabigatran, edoxaban and rivaroxaban are currently licensed in Ireland for the following therapeutic indications:

- Stroke prevention with NVAF with other risk factors
- Treatment of DVT or PE and prevention of recurrent DVT or PE in adults ^{11,12,13,14}

Apixaban, dabigatran and rivaroxaban are also licensed for:

- Thromboprophylaxis post elective hip and knee replacement surgery¹¹⁻¹³

Rivaroxaban (2.5mg) is licensed for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events, in combination with aspirin. Rivaroxaban (10mg) is also licensed for the extended prevention of recurrent VTEs. Rivaroxaban is not currently reimbursed in Ireland for either of these indications.

The indications which are common to both warfarin and the DOACs are stroke prevention in NVAF and prevention and treatment of DVT and PE (discussed below). The use of DOACs for thromboprophylaxis post hip and knee replacement surgery (short-term use) was compared to low molecular weight heparin (LMWH) as warfarin is not used for this indication.

The focus of this recommendation is the pharmacological treatment of stroke prevention in NVAF.

Stroke Prevention in Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia and estimates suggest that as many as 40,000 people in Ireland are affected including 6% of those over 65 years of age. AF is associated with a five-fold increase in the risk of a cerebrovascular event (stroke) and approximately 30% of strokes in Ireland are associated with AF.^{15,16}

1.2 Context for the OAC review

The treatment of stroke prevention in NVAF and the treatment of DVT/PE require anticoagulation therapy and in the case of AF this treatment will be life-long. Warfarin therapy for all indications is adjusted based on a patient's individual INR while the DOACs require varying dosage options and specific administration considerations depending on the indication for treatment and patient factors such as age, renal function and weight.

This document sets out the reasons why the MMP considers well controlled warfarin to be an appropriate anticoagulant treatment for patients with AF when the TTR exceeds 70%.^{6,7,17} Apixaban may also be considered as a first-line treatment option.

As not all patients will be suitable for warfarin therapy due to labile INRs or drug allergies the availability of DOACs affords the opportunity to treat a larger cohort of AF patients than was previously possible. This is demonstrated in current figures from the community drug schemes where the number of patients in receipt of oral anticoagulants has increased overall from approximately 40,000 in January 2013 to just over 73,700 in October 2018.¹⁸

This updated MMP review reclassifies MMP recommendations to include both warfarin and the DOAC of choice, apixaban, as first line treatment options for NVAF. DOACs reviewed as part of this evaluation were all licensed for stroke prevention in NVAF and available for reimbursement in Ireland in March 2019.

There are currently four DOACs with marketing authorisation and approval for reimbursement in Ireland: apixaban, dabigatran, edoxaban and rivaroxaban (as of March 2019).¹¹⁻¹⁴

At the time of writing the first review, PCRS data on DOAC usage was available to the MMP for the period up to and including October 2014. For this updated document, data is available up to October 2018. In the intervening period there has been a marked shift in the anticoagulation landscape in Ireland. The number of people being treated with DOAC

therapies has risen steadily. Analysis of PCRS data relevant to December 2013 found that 10,985 patients were dispensed a DOAC under the GMS, LTI and DP schemes while 32,969 were dispensed warfarin. By October 2018 the numbers on DOAC therapies exceeded those on warfarin, with 57,092 receiving a DOAC and 16,622 patients receiving warfarin.¹⁸ DOACs represent a considerable cost to the Health Service Executive (HSE). Total expenditure on DOAC therapies for 2013-2017 inclusive was €121.9 million versus €22.6 million on warfarin.^{18,19}

Cross-sectional analyses of patient-numbers and total expenditure on oral anticoagulants shows a steady growth in monthly figures over a five-year period (table 1).

Table 1: Changing DOAC vs Warfarin Landscape December 2013-October 2018

	DOAC	Warfarin	Total
Number of Patients			
December 2013	10,985	32,969	43,954
December 2014	17,633	30,844	48,477
December 2015	27,387	27,532	54,919
December 2016	38,017	23,453	61,470
December 2017	48,147	19,588	67,735
October 2018	57,092	16,622	73,714
Total Drug Expenditure per month*			
December 2013	€945,941	€449,512	€1,395,453
December 2014	€1,594,192	€432,351	€2,026,543
December 2015	€2,401,684	€383,318	€2,785,002
December 2016	€3,076,257	€316,237	€3,392,494
December 2017	€3,709,411	€260,688	€3,970,099
October 2018	€4,535,021	€97,207	€4,632,228

* Total Expenditure= cost price & pharmacy fees

2. Aim

In November 2014 the MMP commenced a review of warfarin and the DOACs under the Preferred Drugs initiative. At that time there were four oral anticoagulants licensed for stroke prevention in NVAf; warfarin, apixaban, dabigatran and rivaroxaban. The review has since been updated to consider edoxaban as part of the evidence. In light of constantly evolving guidelines,

emerging evidence and a dynamic prescribing landscape, the MMP reserve the right to review and update the guidance as appropriate.

The selection of a preferred anticoagulant under the MMP is designed to support prescribers in choosing a medicine of proven safety, efficacy and cost effectiveness for stroke prevention in patients with AF. As with previous MMP Preferred Drug initiatives, prescribers are encouraged to consider the preferred drug(s) when initiating anticoagulant therapy.

2.1 Definitions

For the purpose of this evaluation, the use of the term “direct oral anticoagulant” or “DOAC” refers to the oral direct thrombin inhibitors and the oral factor Xa inhibitors that are currently licensed for use (dabigatran etexilate, apixaban, edoxaban and rivaroxaban). These drugs are also known as “new/novel oral anticoagulants” or “non-vitamin K oral anticoagulants” or “NOACs”. The terms “NOAC” and “DOAC” are used interchangeably throughout this document. The terms “dabigatran etexilate” and “dabigatran” are considered interchangeable in this document. Atrial fibrillation refers to non-valvular atrial fibrillation as DOACs are not indicated for use in valvular atrial fibrillation.

The term “labile INRs” refers to unstable or high INRs or poor time in therapeutic range.

Unless otherwise stated, the cost is the reimbursed cost of a drug, as listed on the HSE PCRS website (www.pcrs.ie) in March 2019.

3. Preferred Drug for anticoagulation in stroke prevention in NVAf

3.1 Considerations for Warfarin versus DOAC therapy

The HSE MMP considers that there is little difference in terms of health outcomes between warfarin therapy and DOACs when warfarin is well tolerated and the INR remains (for the most part) between 2 and 3.^{17,20} Warfarin is the established anticoagulant of choice for many patients including those with:

- ✓ Mechanical heart valves
- ✓ Valvular atrial fibrillation
- ✓ Severe renal impairment
- ✓ Cancer related VTE
- ✓ Complicated VTE such as patients with recurrent VTE
- ✓ Patients with antiphospholipid syndrome¹

There are many years of experience with warfarin therapy and the effects of warfarin can be monitored in individuals using the INR. Warfarin has a narrow therapeutic index with food and drug interactions affecting the INR control and so regular monitoring is required.¹ The availability of monitoring allows for closer review of patients at times of co-administration of medications which may interact with warfarin therapy.

All anticoagulants carry the risk of bleeding and therefore regular monitoring and review of INR could be of added benefit for the safe anticoagulation of patients with warfarin. The long half-life of warfarin is also of benefit for potential poor compliance as a missed dose will not result in lack of anticoagulation cover which is a concern for the DOACs. Warfarin anticoagulation has the benefit of being reversible with Vitamin K and PCC. The first direct thrombin inhibitor reversal agent is now available. Idarucizumab, for the reversal of the anticoagulant effects of dabigatran, was introduced in Ireland in 2016.

Non-compliance with warfarin therapy is not considered a suitable reason for choosing a DOAC above warfarin therapy due to the short elimination half-life associated with the DOACs and the consequent risk of reduced anticoagulation if there is poor compliance.²¹ Warfarin is not cleared by the renal pathway and so there is less risk for patients with renal impairment when compared to the new therapies. Warfarin therapy is also less expensive than newer treatments, even when taking account of the cost of monitoring through warfarin clinics or GP practices. For these reasons the MMP considers warfarin to be an appropriate treatment option for patients with AF when the TTR > 70%.

This document reviews the evidence for the use of DOACs for stroke prevention in NVAF to assess which agent may be considered as first line therapy, particularly if INR control on warfarin has been difficult to maintain or there is an allergy to warfarin.

3.2 Preferred Anticoagulants for stroke prevention in NVAF

WARFARIN is an appropriate treatment option when the time in therapeutic range (TTR) is > 70%

The MMP considers APIXABAN to be the preferred DOAC for the treatment of atrial fibrillation and may be considered for first-line treatment particularly when there are tolerability issues and/or labile INRs with warfarin.

4. Consultation for DOAC therapies

A period of consultation was initially undertaken in which submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on 5th September 2014. In 2016 further information was accepted to allow for updated clinical evidence to be submitted for consideration, however as the anticoagulation market is a dynamic and fast changing area the MMP reserves the right to further engage with relevant stakeholders if required.

5. Selection Criteria for DOAC review

A number of key criteria were considered in the selection process:

- Clinical Efficacy
- Adverse effect profiles
- Drug interactions
- Safety
- Patient factors
 - Dosing
 - Administration
 - Storage considerations
- Cost
- National prescribing trends
- Clinical guidelines

5.1 Clinical Efficacy and Safety of DOACs versus warfarin

All licensed DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) have been shown, in noninferiority randomised controlled trials (RCTs) (ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48, ROCKET-AF), to be effective in the prevention of stroke in patients with AF when compared to warfarin (at varying levels of INR control).^{22,23,24,25} Apixaban was also studied versus aspirin in patients unsuitable for warfarin therapy in the AVERROES trial.²⁶ (Table 2)

ARISTOTLE and RE-LY trials were based on the intention to treat (ITT) population while ROCKET-AF used the per-protocol population. ENGAGE AF-TIMI 48 used modified intention to treat (mITT) and ITT populations. Clinical outcome measures in the randomised trials included the primary efficacy outcome of stroke and systemic embolism and secondary efficacy outcomes of death from any cause and myocardial infarction (MI). Safety outcomes included major and minor bleeding events of differing severity and location.²²⁻²⁵

There are no head-to-head RCTs comparing different DOACs. The pivotal AF clinical trials for each of the DOACs compared each agent to warfarin.

Table 2: Pivotal clinical trials for stroke prevention in NVAF

DOAC	Clinical trial for Stroke Prevention in NVAF
Apixaban ^{22,26}	ARISTOTLE (vs. warfarin) AVERROES (vs. aspirin)
Dabigatran ²³	RE-LY (vs. warfarin)
Edoxaban ²⁵	ENGAGE AF-TIMI 48 (vs. warfarin)
Rivaroxaban ²⁴	ROCKET-AF (vs. warfarin)

Within this group of agents there are two distinct drug groups, direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban and rivaroxaban). There are some variations in the efficacy and safety endpoints for the pivotal clinical trials as shown in Table 3. For tabulated details of the pivotal RCTs for stroke prevention in NVAF see Table 4 and Appendix 1.

Table 3: Efficacy and safety endpoints for pivotal trials for stroke prevention in NVAF

Endpoints	ARISTOTLE ²²	RE-LY ²³	ENGAGE AF-TIMI 48 ²⁵	ROCKET-AF ²⁴
Primary efficacy endpoint	Stroke or SEE (ischaemic or haemorrhagic)	Stroke (ischaemic, haemorrhagic or unspecified) or SEE	Stroke (ischaemic or haemorrhagic) or SEE	Composite of stroke (ischaemic or haemorrhagic) and SEE
Secondary efficacy endpoint	1) Death from any cause 2) Rate of MI	1) Stroke 2) SEE 3) Death	1) Composite of stroke, SEE, CV mortality 2) Composite of MI, stroke, SEE, CV mortality 3) Composite of stroke, SEE, all-cause mortality	1) Composite of stroke, SEE or death from CV causes 2) Composite of stroke, SEE, death from CV causes or MI 3) Individual components of the composite end points
Other efficacy outcomes		Rate of MI PE TIA Hospitalisation	Hospitalisation due to CV condition including bleeding Severity of strokes Composite of stroke, SEE, and TIA Number of strokes and SEEs VTE including PE ²⁷	
Primary safety endpoint	Major bleeding* (ISTH criteria)	Major haemorrhage	Major bleeding*	Composite of major and CRNM bleeding*
Secondary safety endpoint	Composite of major bleeding* and CRNM bleeding	1) Bleeding events* (major and minor) 2) Intracerebral haemorrhage 3) Other intracranial haemorrhage 4) Elevation in liver transaminase, bilirubin and hepatic dysfunction and other adverse events	Major or CRNM bleeding	
Other safety outcomes	1) Any bleeding 2) Other adverse events 3) Liver function abnormalities		1) Bleeding events: fatal, CRNM, minor, life threatening, intracranial, GI, bleeding during 30-day transition 2) Other adverse events 3) Liver function abnormalities 4) Bone fractures	Adverse events ALT elevation

SEE: systemic embolic event; CRNM: clinically relevant non-major bleeding; TIA: transient ischaemic attack; ISTH; International Society on Thrombosis and Haemostasis; ALT: alanine aminotransferase

*The definition of major bleeding differs between the pivotal clinical trials

5.1.1 Clinical trial results

Table 4: Outcomes from the pivotal clinical trials for stroke prevention in AF

Outcomes (% per year intention to treat)										
Trial	ARISTOTLE ²²		RE-LY ²³			ENGAGE AF-TIMI 48 ²⁵			ROCKET-AF ²⁴	
Medication and dose	Warfarin (n=9,081)	Apixaban 5 mg BD (or reduction to 2.5 mg BD) (n=9,120)	Warfarin (n=6022)	Dabigatran 150 mg BD (n= 6076)	Dabigatran 110 mg BD (n=6015)	Warfarin (n=7036)	High-dose Edoxaban 60 mg daily (or dose reduction to 30 mg daily) (n=7035)	Low-dose Edoxaban 30 mg daily (or dose reduction to 15 mg daily) (n=7034)	Warfarin (n=7133)	Rivaroxaban 20 mg daily (or reduction to 15 mg daily) (n=7131)
	% outcome	% outcome (HR; 95% CI; P value)	% outcome	% outcome (RR;95%CI; P value)	% outcome (RR;95%CI; P value)	% outcome	% outcome (HR;95%CI; P value)	% outcome (HR;95%CI; P value)	% outcome	% outcome (HR;95%CI; P value)
Primary endpoint Stroke/systemic embolism (% per year) based on ITT population	1.6%	1.27% (0.79;0.66-0.95; P=0.01 for superiority)	1.69%	1.11% (0.66; 0.53-0.82; P for superiority <0.001)	1.53% (0.91; 0.74-1.11; P for noninferiority <0.001)	1.8%(ITT) 1.5% (mITT)	1.57% (0.87; 0.73-1.04; P=0.08 for superiority); 1.18% (mITT) (0.79; 0.63-0.99; P<0.001 for noninferiority, P=0.02 for superiority)	2.04% (1.13; 0.96-1.34; P=0.10 for superiority); 1.61% (mITT) (1.07; 0.87-1.31; P=0.005 for noninferiority P=0.44 for superiority)	2.4%	2.1% (0.88; 0.75-1.03; P <0.001 for noninferiority, P for superiority =0.12) (ITT)
Ischaemic stroke	1.05%	0.97% (0.92; 0.74-1.13; P=0.42)	1.20%	0.92% (0.76; 0.6-0.98; P=0.03)	1.34% (1.11; 0.89-1.40; P =0.35)	1.25%	1.25% (1.00;0.83-1.19; P=0.97)	1.77% (1.41;1.19-1.67; P<0.001)	1.42%	1.34% (0.94; 0.75-1.17; P=0.581)
Haemorrhagic stroke	0.47%	0.24% (0.51; 0.35-0.75; P<0.001)	0.38%	0.10% (0.26; 0.14-0.49; P<0.001)	0.12% (0.31; 0.17-0.56; P<0.001)	0.47%	0.26% (0.54;0.38-0.77; P<0.001)	0.16% (0.33;0.22-0.5; P<0.001)	0.44%	0.26% (0.59; 0.37-0.93; P=0.024)
Primary Safety endpoint (Aristotle, RE-LY, ENGAGE AF-	3.09%	2.13% (0.69; 0.60-0.80; P<0.001 for superiority)	3.36%	3.11% (0.93; 0.81-1.07; P=0.31)	2.71% (0.80; 0.69-0.93; P=0.003)	3.43%	2.75% (0.80;0.71-0.91; P<0.001)	1.61% (0.47;0.41-0.55; P<0.001)	3.4%	3.6% (P=0.58)

Outcomes (% per year intention to treat)										
Trial	ARISTOTLE ²²		RE-LY ²³			ENGAGE AF-TIMI 48 ²⁵			ROCKET-AF ²⁴	
TIMI 48):major bleeding										
Primary Safety endpoint (ROCKET AF) Major and non-major clinically relevant bleeding									14.5%	14.9% (1.03; 0.96-1.11; P= 0.44) Two sided for superiority in rivaroxaban group compared to warfarin group
Intracranial bleeding	0.80%	0.33% (0.42;0.30-0.58; P <0.001)	0.74%	0.30% (0.40; 0.27-0.60; P <0.001)	0.23% (0.31; 0.20-0.47; P<0.001)	0.85%	0.39% (0.47;0.34-0.63; P<0.001)	0.26% (0.30;0.21-0.43; P<0.001)	0.7%	0.5% (0.67; 0.47-0.93; P=0.02)
Extracranial bleeding			2.67%	2.84% (1.07; 0.92-1.25; P=0.38)	2.51% (0.94; 0.80-1.10; P=0.45)					
Other location bleeding	2.27%	1.79% (0.79; 0.68-0.93; P=0.004)				1.37%	0.85% (0.62;0.50-0.78; P<0.001)	0.55% (0.40;0.31-0.52; P<0.001)		
Gastrointestinal bleeding	0.86%	0.76% (0.89; 0.70-1.15; P=0.37)	1.02%	1.51% (1.50; 1.19-1.89; P <0.001)	1.12% (1.10; 0.86-1.41; P=0.43)	1.23%	1.51% (1.23;1.02-1.50;P=0.03)	0.82% (0.67;0.53-0.83;P<0.001)	2.2%	3.2%(P<0.001)
Myocardial infarction	0.61%	0.53% (0.88; 0.66-1.17; P=0.37)	0.64%	0.81% (1.27; 0.94-1.71; P=0.12)	0.82% (1.29; 0.96-1.75; P=0.09)	0.75%	0.70% (0.94;0.74-1.19;P=0.60)	0.89% (1.19;0.95-1.49;P=0.13)	1.1%	0.9% (0.81; 0.63-1.06; P=0.12)
Death from any cause	3.94%	3.52% (0.89; 0.800-0.998; P=0.047)	4.13%	3.64% (0.88; 0.77-1.00; P=0.051)	3.75% (0.91; 0.80-1.03; P=0.13)	4.35%	3.99% (0.92;0.83-1.01; P=0.08)	3.8% (0.87;0.79-0.96; P=0.006)	2.2%	1.9% (0.85; 0.70-1.02; P=0.07)
% discontinuation at end of follow-up	27.5%	25.3%	10.2%	15.5%	14.5%	34.5%	34.4%	33%	22.2%	23.7%
% discontinuation/yr.	15.3%	14.1%	5.1%	7.8%	7.3%	12.3%	12.3%	11.8%	11.7%	12.5%

mITT: modified intention to treat- all randomised subjects who receive at least one dose of randomised study drug; ITT: intention to treat- all randomised subjects whether or not they received drug

Apixaban – ARISTOTLE trial²²

The results of the ARISTOTLE trial can be seen in Table 4 where apixaban was shown to be statistically superior to warfarin for the primary endpoint of ischaemic or haemorrhagic stroke or systemic embolism. Apixaban was also shown to be superior to warfarin for major bleeding.

As is illustrated in Table 4 the rate of the primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) was 1.27% per year in the apixaban group compared with 1.6% per year in the warfarin group (HR, 0.79; 95% CI, 0.66 to 0.95). The trial demonstrated noninferiority and superiority ($p=0.01$) for the primary outcome. The rate of major bleeding was 2.13% per year in the apixaban group compared with 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60 to 0.80; $P<0.001$), and rates of death from any cause were 3.52% and 3.94%, respectively (HR, 0.89; 95% CI, 0.80 to 0.99; $P=0.047$). The rate of haemorrhagic stroke was 0.24% per year in the apixaban group as compared with 0.47% per year for warfarin group (HR, 0.51; 95% CI, 0.35 to 0.75; $P<0.001$), and the rate of ischaemic or uncertain type of stroke was 0.97% per year in apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74 to 1.13; $P=0.42$). The rate of intracranial haemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR, 0.42; 95%CI, 0.30 to 0.58; $p<0.001$).²²

Major bleeding was defined according to International Society of Thrombosis and Haemostasis (ISTH) criteria.²² The ISTH criteria define major bleeding as:

- 1) Fatal bleeding and/or
- 2) Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or
- 3) Bleeding causing a fall in haemoglobin level of 20g/L (1.24mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.²⁸

The ARISTOTLE trial only included major bleeds where there was a decrease in the haemoglobin of 2g/dl in the first 24 hours.

Dabigatran – RE-LY trial²³

As seen in Table 4 dabigatran 150 mg was shown to be statistically superior to warfarin for the primary endpoint with lower rates of stroke or systemic embolism. The rate of the primary outcome (stroke or systemic embolism) was 1.53% per year for dabigatran 110 mg twice daily (BD) compared with 1.69% per year for warfarin (RR, 0.91; 95% CI, 0.74-1.11; P<0.001 for noninferiority) and 1.11% per year for the dabigatran 150 mg twice daily group (RR, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority).²³

In patients with AF, dabigatran at a dose of 110 mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin.²³ Dabigatran at a dose of 150 mg twice daily is the only DOAC to have demonstrated lower rates of ischaemic stroke versus warfarin.

Major bleeding was significantly lower with dabigatran 110 mg twice daily compared to warfarin (2.71% versus 3.36% per year), whereas there was no significant difference in those treated with dabigatran 150 mg twice daily and warfarin (3.11% versus 3.36%). Major bleeding was defined in RE-LY as a reduction in haemoglobin of at least 2g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ.²³

Risk of intracranial bleeding and haemorrhagic stroke were significantly lower in both dabigatran 110 mg twice daily and 150 mg twice daily groups than with warfarin but GI bleeding was more frequent in the 150 mg twice daily dabigatran group as compared to warfarin (1.51% versus 1.02% per year; RR 1.50; 1.19-1.89; P<0.001; Table 4).²³

Edoxaban- ENGAGE AF-TIMI 48 trial²⁵

The results of the ENGAGE AF-TIMI 48 trial can be seen in Table 4. This trial consisted of three treatment arms (Table 5). The low-dose edoxaban treatment regimen (30/15

mg) was not granted approval by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

Table 5: ENGAGE AF-TIMI treatment groups

Treatment group/Regimen	Medication given
Warfarin	Warfarin (INR 2.0-3.0 inclusive)
High-dose Edoxaban	Edoxaban 60 mg daily or dose reduced to 30 mg daily*
Low-dose Edoxaban	Edoxaban 30 mg daily or dose reduced to 15 mg daily*

* Subjects were dose reduced if they had creatinine clearance (CrCl) 30-50 ml/min, body weight of 60kg or less or concomitant use of verapamil, quinidine or dronedarone.

Both strengths of edoxaban demonstrated noninferiority compared with warfarin for the primary endpoint of stroke or SEE in the mITT. The annualised rate of high-dose edoxaban was 1.18% vs. 1.5% for warfarin, (hazard ratio [HR], 0.79; 95% confidence interval [CI] 0.63-0.99; p for noninferiority < 0.001). The annualised rate of low-dose edoxaban was 1.61%, (HR, 1.07; 95% CI, 0.87-1.31; p for noninferiority = 0.005). In the ITT population, superiority testing was performed with borderline results (p = 0.08, p = 0.10, respectively). Low dose edoxaban was associated with a reduced rate of haemorrhagic stroke (HR, 0.33; 95% CI, 0.22-0.50; P<0.001) but a higher rate of ischaemic strokes (HR, 1.41; 95% CI 1.19-1.67, p<0.001) compared with warfarin.

The ITT superiority analysis showed a trend favouring high-dose edoxaban (1.57%) over warfarin (1.8%) (HR, 0.87; 95% CI, 0.73-1.04; P=0.08 for superiority). However this trend was unfavourable for the low-dose edoxaban regimen (2.04%) (HR, 1.13; 95% CI, 0.96-1.34; P=0.10 for superiority).²⁵

The primary safety outcome of major bleeding was higher in the warfarin arm [annualized rate 3.43% (warfarin) vs. 2.75% (edoxaban 60 mg) vs. 1.61% (edoxaban 30 mg), p < 0.001 for both comparisons]. Fatal bleeding and intracranial haemorrhage were also higher in the warfarin arm. Conversely, gastrointestinal (GI) bleeding was higher in the high-dose edoxaban arm, but lower in the low-dose edoxaban arm (1.23% vs. 1.51% vs. 0.82%, p < 0.05).²⁵

Rivaroxaban – ROCKET-AF trial²⁴

Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism in both the per-protocol and the ITT analyses. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

The primary analysis was per-protocol as opposed to the preferred ITT analysis. The primary outcome (composite of ischemic and haemorrhagic stroke) and systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) compared to 241 patients in the warfarin group (2.2% per year); (HR for rivaroxaban, 0.79; 95% CI, 0.66-0.96; $P < 0.001$ for noninferiority). In the ITT analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year; HR, 0.88; 95% CI, 0.75-1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority).²⁴

Major and non-major clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (HR, 1.03; 95% CI, 0.96 to 1.11; $P = 0.44$).²⁴ There were significant reductions in intracranial haemorrhage (0.5% vs. 0.7%, HR 0.67; 95% CI, 0.47-0.93; $P = 0.02$) and fatal bleeding (0.2% vs. 0.5%, $P = 0.003$) in the rivaroxaban group.²⁴

The definition of major bleeding in ROCKET-AF was: clinically overt bleeding associated with a reduction in haemoglobin of at least 2g/dL and/or blood transfusion of two or more units of blood, fatal bleeding, critical anatomic site bleeding or permanent disability. Non-major clinically relevant bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact with a physician, temporary interruption of study drug, pain, or impairment of daily activities.²⁴

Discussion

In reviewing clinical evidence for the DOACs, the MMP remained cognisant of the heterogeneity of the trial design, population characteristics, comparator uniformity (e.g. warfarin TTR variations), analysis approach (per-protocol versus ITT) and definitions of efficacy and safety endpoints of the pivotal clinical trials. These differences in trial design complicate comparisons across the studies. Some examples include:

- RE-LY was an open-label trial as compared to the ROCKET-AF, ENGAGE AF-TIMI 48 and ARISTOTLE trials which were all double-blind trials.
- ROCKET-AF and ENGAGE AF-TIMI 48 recruited higher risk patients. Approximately 87% of the ROCKET-AF population and 53% of the ENGAGE AF-TIMI 48 population had a CHADS₂ score of ≥ 3 (compared with approximately 30% for RE-LY and ARISTOTLE).²⁹
- Variations exist between individual trials in patient follow-up and endpoint determination which may affect final analysis. Comparisons between the pivotal DOAC trials and published meta-analyses must take into account these differences.

Systematic reviews and meta-analyses use pooled data from the clinical trials and allow for a degree of cross interpretation between agents. A number of these reviews have been carried out and will be discussed in section 5.1.4.

In order to appropriately review indirect comparisons of the licensed DOAC therapies it is important to review the variations in clinical trial design including patient selection, inclusion and exclusion criteria and primary and secondary efficacy and safety outcome measures. The four clinical trials reviewed in this section are ARISTOTLE (apixaban), RE-LY (dabigatran), ENGAGE AF-TIMI 48 (edoxaban) and ROCKET-AF (rivaroxaban).²²⁻²⁵

5.1.2 Patient selection in individual trials

In reviewing the main pivotal trials (ARISOTLE, RE-LY, ENGAGE AF-TIMI 48 and ROCKET-AF) we considered the variations in patient cohorts included in the trial design. These patient characteristics can also be compared with real world Irish data where available.

The following patient characteristics were compared across the four clinical trials:

- Age categories
- Stroke risk (CHADS₂ score)
- Renal function

Age categories

As the majority of patients being treated with DOACs for AF will be elderly and given the reduction in renal elimination of drugs in the elderly and dose adjustments recommended for some DOAC therapies due to age, it is appropriate to consider the age of participants in the clinical trials as shown in Table 6.²

Table 6: Age categories in AF clinical trials

Apixaban Trial Data (ARISOTLE)²²				
Age Category	< 80 years	80-89 years	90+ years	Total
Number	15,765	2352	84	18,201
%	86.62	12.92	0.46	100
Dabigatran Trial Data (RE-LY)²³				
Age Category	< 80 years	80-89 years	90+ years	Total
Number	15,097	2,937	79	18,113
%	83.35	16.21	0.44	100
Edoxaban (ENGAGE AF-TIMI 48)*				
Age Category	< 80 years	80-89 years	90+ years	Total
Number	17,514	3,513	78	21,105
%	83	16.6	0.4	100
Rivaroxaban Trial Data (ROCKET-AF)²⁴				
Age Category	< 80 years	80-89 years	90+ years	Total
Number	11,576	2517	78	14,171
%	81.69	17.76	0.55	100

*Age category data for ENGAGE AF-TIMI 48 trial supplied by Daiichi Sankyo Ireland Ltd.³⁰

In the clinical trials there are variances in the percentages of patients within different age ranges and all trials have less than 20% of patients aged 80 years or older.

ARISTOTLE had a lower proportion of older patients with approximately 13.5% of patients over 80 years compared with over 16.5% for RE-LY, 17% for ENGAGE AF-TIMI 48 and approximately 18.3% for ROCKET-AF.^{22-25,30}

GMS prescribing database analysis of new initiations of DOAC therapy between January 2013 and March 2014 (with treatment duration longer than 3 months) showed that 34.8% of patients treated with dabigatran, 37.5% of patients treated with rivaroxaban and 45.4% of patients treated with apixaban were 80 years or over (see section 5.7 for further detail).³¹ Analysis of the PCRS database indicates that in 2015, 34% of patients who applied for reimbursement of a DOAC were ≥ 80 years of age. In each of the four key clinical trials there were less than 20% of the patients aged 80 years or older. Real world data appears to show a larger cohort of patients in the older categories being treated with DOAC therapies as compared with the pivotal clinical trials and careful monitoring of patient outcomes will be an important part of follow up.

More recently studies have investigated the effect of the newer agents in older populations. Kumar et al. (2018) assessed the association between anticoagulation, ischaemic stroke, gastrointestinal and cerebral haemorrhage, and all-cause mortality in older people with AF and chronic kidney disease (CKD).³² The study included patients aged 65 years or older with an estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m² and a new diagnosis of AF. The crude rates of ischaemic stroke and haemorrhage were 4.6 and 1.2 after anticoagulation and 1.5 and 0.4 in patients with no anticoagulation per 100 person years, respectively. Anticoagulation was associated with a lowered rate of all-cause mortality. The increased rate of stroke and haemorrhage associated with anticoagulation in patients with CKD and AF emphasises the need for careful consideration of new DOAC therapies in this patient group.

Subgroup analyses of clinical trial results have been published and a number of points have been noted.

Apixaban

It was reported from ARISTOTLE that there was a lack of interaction in terms of stroke, death and major bleeding between treatment and age in studies with apixaban.³³

Observations from the ARISTOTLE trial published by Halvorsen et al. showed that apixaban as compared with warfarin reduced the risk of stroke, death and major bleeding outcomes in a consistent manner regardless of age. In those aged ≥ 80 years stroke or systemic embolism was reduced from 1.9% per year with warfarin to 1.53% per year with apixaban (HR 0.81, 95% CI, 0.51-1.29), major bleeding from 5.41% per year with warfarin to 3.55% per year with apixaban (HR 0.66, 95% CI, 0.48-0.90) and intracerebral haemorrhage from 1.32% per year with warfarin to 0.47% per year with apixaban (HR 0.36, 95% CI, 0.17-0.77). It was also noted however that this analysis may be limited by the relatively low numbers of patients in the trial who were 80 years or over and the potential for selection bias towards more healthy patients.³³

Age of ≥ 80 years is included in the criteria (which also includes serum creatinine > 133 $\mu\text{mol/L}$ and weight ≤ 60 kg) for lower dose (i.e. 2.5 mg twice daily) selection in patients.¹¹

Dabigatran

A review of RE-LY (dabigatran) found a significant interaction between treatment and age in terms of bleeding where elderly patients were more likely to develop haemorrhagic complications.³⁴ In the RE-LY trial both doses of dabigatran versus warfarin were associated with lower risk of major bleeding in patients < 75 years but similar risk (110 mg) or higher risk (150 mg) of major bleeding in patients ≥ 75 years.³⁴ In patients with AF at risk of stroke, both doses of dabigatran had a lower risk of intracranial bleeding irrespective of age versus warfarin. There was an interaction in terms of extracranial bleeding and age with both doses of dabigatran versus warfarin. Those < 75 years showed lower risk of extracranial haemorrhage than warfarin but in those ≥ 75 years bleeding risk was similar or higher with both doses of dabigatran compared with warfarin.

Age is considered as one criterion for reduced dose of dabigatran (i.e. 110 mg twice daily) with criteria dividing between >80 years or >75 years with increased bleeding risk. Other considerations include renal impairment and bleeding risk, gastro-oesophageal reflux disease/gastritis/oesophagitis and concomitant use of verapamil.¹²

Edoxaban

Approximately 40% of the patients from the ENGAGE AF-TIMI 48 trial were at least 75 years old.³⁵ A subgroup analysis examined the efficacy and safety of edoxaban compared with warfarin in patients under 65, aged 65-74 and ≥ 75 years with AF compared to younger patients. Older patients (≥ 75 years) were found to have similar rates of stroke or embolic event with edoxaban versus warfarin, (HR 0.83, 95% CI, 0.66-1.04) however major bleeding was significantly reduced with edoxaban (HR 0.83, 95% CI, 0.70-0.99). Across all age groups there was consistently lower major bleeding rates with edoxaban than with warfarin.³⁶

Older patients enrolled in the ENGAGE AF-TIMI 48 trial were more likely to be female, with lower body weight and reduced creatinine clearance (CrCl) leading to higher rates of edoxaban dose reduction.³⁶ Further considerations for dose adjustment include concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole.¹⁴ About 30% of the patients who were dose reduced had more than one reason for dose adjustment.³⁵ The decreased drug dose did not alter the efficacy of edoxaban compared with warfarin in the prevention of stroke, systemic embolism or all-cause mortality. However, patients who were dose-reduced had an even greater relative reduction in major bleeding with edoxaban compared with warfarin.³⁵

Rivaroxaban

The ROCKET-AF trial showed no interaction in terms of the primary outcome (in the ITT population) of the composite of stroke (ischaemic or haemorrhagic) and systemic embolism between treatment and age (<75 years versus ≥ 75 years). Older patients

randomised to rivaroxaban had higher rates of the combined endpoint of major or clinically relevant non-major bleeding than those assigned to warfarin. There was no difference in bleeding rates among younger patients.³⁷

Patient age is not considered a criterion for reduced dose with rivaroxaban.¹³

Stroke Risk (CHADS₂ score)

The CHADS₂ score is a patient specific score for stroke risk with AF. The parameters comprising the scoring system include: congestive heart failure history (1), hypertension (1), age ≥ 75 years (1), diabetes mellitus (1), stroke or TIA previously (2) with a total risk score of 6. ROCKET-AF and ENGAGE AF-TIMI 48 enrolled a higher stroke risk population (CHADS₂ score ≥ 2) compared to ARISTOTLE and RE-LY, as shown in Table 7.²⁹ Over 85% of the ROCKET-AF population and over 50% of the ENGAGE AF-TIMI 48 population had a CHADS₂ score of ≥ 3 (compared with approximately 30% for RE-LY and ARISTOTLE).^{29,30}

Table 7: Proportion of patients in CHADS₂ score categories

CHADS ₂ scores	ARISTOTLE (Apixaban)	RE-LY (Dabigatran)	ENGAGE AF-TIMI 48 (edoxaban)	ROCKET-AF (Rivaroxaban)
0	-	31.9%	-	-
1	34%		-	-
2	35.8%	35.63%	46.8%	13.05%
3			30.6%	43.6%
4			15.6%	28.65%
5	(≥3) 30.2%	(≥3) 32.47%	5.8%	12.75%
6			1.2%	1.95%
			(≥3) 53.2%	(≥3) 86.95%

*CHADS₂ scores for ENGAGE AF-TIMI 48 trial supplied by Daiichi Sankyo Ireland Ltd.³⁰

Renal Function

All DOACs have a degree of renal clearance with dabigatran demonstrating the highest proportion with 85% renal clearance. Edoxaban is 50% renally cleared while rivaroxaban and apixaban have renal clearances of 36% and 27% respectively.¹¹⁻¹⁴ Chronic kidney disease (CKD) is an independent risk factor for AF, which is more prevalent among CKD patients than the general population.³⁸ As patients with renal

dysfunction are at greater risk of haemorrhagic complications and in light of the drug clearance through the renal mechanism, it is appropriate to consider the renal function of patients included in the major clinical trials.

- ARISTOTLE excluded patients with a CrCl <25 ml/min or serum creatinine >2.5 mg/dL (220 µmol/L)
- RE-LY excluded patients with a CrCl ≤30 ml/min
- ENGAGE AF-TIMI 48 excluded patients with an estimated CrCl <30 ml/min
- ROCKET-AF excluded patients with a CrCl <30 ml/min

Apixaban

A study by Hohnloser et al. (2012) showed that when compared with warfarin, apixaban treatment reduced the rate of stroke, death, and major bleeding regardless of renal function.³⁹ A further study by Halvorsen et al. (2014) showed that this also applies for the subgroup of patients ≥75 years.³³ This review found that apixaban was superior to warfarin across the range of eGFR, with no significant interaction between the treatment effect and the level of renal dysfunction.

Dabigatran

A review on behalf of RE-LY (2011) found a greater than two fold risk of major bleeding with dabigatran or warfarin in patients with a CrCl less than 50 ml/min as compared with those who had a CrCl greater than or equal to 80 ml/min.³⁴

Edoxaban

Bohula et al. (2016) investigated the impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial.⁴⁰ In patients with moderate renal dysfunction (CrCl 30-50 ml/min), high-dose edoxaban regimen was found to be comparable to warfarin for the prevention of stroke/systemic embolism and had lower rates of major bleeding. Patients with mild or no renal dysfunction (CrCl >50 ml/min) showed results consistent with the main trial population and those with moderate renal dysfunction. The rates of bleeding and stroke/systemic embolism were lowest in patients with

normal renal function (>95 ml/min) for all three treatment arms of the ENGAGE AF-TIMI 48 trial.⁴⁰

The study also performed an exploratory analysis of patients with significantly high CrCl (>95 ml/min) in the ENGAGE AF-TIMI 48 trial and found evidence of lower efficacy for the prevention of thromboembolic events with the high-dose edoxaban regimen compared to warfarin.⁴⁰ However it was noted that patients with CrCl>95 ml/min were at very low risk of both thromboembolic and bleeding complications regardless of the OAC chosen and the small numbers in the analysis may make it difficult to exclude the role of chance in these findings.⁴⁰

The FDA reviewed the data from the ENGAGE AF-TIMI 48 trial and recommended edoxaban should not be used in patients with CrCl >95 ml/min for stroke prevention in AF.⁴¹ In contrast the EMA does not currently have any restrictions on the use of edoxaban in patients with normal renal function, although the European Public Assessment Report (EPAR) for edoxaban (Lixiana®) states that the benefit of edoxaban in preventing stroke in AF patients with high creatinine clearance is less clear and requires further study.⁴²

Rivaroxaban

Fox et al. (2011) reviewed the use of rivaroxaban for stroke prevention in patients with moderate renal impairment and found no evidence of heterogeneity in treatment effect across the dosing groups and results for patients using rivaroxaban 15 mg (reduced dose) for creatinine clearance between 30-49 ml/min were consistent with the overall trial results.⁴³

Discussion

A number of observations were made by Bruins Slot et al. in a clinical evidence synopsis of trial reviews with factor Xa inhibitors versus warfarin for preventing stroke and thromboembolism in patients with AF.⁴⁴ This review found that the available data did

not allow determination of which factor Xa inhibitor is most effective and safe and that potential adverse events may not have been captured due to the relatively short treatment durations (up to 1.9 years). It was also noted that few patients with CrCl <30 ml/min were included in the trials. The evidence for a reduction in major bleeding events associated with factor Xa inhibitors was found to be less robust due to the observed high heterogeneity.⁴⁴

A Cochrane systematic review published in 2017 directly compared the efficacy and safety of the non-vitamin K oral anticoagulants with warfarin in SSE prevention in NVAF patients with CKD. Although their findings indicate that DOACs are as likely as warfarin to prevent SSE events without increasing the risk of major bleeding events in this patient population, the study results chiefly reflect CKD stage G3. The results cannot be applied to stage G4 or G5 without further investigation.³⁸

5.1.3 Clinical trial parameters

Variations in clinical trial parameters and methods for reporting results also make comparison between DOACs difficult. The following parameters are reviewed in relation to the four pivotal clinical trials:

1. Primary efficacy and safety endpoints
2. TTR for trials
3. Number of patients receiving lower/reduced dose in clinical trials for AF
4. Discontinuation rates versus warfarin

1) Primary efficacy and safety endpoints

All four trials (ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48 and ROCKET-AF) use “stroke or systemic embolism” as a primary efficacy endpoint.²²⁻²⁵ The primary safety endpoint for RE-LY, ENGAGE AF-TIMI 48 and ARISTOTLE was major bleeding by ISTH criteria but in ROCKET-AF the primary safety endpoint was the composite of “major and clinically relevant non-major bleeding”. This result was not reported in RE-LY but was in

ARISTOTLE and ENGAGE AF-TIMI 48. “Life-threatening bleeding” was not reported in ARISTOTLE. The combined endpoint of “ischaemic or uncertain type of stroke” was not reported for ROCKET-AF or ENGAGE AF-TIMI 48 where “ischaemic stroke” alone was reported.

RE-LY based all efficacy and safety analysis on the ITT principle. ARISTOTLE published efficacy data based on the ITT population but safety analysis on the ‘on treatment’ (OT) safety population. ENGAGE AF-TIMI 48 published efficacy data based on mITT and also the ITT population. The mITT population was defined as all randomised subjects who received at least one dose of study drug, whereas the ITT population was all randomised subjects whether or not they received a study drug. Safety analyses used the OT safety population.²⁵ Analysis of efficacy in ROCKET-AF was carried out on a per-protocol population to demonstrate noninferiority with superiority and safety analyses carried out on OT population. Efficacy analysis were also conducted on the ITT population and this data is generally used for indirect comparison between trials.²⁴

2) Time in therapeutic range for NVAf (DOAC versus warfarin) clinical trials

The pivotal clinical trials for the DOACs compared each agent to warfarin therapy. As previously mentioned warfarin therapy is guided by monitoring of a patient’s INR and reviewing the percentage of time a patient remains within this defined range, their TTR. Optimal warfarin therapy is considered when the TTR is > 70%.^{6,45} The pivotal clinical trials for stroke prevention in NVAf all obtained mean TTRs of 65% or lower (Table 8).

Table 8: Time in Therapeutic Range (TTR) for warfarin arm in pivotal AF clinical trials

	ARISTOTLE (Apixaban)	RE-LY (Dabigatran)	ENGAGE AF-TIMI 48 (Edoxaban)	ROCKET-AF (Rivaroxaban)
TTR for warfarin	Mean: 62% Median: 66% (interquartile range 52.4-76.5%)	Mean: 64% *	Mean: 64.9% Median: 68.4% (interquartile range 56.5-77.4)	Mean: 55% Median: 58% (interquartile range 43-71%)

*Median values not reported

A number of papers have looked at the efficacy and safety of the new agents at different levels of INR control to review the outcomes of the trial data where lower than optimal TTRs have been observed.^{46,47}

As individual TTR results are not relevant for non-vitamin K antagonist anticoagulants, reviews of warfarin TTR comparisons with DOACs often use centre-based TTR analyses. These analyses evaluate INR measurements for all patients receiving warfarin at a particular site or centre in the clinical trial. The average value can then be compared with those from other sites and allows for a review of the quality of warfarin management across different institutions. Different methodologies may be used to calculate and analyse centre average TTR (cTTR) values.

Apixaban

In the ARISTOTLE trial a cTTR was estimated with the use of a linear mixed model on the basis of the real TTRs in its warfarin-treated patients, with a fixed effect for country and random effect for centre. For each patient, an individual TTR (iTTR) was also predicted with the use of a linear mixed effects model including patient characteristics. A review by Wallentin et al. (2013) concludes that apixaban remains more effective and safer than warfarin across a broad range of warfarin management levels.⁴⁶ A subsequent editorial for *Circulation* questioned the use of predicted cTTR and iTTR in this trial as opposed to actual results but highlighted that the rate of stroke and systemic embolism and mortality, the net clinical benefit, and the composite of the primary efficacy and safety endpoints among patients receiving warfarin were lowest among those with iTTR \geq 71.3%.⁴⁸

Dabigatran

Wallentin L et al. (2010) reviewed the efficacy and safety of dabigatran and found that there was a significant interaction in terms of major bleeding and the cTTR when comparing dabigatran 150 mg and warfarin.⁴⁷ Less bleeding events were observed for dabigatran at lower cTTR but similar events at higher cTTR. The rates of major bleeding

were lower with dabigatran 110 mg irrespective of the cTTR in this group. Dabigatran 150 mg was not found to be superior to warfarin at reducing the risk of non-haemorrhagic stroke at higher cTTR quartiles however intracranial bleeds were lower with both doses of dabigatran than warfarin irrespective of the cTTR.

Edoxaban

In the ENGAGE AF-TIMI 48 trial TTR for the warfarin group was estimated using the linear interpolation method of Rosendaal. The mean TTR for the warfarin group was $64.9\% \pm 18.7\%$ (median 68.4%, interquartile range 56.5-77.4%). The INR was 1.8-3.2 for 83.1% of the treatment period. No significant interaction was found between cTTR and treatment effect for either the high-dose or low-dose edoxaban trial arms.²⁵

Rivaroxaban

Piccini et al. (2014), ROCKET AF investigators, reviewed the relationship between TTR and comparative treatment effect of rivaroxaban and warfarin based on cTTR. Mean iTTR in ROCKET-AF was 55% and mean cTTR was 59% (with median cTTR of 61%, interquartile range 51%-69%). This review concluded that there was no evidence that the relative efficacy of rivaroxaban versus warfarin varied with cTTR.⁴⁹

In 2015 the ROCKET-AF study data underwent further analyses by the EMA's committee for medicinal products for human use (CHMP), after the INR device used in the warfarin treatment arm was found to have a defect. There were concerns that the INR device could have provided lower INR values in some patients in the warfarin treatment group. Following an investigation the CHMP concluded that any incorrect measurements from the device would have had only a marginal effect on the study results and the safety of rivaroxaban remains unchanged.⁵⁰

3) Number of patients receiving lower/reduced DOAC dose in NVAF clinical trials

It is important to consider the evidence from clinical trials for lower doses of DOACs as reduced doses are recommended for patients of older age (>80 years) and/or reduced renal function, and many patients with AF will fall into these categories.

The RE-LY and ENGAGE AF-TIMI 48 trials, in contrast to the ARISTOTLE and ROCKET-AF trials, obtained trial data for full cohorts of both doses of dabigatran (150 mg and 110 mg) and edoxaban (60 mg and 30 mg) versus warfarin. There were over 6,000 patients in each category in the RE-LY trial and 7,000 patients in each category in the ENGAGE AF-TIMI 48 trial.^{23,25} However the edoxaban low-dose regimen did not receive approval from the FDA or the EMA. ARISTOTLE and ROCKET-AF trials used reduced doses of apixaban 2.5 mg twice daily and rivaroxaban 15 mg once daily respectively in a predefined cohort of higher risk patients (Table 9).^{22,24}

Table 9: Breakdown of doses in pivotal trials

	ARISTOTLE (Apixaban)	RE-LY (Dabigatran)	ENGAGE AF-TIMI 48 (Edoxaban)		ROCKET-AF (Rivaroxaban)
	Regular dose: 5 mg BD Reduced dose: 2.5 mg BD	Regular dose: 150 mg BD Reduced dose: 110 mg BD	High-dose regimen: Regular dose:60 mg OD Reduced dose:30 mg OD	Low-dose regimen: Regular dose:30 mg OD Reduced dose:15 mg OD	Regular dose: 20 mg OD Reduced dose: 15 mg OD
Total numbers on DOAC	9,120	12,091	7,035	7,034	7,111
Regular dose	~ 8,692	~ 6,076	~ 5,251	~5,249	~ 5,637
Reduced dose	428 (4.7%)	6,015 (50%)	1,784 (25.4%)	1,785 (25.4%)	1,474 (20.7%)
Numbers on warfarin	9,081	6,022	7,036		7,116

Apixaban

For apixaban the reduced dose was given to patients with two or more of the following factors: age ≥80 years, bodyweight ≤60 kg, and serum creatinine ≥133 μmol/L (≥1.5 mg/dL). Most of the patients receiving the reduced dose were ≥75 years.³³ Less than 5%

of all patients receiving apixaban in the ARISTOTLE trial were treated with the lower dose of 2.5 mg twice daily. Analysis of GMS dispensing data from January 2013 to March 2014 (see section 5.7 for further details) showed that over 50% of all patients in the analysed cohort received the 2.5 mg dose and approximately 74% of these patients were 80 years or older.

Dabigatran

In the RE-LY trial dabigatran patients were assigned into two treatment groups and given either 150 mg dabigatran or 110 mg dabigatran. Patients then remained on that dose for the duration of the study.²³

Edoxaban

In the ENGAGE AF-TIMI 48 trial patients on edoxaban were dose reduced in either the high-dose or low-dose treatment regimen if they had creatinine clearance between 30-50 ml/min, body weight of 60 kg or less or concomitant use of the P-gp inhibitors verapamil, quinidine or dronedarone. A total of 5,330 (25.3%) patients received a reduced dose of edoxaban or matching placebo at randomisation. During the trial a further 7.1% of the total study group received a dose reduction.²⁵

Rivaroxaban

Rivaroxaban 15 mg once daily was given to patients with creatinine clearance of 30-49 ml/min at enrolment and there was no dose adjustments post-baseline for changing CrCl (however those with CrCl<30 ml/min were removed from the study).⁴³

Those patients randomised with moderate renal impairment had a median age of 79 years, a mean CHADS₂ of 3.7 and 62% had previously been on warfarin whilst 36% were taking aspirin. In total 1,474 patients (20.7%) were treated with the 15 mg dose in ROCKET-AF trial with a corresponding 1,476 patients treated with warfarin (with CrCl 30-49ml/min). Some 5,637 patients were treated with rivaroxaban 20 mg once daily (CrCl ≥ 50 ml/min).⁴³ GMS prescribing database analysis indicates similar findings with

approximately 30% of patients analysed receiving the 15 mg daily dose (see section 5.7 for details).

4) Discontinuation rates versus warfarin

Withdrawal rates for treatment at the end of the studies exceeded 20% in ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48 and the dabigatran arms of RE-LY.

In the ARISTOTLE trial 25% of patients treated with apixaban discontinued use during the trial and 27% discontinued treatment in the warfarin arm. Reasons for discontinuation included patient request, adverse events, death and “other reasons” as per ARISTOTLE supplementary material.⁵¹ The most common reason for discontinuation in ARISTOTLE was for bleeding-related adverse reactions and this occurred in 1.7% of patients treated with apixaban (versus 2.5% on warfarin).

There was a difference in study drug discontinuation rates between dabigatran (21%) and warfarin (17%) in RE-LY. Ru San et al. (2012) suggest this may be due to the open-label design of the RE-LY study and the higher rates of dyspepsia noted with dabigatran. Dyspepsia occurred in 5.8% of the warfarin group compared with 11.8% and 11.3% for dabigatran 110 mg and 150 mg respectively.⁵²

In the ENGAGE AF-TIMI 48 trial discontinuation rates were similar between treatment arms, with 34% of patients on the high-dose edoxaban regimen (60 mg/30 mg), 33% of patients on the low-dose edoxaban regimen (30 mg/15 mg) and 35% of patients on warfarin discontinuing treatment during the study. The most common reason for discontinuation was an adverse event or suspected endpoint event which occurred in 17.2% of patients on the high-dose edoxaban regimen and 15.6% of patients on the low-dose edoxaban regimen compared to 16.7% of patients on warfarin. Other reasons for discontinuation of treatment during the trial included death, investigator or subject decision or the patient refused routine follow-up.⁵³

In ROCKET-AF 23.9% of patients on rivaroxaban and 22.4% of patients on warfarin discontinued treatment during the study. Reasons for discontinuation included an adverse event, withdrawn consent from study drug and follow-up, patient decision to stop drug but continue follow-up, patient lost to follow-up, experiencing the primary endpoint and death.²⁴

5.1.4 Comparative efficacy and safety

Systematic reviews and meta-analyses

Indirect analyses have been carried out but must be interpreted with a level of caution due to the heterogeneity in the clinical trial designs for DOAC therapies as highlighted in sections 5.1.2 and 5.1.3.

Systematic reviews and meta-analyses utilise pooled data from clinical trials and provide an additional means of assessing the general and comparative efficacy of DOACs. Network meta-analysis requires that studies are sufficiently similar in order to effectively pool the results. In reviewing the DOAC pivotal clinical trials it is noted that there is heterogeneity in both clinical and methodological aspects of the individual trials. As previously noted some areas of heterogeneity include differences in TTR for warfarin arm, variations in proportions of patients with CHADS₂ scores and differences in clinical outcomes measured. In order to take account of these differences, meta-analysis may include pre-specified sub-group analysis. It is also noted that the small number of studies limits analysis for heterogeneity.⁵⁴ The potential for bias in analysis carried out on behalf of a particular product or manufacturer is recognised.

Publications were obtained in the course of database searches (Medline and CINAHL) and the search was limited to analyses of the pivotal clinical trials for stroke prevention in AF including subgroup analyses. This search was updated in 2018 to include edoxaban.

Lip GY (2012) carried out an indirect comparison reviewing dabigatran, rivaroxaban and apixaban in their three main phase 3 clinical trials for stroke prevention in AF (RE-LY, ROCKET-AF and ARISTOTLE) using warfarin as a single common comparator and using results from ITT analysis.⁵⁵ The focus of this analysis was on the primary efficacy and safety endpoints. ARISTOTLE, RE-LY and ROCKET-AF clinical trials were reviewed for comparability and consistency of definitions. This review noted the differences in trial design (RE-LY was open label for the warfarin arm while ARISTOTLE and ROCKET-AF were double blind) and variations in terminology for the primary safety endpoints. Lip et al. noted the important risk differences between the trials e.g. greater than 50% point difference in the CHADS₂ score and greater than 35% point difference in the proportion of use for secondary prevention (i.e. previous stroke or TIA) between the ROCKET-AF trial and the other two trials (ARISTOTLE and RE-LY). ROCKET-AF also had a higher proportion of patients with heart failure, diabetes and hypertension than the other trials (62.5%, 40% and 90.5% respectively for ROCKET-AF). RE-LY and ARISTOTLE were broadly similar in patient demography and baseline stroke risk.⁵⁵

No significant difference for apixaban versus dabigatran (both doses) or rivaroxaban, or rivaroxaban versus dabigatran 110 mg twice daily in preventing stroke and systemic embolism was found. No significant differences were reported between individual DOACs for the ischaemic stroke endpoint. The review showed a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran 150 mg twice daily compared with rivaroxaban and lower risk of haemorrhagic stroke (by 56%, $p=0.039$) and non-disabling stroke (by 40%, $p=0.038$). For major bleeding a significantly lower risk was found with apixaban versus dabigatran 150 mg twice daily (by 26%, 95% CI 0.61-0.91; $p=0.003$) and a significantly lower risk with apixaban versus rivaroxaban (by 34%; 95% CI, 0.54-0.81; $p<0.001$). No significant difference was noted for apixaban versus dabigatran 110 mg twice daily for major bleeding (HR, 0.86; 95% CI, 0.7-1.06). Dabigatran 110 mg twice daily showed less major bleeding (by 23%; 95% CI, 0.63-0.94; $p=0.011$) and less intracranial bleeding (by 54%; 95% CI, 0.27-0.80; $p=0.006$) than rivaroxaban. Gastrointestinal and extracranial bleeding was found to be significantly

less with apixaban compared with dabigatran 150 mg twice daily by 41% ($p=0.003$) and 25% ($p=0.007$) respectively. Apixaban was found to have lower major or clinically relevant bleeding (by 34%, $p<0.001$) compared with rivaroxaban. No significant difference was seen in the risk of MI between both doses of dabigatran and apixaban but more MI events were seen with dabigatran (>50%) compared to rivaroxaban. Limitations were addressed in relation to differences in trial design and patient populations and the inability to adjust analysis for these trial variables.⁵⁵

Cameron et al. (2014) carried out a systematic review and network meta-analysis to compare antithrombotic agents for the prevention of stroke and major bleeding in patients with NVAF and among sub-populations.⁵⁴ This review included 16 individual RCTs with five large multicentre trials which included: ARISTOTLE, RE-LY, ROCKET-AF and ENGAGE AF-TIMI 48. Dabigatran 150 mg twice daily and apixaban showed reductions relative to warfarin for stroke and systemic embolism (OR, 0.66; 95% CI, 0.53-0.82 and OR, 0.78; 95% CI, 0.65-0.94 respectively). In relation to major bleeding apixaban, edoxaban (both high-dose and low-dose regimens) and dabigatran 110 mg showed reductions in major bleeding compared with warfarin.⁵⁴

Apixaban and dabigatran 110 mg had fewer major bleeding events versus dabigatran 150 mg and rivaroxaban. Edoxaban high-dose (60 mg) had fewer major bleeding events compared with rivaroxaban. No difference was seen in major bleeding between warfarin and dabigatran 150 mg or rivaroxaban. The review group noted that results between individual treatments of DOACs should be interpreted with caution due to limitations associated with using a fixed-effects model.⁵⁴

A meta-analysis carried out by Ruff CT et al. (2014) was limited to phase III, randomised trials of patients with AF who were randomised to receive DOACs or warfarin where both efficacy and safety outcomes were reported. The trials included were RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48.⁵⁶ The overall finding was that DOACs decreased stroke and systemic embolism by 19% compared with warfarin (RR 0.81; 95%

CI, 0.73-0.91; $p < 0.0001$), mainly driven by reduced haemorrhagic stroke (0.49; 0.38-0.64; $p < 0.0001$). DOACs were found to reduce all-cause mortality and intracranial haemorrhage but showed an increase in gastrointestinal bleeding. No heterogeneity was noted for stroke or systemic embolism in important subgroups but there was a greater relative reduction in major bleeding with DOACs when the cTTR was less than 66% than when it was 66% or greater. It was also reported that low-dose DOACs had similar efficacy to warfarin for the composite of stroke or systemic embolism but were associated with an increase in ischaemic stroke compared with warfarin (and a subsequent reduction in haemorrhagic stroke). It was noted that each trial can only offer partial reassurance that the overall balance of efficacy and safety is preserved.⁵⁶

The Canadian agency for Drugs and Technologies in Health carried out a systematic review and indirect comparison of antithrombotic agents for the prevention of stroke and systemic embolism in patients with AF in 2013. DOACs included in this review were dabigatran, rivaroxaban and apixaban.⁵⁷ The review also assessed the impact of age, CHADS₂ score and TTR on the clinical safety and efficacy of antithrombotic agents. The review found that absolute risk differences (ARD) for the DOACs versus warfarin were small although there were statistically significant differences for some outcomes. In the main analysis of patients aged 75 years or older it was found that apixaban 5 mg twice daily and dabigatran 150 mg twice daily were associated with statistically significantly lower rates of stroke and systemic embolism (SSE) compared with dose adjusted warfarin. Results from the network meta-analysis showed apixaban 5 mg twice daily and dabigatran 110 mg twice daily were associated with statistically significantly lower rates of major bleeding compared with warfarin. Dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily were associated with statistically significantly higher rates of major bleeding compared with apixaban 5 mg twice daily and dabigatran 110 mg twice daily.⁵⁷

Subgroup analysis of CHADS₂ scores showed no statistically significant differences between warfarin and each DOAC for SSE in CHADS₂ <2 while apixaban 5 mg twice daily

and dabigatran 110 mg twice daily were associated with lower rates of major bleeding compared to warfarin. For higher risk patients (CHADS₂ ≥2) apixaban 5 mg twice daily and dabigatran 150 mg twice daily were associated with lower risks of SSE compared with warfarin. Apixaban 5 mg twice daily was associated with a statistically significant lower rate of major bleeding compared with warfarin, dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily.⁵⁷

Age categories and TTR was also reviewed in subgroup analyses. A number of limitations to this review are highlighted including the heterogeneity among the trials for both patient characteristics and trial methodology, the small number of trials available and that no direct comparisons of the different DOACs are available.

This report concluded that, based on the available evidence and taking into account the limitations of the analysis, dabigatran 150 mg twice daily may be a suitable choice for patients with moderate risk of stroke (CHADS₂ = 1) or who are relatively young (≤70 years) or who cannot be adequately controlled on warfarin (TTR<66%) and that “apixaban 5 mg twice daily would likely be the optimal DOAC in patients with a higher risk of stroke (CHADS₂≥2) or are relatively old (≥80 years old)”.⁵⁷

More recently, Lip et al. (2016) carried out a fixed-effects network meta-analysis on the relative safety and efficacy of apixaban compared with dabigatran, rivaroxaban and edoxaban for stroke prevention in patients with NVAf.⁵⁸ Three subgroup analyses were also performed to minimise inter-trial heterogeneity:

- i) patients with a CHADS₂ score ≥2,
- ii) secondary prevention population- patients with a previous stroke or transient ischaemic attack
- iii) patients with high quality anticoagulation control with warfarin (in ROCKET-AF only the North American population with a mean TTR 64% was included).

Results from the base case analysis found few statistically significant differences between DOACs for efficacy outcomes. Hazard ratios for stroke/systemic embolism were significantly lower for apixaban, high-dose edoxaban, rivaroxaban and dabigatran 150 mg than edoxaban low-dose. Dabigatran 150 mg was significantly more efficacious than rivaroxaban, edoxaban high-dose and dabigatran 110 mg, but not apixaban.

Apixaban and edoxaban low-dose had significantly lower hazard ratios of major bleeding and gastrointestinal bleeding compared to rivaroxaban and dabigatran 150 mg. Rivaroxaban was associated with a greater hazard of clinically relevant non-major bleeding than all other DOACs and a greater hazard of intracranial haemorrhage than all DOACs, except high-dose edoxaban.

Sub-group analysis results were broadly similar to the base case results. Differences included:

- i) Patients with a CHADS₂ score ≥ 2 did not show significantly better efficacy and safety outcomes with dabigatran compared to rivaroxaban. Apixaban was the only DOAC to demonstrate significantly reduced hazards for both safety and efficacy compared to warfarin.
- ii) The secondary prevention subgroup had less statistically significant differences between treatment groups than reported in the base case analysis.
- iii) The high quality anticoagulation control subgroup did not have statistically significant differences with efficacy and safety comparisons with rivaroxaban.

This network meta-analysis was limited by heterogeneity in trial design and baseline characteristics and caution was advised when comparing results across trials. However the authors stated that, despite these methodological challenges, results suggested that all DOACs are comparable to warfarin for safety and efficacy and apixaban has the most favourable safety and efficacy profile of the DOACs for the overall population and subgroups.⁵⁸

Fernandez et al. (2015) carried out a systematic review and network meta-analysis of edoxaban versus other DOACs in NVAF patients with a CHADS₂ score ≥ 2 .²⁹ This meta-analysis found that the risk of stroke and systemic embolism for high-dose edoxaban was similar to dabigatran (both doses), apixaban and rivaroxaban. The low-dose edoxaban regimen had a significantly higher risk of stroke and systemic embolism than apixaban and dabigatran 150 mg and similar risk to rivaroxaban.²⁹

For the primary safety endpoint of major bleeding the high-dose edoxaban regimen had a significantly lower risk than rivaroxaban and dabigatran (both strengths) and a similar risk to apixaban. The low-dose edoxaban regimen had significantly lower rate of major bleeding than the other DOACs. Intracranial haemorrhage risk was the same for the edoxaban high-dose regimen, apixaban, dabigatran (both strengths) and rivaroxaban. Compared to rivaroxaban the high-dose edoxaban regimen had significantly lower rates of the composite of major bleeding and clinically relevant bleeding, major gastrointestinal bleeding and clinically relevant nonmajor bleeding.²⁹

In addition to DOAC inter-trial heterogeneity there were further limitations to this network meta-analysis including: a lack of data for patients with a CHADS₂ score ≥ 2 for many endpoints in the RE-LY and ARISTOTLE trials, the small number of available pivotal trials (four) affecting the ability to control for multiple treatment effect modifiers and an inability to adjust for differences in TTR between the trials. Further head-to-head comparisons are required to confirm the findings of this meta-analysis.²⁹

López-López et al. (2017) carried out a systematic review, network meta-analysis and cost-effectiveness analysis to compare the efficacy, safety and cost-effectiveness of DOACs for patients with NVAF. This review, involving 94,656 patients, identified 23 individual RCTs including ARISTOTLE, RE-LY, ROCKET-AF and ENGAGE AF-TIMI 48. Dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, edoxaban 60 mg once daily and apixaban 5 mg twice daily showed reductions relative to warfarin for stroke and systemic embolism (OR, 0.65; 95% CI, 0.52-0.81; OR, 0.88; 95% CI, 0.74-1.03; OR,

0.86; 95% CI, 0.74-1.01 and OR, 0.79; 95% CI, 0.66-0.94 respectively). In relation to major bleeding apixaban, edoxaban (both high-dose and low-dose regimens) and dabigatran 110 mg showed reductions in major bleeding compared with warfarin. Apixaban 5 mg twice daily showed reductions in major bleeding compared with dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily. Most of the DOACs showed a decrease in intracranial bleeding and an increase in gastrointestinal bleeding compared with warfarin. Apixaban 5 mg twice daily was ranked the highest for most outcomes.⁵⁹

5.1.5 Observational studies

A number of real-world studies have been published or are on-going in the review of DOACs in both stroke prevention in NVAf and other indications and these studies will help to support safety and efficacy data shown in the pivotal clinical trials. While patient cohorts differ in these analyses and no information on efficacy outcomes are presented, real world safety data is useful to assess the benefit of these new therapies.

An FDA Medicare study published in *Circulation* (2015) looked at 134,000 patients in the US and showed that patients aged 65 years and over had reduced risk of ischaemic stroke, intracranial haemorrhage and death with dabigatran when compared with warfarin for NVAf; however major GI bleeding rates were higher. It should be noted that the licensed doses of dabigatran for NVAf in the USA are 150 mg and 75 mg twice daily. The majority (83%) of patients on dabigatran in the Medicare study were treated with the 150 mg twice daily dose.⁶⁰

An observational safety surveillance study published in 2014 provided results from 27,467 patients treated with rivaroxaban and followed up for 15 months. The results of this study focused on major bleeding and found rates to be generally consistent with clinical trial results. There were variations in the patient population for this review

compared with ROCKET-AF but in general it was found that patients with major bleeding were older (mean age 78.4 years compared with 75.7 years for no bleed). Mean CHADS₂ score for this patient population was 2.2 in the patients who did not bleed and 3 in the patients who did bleed as compared with 3.5 for ROCKET-AF.⁶¹ The publication elucidates on the real world rates of major bleeding in comparison to ROCKET-AF for specific age categories and demonstrates generally lower rates of bleeding.⁶¹

In 2016 an observational FDA Medicare study was published which compared stroke, bleeding and mortality risks in 118,891 patients who were over 65 years and initiated on dabigatran 150 mg twice daily or rivaroxaban 20 mg daily for NVAf. Data analysis showed a significant increase in the risks of intracranial haemorrhage and major extracranial bleeding, including major gastrointestinal bleeding in patients treated with rivaroxaban compared to dabigatran. Mortality risk was significantly increased in rivaroxaban patients 75 years or older or with a CHADS₂ score greater than 2, compared to dabigatran.⁶²

Lip et al. (2016) completed a propensity score-matched analysis of major bleeding risk in 45,361 NVAf patients initiated on apixaban, dabigatran, rivaroxaban and warfarin using a US claims database. Initiation with apixaban and dabigatran had significantly lower rates of major bleeding compared to warfarin. When the DOACs were compared, initiation with rivaroxaban was associated with a significantly increased risk of major bleeding compared to apixaban.⁶³

In 2018, Vinogradova et al published a prospective open cohort study investigating the associations between DOACs and risks of bleeding, ischaemic stroke, VTE and all-cause mortality compared with warfarin. Patients were initiated on warfarin, apixaban, rivaroxaban or dabigatran and sub grouped into patients with and without AF. In patients with AF, compared with warfarin, apixaban was associated with a decreased risk of major bleeding and intracranial bleeding; dabigatran was associated with a decreased risk of intracranial bleeding. Overall, apixaban was found to be the

safest drug with reduced risks of major, intracranial and GI bleeding compared with warfarin. However, rivaroxaban and low dose apixaban were associated with increased risk of all-cause mortality compared with warfarin.⁶⁴

Discussion

Following a comprehensive review of the clinical trial data and observational studies, the MMP has concluded that the clinical efficacy of individual DOACs is generally comparable with some differences for certain sub-groups. Therefore, it is challenging to recommend a particular DOAC on the basis of clinical efficacy alone at this point in time. In terms of safety outcome data it is possible to make a recommendation.

**Favoured OAC- Clinical Efficacy and Safety: APIXABAN or WARFARIN
(when TTR is > 70%)**

Favoured DOAC- Clinical Efficacy data: No preference of DOAC

Favoured DOAC- Clinical Safety data (major bleeding): APIXABAN

5.2 Adverse Effects

The most commonly reported adverse effect with DOAC therapy is bleeding.¹ All oral anticoagulant use carries a risk of bleeding (including GI and intracranial). See Table 10 for the common adverse effects as listed in the individual SmPCs for DOACs. Overall, the DOACs are broadly similar in terms of adverse effects though these effects may occur to a lesser or greater extent depending on the particular DOAC. There is evidence to suggest that dabigatran, rivaroxaban and the high-dose edoxaban regimen are associated with an increased risk of GI haemorrhage as compared to warfarin whereas apixaban has a similar risk to warfarin and the low-dose edoxaban regimen has a

reduced risk of GI haemorrhage compared to warfarin (although not licensed for use).

25,51,56

Table 10: Common adverse effects of DOAC therapies

DOAC	Apixaban ¹¹	Dabigatran ¹²	Edoxaban ¹⁴	Rivaroxaban ¹³
Common adverse effects	Haemorrhage (including eye, GI and rectal haemorrhage), haematuria, contusion, epistaxis, haematoma	Anaemia, epistaxis, GI haemorrhage, dyspepsia, skin and genito-urological haemorrhage	Anaemia, dizziness, headache, epistaxis, abdominal pain, nausea, GI, oral/pharyngeal, cutaneous soft tissue haemorrhage; urethral or vaginal haemorrhage, puncture site haemorrhage, increased GGT and blood bilirubin, abnormal LFTs, rash, pruritus	Anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, GI haemorrhage, dyspepsia, subcutaneous and urogenital tract haemorrhage

GGT: gamma-glutamyltransferase;

LFTs: Liver function tests

GI: gastrointestinal

Haemorrhagic complications at various sites are the predominant adverse effects of all DOAC therapies. There was a non-significant trend to a higher incidence of MI with both doses of dabigatran compared with warfarin in the RE-LY study.²³ Subsequent real-world studies did not show an increased risk of MI for dabigatran versus warfarin.⁶⁰ Due to the relatively short duration of available clinical trial data (approximately 2 years) long-term adverse effects may only be seen as more real-life data becomes available. Longer term follow-up (up to 6.7 years) for dabigatran in the RELY-ABLE study (where patients enrolled in RE-LY were permitted to continue on dabigatran) did not identify new safety signals.⁶⁵ One indirect comparison analysis suggested that there were no significant differences in MI events between dabigatran (both doses) and apixaban.⁵⁵ However, a lower rate of MI with rivaroxaban as compared with dabigatran has been reported. Edoxaban was not found to have a significantly different rate of MI compared

to warfarin, although annualised rates of death from cardiovascular causes were lower with the high-dose edoxaban regimen (2.74%) and the low-dose edoxaban regimen (2.71%) compared to warfarin (3.17%).²⁵ A network meta-analysis by Fernandez et al. (2015) did not find any significant differences between the high-dose edoxaban regimen, rivaroxaban and apixaban for the endpoint of MI.²⁹

Dabigatran had a higher incidence of dyspepsia than warfarin in the RE-LY trial with 11.8% and 11.3% of patients in the dabigatran 110 mg and 150 mg groups and 5.8% of warfarin patients reporting the adverse event. There was also an increase in the rate of GI bleeding with dabigatran 150 mg despite overall lower bleeding rates at other sites. These adverse events may be due to the formulation of dabigatran. To enhance the absorption of dabigatran the capsule contains dabigatran-coated pellets with a tartaric acid core which may explain the increased incidents of dyspepsia and GI bleeding.²³

Anticoagulation treatment is considered a life-long intervention for stroke prevention in NVAf so abrupt discontinuation (without replacement with another anticoagulant) should not be a feature of treatment unless a patient’s bleeding risk is significantly increased or significant bleeding has occurred. Table 11 highlights the percentage of patients discontinuing the study drug in the pivotal NVAf clinical trials.²²⁻²⁵ Of the patients who discontinued treatment, adverse events were responsible 30-50% of the time.

Table 11: Discontinuation of study drug in clinical trials

Discontinued study drug early	Apixaban (N=9088)	Dabigatran 110 mg (N=6015)	Dabigatran 150 mg (N=6076)	Edoxaban High-dose (N=7012)	Edoxaban Low-dose (N=7002)	Rivaroxaban (N=7111)
Total discontinued	2310 (25.4%)	1161 (21%)	935 (16%)	2415 (34.4%)	2309 (33%)	1693 (23.9%)
% (of total discontinued) who discontinued due to adverse event	679 (30%)	355 (31%)	376 (40%)	1204 (49.9%)	1093 (47.3%)	594 (35%)

The trial data for the DOACs highlights that premature discontinuation of any OAC increases the risk of thrombotic events. The FDA included warnings for all

anticoagulants of the increased risk of thrombotic events if treatment is discontinued prematurely.

5.3 Drug Interactions

There is potential for both pharmacokinetic and pharmacodynamic drug interactions to occur with the DOACs. Before considering the drug interactions, it is useful to review the individual characteristics of each drug and their pharmacokinetic and pharmacodynamic profiles.

Pharmacokinetic profile

The DOACs all exhibit a rapid onset of action and have relatively short half-lives when compared with warfarin. While onset and duration of the four agents is relatively consistent the modes of metabolism and elimination vary (see Table 12). The direct thrombin inhibitor, dabigatran, is not metabolised by the cytochrome P450 enzymes but factor Xa inhibitors (apixaban, rivaroxaban and edoxaban) are metabolised by CYP3A4. Drug interactions may occur if these agents are co-administered with inducers or inhibitors of CYP3A4. Apixaban, dabigatran, rivaroxaban and edoxaban are all substrates for the efflux transporter P-gp. P-gp is extensively distributed in the intestinal epithelium and has a protective action in relation to its substrates. Drugs that induce or inhibit P-gp will have an effect on the concentration of the DOACs and may increase the risk of thrombosis or bleeding respectively (see Table 12).

Table 12: Pharmacokinetic profile of DOACs

Drug Characteristics	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Mechanism of action	Oral direct factor Xa inhibitor	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability %	50%	Approximately 6.5%	Approximately 62%	60-80% (66% for 20 mg dose fasting; increased to over 90% with food)
Time to peak levels (hours)	3-4 hours	0.5-2 hours	1-2 hours	2-4 hours
Half-life (hours)	Approximately 12 hours	12-14 hours	10-14 hours	5-12 hours in younger patients 11-13 hours if older age
Metabolism	CYP3A4/5 (major pathway)	Conjugation, eliminated primarily unchanged in the urine	Hydrolysis, conjugation or oxidation by CYP3A4/5 (<10%)	CYP3A4 (major pathway), CYP2J2, oxidative degradation and hydrolysis
Effect on P-glycoprotein	Substrate for P-gp. Interactions with inhibitors and inducers of P-gp	Substrate for P-gp. Interactions with inhibitors and inducers of P-gp	Substrate for P-gp. Interactions with inhibitors and inducers of P-gp	Substrate for P-gp. Interactions with inhibitors and inducers of P-gp
Cytochrome P450 enzymes	Partially metabolised by CYP450 3A4	Not metabolised by CYP450 enzymes	Partially metabolised by CYP3A4/5 (<10%)	Partially metabolised by CYP450 3A4
Standard dose	5 mg BD	150 mg BD	60 mg OD	20 mg OD
Dose in renal impairment	2.5 mg BD (and age/ weight considerations)	150 mg BD or 110 mg BD if high bleeding risk (or age considerations: 75-80 years or >80 years)	30 mg OD if moderate or severe renal impairment (CrCl 15-50 ml/min), body weight considerations	15 mg OD
Special considerations		Do not open capsules – must be swallowed whole		15 mg and 20 mg must be taken with food
Excretion	27% renal; 25% faecal	85% renal	50% renal	67% renal and faecal route; 33% unchanged eliminated via renal route

Pharmacodynamic profiles

Apixaban inhibits free and clot-bound factor Xa and prothrombinase activity. It has no direct effects on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin.¹¹ Apixaban prolongs prothrombin time (PT), INR and activated partial thromboplastin time (aPTT).

Dabigatran etexilate is a small molecule prodrug which must be converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.¹² Dabigatran prolongs the thrombin clotting time, ecarin clotting time and the aPTT.

Edoxaban inhibits factor Xa and prothrombinase activity. Inhibition of factor Xa reduces thrombin generation, prolongs clotting time (PT and aPTT) and reduces the risk of thrombin formation.¹⁴

Rivaroxaban inhibits factor Xa which interrupts the intrinsic and extrinsic pathway inhibiting both thrombin formation and the development of thrombi. Rivaroxaban also inhibits free and clot-bound factor Xa and prothrombinase activity. It does not inhibit thrombin and no effects on platelets were observed.¹³ Prothrombin time is influenced by rivaroxaban, and aPTT and HepTest are also prolonged.

For all DOACs the coagulation tests mentioned above are not recommended to assess the pharmacodynamic effects of the agents; however due to the predictable pharmacokinetic profile of these agents, routine monitoring of the anticoagulant effect of DOACs is not required.

Pharmacodynamic drug interactions

Factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) have a common mechanism of action and pharmacodynamic interactions with other medications are likely to occur with all factor Xa inhibitors. Caution is required with other medications which will

increase the risk of bleeding (NSAIDs, anti-platelet drugs) and they are contraindicated with other anticoagulants. For the direct thrombin inhibitor dabigatran the pharmacodynamic interactions are considered to be similar to factor Xa inhibitors but also include a documented increased bleeding risk with concomitant use of Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs).¹¹⁻¹⁴ However, care should be taken with the concomitant use of all anticoagulants with SSRIs/SNRIs as individual SmPCs for these agents note there are reports of bleeding with SSRI/SNRI use and advise caution with concomitant use with anticoagulants.^{66,67}

Pharmacokinetic drug interactions

Apixaban, dabigatran, edoxaban and rivaroxaban are all substrates for the efflux transporter P-gp. Concomitant use of a medication that inhibits or induces P-gp may have an effect on plasma levels of the DOACs and care should be exercised. The factor Xa inhibitors apixaban, edoxaban and rivaroxaban are partially metabolised by the CYP450 enzyme system and interactions may occur with co-administration of medications which induce or inhibit the CYP450 3A4 enzyme.¹¹⁻¹⁴

Clinically important **pharmacokinetic and pharmacodynamic** drug-drug interactions for each DOAC are outlined in tables 13-16.

Table 13: Apixaban drug interactions

Recommendation	Drug group	Reason
Contraindicated	Other anticoagulants (unless switching, then refer to individual SmPC)	Increased risk of bleeding, pharmacodynamic interaction
Avoid Concurrent Use	Ketoconazole, itraconazole, posaconazole, voriconazole, anti-retrovirals	Strong CYP3A4 and P-gp inhibitors - increased concentration of apixaban, increased bleeding risk
Caution	Carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort	CYP3A4 and P-gp inducers- reduced apixaban concentration
Caution	NSAIDs including aspirin, platelet aggregation inhibitors	Increased bleeding risk, pharmacodynamic interaction

Table 14: Dabigatran drug interactions

Recommendation	Drug group	Reason
Contraindicated	Other anticoagulants (unless switching, then refer to individual SmPC)	Increased risk of bleeding, pharmacodynamic interaction
Contraindicated	Ciclosporin, dronedarone, itraconazole, ketoconazole	Strong P-gp inhibitors – increased bleeding risk
Avoid Concurrent Use	Carbamazepine, phenytoin, rifampicin, St Johns Wort	P-gp inducers – reduced dabigatran concentration, reduced efficacy
Caution	Amiodarone, quinidine, verapamil, ticagrelor, clarithromycin, tacrolimus	P-gp inhibitors – increased dabigatran concentration, increased risk of bleeding
Caution	NSAIDs including aspirin, platelet aggregation inhibitors, SSRI/SNRI	Increased bleeding risk, pharmacodynamic interaction

Table 15: Edoxaban drug interactions

Recommendation	Drug group	Reason
Contraindicated	Other anticoagulants (unless switching, then refer to individual SmPC), chronic use of NSAIDs	Increased risk of bleeding, pharmacodynamic interaction
Avoid Concurrent Use	High dose aspirin	Increased risk of bleeding
Caution	Ciclosporin, dronedarone, erythromycin, ketoconazole	P-gp inhibitors- increased edoxaban concentration, requires dose reduction to 30 mg
Caution	Rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns Wort	P-gp inducers- reduced edoxaban concentration
Caution	Low dose aspirin, platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy	Increased risk of bleeding

Table 16: Rivaroxaban drug interactions

Recommendation	Drug group	Reason
Contraindicated	Other anticoagulants (unless switching, then refer to individual SmPC)	Increased risk of bleeding, pharmacodynamic interaction
Avoid Concurrent Use	Ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors	Strong CYP3A4 and P-gp Inhibitors (increased rivaroxaban concentration, increased bleeding risk)
Avoid Concurrent Use	Dronedarone	Limited clinical data (P-gp inhibitor)
Caution	Carbamazepine, phenytoin, rifampicin, St Johns Wort, phenobarbitone	CYP3A4 and P-gp inducers (reduced rivaroxaban concentration)
Caution	NSAIDs including aspirin Platelet aggregation inhibitors	Increased bleeding risk, pharmacodynamic interaction

Favoured OAC- Drug interactions: DOAC (no preference)

5.4 Safety

The use of anticoagulants is known to increase a patient’s risk of both significant and non-significant bleeding.^{1,11-14} Reduced renal function can increase bleeding risk and dose reduction is recommended for all DOAC therapies in patients with significant renal dysfunction. Patients should have renal function tests carried out at regular intervals. The 2012 update on the European Society of Cardiology (ESC) guidelines for the management of AF recommends annual renal function measurements in patients with normal (CrCl \geq 80ml/min) or mild (50-79 ml/min) renal dysfunction. For patients with moderate renal dysfunction (CrCl 30-49 ml/min), renal function should be assessed 2-3 times per year.¹⁶ These guidelines were further updated in 2016 and now advise that all AF patients treated with OACs are assessed **at least annually** to detect CKD.⁶⁸ The MMP advises regular monitoring of patients with renal dysfunction before initiation and while taking DOACs as dose adjustment may be necessary.

Due to the complex pharmacology associated with the new agents and the variety of dosing options across the range of indications and co-administered medications it is vital that prescribers refer to the relevant SmPCs for individual agents or access appropriate decision aids to ensure appropriate dose choice.^{11-14, 17}

It must also be noted that in all the studies of new DOACs with warfarin as a comparator, participants had to be eligible for both treatments. Therefore these existing studies do not provide evidence regarding the safety or efficacy of the new agents in patients where the bleeding risk is considered to be too high to safely use warfarin.⁵⁶ The AVERROES trial was carried out among people with AF, none of whom were considered appropriate for warfarin. In this trial apixaban was superior to aspirin in the prevention of thromboembolism.²⁶

Over the last number of years, the Health Products Regulatory Authority (HPRA) (formerly the Irish Medicines Board (IMB)), the Irish Medication Safety Network (IMSN), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the EMA and the MMP have issued warnings about the safety of anticoagulants including DOACs. While undertaking this review, we remained cognisant of these safety alerts.

Regulatory agency alerts

- ***IMB Pradaxa® (dabigatran etexilate) (Notice for MIMS December 2011)***

Recommendations for assessment of renal function and monitoring in the elderly

<http://www.hpra.ie/docs/default-source/Safety-Notices/mims-december--imb-page-final.pdf>

- ***MHRA Drug Safety Update (July 2012)***

Dabigatran (Pradaxa®): risk of serious haemorrhage – contraindications clarified and reminder to monitor renal function

<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON175429>

- **MHRA Drug Safety Update (October 2013, updated September 2016)**

2013: New oral anticoagulants apixaban, dabigatran and rivaroxaban: risk of serious haemorrhage – clarified contraindications apply to all three medicines.

2016 update: Idarucizumab (Praxbind®) was granted a European licence in November 2015 as specific reversal agent for dabigatran

<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON322347>

- **HPRA Drug Safety Newsletter (November 2014)**

Oral anticoagulants – Update on National Monitoring Experience

<http://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-dsn-64th-edition.pdf?sfvrsn=11>

Special interest group alerts

- **IMSN Safety Alert (August 2011)**

Safety alert for NOACs and antiplatelet agents (rivaroxaban, dabigatran and prasugrel)
August 2011 available on:

<http://www.imsn.ie/images/alerts/imsn-anticoag-and-antiplatelet-alert-aug-2011.pdf>

- **IMSN Safety Alert (May 2018)**

Safety alert for DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) available at:

<http://www.imsn.ie/images/alerts/DOACA2018.pdf>

- **MMP letter to GPs (5th March 2014):**

Re: Issues in relation to prescribing safety of New Oral Anticoagulants (NOACs)

<http://www.hse.ie/eng/about/Who/clinical/natclinprog/medicinemanagementprogrammme/NOACs.pdf>

5.5 Patient factors

5.5.1 Dosing

There are two standard dosing frequencies for DOACs in the treatment of AF. Apixaban and dabigatran are both administered twice daily while rivaroxaban and edoxaban are given once daily.¹¹⁻¹⁴

In the absence of clinical outcome data demonstrating superiority of one drug over another, drugs taken once daily may be preferred to those requiring multiple daily doses as stated in the EHRA guidelines on AF.²¹ These guidelines state that a once-daily dosing regimen has been shown to be related to greater adherence versus twice-daily dosing for hypoglycaemic and antihypertensive therapies in patients with AF and cardiovascular disease. While once-daily dosing may be considered advantageous for many drug treatments, it must be considered carefully in relation to anticoagulation where newer agents have short half-lives and hence there is an increased risk of thrombosis if abrupt discontinuation or missed doses occurs.¹¹⁻¹⁴ In 2014, the American Heart Association in conjunction with the American College of Cardiology and the Heart Rhythm Society (AHA/ACC/HRS) produced guidelines for the management of patients with AF and recommend strict compliance with the new agents as missing even one dose could result in a period without anticoagulant protection.⁶⁹

A number of analyses looked specifically at the dosing frequency of DOACs and have found conflicting results. One meta-analysis carried out on behalf of Boehringer (twice-daily dabigatran) looked at dosing frequency of DOACs and noted that twice-daily dosing appears to offer a more balanced risk-benefit profile with respect to stroke prevention and intracranial haemorrhage.⁷⁰ The potential for bias in analysis carried out on behalf of a particular product or manufacturer is recognised. Another meta-analysis published in 2014 found that the pooled analysis from phase III randomised clinical trials did not support the hypothesis that there was a specific class effect of the direct

thrombin inhibitors or the factor Xa inhibitors and did not show a benefit of once-daily versus twice-daily dosing for AF.⁷¹

It is clear that, regardless of whether a DOAC with once-daily or twice-daily dosing is chosen, thorough patient education and counselling are required to ensure compliance. It is vital that patients have a clear understanding of the dosage regimen, the importance of compliance and the risks of missed doses.

Warfarin is a once-daily oral medication. It can be taken at any time during the day but is often recommended to be taken in the afternoon or evening. It should be taken at the same time every day. The long half-life of warfarin is also of benefit for potential poor compliance, as a missed dose will not result in lack of anticoagulation cover which is a concern for the DOACs.

Favoured OAC- Dosing: WARFARIN (long half-life and once daily dosing)

Favoured DOAC- Dosing: No preference of DOAC

5.5.2 Administration

There are a number of important administration considerations in relation to the DOACs (Table 17 and 18).

Table 17: Administration with food

Apixaban	No specific requirements for drug administration and can be taken with or without food. ¹¹
Dabigatran etexilate	Food does not affect the bioavailability but delays the time to peak plasma concentrations by two hours. ¹²
Edoxaban	Food has minimal effect on total exposure of drug. Can be taken with or without food. ¹⁴
Rivaroxaban (15 mg and 20 mg)	Food increases the bioavailability of the 15 and 20 mg doses from 66% to 80% so they should be taken with food to ensure appropriate drug absorption. ¹³

Table 18: Information on crushing medication

Apixaban	Can be crushed and mixed with water, 5% dextrose, apple juice or apple puree. Evidence suggests that crushing the tablets for administration leads to comparable exposure of apixaban. ^{11,72}
Dabigatran	Capsules must not be opened and must be swallowed whole. Formulated in hydroxyl-propyl-methyl-cellulose capsules containing pellets of dabigatran coated with a tartaric acid core as low pH is required to enhance the absorption of dabigatran. ⁶⁹
Edoxaban	No data is available on the bioavailability of edoxaban on crushing and/or mixing into foods/liquids or administration through feeding tubes in the SmPC. Therefore crushing is not currently recommended. ¹⁴
Rivaroxaban	Can be crushed and mixed with water or apple puree immediately prior to use and dosing with 15 mg or 20 mg must be followed immediately by food. ¹³ Can be administered (crushed and mixed with a small amount of water) via gastric tube once the tube is correctly placed. Dosing in this way should be immediately followed by enteral feeding. It should not be given via feeding tubes that are placed distal to the stomach (small intestine) due to decreased absorption in this location. ¹³

Timing of doses

- All DOACs should be taken at the same time each day (whether once or twice daily) to ensure stable drug concentrations. Twice-daily dosing should be taken 12 hourly.
- Warfarin should be taken at the same time each day, preferably in the evening, to facilitate INR monitoring.

Considerations in relation to administration with other medications

- For concomitant use of verapamil and dabigatran the lower dose of 110 mg dabigatran twice daily should be used and both should be taken at the same time each day.¹²
- Intestinal absorption of dabigatran is pH dependent and may be reduced in patients taking proton pump inhibitors (PPIs) - concomitant PPI use in RE-LY did not appear to reduce the efficacy of dabigatran however pantoprazole reduced the concentration of dabigatran by 30% and caution should be observed.¹²

- The dose of edoxaban should be reduced to 30 mg when used concomitantly with the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole.¹⁴
- Apixaban and rivaroxaban do not have any specific considerations in relation to administration with other medications except for documented drug interactions.^{11,13}

Favoured OAC- Administration: WARFARIN or APIXABAN

5.5.3 Storage considerations

- Apixaban, edoxaban and rivaroxaban do not have any special storage conditions.^{11,13,14}
- Dabigatran capsules should be stored in their original packaging to protect against moisture and are therefore not suitable for blister packaging.^{12,73}

Favoured OAC- Storage: WARFARIN or APIXABAN or EDOXABAN or RIVAROXABAN

5.5.4 Reversibility

The availability of a reversal agent is an important safety development for DOAC use. Idaricuzumab (Praxbind®) is a specific reversal agent for dabigatran and the first reversal agent developed for any DOAC. It is indicated for emergency surgery/urgent procedures and life threatening or uncontrolled bleeding.⁷⁴ It was approved by the FDA in October 2015, under the accelerated approval pathway. This was updated to full approval in April 2018.⁷⁵ Marketing authorisation within the European Union was granted in November 2015.⁷⁶ In December 2015, the NCPE undertook a rapid review of Praxbind® and recommended it for reimbursement in Ireland.

Idarucizumab (Praxbind®) is a humanised mouse monoclonal antibody fragment which binds with high affinity to dabigatran. In preclinical studies, idarucizumab rapidly reversed the anticoagulant effects of dabigatran and attenuated dabigatran-induced bleeding in various animal models, while showing no evidence of thrombogenicity.⁷⁷ The RE-VERSE AD study was designed to evaluate the effectiveness of idarucizumab in patients treated with dabigatran who were in need of emergency intervention, or who experienced an uncontrolled or life-threatening bleeding event. The interim analysis (90 patients) reported that idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88-98% of patients, with no safety concerns identified.⁷⁸ In the full cohort analysis which was published in August 2017, the median maximum percentage reversal of dabigatran within four hours of idarucizumab administration was 100% (95% confidence interval), as assessed on the basis of either the diluted thrombin time or the ecarin clotting time (n=503).⁷⁹

Another reversal agent, designed to neutralise the anticoagulant effects of both direct and indirect factor Xa inhibitors, has also been developed. This agent, andexanet alfa is a recombinant modified human factor Xa protein that lacks the enzymatic activity of factor Xa. Thus it acts as a decoy protein, binding and inactivating factor Xa inhibitors with high affinity. Results from the Phase III ANNEXA-R and ANNEXA-A studies demonstrated that andexanet alfa rapidly and significantly reversed the anticoagulant effect of the factor Xa inhibitors rivaroxaban and apixaban, shown as a reduction in anti-Factor Xa activity.⁸⁰ A phase IV confirmatory study (ANNEXA-4) in patients receiving apixaban, rivaroxaban, edoxaban or enoxaparin, who presented with an acute major bleed was initiated in January 2015.⁸¹ The study was designed to support andexanet alfa's approval by the FDA, under an accelerated pathway and is currently ongoing. The estimated primary completion date is November 2022. Results of the most recent preliminary analysis showed that excellent or good clinical haemostasis was achieved in 83% of patients.⁸²

The effects of warfarin can be reversed using vitamin K or prothrombin complex concentrate (PCC). The choice of reversal agent is dependent on whether the haemorrhage is life-threatening or not.³

Favoured OAC- Reversibility: WARFARIN or DABIGATRAN

5.6 Cost

The MMP recognises the complex and multi-faceted nature of the costs associated with stroke prevention in NVAF. Individual drug acquisition costs for the OACs were compared for treatment of AF.

The daily maintenance dose of warfarin is usually in the range 3 to 9 mg, thus costs were calculated using an average dose of 6 mg per day.⁴

Table 19: Cost of OAC therapies per daily dose based on reimbursed price*

	Apixaban 5 mg	Apixaban 2.5 mg	Dabigatran 150 mg	Dabigatran 110 mg	Edoxaban 60 mg	Edoxaban 30 mg	Rivaroxaban 20 mg	Rivaroxaban 15 mg	Warfarin** (6 mg per day)
Cost Per day⁸³	€2.25	€2.24	€2.28	€2.26	€2.16	€2.16	€2.29	€2.29	€0.20 (6 x 1 mg) €0.11 (2 x 3 mg)

*Costs are originator-brad costs and are based on reimbursed price on www.pcrs.ie 05/03/2019 ** Warfarin costs do NOT include monitoring costs

Licenses were granted for apixaban, dabigatran and rivaroxaban from 2008 (from 2011 for AF indication), with edoxaban becoming licensed in 2015, as such all products are currently under patent protection.

Pharmacoeconomic Evaluations in Ireland

The NCPE reviewed the four DOACs for cost-effectiveness for the indication of stroke and systemic embolism prevention in NVAF. In August 2011, the NCPE recommended reimbursement of dabigatran at a price significantly below €2.80 per day to ensure value for money for the HSE.⁸⁴ The current price per day for dabigatran is €2.28 for the 150 mg strength and €2.26 for the 110 mg strength.⁸³

In March 2012 the NCPE did not find rivaroxaban to be cost-effective for the prevention of stroke and systemic embolism in adult patients with NVAf with one or more risk factors.⁸⁵ Subsequent to this the company reviewed its pricing policy and a positive reimbursement recommendation was made in June 2012.

Cost-effectiveness of apixaban was reviewed in May 2013 for the indication of stroke prevention and prevention of systemic embolism in people with NVAf. The evaluation found that apixaban 5 mg twice daily could be considered cost-effective for the prevention of stroke and systemic embolism and is currently reimbursed at a price of €2.25 per day.^{83,86}

In June 2015 the cost-effectiveness of edoxaban for the prevention of stroke and systemic embolism in people with NVAf was reviewed. The rapid review was completed in July 2015 and the NCPE stated that a full pharmacoeconomic evaluation was not recommended.⁸⁷ The current reimbursement cost for edoxaban is €2.16 per day.⁸³

5.6.1 Cost Summary

Significantly increased costs for anticoagulant therapy should correspond to significantly better clinical outcomes for more patients. The number of patients receiving anticoagulant therapy has almost doubled in the years between 2013 and 2018. Expenditure on OACs has increased from €1 million per month to €4.6 million per month in the same period.

Apixaban and dabigatran were subject to price reductions in August 2016 in line with the Irish Pharmaceutical Healthcare Association (IPHA) agreement and edoxaban now has the lowest acquisition cost, followed by apixaban.

Favoured OAC- Cost: WARFARIN

Favoured DOAC- Cost: EDOXABAN

5.7 National Prescribing Trends

The MMP recognise that clinical experience is an important factor for prescribers when choosing a medication. In the case of the DOAC drugs, apixaban, dabigatran and rivaroxaban all came to market for stroke prevention in AF between the years 2011 - 2013. Edoxaban came to market for this indication in 2015. This review includes analysis of prescribing trends up to, and including, October 2018.

5.7.1 Data sources

Data from the following pharmaceutical reimbursement schemes were analysed in order to examine recent trends in the prescribing of oral anticoagulants: (i) General Medical Services (GMS) scheme, (ii) Drugs Payment (DP) scheme; (iii) Long Term Illness (LTI) scheme. These schemes are managed by the HSE PCRS, through which data was made available to the MMP for analysis. Detailed information regarding the above schemes is available through the following HSE webpages:

- General information for the public regarding the PCRS schemes
<http://www.hse.ie/eng/services/list/1/schemes/>
- PCRS Financial and Statistical Analyses
http://www.hse.ie/eng/staff/PCRS/PCRS_Publications/

In this section, the term 'GMS data' refers to pharmacy claims data submitted to the PCRS by community pharmacists who dispense medications under the GMS scheme. GMS data is expected to capture all incidences of a drug being dispensed to a patient under this scheme, (except where a patient receives a drug relating to a specific condition which is covered under the Long Term Illness scheme, in which case the

dispensing of the drug is captured through the LTI data). In the case of the Drugs Payment scheme, data is only available for patients whose monthly prescription drug expenditure exceeded the threshold above which the PCRS provides reimbursement (this threshold stood at €144 per month as of January 2013 onwards. It was reduced to €134 per family per month from January 1st, 2018. It will be further reduced to €124 per family per month on 1st April 2019). As such, the DP scheme is a less complete source of information than the GMS data for studies of individual patient dispensing patterns.

For the purposes of this analysis, data from the above schemes are referred to collectively as 'PCRS data'.

5.7.2 Overall dispensing trends for OACs under the community drug schemes

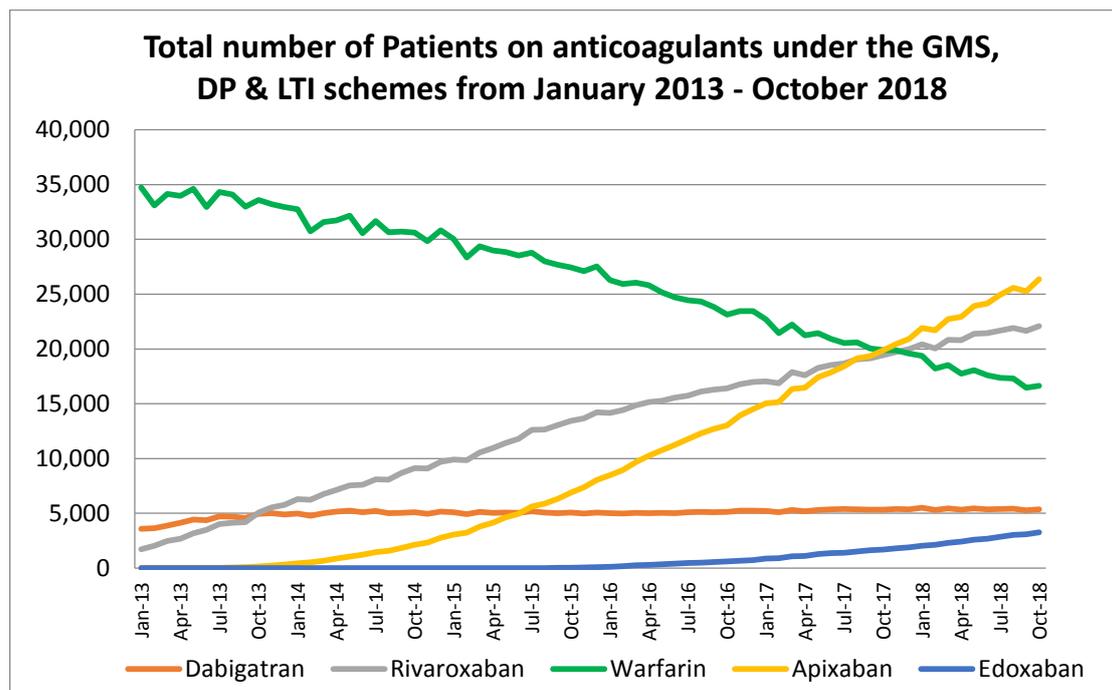


Figure 1: Number of patients in receipt of each oral anticoagulant. GMS, DP and LTI scheme data, January 2013- October 2018 inclusive

Figure 1 demonstrates clearly how prescribing trends have changed over the last five years. The emergence of DOACs has resulted in a fast-moving and changing OAC

market in recent years, which is likely to continue to adjust with time and as further clinical evidence becomes available.

The introduction of the newer agents has resulted in a dramatic decrease in the number of patients prescribed warfarin. Patient numbers have halved from almost 35,000 in January 2013 to 16,600 in October 2018. Conversely, the newer agents have seen a rapid increase in prescribing frequency. The number of patients on rivaroxaban has increased from 1,710 to 22,084 in the same period. Rivaroxaban has been consistently the most commonly prescribed DOAC over the last few years. However since August 2017 it has been surpassed by apixaban. Over 26,000 patients were prescribed apixaban in October 2018. Edoxaban was made available to patients in September 2015. The number of patients prescribed edoxaban in October 2018 was 3,267.¹⁸ Figures 2 and 3 illustrate how the anticoagulant landscape has changed in the period between January 2013 and October 2018.¹⁸

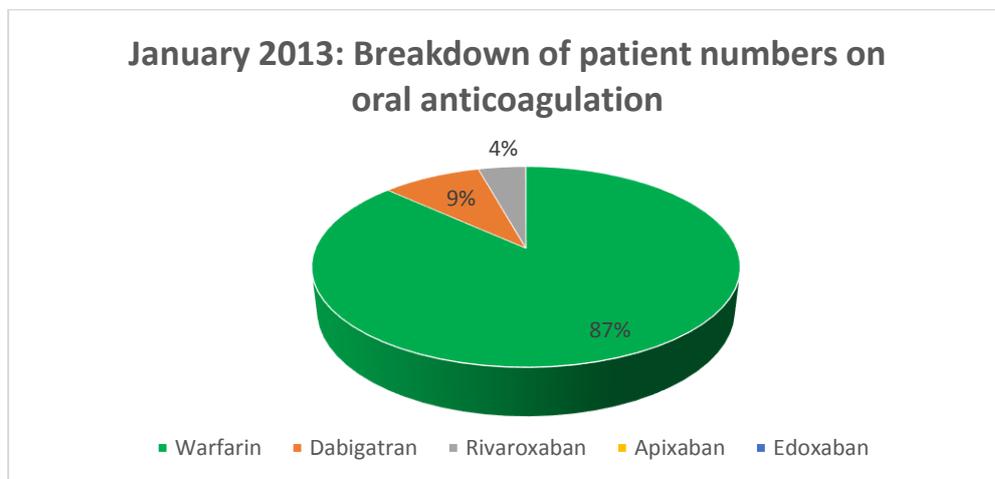


Figure 2: Distribution of oral anticoagulation patient numbers January 2013

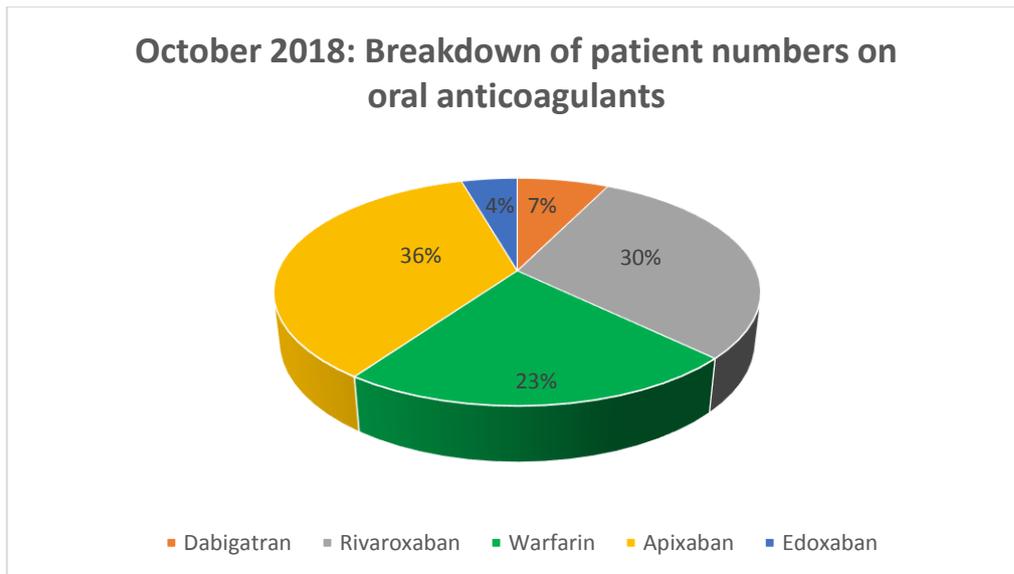


Figure 3: Distribution of oral anticoagulation patient numbers October 2018

The PCRS Statistical Analysis of Claims and Payments 2017 provides further data on the usage of anticoagulants. It ranks the top 100 most commonly prescribed drugs in order of prescribing frequency. Absence of a corresponding ranking number in tables 20 and 21 below indicates that the drug was not in the top 100. Limited information was available for edoxaban as it was not listed in the top 100 in terms of prescribing frequency or ingredient cost on the GMS and LTI schemes.⁸⁸

Table 20: Prescribing frequency of OACs dispensed in 2017 under Community Drugs Schemes

	Prescribing frequency	Rank	% of Scheme Total
Warfarin			
GMS	416,514	34	0.71%
DPS	36,236	45	0.51%
LTI	45,753	36	0.55%
Rivaroxaban			
GMS	197,378	73	0.34%
DPS	43,661	35	0.61%
LTI	22,647	51	0.27%
Apixaban			
GMS	200,280	71	0.34%
DPS	37,879	43	0.53%
LTI	20,868	55	0.25%
Dabigatran			
GMS	55,443	*	0.10%
DPS	11,597	*	0.16%
LTI	6,030	*	0.07%
Edoxaban**			
DPS	4,429	*	0.06%

* Drug was not listed in top 100

** Prescribing frequency figures not listed for edoxaban for GMS and LTI

Table 21: Reimbursed ingredient cost of OACs dispensed in 2017 under Community Drugs Schemes

	Ingredient Cost	Rank	% of Scheme Total
Warfarin			
GMS	€902,619	*	0.14%
DPS	€82,307	*	0.08%
LTI	€100,347	*	0.06%
Rivaroxaban			
GMS	€12,514,477	6	1.95%
DPS	€2,864,274	4	2.61%
LTI	€1,422,630	25	0.86%
Apixaban			
GMS	€12,478,694	7	1.24%
DPS	€2,439,236	10	1.59%
LTI	€1,284,795	27	0.48%
Dabigatran			
GMS	€3,621,682	36	0.57%
DPS	€781,395	25	0.71%
LTI	€396,999	60	0.24%
Edoxaban**			
DPS	€282,497	88	0.26%

*Drug was not listed in Top 100

** Ingredient cost (alone) figures not listed for edoxaban for GMS and LTI

Comparison of tables 20 and 21 highlights the large discrepancies between prescribing frequency and cost. Rivaroxaban was ranked as the 73rd most frequently prescribed drug on the GMS scheme. However, it was the 6th highest drug in terms of reimbursed ingredient cost, which equated to over €12.5 million. Similarly for the DP scheme, rivaroxaban was ranked 35th in terms of prescribing frequency, yet it was the 4th highest in terms of cost. Apixaban is listed as the 43rd most frequently prescribed drug on the DPS. However it is ranked as 10th in terms of expenditure, corresponding to a

figure of €2.4 million. Expenditure on apixaban on the GMS scheme was just under €12.5 million. Conversely, warfarin, although ranked in the top 35 in terms of prescribing frequency for all three schemes, is not included in the list of the top 100 products by ingredient cost.⁸⁸

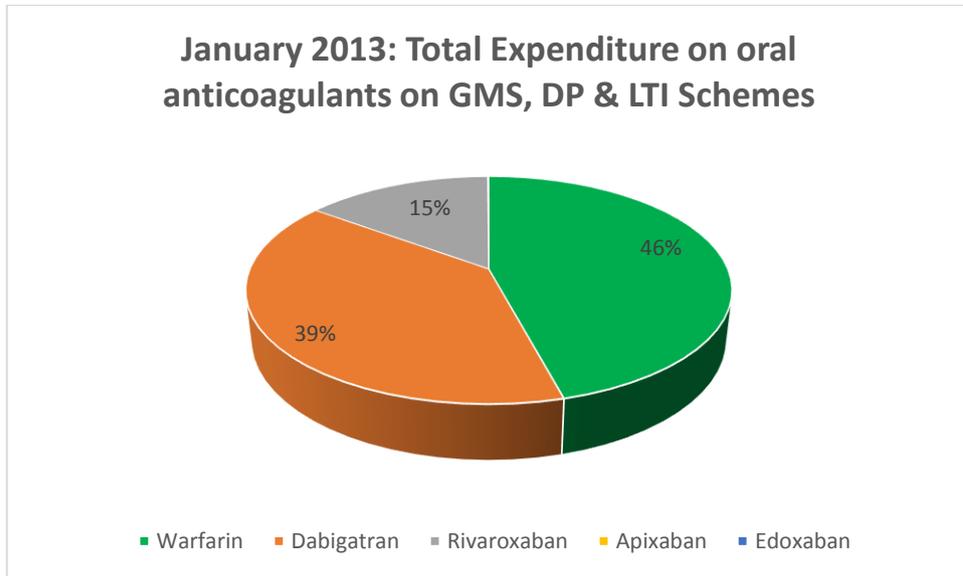


Figure 4: Total expenditure on oral anticoagulants on GMS, DP and LTI schemes January 2013

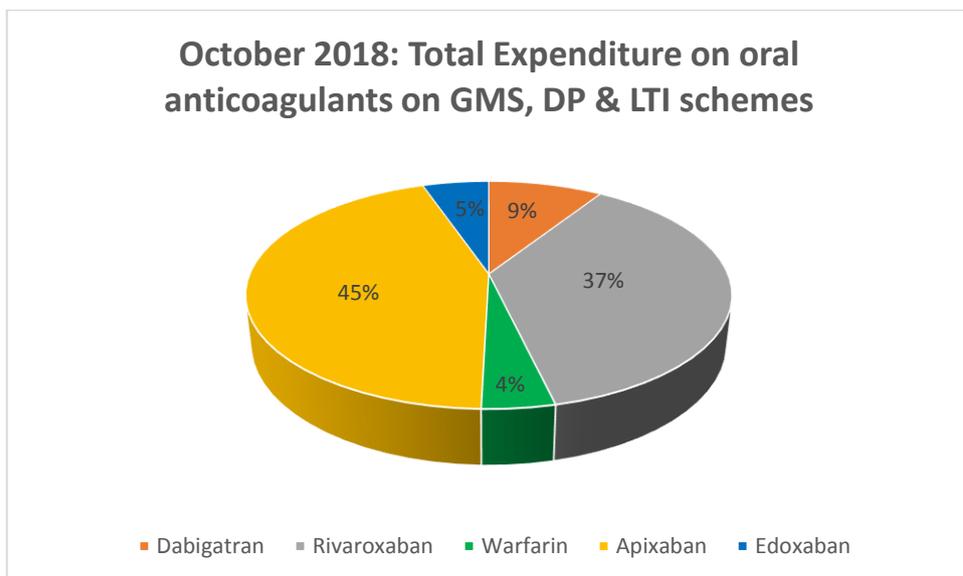


Figure 5: Total expenditure on oral anticoagulants on GMS, DP and LTI schemes October 2018

Total expenditure on DOACs has increased from €8.9 million in 2013 to €41.8 million in 2017.¹⁸ Total expenditure is the price paid to pharmacies and includes cost price and pharmacy fees. This five year period has seen a marked change in expenditure trends for anticoagulants. Data from October 2018 demonstrates that warfarin spend has decreased from 46% to 4% of total expenditure on OACs. Spend on rivaroxaban and apixaban has increased from 15% to 37% and from 0.09% to 45% respectively.¹⁸

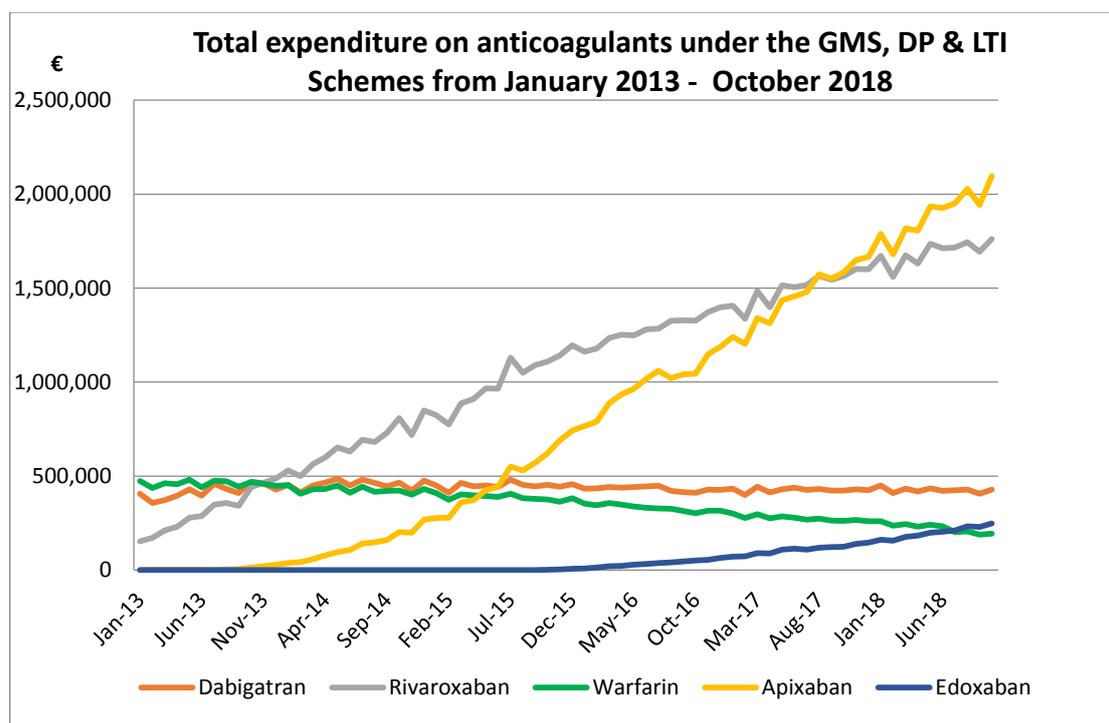


Figure 6: Oral anticoagulant expenditure January 2013-October 2018

5.8 Clinical Guidance

Over the last number of years there have been a large number of newly published guidelines in relation to anticoagulation and stroke prevention in NVAf. In general international recommendations do not choose one DOAC above another and this is often due to the current lack of clear evidence of superiority of both clinical and safety data for one DOAC over another. The lack of head to head comparisons is a limiting factor as is the heterogeneity of the individual clinical trials. References are made to

the levels of evidence available for each agent in a number of guidelines and this relates to additional trial data which can be considered. Table 22 lists a number of national and international guidelines and their recommendations in relation to warfarin and DOAC use for NVAF.

Table 22: Clinical Guidelines/Recommendations

Group	Year	Guideline	Recommended Drug (if applicable)	Excerpt/Comment
Irish College of General Practitioners ⁸⁹	2014	Anticoagulation in General Practice/Primary Care. Part 2: New/novel oral anticoagulants	Warfarin preferred OAC (see comment) No preference for DOAC	Warfarin is the anticoagulant of choice unless people have an allergy, poor INR control or require treatment with medications that interact with warfarin
Irish Heart Foundation Ireland ⁹⁰	2010 (no recent update)	Council for Stroke National Clinical Guidelines and recommendations for the care of people with stroke and TIA	Warfarin (pre DOAC licenses)	
NICE UK ⁸	2014	Clinical Guideline (CG 180) Atrial fibrillation: the management of atrial fibrillation	Warfarin or DOAC DOAC should be chosen based on results of patient TTR on warfarin	
Royal College of Physicians UK ⁹¹	2016 (5 th edition)	National Clinical Guideline for stroke	None specified	
SIGN Scotland ⁹²	2013	SIGN 129: Antithrombotics: indications and management. A national clinical guideline	Apixaban, dabigatran and rivaroxaban can be considered as alternatives to warfarin in the management of patients with AF with one or more risk factors for stroke	Give consideration to: <ul style="list-style-type: none"> • The relative lack of experience of long term use of NOACs compared to VKA • The lack of a licensed product for rapid reversal of DOACs • The limited data on use in patients at the extremes of body weight and those with hepatic impairment
SIGN Scotland ⁹³	2014	Prevention of stroke in patients with atrial fibrillation – a guide for primary care	None specified	Recommend if selecting a DOAC instead of warfarin; consideration be given to the points raised in SIGN 129

Group	Year	Guideline	Recommended Drug (if applicable)	Excerpt/Comment
All Wales Medicines Strategy Group Wales ⁹⁴	2016	All Wales Advice on the Role of Oral Anticoagulants	Anticoagulation with warfarin or DOAC choice based on clinical features and preferences, based on discussion with the patient	Ref. NICE CG180 and SIGN 129 Recommend use of NICE Patient Decision Aid
European Society of Cardiology (ESC) ⁶⁸	2016	ESC Guidelines for management of atrial fibrillation in collaboration with the European Society for Cardio-Thoracic Surgery (EACTS), (updated from 2012 guidelines)	Either warfarin (INR 2-3, TTR ≥70%) or DOAC (none specified) Patients at high risk of GI bleed: Recommend VKA or another DOAC over dabigatran 150 mg, rivaroxaban 20 mg and edoxaban 60 mg	When OAC is initiated in a patient with AF who is eligible for a DOAC, recommend DOAC in preference to a VKA. AF patients already on treatment with a VKA may be considered for DOAC if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to DOAC (e.g. prosthetic valve).
ASA/AHA USA ⁹⁵	2014	Guideline for the primary prevention of stroke	NVAF with CHA ₂ DS ₂ -VASc ≥ 2 and low risk of haemorrhagic complications Warfarin (Class 1; level of evidence A) Apixaban, dabigatran, rivaroxaban (Class 1; level of evidence B)	Individualise on the basis of patient risk factors (risk for intracranial haemorrhage), cost, tolerability, patient preference, potential for drug interactions and other clinical characteristics, including TTR for warfarin
AHA/ACC/HRS USA ⁹⁶	2019	Focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation	No preference between DOACs.	When OAC is initiated in a patient with AF who is eligible for a DOAC, recommend DOAC in preference to a VKA.
ASA/AHA USA ⁹⁷	2014	Guidelines for the prevention of stroke in patients with stroke and transient	Prevention of recurrent stroke in patients with NVAF (paroxysmal or permanent) Warfarin and apixaban	The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability,

Group	Year	Guideline	Recommended Drug (if applicable)	Excerpt/Comment
		ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association	(Class 1; level of evidence A)* Dabigatran (Class 1; level of evidence B)* Rivaroxaban is reasonable (Class IIa; level of evidence B)*	patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.
CHEST ⁹⁸	2018	Antithrombotic therapy for atrial fibrillation. CHEST guideline and expert panel report	DOACs are the recommended drug class over warfarin. If warfarin is appropriate, aim to achieve a TTR > 70%.	When OAC is initiated in a patient with AF who is eligible for a DOAC, recommend DOAC in preference to a VKA.
NHFA/CSANZ ⁹⁹	2018	Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018	No preference of DOAC	When OAC is initiated in a patient with AF who is eligible for a DOAC, recommend DOAC in preference to a VKA.

* Classification of recommendation and level of evidence in AHA/ASA guidelines

American guidelines use classifications based on estimates on the certainty of the treatment effects (Level A- C, where Level A represents multiple populations evaluated and data is derived from multiple clinical trials or meta-analyses) and the size of treatment effect (Class I, IIa, IIb, III, where Class I represents increased benefit over risk and Class III represents no benefit or risk of harm). Level of evidence B or C does not imply that the recommendation is weak but that multiple randomised trial evidence is not available.

The All Wales Medicines Strategy Group (2016) recommends that the decision to start treatment with warfarin or a DOAC should be made after an informed discussion between the clinician and the person about the risks and benefits. It notes that warfarin has been used for over 60 years and its short-, and long-term side-effect profiles are well described. No individual DOAC is given preference in this guide.⁹⁴ The Scottish Intercollegiate Guidelines Network (SIGN) considered the DOACs as alternatives to warfarin, however they recommend that consideration be given to the relative lack of experience in long-term use of the new agents and the lack of products for rapid reversal. They also note the lack of experience in patients at extremes of body weight and those with hepatic impairment.⁹²

Some of the most recently published guidelines recommend the use of DOACs over warfarin to reduce stroke risk in appropriate AF patients. The CHEST guidelines issued a strong recommendation (based on moderate-quality evidence), that DOACs should be chosen over VKA in patients eligible for an OAC. CHEST also recommend that interventions to improve TTR or switching to a DOAC be considered for patients on VKAs with consistently low time in INR therapeutic range (e.g. TTR <65%).⁹⁸

Similarly, Australian guidelines made a strong recommendation (based on moderate-quality evidence) that when an OAC is initiated in a patient with NVAf, a DOAC- apixaban, dabigatran or rivaroxaban- is recommended in preference to warfarin.⁹⁹

The 2019 guidelines issued by the AHA/ACC/HRS USA recommend the use of DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) over warfarin in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve). The recommendation was made by considering the DOAC trials as a group. The guidelines concluded that the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.⁹⁶

Favoured OAC- Clinical guidelines: DOAC

Favoured DOAC- Clinical guidelines: No preference

6. Summary

The following summaries are based on the evidence reviewed and represent the views of the MMP. Further details and references may be found in the relevant sections of the evaluation.

WARFARIN

Benefits of Warfarin:

- ✓ Many years of experience using warfarin as an anticoagulant
- ✓ New therapies have not been shown to be superior to warfarin therapy with TTR >70%
- ✓ It is possible to monitor the efficacy of warfarin therapy through INR monitoring
- ✓ It is possible to reverse the effect of warfarin using Vitamin K and/or PCC
- ✓ All doses are individualised based on INR results
- ✓ Warfarin has the lowest acquisition cost of any OAC
- ✓ Long half-life ensures a level of underlying anticoagulant cover if a dose is missed

DOACs

- ✓ There is little difference in terms of efficacy for the four DOACs, apixaban, dabigatran, edoxaban and rivaroxaban
- ✓ Apixaban and dabigatran 150 mg dose were superior to warfarin for the primary efficacy endpoint of stroke or systemic embolism in the ITT analysis. High dose edoxaban was superior to warfarin for this primary endpoint in the mITT analysis during the treatment period (but not over entire study period)
- ✓ The rates of ischaemic and haemorrhagic stroke were significantly lower with dabigatran 150 mg twice daily as compared to warfarin therapy
- ✓ Apixaban appears to have an advantage in terms of safety and reduced bleeding, compared to warfarin and other DOACs
- ✓ Major bleeding seems to be reduced with apixaban, dabigatran 110 mg twice daily and edoxaban
- ✓ Apixaban and rivaroxaban have favourable evidence in terms of administration however rivaroxaban 15 mg and 20 mg doses must be taken with food to ensure appropriate absorption
- ✓ There is evidence that rivaroxaban and apixaban can be crushed and mixed with water/apple juice for administration
- ✓ Rivaroxaban and edoxaban are licensed for once-daily administration while apixaban and dabigatran are twice daily
- ✓ Dabigatran is currently the only DOAC with a licensed reversibility agent

7. Conclusion

Having reviewed the available evidence, considered pivotal clinical trials, international guidelines and patient factors such as dosing, administration and safety issues the MMP recommends:

Warfarin is an appropriate first-line treatment option for stroke prevention with Atrial Fibrillation when the time in therapeutic range (TTR) > 70%.

APIXABAN is the preferred direct oral anticoagulant (DOAC) for stroke prevention with Atrial Fibrillation and may be considered for first-line treatment, particularly if there are tolerability issues and/or labile INRs with warfarin.

References

1. National Medicines Information Centre (NMIC). Update on Oral Anticoagulation Therapy. 2012;18(6).
[http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2012/Final NMIC UPDATE ON ORAL ANTICOAGULATION THERAPY PRINT.pdf](http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2012/Final%20NMIC%20UPDATE%20ON%20ORAL%20ANTICOAGULATION%20THERAPY%20PRINT.pdf). Accessed May 9, 2018.
2. Department of Health and Children. Changing Cardiovascular Health. National Cardiovascular Health Policy 2010-2019. http://health.gov.ie/wp-content/uploads/2016/04/changing_cardiovascular_health.pdf. Published 2010. Accessed April 24, 2018.
3. Warfant® (warfarin) Summary of Product Characteristics. 2017.
https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0073-139-001_15052017144039.pdf. Accessed April 24, 2018.
4. Warfarin Teva® (warfarin) Summary of Product Characteristics. 2018.
https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA2050-001-001_09032018163210.pdf. Accessed April 24, 2018.
5. Primary Care Reimbursement Service (PCRS). PCRS Database: Number of Patients on Warfarin (Dec 17)- GMS, DPS combined. 2017.
6. Lip GYH. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? *Eur Heart J*. 2013;34(14):1041-1049.
7. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *Circ Cardiovasc Qual Outcomes*. 2011;4(1):22-29.
8. NICE CG180. Atrial fibrillation: management | Guidance and guidelines | NICE. 2014. <https://www.nice.org.uk/guidance/cg180/chapter/patientcentred-care>. Accessed April 24, 2018.
9. National Institute for Health and Care Excellence (NICE). Patient Decision Aid. Atrial fibrillation: medicines to help reduce your risk of a stroke – what are the

- options? 2014.
<http://guidance.nice.org.uk/CG180/PatientDecisionAid/pdf/English>. Accessed May 9, 2018.
10. British National Formulary (BNF). Warfarin sodium.
https://www.new.medicinescomplete.com/#/content/bnf/_107604022?hspl=warfarin&hspl=indications. Published 2017. Accessed May 9, 2018.
 11. Eliquis® (Apixaban): Summary of Product Characteristics.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed May 9, 2018.
 12. Pradaxa® (Dabigatran): Summary of Product Characteristics.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. Accessed May 9, 2018.
 13. Xarelto® (Rivaroxaban): Summary of Product Characteristics.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. Accessed May 9, 2018.
 14. Lixiana® (Edoxaban): Summary of Product Characteristics.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf. Accessed May 9, 2018.
 15. Irish Heart Foundation. Atrial Fibrillation. <https://irishheart.ie/heart-and-stroke-conditions-a-z/atrial-fibrillation/>. Accessed April 24, 2018.
 16. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2012;33(21):2719-2747.
 17. Anticoagulation Prescribing Tips Version 1.4 MMP 2017.
doi:10.1056/NEJMoa0906598.
 18. PCRS database analysis 2013-2018. Total expenditure, total number of

- prescriptions and total number of patients dispensed warfarin, dabigatran, rivaroxaban, apixaban and edoxaban January 2013- October 2018. GMS and DPS combined. Internal communication. On file.
19. Clarke S, Geraghty N, Barry M. The Uptake of Non-Vitamin K Oral Anticoagulants in Ireland: Balancing cost-effectiveness and budget impact. Presented at ISPOR Washington. In: ; 2016.
<https://www.ispor.org/ScientificPresentationsDatabase/Presentation/62994>. Accessed May 10, 2018.
 20. National Medicines Information Centre (NMIC). Update on Management of Non-Valvular Atrial Fibrillation. 2013;19(1).
http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2013/NMIC_UPDATE_ON_MANAGEMENT_OF_NON_VALVULAR_ATRIAL_FIBRILLATION.pdf. Accessed May 10, 2018.
 21. Heidbuchel H, Verhamme P, Alings M, et al. EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. 2013;(15):625-651.
 22. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2011;365(11):981-992.
 23. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
 24. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med*. 2011;365(10):883-891.
 25. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2013;369:2093-2104.
 26. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in Patients with Atrial Fibrillation. *N Engl J Med*. 2011;364(9):806-817.
 27. ENGAGE AF-TIMI 48 (NCT00781391) CLINICAL STUDY PROTOCOL. *N Engl J Med*. 2013;369:2093-2104.
 28. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb*

- Haemost.* 2005;3(4):692-694.
29. Fernandez MM, Wang J, Ye X, et al. Systematic review and network meta-analysis of the relative efficacy and safety of edoxaban versus other nonvitamin K antagonist oral anticoagulants among patients with nonvalvular atrial fibrillation and CHADS2 score ≥ 2 . *SAGE open Med.* 2015;3:2050312115613350.
 30. Medical Information: Age category data from ENGAGE-AF TIMI 48 trial. Daiichi Sankyo Ireland Ltd. 2016.
 31. PCRS database analysis of new NOAC initiations January 2013-March 2014. Internal Communication with MMP, on file.
 32. Kumar S, de Lusignan S, McGovern A, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. *BMJ.* 2018;360:k342.
 33. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J.* 2014;35(28):1864-1872.
 34. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation Clinical Perspective. *Circulation.* 2011;123(21):2363-2372.
 35. Eisen A, Ruff CT. Edoxaban in patients with atrial fibrillation. *Ther Adv Cardiovasc Dis.* 2017;11(3):81-90.
 36. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and Safety of Edoxaban in Elderly Patients With Atrial Fibrillation in the ENGAGE AF–TIMI 48 Trial. *J Am Heart Assoc.* 2016;5(5):e003432.
 37. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the ROCKET AF Trial. *Circulation.* 2014;130(2):138-146.
 38. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic

- events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev*. November 2017.
39. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33(22):2821-2830.
 40. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation*. 2016;134(1):24-36.
 41. US Food and Drug Administration. Prescribing Information for Savaysa (edoxaban). 2015.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed May 11, 2018.
 42. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Lixiana: EPAR Public Assessment Report. 2015.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002629/WC500189047.pdf. Accessed May 11, 2018.
 43. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32(19):2387-2394.
 44. Bruins Slot KMH, Berge E. Factor Xa Inhibitors vs Warfarin for Preventing Stroke and Thromboembolism in Patients With Atrial Fibrillation. *JAMA*. 2014;311(11):1150.
 45. De Caterina R, Husted S, Wallentin L, et al. New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes: ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper. *J Am Coll Cardiol*. 2012;59(16):1413-1425.
 46. Wallentin L, Lopes RD, Hanna M, et al. Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International

- Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation. *Circulation*. 2013;127(22):2166-2176.
47. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376(9745):975-983.
48. Gallego P, Vilchez JA, Lane DA. Apixaban compared with warfarin for stroke prevention in atrial fibrillation: implications of time in therapeutic range. *Circulation*. 2013;127(22):2163-2165.
49. Piccini JP, Hellkamp AS, Lokhnygina Y, et al. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. *J Am Heart Assoc*. 2014;3(2):e000521.
50. European Medicines Agency. EMA concludes defective device in ROCKET study does not impact Xarelto's® safety. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002465.jsp&mid=WC0b01ac058004d5c1. Accessed May 11, 2018.
51. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. Supplementary Material. *N Engl J Med*. 2011;365(11):981-992.
52. Ru San T, Chan MYY, Wee Siong T, et al. Stroke Prevention in Atrial Fibrillation: Understanding the New Oral Anticoagulants Dabigatran, Rivaroxaban, and Apixaban. *Thrombosis*. 2012;2012:1-10.
53. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. Supplementary Material. *N Engl J Med*. 2013;369(22):2093-2104.
54. Cameron C, Coyle D, Richter T, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ Open*.

- 2014;4(6):e004301-e004301.
55. Lip GYH, Larsen TB, Skjøth F, Rasmussen LH. Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol*. 2012;60(8):738-746.
 56. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.
 57. *Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review: Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients With Atrial Fibrillation*. 1.1B. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013.
<http://www.ncbi.nlm.nih.gov/pubmed/24199270>. Accessed May 11, 2018.
 58. Lip GYH, Mitchell SA, Liu X, et al. Relative efficacy and safety of non-Vitamin K oral anticoagulants for non-valvular atrial fibrillation: Network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. *Int J Cardiol*. 2016;204:88-94.
 59. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *bmj BMJ*. 2017;359.
 60. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular bleeding and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation*. 2015;131(2):157-164.
 61. Tamayo S, Frank Peacock W, Patel M, et al. Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban. *Clin Cardiol*. 2015;38(2):63-68.
 62. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. *JAMA Intern Med*. 2016;176(11):1662.

63. Lip GYH, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. *Thromb Haemost.* 2016;116(11):975-986.
64. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ.* 2018;362:2505.
65. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. *Circulation.* 2013;128(3):237-243.
66. Cipramil® (Citalopram) 10mg. Summary of Product Characteristics. http://www.medicines.ie/31636_cipramil-10mg-tablets?page=1&per-page=25. Accessed May 11, 2018.
67. Efexor® (venlafaxine) XL 75mg Summary of Product Characteristics. http://www.medicines.ie/31965_efexor-xl-75-mg-hard-prolonged-release-capsules?page=1&per-page=25. Accessed May 11, 2018.
68. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962.
69. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130(23):e199-267.
70. Clemens A, Noack H, Brueckmann M, Lip GYH. Twice- or Once-Daily Dosing of Novel Oral Anticoagulants for Stroke Prevention: A Fixed-Effects Meta-Analysis with Predefined Heterogeneity Quality Criteria. Kiechl S, ed. *PLoS One.* 2014;9(6):e99276.
71. Providência R, Grove EL, Husted S, Barra S, Boveda S, Morais J. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: Comparisons between direct thrombin inhibitors vs. factor Xa

- inhibitors and different dosing regimens. *Thromb Res.* 2014;134(6):1253-1264.
72. Song Y, Chang M, Frost C, et al. Relative bioavailability of crushed apixaban tablets administered with water of applesauce in healthy subjects. Presented at the American Society of Clinical Pharmacology and Therapeutics (ASCPT) Annual meeting; March 3-7, 2015; New Orleans, USA. 2015;97:S21-S56.
73. Medical information Boehringer Ingelheim May 2014. On file.
74. Praxbind® (Idarucizumab) Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003986/WC500197462.pdf. Accessed April 24, 2018.
75. Boehringer Ingelheim 2018. FDA Provides Full Approval to Praxbind, Specific Reversal Agent for Pradaxa. <https://www.boehringer-ingelheim.us/press-release/fda-provides-full-approval-praxbind-specific-reversal-agent-pradaxa>. Published 2018. Accessed May 21, 2018.
76. European Medicines Agency. Praxbind, EPAR summary for the public. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003986/WC500197464.pdf. Accessed May 21, 2018.
77. Pollack C V., Reilly PA, Bernstein R, et al. Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran. *Thromb Haemost.* 2015;114(07):198-205.
78. Pollack C V., Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med.* 2015;373(6):511-520.
79. Pollack C V., Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal — Full Cohort Analysis. *N Engl J Med.* 2017;377(5):431-441.
80. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med.* 2015;373(25):2413-2424.
81. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med.* 2016;375(12):1131-1141.

82. American College of Cardiology. ANNEXA-4 Suggests Experimental Drug Controls Bleeding in Patients Taking Factor Xa Inhibitors.
<http://www.acc.org/latest-in-cardiology/articles/2018/03/07/15/53/mon-1045am-annexa-4-andexanet-for-reversal-of-anticoagulation-in-factor-xa-acc-2018>. Published 2018. Accessed May 22, 2018.
83. HSE PCRS Reimbursable Items. <https://www.sspcrs.ie/druglist/pub>. Accessed March 5, 2019.
84. National Centre for Pharmacoeconomics (NCPE) Review. Dabigatran etexilate (Pradaxa®) for the Prevention of Stroke and Systemic Embolism in Adult Patients with Atrial Fibrillation. 2011. <http://www.ncpe.ie/wp-content/uploads/2012/03/Dabigatran-Etexilate-Pradaxa-in-AFsummary.pdf>. Accessed April 24, 2018.
85. National Centre for Pharmacoeconomics (NCPE) Review. Economic Evaluation of Rivaroxaban (Xarelto®) for the Prevention of Stroke and Systemic Embolism in adult patients with Non-Valvular Atrial Fibrillation with one or more risk factors, such as Congestive. 2012. <http://www.ncpe.ie/wp-content/uploads/2012/04/Rivaroxaban-for-AT-web-summary.pdf>. Accessed April 24, 2018.
86. National Centre for Pharmacoeconomics. Cost Effectiveness of Apixaban (Eliquis®) for the Prevention of Stroke and Systemic Embolism in People with Non-Valvular Atrial Fibrillation. 2013. <http://www.ncpe.ie/wp-content/uploads/2012/12/Apixaban-in-NVAF-Summary-21.pdf>. Accessed April 24, 2018.
87. National Centre for Pharmacoeconomics. Edoxaban (Lixiana®) for the prevention of stroke/SE in adults with NVAF and for the secondary treatment/secondary prevention of DVT and PE in adults.
<http://www.ncpe.ie/drugs/edoxaban-lixiana/>. Accessed April 24, 2018.
88. PCRS. Statistical Analysis of Claims and Payments 2016.
<https://www.hse.ie/eng/staff/pcrs/pcrs-publications/pcrs-annual-report-20161.pdf>. Accessed May 25, 2018.

89. Kildea-Shine P, O’Riordan M. *Anticoagulation in General Practice/Primary Care Part 2:New/Novel Oral Anticoagulants.*; 2014.
<https://www.icgp.ie/go/library/catalogue/item/C3D473F5-F329-85D1-6DDE8A051E730C73>. Accessed May 11, 2018.
90. Irish Heart Foundation: Council for Stroke 2010 (revised) National Clinical Guidelines and Recommendations for the Care of People with Stroke and Transient Ischaemic Attack. 2010. <http://irishheart.ie/wp-content/uploads/2017/04/guidelines.pdf>. Accessed May 11, 2018.
91. Royal College of Physicians UK. *National Clinical Guideline for Stroke, 5th Edition.*; 2016.
[https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-\(1\).aspx](https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx). Accessed June 22, 2018.
92. Scottish Intercollegiate Guidelines Network (SIGN). Antithrombotics: indications and management. 2013.
<http://www.sign.ac.uk/assets/sign129.pdf>. Accessed April 24, 2018.
93. Scottish Intercollegiate Guidelines Network (SIGN). Prevention of stroke in patients with atrial fibrillation. 2014.
http://www.sign.ac.uk/assets/af_publication.pdf. Accessed April 24, 2018.
94. All Wales Medicines Strategy Group. All Wales Advice on the Role of Oral Anticoagulants. February. 2016.
[http://www.awmsg.org/docs/awmsg/medman/All Wales Advice on the Role of Oral Anticoagulants.pdf](http://www.awmsg.org/docs/awmsg/medman/All%20Wales%20Advice%20on%20the%20Role%20of%20Oral%20Anticoagulants.pdf). Accessed April 24, 2018.
95. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-3832.
96. January CT, Group W, Samuel Wann L, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. 2019.
97. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the Prevention of

- Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236.
98. Lip GYH, Banerjee ; Amitava, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. 2018.
99. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Hear Lung Circ*. 2018;27(10):1209-1266.

Bibliography

- Bauersachs R, Berkowitz SD, Brenner B, et al, for the EINSTEIN-DVT investigators. Oral Rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine*, 2013; 363 (26): 2499–2510. Clinical Trials.gov Identifier NCT00440193.
- Bin J, Henry L, Fen R et al. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with Atrial Fibrillation. *Journal of Cardiovascular Pharmacology* 2014;64:4;368-374.
- Bounameaux H, Camm A. Edoxaban: An update on the new oral direct factor Xa inhibitor. *Drugs* 2014; 74: 1209-1231.
- EINSTEIN-PE investigators, Buller HE, Prins MH et al; Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*, 2013;366(14):1287-1297.
- Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358 (26): 2765–2775.
- Eriksson BI, Dahl OE, Huo MH, et al; RE-NOVATE II Study Group. Oral Dabigatran Etxilate versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). A randomised, double-blind, non-inferiority trial. *ThrombHaemost* 2011;105 (4): 721–729.
- Eriksson BI, Dahl OE, Rosencher N, et al; RE-MODEL Study Group. Oral Dabigatran Etxilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomised trial. *Thromb Haemost* 2007; 5 (11): 2178–2185.
- Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 2011; 154:1–11.
- Goette A, Merino J, Ezekowitz M et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *The Lancet* 2016; 388(10055):1995-2003.
- Guyatt GH, Ak EA, Crowther M et al. For the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines CHEST 2012; 141(2)(Suppl):7S–47.
- Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration Rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double blind randomised controlled trial. *Lancet*, 2008; 372 (9632): 31–39.

- Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? *Am J Med* 2010; 123:785–789.
- Lip GY, Lane DA. Stroke Prevention in Atrial Fibrillation. A systematic review. *JAMA*. 2015;313(19):1950-1962.
- Patel MR, Hellkamp AS, Lokhnygina Y et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation. Analysis from the ROCKET AF trial. *J AM Coll Cardiol*. 2013; 61(6):651-658.
- Peterson J, Hoehns J. Administration of direct oral anticoagulants through enteral feeding tubes. *Journal of Pharmacy Technology* 2016; 32(5):196-200.
- Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate vs. warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. *BMJ* 2011; 343:d6333.
- Plitt A, Ezekowitz M, De Caterina R et al. Cardioversion of atrial fibrillation in ENGAGE AF-TIMI 48. *Clinical Cardiology* 2016; 39(6):345-346.
- Riemsmma R, Joore M, Grutters J et al. Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery, Southampton: NETSCC; 2012.
- Sardar P, Chatterjee S, Chaudhari S et al. New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials. *J Am Geriatr Soc* 2014;62(5):857-864.
- Schulman S, Kearon C, Kakkar AK et al. and RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361(24):2342-52.
- Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 2011; 123:2562–2570.
- Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *ThrombHaemost* 2011; 105:908–919.
- Turagam M, Velagapudi P, Flaker G. Stroke prevention in the elderly atrial fibrillation patient with comorbid conditions; focus on non-vitamin k antagonist oral anticoagulants. *Clinical Interventions in Aging* 2015; 10:01431-44.
- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. 2012 NICE clinical guideline 144 guidance.nice.org.uk/cg14

Appendix 1: Pivotal clinical trials for stroke prevention in non-valvular atrial fibrillation for NOACs

Table 22: Trial design information for Aristotle, RE-LY and ROCKET-AF

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
Study design	Randomised Double-blind, double dummy	Randomised Open label, single blind	Randomised Double-blind, double dummy	Randomised Double-blind, double dummy
Study population	AF or flutter and at least one of the following risk factors: <ul style="list-style-type: none"> • ≥ 75 • Previous stroke, TIA or SE • Symptomatic heart failure (previous 3 months or LVEF\leq40%) • Diabetes • Hypertension 	Atrial fibrillation documented on ECG at screening or within 6 months beforehand and at least one of: <ul style="list-style-type: none"> • Previous stroke or TIA • LVEF$<$40% • NYHA class II or more heart failure • At least 75 years • 65-74 + diabetes, hypertension or coronary artery disease 	<ul style="list-style-type: none"> • Male or female \geq 21 years • Atrial fibrillation documented on ECG tracing within 12 months preceding randomisation • A score of 2 or higher on the CHADS₂ risk assessment • Anticoagulation therapy planned for trial duration • Able to provide written informed consent 	Non-valvular atrial fibrillation with moderate-high risk of stroke indicated by: <ul style="list-style-type: none"> • History of prior stroke • TIA or non CNS systemic embolism cardioembolic in origin • 2 or more of the following risk factors: heart failure and/or LVEF\leq35%, hypertension, age \geq75, diabetes mellitus
Number of patients	18,201	18,113	21,105	14,264
Follow-up period (years)	1.8 (median)	2.0 (median)	2.8 (median)	1.94 (707 days median follow-up)
Randomized groups	Dose adjusted warfarin vs. apixaban 5mg BD	Dose adjusted warfarin vs. blinded doses of dabigatran 110mg BD and 150mg BD	Dose adjusted warfarin vs. edoxaban high-dose regimen (60/30mg daily) and edoxaban low-dose regimen (30/15mg daily)	Dose adjusted warfarin vs. rivaroxaban 20mg OD
TTR for warfarin	62.2% (mean) 66% (median)	64% (mean)	64.9% (mean) 68.4% (median)	55% (mean) 58% (median; interquartile range 43-71)

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
Primary efficacy endpoint	Ischaemic or haemorrhagic stroke or systemic embolism	Stroke or systemic embolism	Ischaemic or haemorrhagic stroke or systemic embolic event (SEE)	Composite of stroke (ischaemic or haemorrhagic) and systemic embolism
Secondary efficacy endpoint	Death from any cause Rate of MI	Death from any cause Rate of MI	1) Composite of stroke, SEE, CV mortality 2) Composite of non-fatal MI, non-fatal stroke, non-fatal SEE, CV mortality 3) Composite of stroke, SEE, all-cause mortality	Stroke, systemic embolism or death from cardiovascular causes A composite of stroke, systemic embolism, death from cardiovascular causes or MI Individual components of the composite end points
Safety endpoints	Major bleeding (according to the criteria of the international society on thrombosis and haemostasis (ISTH)) Composite of major bleeding and clinically relevant non major bleeding Any bleeding Other adverse events Liver function abnormalities	Major bleeding Life-threatening bleeding Intracranial bleeding Major and minor GI bleeding	Major bleeding* (modified ISTH) ≥ 1 of: Bleeding that contributed to death; symptomatic bleeding in critical area or organ; clinically overt bleeding event Major and clinically relevant non-major bleeding All bleeding New bone fractures All other clinical and lab safety assessments including liver enzyme and bilirubin abnormalities	Composite of major and non-major clinically relevant bleeding events

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
Exclusion criteria	<ol style="list-style-type: none"> 1. AF due to a reversible cause (e.g. thyrotoxicosis or pericarditis) 2. Clinically significant moderate or severe mitral valve stenosis 3. Prosthetic mechanical heart valve; conditions other than AF needing anticoagulation 4. Stroke within previous 7 days 5. Planned major surgery; 6. Platelet count $\leq 100,000/\text{mm}^3$; 7. Uncontrolled hypertension (sbp $\geq 180\text{mmHg}$ and/or diastolic blood pressure $\geq 100\text{mmHg}$) 8. Planned AF ablation procedure 9. Treatment with aspirin $>165\text{mg}$ a day or for both aspirin and clopidogrel or investigational drug within 30 days 10. Severe renal insufficiency (serum creatinine 221micromol/L or $>2.5\text{mg/dL}$) or calculated creatinine clearance of 	<ol style="list-style-type: none"> 1. History of heart valve disorder (i.e. prosthetic heart valves or hemodynamically relevant valve disease) 2. Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days 3. Conditions associated with an increased risk of bleeding <ol style="list-style-type: none"> a. Major surgery within the previous month. b. Planned surgery or intervention within the next 3 months. c. History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding. d. Gastrointestinal haemorrhage within the past year. e. Symptomatic or endoscopically documented gastroduodenal ulcer 	<ol style="list-style-type: none"> 1. Atrial fibrillation secondary to other reversible disorders 2. Moderate/severe mitral stenosis, unresected atrial myxoma or mechanical heart valve 3. History of left atrial appendage exclusion 4. Intracardial mass or left ventricular thrombus 5. Subjects who may discontinue chronic anticoagulation therapy if planned procedure was successful in converting the subject to normal sinus rhythm 6. Any contraindications for anticoagulation 7. Creatinine clearance $<30\text{ml/min}$ 8. Any conditions associated with a high risk of bleeding 9. Use of dual antiplatelet therapy 10. Subjects receiving chronic cyclosporine therapy 11. Subjects receiving prohibited concomitant medications 12. Acute MI, stroke, acute coronary syndrome or percutaneous coronary intervention in the last 30 days 	<p><u>Cardiac-related conditions</u></p> <ol style="list-style-type: none"> 1. Haemodynamically significant mitral valve stenosis 2. Prosthetic heart valves 3. Planned cardioversion 4. Transient AF caused by reversible disorder such as thyrotoxicosis, PE, MI, recent surgery. 5. Known atrial myxoma or LV thrombus 6. Active endocarditis <p><u>Haemorrhage risk-related criteria</u></p> <ol style="list-style-type: none"> 7. Active internal bleeding 8. History of or condition associated with increased bleeding risk – major surgery 30 days prior to randomisation, clinically significant GI bleed within 6 months, intracranial, intraocular, spinal or a traumatic intra-articular bleed 9. Planned invasive procedure with potential for uncontrolled bleeding.

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
	<p><25ml/min</p> <p>11. ALT or AST>2ULN;</p> <p>12. Total bilirubin > 1.5 ULN;</p> <p>13. Haemoglobin level <9g/dL;</p> <p>Pregnancy</p> <p>14. Severe comorbid condition with life expectancy ≤1 year</p> <p>15. Substance abuse disorder</p> <p>16. Inability to comply with INR monitoring</p>	<p>disease in the previous 30 days.</p> <p>f. Haemorrhagic disorder or bleeding diathesis.</p> <p>g. Need for anticoagulant treatment of disorders other than atrial fibrillation.</p> <p>h. Fibrinolytic agents within 48 hours of study entry.</p> <p>i. Uncontrolled hypertension (systolic blood pressure greater than 180 mmHg and/or diastolic blood pressure greater than 100 mmHg).</p> <p>j. Recent malignancy or radiation therapy (within six months) and not expected to survive three years.</p> <p>4. Contraindication to warfarin treatment</p> <p>5. Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism,</p>	<p>13. Active liver disease or persistent elevation of liver enzymes/bilirubin</p> <p>14. History of HIV</p> <p>15. History of hepatitis B or C</p> <p>16. Other clinically relevant lab abnormalities</p> <p>17. Hb<10g/dl, platelets <100,000 cells/μl or WBC<3,000 cells/μl</p> <p>18. Pre-planned invasive procedures or surgeries in which bleeding anticipated during the study</p> <p>19. Subjects who received any investigational drug or device within 30 days prior to randomisation or plan to receive such therapy during the study</p> <p>20. Subject previously randomised in a DU-176b study</p> <p>21. Females of child-bearing potential including history of tubal ligation or <2 years postmenopausal</p> <p>22. Subjects with active malignancy, treatment for cancer in the last 5 years, concurrent active medical illness or infection, life expectancy <12 months</p>	<p>10. Platelet count <90,000/microliter at screening</p> <p>11. Sustained uncontrolled hypertension (systolic BP≥180mmHg or diastolic BP≥100mmHg)</p> <p><u>Concomitant conditions and therapies</u></p> <p>12. Severe disabling stroke within 3 months or any stroke within 14 days before randomization</p> <p>13. TIA within 3 days of randomisation.</p> <p>14. Indication for anticoagulation other than AF (e.g. VTE)</p> <p>15. Treatment with aspirin >100mg/day, aspirin in combination with thienopyridines within 5 days of randomisation, IV antiplatelets within 5 days, fibrinolytics within 10 days.</p> <p>16. Anticipated need for chronic NSAID therapy</p> <p>17. Systemic treatment with strong inhibitors of CYP3A4 (ketoconazole or protease inhibitors) within 4 days</p> <p>18. Treatment with strong inducers of CYP3A4 (rifampicin) within 4 days before randomization.</p>

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
		<p>untreated hyperthyroidism).</p> <p>6. Plan to perform a pulmonary vein ablation or surgery for cure of the AF</p> <p>7. Severe renal impairment (estimated creatinine clearance ≤ 30 mL/min)</p> <p>8. Active infective endocarditis</p> <p>9. Active liver disease, including but not limited to: a) persistent ALT, AST, Alk Phos greater than twice the upper limit of normal, b) Active hepatitis A, B and C</p> <p>10. Women who are pregnant, lactating, or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study</p> <p>11. Anaemia (haemoglobin < 100g/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L)</p> <p>12. Patients who have developed transaminase</p>	<p>23. Inability to adhere to study procedures</p> <p>24. Known alcohol or drug dependence within the past 12 months</p> <p>25. Increased risk of harm by participating in the study</p>	<p>19. Anaemia (haemoglobin < 10g/dL)</p> <p>20. Pregnant or breast feeding.</p> <p>21. Any other contraindication to warfarin.</p> <p>22. Known HIV at screening.</p> <p>23. CrCl < 30ml/min.</p> <p>24. Known significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis, of ALT > 3 x the ULN</p> <p>25. Serious concomitant illness associated with life expectancy of less than 2 years, drug addiction or alcohol abuse within 3 years before randomization, received experimental drug within 30 days. Previous randomization in present or other study of rivaroxaban, known allergy to any component of rivaroxaban or warfarin, inability to comply with study procedures, employees of the investigator or study centre</p>

Study Characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
		<p>elevations upon exposure to ximelagatran</p> <p>13. Patients who have received an investigational drug in the past 30 days or are participating in another drug study</p> <p>14. Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, life expectancy less than the expected duration of the trial due to concomitant disease or having any condition which in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse)</p>		

Baseline patient characteristics	Apixaban (ARISTOTLE)	Dabigatran (RE-LY)	Edoxaban (ENGAGE AF-TIMI 48)	Rivaroxaban (ROCKET-AF)
Age (years)	70 (median) (63-76 interquartile range)	71.5 (150mg) (mean) ±SD (8.7)	72 (64-78)	73 (median) (65-78 interquartile range)
Female	35% (warf) 35.5% (apix)	36.4% (average of 3 groups)	38.1% (average of 3 groups)	39.7%
Weight (kg)	82kg (median) (70-96 interquartile range)	82.7kg (mean) ±19.7 (average SD?)	Mean and median weight not stated, 9.9% of patients were <60kg	BMI median and interquartile 28.3 and 28.1 (w) 25.2-32.1, 25.1-31.8)
CHADS₂ scores				
0	-	} 31.9%	-	-
1	34%	} }	0.1%	-
2	35.8%	} 35.63%	46.5%	13.05%
3	} }	} }	} }	43.6%
4	} (≥3) 30.2%	} (≥3) 32.47%	} (≥3) 53.2%	28.65%
5	} }	} }	} }	12.75%
6	} }	} }	} }	1.95%
Renal Function proportions	% (excluded <25ml/min)	(excluded <30ml/min)	(excluded <30ml/min) Results from prespecified analysis of renal function in ENAGE AF-TIMI 48, low-dose edoxaban regimen was excluded	67 (median) interquartile range 52-88(86) (excluded < 30ml/min)
Normal (>80ml/min)	41.3	Dabigatran dose was not stratified by CrCl in RE-LY	CrCl>95ml/min 22.2%	32.2%
Mild impair (>50-80ml/min)	41.7		CrCl >50-95ml/min 58.3%	46.6%
Moderate impair (>30-50ml/min)	15.1 (4.7% and 4.4% in active and control groups received renal dose of 2.5mg)		CrCl 30-50 ml/min 19.5%	21.1%
Severe (≤30ml/min)	1.5			0.06%
Not reported	0.4			

Outcomes (% per year intention to treat)										
Trial	ARISTOTLE		RE-LY			ENGAGE AF-TIMI 48			ROCKET-AF	
Medication and dose	Warfarin (n=9,081)	Apixaban 5mg BD (or reduction to 2.5mg BD) (n=9,120)	Warfarin (n=6022)	Dabigatran 150mg BD (n= 6076)	Dabigatran 110mg BD (n=6015)	Warfarin (n=7036)	High-dose Edoxaban 60mg daily (or dose reduction to 30mg daily) (n=7035)	Low-dose Edoxaban 30mg daily (or dose reduction to 15mg daily) (n=7034)	Warfarin (n=7133)	Rivaroxaban 20mg daily (or reduction to 15 mg daily) (n=7131)
	% outcome	% outcome (HR; 95% CI; P value)	% outcome	% outcome (RR;95% CI; P value)	% outcome (RR;95% CI; P value)	% outcome	% outcome (HR;95% CI; P value)	% outcome (HR;95% CI; P value)	% outcome	% outcome (HR;95% CI; P value)
Primary endpoint Stroke/systemic embolism (% per year) based on ITT population	1.6%	1.27% (0.79;0.66-0.95; P=0.01 for superiority)	1.69%	1.11% (0.66; 0.53-0.82; P for superiority <0.001)	1.53% (0.91; 0.74-1.11; P for noninferiority <0.001)	1.8%	1.57% (0.87; 0.73-1.04; P=0.08)	2.04% (1.13; 0.96-1.34; P=0.10)	2.4%	2.1% (0.88; 0.75-1.03; P <0.001 for non-inferiority, P for superiority =0.12) (ITT)
Ischaemic stroke	1.05%	0.97% (0.92; 0.74-1.13; P=0.42)	1.20%	0.92% (0.76; 0.6-0.98; P=0.03)	1.34% (1.11; 0.89-1.40; P =0.35)	1.25%	1.25% (1.00;0.83-1.19; P=0.97)	1.77% (1.41;1.19-1.67; P<0.001)	1.42%	1.34% (0.94; 0.75-1.17; P=0.581)
Haemorrhagic stroke	0.47%	0.24% (0.51; 0.35-0.75; P<0.001)	0.38%	0.10% (0.26; 0.14-0.49; P<0.001)	0.12% (0.31; 0.17-0.56; P<0.001)	0.47%	0.26% (0.54;0.38-0.77; P<0.001)	0.16% (0.33;0.22-0.5; P<0.001)	0.44%	0.26% (0.59; 0.37-0.93; P=0.024)
Primary Safety endpoint (Aristotle, RE-LY, ENGAGE AF-TIMI 48): major bleeding	3.09%	2.13% (0.69; 0.60-0.80; P<0.001 for superiority)	3.36%	3.11% (0.93; 0.81-1.07; P=0.31)	2.71% (0.80; 0.69-0.93; P=0.003)	3.43%	2.75% (0.80;0.71-0.91; P<0.001)	1.61% (0.47;0.41-0.55; P<0.001)	3.4%	3.6% (P=0.58)
Primary Safety endpoint									14.5%	14.9% (1.03; 0.96-1.11; P=

Outcomes (% per year intention to treat)										
Trial	ARISTOTLE		RE-LY			ENGAGE AF-TIMI 48			ROCKET-AF	
(ROCKET AF) Major and non-major clinically relevant bleeding										0.44) Two sided for superiority in the rivaroxaban group as compared with the warfarin group
Intracranial bleeding	0.80%	0.33% (0.42;0.30-0.58; P<0.001)	0.74%	0.30% (0.40; 0.27-0.60; P<0.001)	0.23% (0.31; 0.20-0.47; P<0.001)	0.85%	0.39% (0.47;0.34-0.63; P<0.001)	0.26% (0.30;0.21-0.43; P<0.001)	0.7%	0.5% (0.67; 0.47-0.93; P=0.02)
Extracranial bleeding			2.67%	2.84% (1.07; 0.92-1.25; P=0.38)	2.51% (0.94; 0.80-1.10; P=0.45)					
Other location bleeding	2.27%	1.79% (0.79; 0.68-0.93; P=0.004)				1.37%	0.85% (0.62;0.50-0.78;P<0.001)	0.55% (0.40;0.31-0.52;P<0.001)		
Gastrointestinal bleeding	0.86%	0.76% (0.89; 0.70-1.15; P=0.37)	1.02%	1.51% (1.50; 1.19-1.89; P<0.001)	1.12% (1.10; 0.86-1.41; P=0.43)	1.23%	1.51% (1.23;1.02-1.50;P=0.03)	0.82% (0.67;0.53-0.83;P<0.001)	2.2%	3.2%(P<0.001)
Myocardial infarction	0.61%	0.53% (0.88; 0.66-1.17; P=0.37)	0.64%	0.81% (1.27; 0.94-1.71; P=0.12)	0.82% (1.29; 0.96-1.75; P=0.09)	0.75%	0.70% (0.94;0.74-1.19;P=0.60)	0.89% (1.19;0.95-1.49;P=0.13)	1.1%	0.9% (0.81; 0.63-1.06; P=0.12)
Death from any cause	3.94%	3.52% (0.89; 0.800-0.998; P=0.047)	4.13%	3.64% (0.88; 0.77-1.00; P=0.051)	3.75% (0.91; 0.80-1.03; P=0.13)	4.35%	3.99% (0.92;0.83-1.01; P=0.08)	3.8% (0.87;0.79-0.96; P=0.006)	2.2%	1.9% (0.85; 0.70-1.02; P=0.07)
% discontinuation at end of follow-up	27.5%	25.3%	10.2%	15.5%	14.5%	34.5%	34.4%	33%	22.2%	23.7%
% discontinuation/yr.	15.3%	14.1%	5.1%	7.8%	7.3%	12.3%	12.3%	11.8%	11.7%	12.5%

Appendix 2: Anticoagulation Prescribing Tips -Warfarin and DOACs

ANTICOAGULATION PRESCRIBING TIPS

These prescribing tips are intended to assist prescribers, and advise on the appropriate dosing, when a direct oral anticoagulant (DOAC) is selected for treatment. Dosing recommendations are based on the *Summary of Product Characteristics (SmPC)* for each product (available on www.hpra.ie and www.medicines.ie)

The Medicines Management Programme consider **WARFARIN** or **APIXABAN** to be the agents of choice for most patients with **Non- Valvular Atrial Fibrillation (NVAF)¹**

WARFARIN is an appropriate first-line treatment option for stroke prevention in NVAF when time in therapeutic range (TTR) > 70%
APIXABAN is the preferred DOAC for stroke prevention in NVAF and may be considered 1st line treatment, particularly if there are tolerability issues and/or labile international normalised ratios (INRs) with warfarin

The following points should be considered prior to prescribing an oral anticoagulant:

1. Warfarin is the established anticoagulant of choice for many patients including those with: mechanical heart valves, valvular atrial fibrillation, severe renal impairment, cancer related venous thromboembolism (VTE), complicated VTE such as patients with recurrent VTE, patients with antiphospholipid syndrome²
2. Warfarin dosing and monitoring: Refer to ICGP guidance: "Anticoagulants in general practice/primary care Part 1: Warfarin (2014)" (available on www.icgp.ie)
3. **Clinical Trials for DOACs:**
 - The DOACs were not shown to be superior to optimal warfarin therapy in clinical trials for stroke prevention in Atrial Fibrillation i.e. where TTR for warfarin > 70%^{3,4}(ROCKET-AF: mean TTR=55%³, RE-LY: mean TTR=64%⁵, ENGAGE AF-TIMI: mean TTR: 68.4%⁷, ARISTOTLE: mean TTR= 62%⁸)
 - The pivotal clinical trial for rivaroxaban for stroke prevention in AF was a non-inferiority trial (ROCKET-AF) with a TTR of 55%
 - Patients with severe renal dysfunction were excluded from the pivotal clinical trials in AF i.e. exclusion criteria for ROCKET-AF (rivaroxaban)³, RE-LY (dabigatran)⁵ and ENGAGE AF-TIMI (edoxaban)⁷: Creatinine clearance (CrCL) < 30 ml/min; ARISTOTLE (apixaban) exclusion criteria was CrCl < 25 ml/min⁸Therefore the Medicines Management Programme advises extreme caution when using DOACs in patients with CrCl of 15-30 ml/min. Apixaban, edoxaban and rivaroxaban are contraindicated with CrCl < 15ml/min while dabigatran is contraindicated with CrCl < 30 ml/min

Patients on DOAC therapy should have regular assessment of their renal function and their dose adjusted or therapy reviewed as appropriate (at least 6 monthly review and more frequently if renal impairment or risk factors for impaired renal function).

- Similar exclusion criteria for renal dysfunction were used in VTE prophylaxis trials and treatment of DVT/PE trials⁹⁻¹⁷
 - The trials for treatment of DVT/PE with dabigatran and rivaroxaban studied the standard treatment doses only (150mg BD and 20mg OD respectively). The lower doses of 110mg BD dabigatran and 15mg OD rivaroxaban to treat DVT/PE have not been studied in a clinical setting^{13,15,18,19}
 - Trials for the treatment of DVT and PE (for rivaroxaban and dabigatran) were non-inferiority trials¹³⁻¹⁵
4. Significant drug interactions may occur with DOAC therapy and the most common of these are highlighted in this prescribing aid¹⁸⁻²¹
 5. Poor compliance with DOAC therapies carries a risk of thrombotic events due to the short half-life of these agents¹⁸⁻²¹
 6. Reversal agents: an antidote (idarucizumab) is now available for the direct thrombin inhibitor, dabigatran. There is currently no antidote available for the haemorrhagic complications associated with the factor Xa inhibitors.

References

1. National Institute for Health and Care Excellence (NICE). Atrial fibrillation: diagnosis and management. NICE guideline [NG106]. London: NICE; 2017.
2. National Institute for Health and Care Excellence (NICE). Venous thromboembolism: diagnosis and management. NICE guideline [NG143]. London: NICE; 2017.
3. Ezekowitz SD, Yusuf S, Avezub M, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2010;363:2537-46.
4. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
5. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
6. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
7. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
8. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
9. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
10. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
11. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
12. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
13. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
14. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
15. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
16. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
17. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
18. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
19. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
20. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.
21. Granger CB, Alexander H, McMurray JJ, et al. Comparison of warfarin and dabigatran for the prevention of stroke and embolism in patients with atrial fibrillation. *N Engl J Med*. 2011;365:975-82.



Version 1.5 MMP March 2019

Available on www.hpra.ie/yourmedicines

Contact icgp@hpra.ie for more details

Appendix 3: Prescribing tips for the preferred DOAC for stroke prevention in AF

Prescribing tips for APIXABAN

These prescribing tips only relate to the indication of stroke prevention in non-valvular atrial fibrillation (NVAf). For dosing information for other indications for APIXABAN please refer to the Summary of Product Characteristics (SmPC), which may be accessed freely online at www.hpra.ie and www.medicines.ie

The MMP DOAC prescribing tips can also be accessed for to ensure correct dose selection (www.hse.ie/yourmedicines)

Onset of Action: Apixaban has a very fast onset of action (3-4 hours after first dose)

Frequency: MUST be taken TWICE DAILY every 12 hours

Duration of Treatment: Anticoagulation for stroke prevention in AF will be considered life-long therapy. As patients get older, regular review of appropriate doses, renal function and age considerations should be taken into account.

Atrial Fibrillation: Dosing & Administration

Please consult individual SmPCs for guidance on prescribing for other indications and in special patient populations

Adjust dose for:

AGE, BODY WEIGHT, RENAL IMPAIRMENT and consider any potential DRUG INTERACTIONS

DOSING		Stroke prevention in NVAf
Standard dose		5 mg twice daily (BD)
Serum creatinine > 133micromol/L (measured) AND ≥80yrs OR weight ≤60kg (or any two of three above i.e. serum creatinine, age ≥80, weight ≤60kg)		2.5mg BD
CrCl 15-29ml/min [use Cockcroft-Gault equation (SI units)] (regardless of age or weight)		2.5mg BD – EXTREME CAUTION , consider alternative (review HAS-BLED and other risk factors)
CONTRAINDICATED in CrCl < 15ml/min		
SPECIAL REQUIREMENTS		
Food	There are no specific requirements for apixaban administration and the medication can be taken with or without food	
Crushing	There are no recommendations on crushing the tablets in the current SPC but there is published evidence that crushing apixaban has led to comparable exposure of apixaban to the solid dosage form.	

DRUG INTERACTIONS

- **CONTRAINDICATED** with other anticoagulants
- **AVOID CONCURRENT USE** (increased bleeding risk): Strong **inhibitors** of CYP3A4 and P-gp, such asazole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details
- **CAUTION** (risk of reduced efficacy): Strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort)
- **CAUTION** (increased bleeding risk): NSAIDs including aspirin
- Antiplatelet agents including **aspirin** will increase risk of bleeding

Contraindicated in patients with **hepatic disease** associated with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment.