Medicines Management Programme

Oral anticoagulants for stroke prevention in non-valvular atrial fibrillation

Drugs in this review include:

- Warfarin
- Apixaban
- Dabigatran
- Rivaroxaban

Approved by: Prof. Michael Barry, Clinical Lead, MMP.
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List of abbreviations

AHA/ACC/HRS American Heart Association/American College of Cardiology/Heart Rhythm Society
AHA/ASA American Heart Association/American Stroke Association
ARD Absolute Risk Difference
ARISTOTLE Apixaban for the Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation
CINAHL Cumulative Index to Nursing and Allied Health Literature
CYP450 Cytochrome P450
DDD Defined daily dose
DTI Direct Thrombin Inhibitor
DPS Drug Payment Scheme
DVT Deep Vein Thrombosis
EMA European Medicines Agency
ESC European Society of Cardiology
GMS General Medical Service
GP General Practitioner
HPRA Health Products Regulatory Agency
HSE Health Service Executive
ICGP Irish College of General Practitioners
ISTH International Society on Thrombosis and Haemostasis
IHF Irish Heart Foundation
IMB Irish Medicines Board
LVEF Left Ventricular Ejection Fraction
NYHA New York Heart Association
MHRA Medicines and Healthcare products Regulatory Authority
MI Myocardial Infarction
MMP Medicines Management Programme
NCPE National Centre for Pharmacoeconomics
NICE National Institute for Health and Care Excellence
NMIC National Medicines Information Centre
NOAC New Oral Anticoagulant
NVAF Non-Valvular Atrial Fibrillation
PCC Prothrombin Complex Concentrate
PCRS Primary Care Reimbursement Service
PE Pulmonary Embolism
P-gp P-glycoprotein
PPI Proton pump inhibitor
RCT Randomised controlled trial
RE-LY Randomised Evaluation of Long-term Anticoagulant therapy (Dabigatran)
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
SIGN Scottish Intercollegiate Guidelines Network
SmPC Summary of Product Characteristics
SSE Stroke and Systemic Embolism
TTR Time in therapeutic range
VKA Vitamin K Antagonist
XaI Factor Xa Inhibitors
1. Background
Oral anticoagulants 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 is the most common cardiac arrhythmia worldwide occurring in approximately 1-2% of the general population.\(^2\) Atrial fibrillation (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 oral anticoagulants available. Warfarin is indicated for prophylaxis of systemic embolization in patients with rheumatic heart disease and atrial fibrillation. It is also indicated for prophylaxis of venous thrombosis and pulmonary embolism and for use in the treatment of these conditions to prevent their extension.\(^3\)

Warfarin has been licensed for use as an anticoagulant since 1954 and there are over 30,000 patients on warfarin treatment on the GMS and DPS schemes according to a recent review of the PCRS database (October 2014).\(^4\) Treatment with warfarin requires regular monitoring of the International Normalised Ratio (INR) to ensure the patients 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, ‘time in therapeutic range’ (TTR) with optimal therapy considered when the TTR is > 70%.\(^5,6\)
The non-vitamin K oral anticoagulants (NOACs) first became available in Ireland 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 non-valvular atrial fibrillation and treatment of VTE i.e. deep vein thrombosis (DVT) and pulmonary embolism (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. It is anticipated that a fourth NOAC, edoxaban, a factor Xa inhibitor, will be licensed for stroke prevention in NVAF in 2015.

Patients who are being started on oral anticoagulation therapy should be given full information with regard to all anticoagulant options prior to the prescribing of a particular agent. The National Institute for Health and Care Excellence in the United Kingdom have recently published a patient decision aid to inform patients prior to anticoagulation choice.

1.1. Therapeutic Indications

Warfarin is licensed in Ireland for the following therapeutic indications:
- Prophylaxis of systemic embolism in patients with rheumatic heart disease and both valvular and non-valvular atrial fibrillation
- Prophylaxis of prosthetic heart valves
- Prophylaxis and treatment of venous thrombosis and pulmonary embolism
- Transient cerebral ischaemic attacks

Apixaban, dabigatran and rivaroxaban are currently licensed in Ireland for the following therapeutic indications:
- Stroke prevention with non-valvular atrial fibrillation with other risk factors
- Treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Thromboprophylaxis post elective hip and knee replacement surgery
Warfarin therapy has a wider range of therapeutic indications than the NOACs including valvular AF and use with prosthetic heart valves. The two indications which are common to both warfarin and the NOACs are stroke prevention in non-valvular atrial fibrillation and prevention and treatment of DVT and PE (discussed below). The use of NOACs 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 non-valvular atrial fibrillation.

**Stroke Prevention in Atrial Fibrillation**

Atrial fibrillation (AF) 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.\(^{12}\) 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 atrial fibrillation.\(^{12,13}\)

**Treatment of DVT/PE**

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolic diseases cover a spectrum ranging from asymptomatic calf vein thrombosis to symptomatic DVT. DVTs can be fatal if they lead to PE. Non-fatal VTE can cause serious long-term conditions such as post-thrombotic syndrome.\(^{14}\)

**Prophylaxis of VTE post hip and knee replacement surgery**

Apixaban, dabigatran and rivaroxaban are all licensed for thromboprophylaxis post elective hip and knee replacement surgery. The use of NOACs for this indication is short-term (from 14 to approximately 35 days) and can replace the need for subcutaneous thromboprophylactic treatment following these procedures. Pharmacoeconomic evaluations carried out by the NCPE found NOAC therapies to be
The treatment of DVT/PE and the prophylaxis of VTE post orthopaedic surgery are not the focus of this document.

**1.2 Context for this review**

The treatment of stroke prevention in NVAF and the other licensed indications mentioned above (treatment of DVT/PE) require anticoagulation therapy and in the case of atrial fibrillation this treatment will be life-long. Warfarin therapy for all indications is adjusted based on a patient's individual INR while the NOACs require varying dosage options and specific administration considerations depending on the indication for treatment and patient factors such as age, renal function and weight. A recent review of PCRS claims data for GMS and DPS community drug schemes (March 2014) revealed concerns in relation to the potentially inappropriate prescribing associated with the NOACs while their use in practice was growing steadily. Potentially inappropriate prescribing of NOAC therapy may have serious implications for patient safety.

This document will set out the reasons why the MMP considers well controlled warfarin to be the agent of choice and the first line anticoagulant for patients with AF when the TTR exceeds 70%. As not all patients will be suitable for warfarin therapy due to labile INRs or drug allergies the availability of NOACs afford the opportunity to treat a larger cohort of AF patients than was previously possible. This review looks at the evidence for the NOACs currently licensed and with reimbursement approval in Ireland and aims to recommend a NOAC of choice for second line anticoagulation therapy when warfarin therapy is not suitable.
This review will focus on the treatment of stroke prevention in atrial fibrillation. The NOACs reviewed as part of this evaluation are currently all licensed for the treatment of non-valvular atrial fibrillation in Ireland.9,10,11

There are currently three NOACs with marketing authorisation in Ireland, apixaban, dabigatran and rivaroxaban.9,10,11

At the time of writing, PCRS data on NOAC usage was available to the MMP for the period up to and including the month October 2014. In the first ten months of 2014 some 166,070 prescriptions were issued for NOACs under the GMS, DP and LTI schemes. This represented an 80% increase in NOAC prescription claims versus the corresponding months in 2013.20 The number of people being treated with NOAC therapies has risen steadily; in October 2014, 16,272 patients were dispensed a NOAC under the PCRS schemes, while 30,620 patient were dispensed warfarin. Corresponding figures for October 2013 found that 10,131 patients were dispensed a NOAC while 33,585 were dispensed warfarin. The NOACs represent a considerable cost to the Health Service Executive (HSE); total drug expenditure on NOACs amounted to €1.5 million for the month of October 2014 alone, in comparison to a total drug expenditure on warfarin of €0.4 million during this time.

2. Aim

There are four oral anticoagulants currently licensed for stroke prevention in non-valvular atrial fibrillation, warfarin, apixaban, dabigatran and rivaroxaban. In November 2014 the Medicines Management Programme (MMP) commenced a review of warfarin and the NOACs under the Preferred Drugs initiative. 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 atrial fibrillation.
As with previous MMP Preferred Drugs initiatives, prescribers are encouraged to consider the preferred drug when initiating anticoagulant therapy.

2.1 Definitions

For the purpose of this evaluation, the use of the term “new oral anticoagulant” or “non-vitamin K oral anticoagulant” or “NOAC” refers to the oral direct thrombin inhibitors and the oral factor Xa inhibitors that are currently licensed for use (dabigatran etexilate, apixaban and rivaroxaban). The terms “dabigatran etexilate” and “dabigatran” are considered interchangeable in this document. In this document atrial fibrillation (AF) refers to non-valvular atrial fibrillation (NVAF) as NOACs are not indicated for use in valvular atrial fibrillation. Unless otherwise stated, the cost is the reimbursed cost of a drug, as listed on the HSE PCRS website (www.pcrs.ie) on April 2015.

3. Preferred Drug for anticoagulation in stroke prevention in NVAF

3.1 Considerations for Warfarin versus NOAC therapy

The HSE MMP considers that there is little difference in terms of health outcomes between warfarin therapy and NOACs when warfarin is well tolerated and the INR remains (for the most part) between 2 and 3.\textsuperscript{19,21} 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 syndrome\textsuperscript{1}
There are many years of experience with warfarin therapy and the effects of warfarin can be monitored in individuals using the international normalised ratio (INR). Warfarin has a narrow therapeutic index with food and drug interactions affecting the INR control and so regular monitoring is required. 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 NOACs. Warfarin anticoagulation has the benefit of being reversible with Vitamin K and prothrombin complex concentrate (PCC).

Non-compliance with warfarin therapy is not considered a suitable reason for choosing a NOAC above warfarin therapy due to the short elimination half-life associated with the NOACs and the consequent risk of reduced anticoagulation if there is poor compliance. 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 Medicines Management Programme considers warfarin to be the agent of first choice for most patients with atrial fibrillation.

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

Under the MMP, the preferred anticoagulant for stroke prevention in NVAF is **WARFARIN**

Where there are issues of tolerability and/or labile INRs with warfarin, an alternative oral anticoagulant (NOAC) may be considered second line.

Under the MMP, the preferred NOAC for second line use for stroke prevention with atrial fibrillation, where warfarin is unsuitable, is **APIXABAN**

Where there are issues of tolerability and/or suitability with APIXABAN, an alternative oral anticoagulant may be considered third line. Patients should be provided with sufficient information on ALL AVAILABLE THERAPIES when anticoagulation is being commenced*

Care should be taken at times where anticoagulation therapy is being changed

*NICE CG180 Atrial Fibrillation (update): Patient decision aid*
4. Consultation for NOAC therapies

A period of consultation was 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 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 during the evaluation process.

5. Selection Criteria for NOAC 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 NOACs versus warfarin

All licensed NOACs (apixaban, dabigatran and rivaroxaban) have been shown, in non-inferiority randomised controlled trials (ARISTOTLE, RE-LY, ROCKET-AF), to be effective in the prevention of stroke in patients with atrial fibrillation when compared to warfarin (at varying levels of INR control). Apixaban was also studied versus aspirin in patients unsuitable for warfarin therapy (AVERROES). (see table 1) ARISTOTLE and RE-LY trials were based on the intention to treat (ITT) population while ROCKET-AF used the per protocol population. 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.\textsuperscript{23-25}

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

**Table 1: Pivotal clinical trials for stroke prevention in non-valvular atrial fibrillation**\textsuperscript{23-26}

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Clinical trial for Stroke Prevention in NVAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>ARISTOTLE (vs. warfarin)</td>
</tr>
<tr>
<td></td>
<td>AVERROES (vs. aspirin)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-LY (vs. warfarin)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>ROCKET-AF (vs. warfarin)</td>
</tr>
</tbody>
</table>

Within this group of agents there are two distinct drug groups, direct thrombin inhibitors (DTIs) (dabigatran) and factor Xa inhibitors (XaI) (apixaban and rivaroxaban). The DTI dabigatran is predominantly cleared by the renal pathway and there may be specific concerns in renal impairment (contraindicated in CrCl<30ml/min) but this agent is also the only NOAC with large-clinical trial data for each of the two licensed doses of 150mg and 110mg BD.\textsuperscript{24} There are some variations in the efficacy and safety endpoints for the pivotal clinical trials as shown in table 2. For tabulated details of the pivotal RCTs for stroke prevention in NVAF see Table 3 and Appendix 1.
Table 2: Efficacy and safety endpoints for pivotal trials for Stroke prevention in NVAF

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>ARISTOTLE(^{23})</th>
<th>RE-LY(^{24})</th>
<th>ROCKET-AF(^{25})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td>Stroke or systemic embolism (ischaemic or haemorrhagic)</td>
<td>Stroke (ischaemic, haemorrhagic or unspecified) or systemic embolism</td>
<td>Composite of stroke (ischaemic or haemorrhagic) and systemic embolism</td>
</tr>
<tr>
<td><strong>Secondary efficacy endpoint</strong></td>
<td>Death from any cause Rate of MI</td>
<td>Stroke Systemic embolism Death</td>
<td>1) Composite of stroke, systemic embolism or death from cardiovascular causes 2) Composite of stroke, systemic embolism, death from cardiovascular causes or MI 3) Individual components of the composite end points</td>
</tr>
<tr>
<td><strong>Other efficacy outcomes</strong></td>
<td>Rate of MI Pulmonary embolism Transient ischaemic attack Hospitalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary safety endpoint</strong></td>
<td>Major bleeding* (ISTH criteria)</td>
<td>Major haemorrhage</td>
<td>Composite of major and non-major clinically relevant bleeding*</td>
</tr>
<tr>
<td><strong>Secondary safety endpoint</strong></td>
<td>Composite of major bleeding* and clinically relevant non-major bleeding</td>
<td>Bleeding events* (major and minor) Intracerebral haemorrhage Other intracranial haemorrhage Elevation in liver transaminases, bilirubin and hepatic dysfunction and other adverse events</td>
<td></td>
</tr>
<tr>
<td><strong>Other safety outcomes</strong></td>
<td>Any bleeding Other adverse events Liver function abnormalities</td>
<td></td>
<td>Adverse events ALT elevation</td>
</tr>
</tbody>
</table>

* The definition of major bleeding differs between the pivotal clinical trials
### 5.1.1 Clinical trial results

Table 3: Outcomes from the pivotal clinical trials for stroke prevention in AF

<table>
<thead>
<tr>
<th>Outcomes (% per year intention to treat)</th>
<th>ARISTOTLE</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
<td>Warfarin (n=9,081)</td>
<td>Apixaban (n=9,120)</td>
<td>Warfarin (n=6022)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>% outcome</td>
<td>% outcome (HR; 95% CI; P value)</td>
<td>% outcome</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong> Stroke/systemic embolism (% per year) based on intention to treat population</td>
<td>1.6%</td>
<td>1.27% (0.79;0.66-0.95; P=0.01 for superiority)</td>
<td>1.69%</td>
</tr>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td>1.05%</td>
<td>0.97% (0.92; 0.74-1.13; P=0.42)</td>
<td>1.20%</td>
</tr>
<tr>
<td><strong>Haemorrhagic stroke</strong></td>
<td>0.47%</td>
<td>0.24% (0.51; 0.35-0.75; P&lt;0.001)</td>
<td>0.38%</td>
</tr>
<tr>
<td><strong>Primary Safety endpoint (Aristotle and RE-LY)</strong> Major bleeding</td>
<td>3.09%</td>
<td>2.13% (0.69; 0.60-0.80; P&lt;0.001 for superiority)</td>
<td>3.36%</td>
</tr>
<tr>
<td><strong>Primary Safety endpoint (ROCKET AF)</strong> Major and non-major clinically relevant</td>
<td>14.5%</td>
<td>14.9% (1.03; 0.96-1.11; P= 0.44) Two sided for superiority in the rivaroxaban group as compared with the</td>
<td></td>
</tr>
<tr>
<td>bleeding</td>
<td>warfarin group</td>
<td></td>
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<tr>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
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<tr>
<td>Intracranial bleeding</td>
<td>0.80% (0.42; 0.30-0.58; P &lt;0.001)</td>
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<tr>
<td></td>
<td>0.74% (0.30; 0.27-0.60; P =0.701)</td>
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<tr>
<td></td>
<td>0.23% (0.31; 0.20-0.47; P&lt;0.001)</td>
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<td></td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>0.74 % (0.40; 0.30-0.58; P =0.701)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.74% (0.40; 0.30-0.58; P =0.701)</td>
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<tr>
<td></td>
<td>0.74% (0.40; 0.30-0.58; P =0.701)</td>
<td></td>
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<tr>
<td>Other location bleeding</td>
<td>2.67% (1.07; 0.92-1.25; P=0.38)</td>
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<tr>
<td></td>
<td>2.51% (0.94; 0.80-1.10; P=0.45)</td>
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<tr>
<td>Gastrointestinal bleeding</td>
<td>1.02% (1.50; 1.19-1.89; P &lt;0.001)</td>
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<td></td>
<td>1.12% (1.10; 0.86-1.41; P=0.43)</td>
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<tr>
<td>Myocardial infarction</td>
<td>0.64% (1.27; 0.94-1.71; P=0.12)</td>
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<td></td>
<td>0.82% (1.29; 0.96-1.75; P=0.09)</td>
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<tr>
<td>Death from any cause</td>
<td>4.13% (0.88; 0.77-1.00; P=0.051)</td>
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<tr>
<td></td>
<td>3.75% (0.91; 0.80-1.03; P =0.13)</td>
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<tr>
<td>% discontinuation at end of follow-up</td>
<td>27.5% (10.2% 15.5% 14.5% 22.2% 23.7%)</td>
<td></td>
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</tr>
<tr>
<td>% discontinuation/yr.</td>
<td>15.3% (5.1% 7.8% 7.3% 11.7% 12.5%)</td>
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</tr>
</tbody>
</table>
Apixaban – ARISTOTLE trial

The results of the ARISTOTLE trial can be seen in table 3 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 3 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 non-inferiority and superiority (p=0.01) for the primary outcome – see table 3. 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).

Major bleeding was defined according to International Society of Thrombosis and Haemostasis (ISTH) criteria. 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.

In the ARISTOTLE trial only major bleeds where there was a decrease in the haemoglobin of 2g/dl in the first 24 hours were included.
Dabigatran – RE-LY trial

As seen in table 3 dabigatran 150mg 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 110mg twice daily 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 150mg twice daily group (RR, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority).

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

Major bleeding was significantly lower with dabigatran 110mg BD compared to warfarin (2.71% versus 3.36% per year), whereas there was no significant difference in those treated with dabigatran 150mg BD and warfarin (3.11% versus 3.36%). Major bleeding was defined in RE-LY as a reduction in haemoglobin of at least 2.0 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ.

Risk of intracranial bleeding and haemorrhagic stroke were significantly lower in both dabigatran 110mg BD and 150mg BD groups than with warfarin but GI bleeding was more frequent in the 150mg BD dabigatran group as compared to warfarin (1.51% versus 1.02% per year; RR 1.50; 1.19-1.89; P<0.001; table 3).
Rivaroxaban – ROCKET-AF trial

Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism in both the per-protocol and the intention-to-treat 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.25

The primary analysis was per protocol as opposed to the preferred intention to treat (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 non-inferiority). In the intention-to-treat analysis, and comparative to other published studies, 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 non-inferiority; P=0.12 for superiority).25

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).26 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.25

The definition of major bleeding in ROCKET-AF was: clinically overt bleeding associated with a reduction in haemoglobin of at least 2.0 g/dL and/or blood transfusion of two or more units of blood, fatal bleeding, critical anatomic site bleeding or permanent disability.25
Discussion

In reviewing clinical evidence for the NOACs 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 intention to treat) 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 and ARISTOTLE trials which were both double blind trials.
- ROCKET-AF recruited higher risk patients with over 85% of their patient population having a CHADS\textsubscript{2} score of ≥3 (compared with approximately 30% for RE-LY and ARISTOTLE).
- Variations exist between individual trials in patient follow-up and endpoint determination which may affect final analysis. Comparisons between the pivotal NOAC 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 6.1.4

In order to appropriately review indirect comparisons of the licensed NOAC 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 three clinical trials reviewed in this section are ARISTOTLE (apixaban), RE-LY (dabigatran) and ROCKET-AF (rivaroxaban).\textsuperscript{23-25}
5.1.2 Patient selection in individual trials

In reviewing the main pivotal trials (ARISOTLE, RE-LY, 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 three clinical trials:

- Age categories
- Stroke Risk (CHADS2 score)
- Renal Function

**Age categories**

As the majority of patients being treated with NOACs for AF will be elderly and given the reduction in renal elimination of drugs in the elderly and dose adjustments recommended for some NOAC therapies due to age, it is appropriate to consider the age of participants in the clinical trials as shown in table 4.²

**Table 4: Age categories in AF clinical trials**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban Trial Data (ARISTOTLE)</th>
<th>Dabigatran Trial Data (RE-LY)</th>
<th>Rivaroxaban Trial Data (ROCKET-AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Category</strong></td>
<td>&lt; 80 years</td>
<td>80-89 years</td>
<td>90+ years</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>15,765</td>
<td>2352</td>
<td>84</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>86.62</td>
<td>12.92</td>
<td>0.46</td>
</tr>
</tbody>
</table>

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 and approximately 18.3% for ROCKET-AF.²³⁻²⁵
GMS prescribing database analysis of new initiations of NOAC 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). It appears from this analysis that real world data may see a larger cohort of patients in the older categories being treated with NOAC therapies as compared with the pivotal clinical trials and careful monitoring of patient outcomes will be an important part of follow up.

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. 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, including in the group at least 80 years of age. In those aged ≥ 80 years where 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.

Age of ≥80 years is included in the criteria (which also includes serum creatinine > 133micromol/L and weight ≤60kg) for lower dose (i.e. 2.5mg twice daily) selection in patients.
**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. 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 (110mg) or higher risk (150mg) of major bleeding in patients ≥75 years. In patients with atrial fibrillation at risk for 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. 110mg twice daily) with criteria dividing between >80 years or >75 years with increased bleeding risk. Other considerations include renal impairment and bleeding risk, GORD/gastritis/oesophagitis and concomitant use of verapamil.

**Rivaroxaban**

The ROCKET-AF trial showed no interaction in terms of the primary outcome (in the intention to treat (ITT) population) of the composite of stroke (ischaemic or haemorrhagic) and systemic embolism between treatment and age (<75 years versus ≥75 years) nor for major and non-major clinically relevant bleeding while on treatment.

Patient age is not considered a criterion for reduced dose with rivaroxaban.
**Stroke Risk (CHADS₂ score)**

The CHADS₂ score is a patient specific score for stroke risk with atrial fibrillation. 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 had a higher proportion of patients with CHADS₂ scores of ≥3 compared to RE-LY and ARISTOTLE as shown in table 5 and had a reduced proportion of lower risk patients (CHADS₂ 0-2).

<table>
<thead>
<tr>
<th>CHADS₂ scores</th>
<th>ARISTOTLE (Apixaban)</th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>34%</td>
<td>31.9%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35.8%</td>
<td>35.63%</td>
<td>13.05%</td>
</tr>
<tr>
<td>3</td>
<td>(≥3) 30.2%</td>
<td>(≥3) 32.47%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>(≥3) 86.95%</td>
</tr>
<tr>
<td>5</td>
<td>1.95%</td>
<td>12.75%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Renal Function**

All NOACs have a degree of renal clearance with dabigatran demonstrating the highest proportion with 80% renal clearance. Rivaroxaban has a 33% renal clearance and apixaban has a 27% renal clearance.²² 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.

- **RE-LY** excluded patients with a creatinine clearance ≤30ml/min
- **ROCKET-AF** excluded patients with a creatinine clearance <30ml/min
- **ARISTOTLE** excluded patients with a creatinine clearance <25ml/min or serum creatinine>2.5mg/dL (220µmol/L)
**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. A further study by Halvorsen et al. (2014) showed that this also applies for the subgroup of patients ≥75 years. This review found that apixaban was superior to warfarin across the range of estimated GFR, with no significant interaction between the treatment effect and the level of renal dysfunction.

**Dabigatran**

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

**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 15mg (reduced dose) for creatinine clearance between 30-49ml/min were consistent with the overall trial results.

**Discussion**

A number of observations were made by Karsten et al. in a clinical evidence synopsis of trial reviews with factor Xa inhibitors versus warfarin for preventing stroke and thromboembolism in patients with atrial fibrillation. This review estimated 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 creatinine clearance <30ml/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.
5.1.3 Clinical trial parameters

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

1. Primary efficacy endpoint and safety end-points
2. Time in therapeutic range for trials
3. Number of patients receiving lower/reduced dose in clinical trials for AF
4. Discontinuation rates versus warfarin

1) Primary efficacy endpoint and safety end-points

All three trials (ARISTOTLE, RE-LY and ROCKET-AF) use “all stroke or systemic embolism” as a primary efficacy endpoint. The primary safety end-point for RE-LY and ARISTOTLE was major bleeding by international society on thrombosis and haemostasis (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. “Life-threatening bleeding” was not reported in ARISTOTLE. The combined endpoint of “ischaemic or uncertain type of stroke” was not reported for ROCKET-AF where “ischaemic stroke” alone was reported.

RE-LY based all efficacy and safety analyses on the intention to treat (ITT) principle. ARISTOTLE published efficacy data based on Intention to treat (ITT) population but safety analyses on the ‘on treatment’ (OT) safety population. Analysis of efficacy in ROCKET-AF was carried out on a per protocol (PP) population to demonstrate non-inferiority with superiority and safety analyses carried out on OT population. Efficacy analyses were also conducted on the ITT population and this data is generally used for indirect comparison between trials.

2) Time in therapeutic range for NVAF (NOAC versus warfarin) clinical trials

The pivotal clinical trials for the NOACs compared each agent to warfarin therapy. As previously mentioned warfarin therapy is guided by monitoring of a patient’s international normalised ratio (INR) and reviewing the percentage of time a patient
remains within this defined range, their ‘time in therapeutic range’ (TTR). Optimal warfarin therapy is considered when the TTR is > 70%. The pivotal clinical trials for stroke prevention in NVAF all obtained mean TTRs of less than 65% (table 6).

Table 6: Time in Therapeutic Range (TTR) for warfarin arm in pivotal AF clinical trials

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE (Apixaban)</th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR (time in therapeutic range) for warfarin</td>
<td>Mean: 62% Median: 66% (interquartile range 52.4-76.5%)</td>
<td>64% mean</td>
<td>Mean: 55% Median: 58% (interquartile range 43-71%)</td>
</tr>
</tbody>
</table>

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.

As individual TTR results are not relevant for non-vitamin K antagonist anticoagulants reviews of warfarin TTR interactions with NOACs 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 cTTR values.

Apixaban

In the ARISTOTLE trial a centre average TTR (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 concludes that apixaban remains more effective and safer than warfarin across a broad range of warfarin management levels. 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≥71.3%.  

**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 centre TTR (cTTR) when comparing dabigatran 150mg and warfarin. 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 110mg irrespective of the cTTR in this group. Dabigatran 150mg 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.

**Rivaroxaban**

Piccini et al. (2014), ROCKET AF investigators, reviewed the relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin based on cTTR. Mean individual TTR (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.

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

It is important to consider the evidence from clinical trials for lower doses of NOACs 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 trial, in contrast to the ARISTOTLE and ROCKET-AF trials, obtained trial data for full cohorts of both doses of dabigatran (150mg and 110mg) versus warfarin with over 6,000 patients in each category. ARISTOTLE and ROCKET-AF trials used reduced
doses of apixaban 2.5mg twice daily and rivaroxaban 15mg once daily respectively in a predefined cohort of higher risk patients (table 7).23,25

Table 7: Numbers of patients (and percentage) on reduced dose therapy in trials

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE (Apixaban)</th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular dose:</td>
<td>Regular dose:</td>
<td>Regular dose:</td>
</tr>
<tr>
<td></td>
<td>5mg BD</td>
<td>150mg BD</td>
<td>20mg OD</td>
</tr>
<tr>
<td></td>
<td>Reduced dose:</td>
<td>Reduced dose:</td>
<td>Reduced dose:</td>
</tr>
<tr>
<td></td>
<td>2.5mg BD</td>
<td>110mg BD</td>
<td>15mg OD</td>
</tr>
<tr>
<td>Total numbers on NOAC</td>
<td>9120</td>
<td>12091</td>
<td>7111</td>
</tr>
<tr>
<td>Regular dose</td>
<td>~ 8692</td>
<td>~ 6076</td>
<td>~ 5637</td>
</tr>
<tr>
<td>Reduced dose</td>
<td>428 (4.7%)</td>
<td>6015 (50%)</td>
<td>1474 (20.7%)</td>
</tr>
<tr>
<td>Numbers on warfarin</td>
<td>9081</td>
<td>6022</td>
<td>7116</td>
</tr>
</tbody>
</table>

**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.29 Less than 5% of all patients receiving apixaban in the ARISTOTLE trial were treated with the lower dose of 2.5mg 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 2.5mg dose and approximately 74% of these patients were 80 years or older.

**Rivaroxaban**

Rivaroxaban 15mg once daily was given to patients with creatinine clearance of 30-49ml/min at enrolment and there was no dose adjustments post-baseline for changing CrCl (however those with CrCl<30ml/min were removed from the study).32 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 1474 patients (20.7%) were treated with the 15mg dose in ROCKET-AF trial with a corresponding 1476 patients treated with warfarin (with CrCl 30-49ml/min). Some 5637 patients were treated with rivaroxaban 20mg once daily
(CrCl ≥ 50ml/min). GMS prescribing database analysis indicates similar findings with approximately 30% of patients analysed receiving the 15mg 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 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. 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. San TR et al. 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% or the warfarin group compared with 11.8% and 11.3% for dabigatran 110mg and 150mg respectively.

In ROCKET-AF 23.9% of patients on rivaroxaban and 22.4% of patients on warfarin discontinued treatment during the study.
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 NOAC 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 NOACs. Network meta-analysis requires that studies are sufficiently similar in order to effectively pool the results. In reviewing the NOAC 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 CHADS\textsubscript{2} 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.\textsuperscript{41}

Publications were obtained in the course of database searches: Medline and CINAHL (2010-2014) and the search was limited to analyses of the pivotal clinical trials for stroke prevention in atrial fibrillation including subgroup analyses.

Lip GY (2012) carried out an indirect comparison reviewing the 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 intention-to-treat (ITT) analyses.\textsuperscript{42} 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 CHADS\textsubscript{2} 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.

No significant difference for apixaban versus dabigatran (both doses) or rivaroxaban, or rivaroxaban versus dabigatran 110mg BD in preventing stroke and systemic embolism was found. No significant differences were reported between individual NOACs for the ischaemic stroke endpoint. The review showed a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran 150mg BD 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 150mg BD (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 110mg BD for major bleeding (HR 0.86 95\% CI 0.7-1.06). Dabigatran 110mg BD 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 150mg BD 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.
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 non-valvular AF and among sub-populations. This review included 16 individual RCTs with five large multicentre trials which included: ARISTOTLE, RE-LY and ROCKET-AF as three of these. Dabigatran 150mg BD 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 and dabigatran 110mg showed reductions in major bleeding compared with warfarin. Apixaban and dabigatran 110mg had fewer major bleeding events versus dabigatran 150mg and rivaroxaban. No difference was seen in major bleeding between warfarin and dabigatran 150mg or rivaroxaban. The review group noted that results between individual treatments of NOACs should be interpreted with caution due to limitations associated with using a fixed-effects model.

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 NOACs or warfarin where both efficacy and safety outcomes were reported for trials including RE-LY, ROCKET-AF and ARISTOTLE. The overall finding was that NOACs 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). NOACs 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 NOACs when the centre-based TTR was less than 66% than when it was 66% or greater. It was also reported that low-dose NOACs 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.
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 atrial fibrillation in 2013. This review also assessed the impact of age, CHADS\textsubscript{2} score and time spent in therapeutic range (TTR) on the clinical safety and efficacy of antithrombotic agents. The review found that absolute risk differences (ARD) for the NOACs 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 5mg twice daily and dabigatran 150mg 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 5mg twice daily and dabigatran 110mg twice daily were associated with statistically significantly lower rates of major bleeding compared with warfarin. Dabigatran 150mg twice daily and rivaroxaban 20mg once daily were associated with statistically significantly higher rates of major bleeding compared with apixaban 5mg twice daily and dabigatran 110mg twice daily.

Subgroup analysis of CHADS\textsubscript{2} scores showed no statistically significant differences between warfarin and each NOAC for SSE in CHADS\textsubscript{2} <2 while apixaban 5mg twice daily and dabigatran 110mg twice daily were associated with lower rates of major bleeding compared to warfarin. For higher risk patients (CHADS\textsubscript{2} \geq 2) apixaban 5mg twice daily and dabigatran 150mg twice daily were associated with lower risks of SSE compared with warfarin. Apixaban 5mg twice daily was associated with a statistically significant lower rate of major bleeding compared with warfarin, dabigatran 150mg twice daily and rivaroxaban 20mg once daily.

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 NOACs are available.
This report concluded that, based on the available evidence and taking into account the limitations of the analysis, that dabigatran 150mg twice daily may be a suitable choice for patients with moderate risk of stroke (CHADS$_2$ = 1) or who are relatively young (≤70 years) or who cannot be adequately controlled on warfarin (TTR<66%) and that “apixaban 5mg twice daily would likely be the optimal NOAC in patients with a higher risk of stroke (CHADS$_2$≥2) or are relatively old (≥80 years old)”\textsuperscript{44}.

**Discussion**

Following a comprehensive review of the literature, the MMP has concluded that the clinical efficacy of individual NOACs is generally comparable with some differences for certain sub-groups. Therefore, it is difficult to recommend a particular NOAC 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.

<table>
<thead>
<tr>
<th>Favoured OAC - Clinical Efficacy and Safety: WARFARIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>(when TTR is maintained &gt;70%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Favoured NOAC - Clinical Efficacy data: No preference of NOAC</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Favoured NOAC - Clinical safety data (major bleeding): Apixaban</th>
</tr>
</thead>
</table>
5.1.5 Observational studies

A number of real-world studies have been published and are on-going in the review of NOACs 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 150mg and 75mg BD. The majority (83%) of patients on dabigatran in the Medicare study were treated with the 150mg BD dose.

A recently published observational safety surveillance study 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 CHADS 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. 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.
5.2 Adverse Effects
The most commonly reported adverse effect with NOAC therapy is bleeding. All oral anticoagulant use carries a risk of bleeding (including gastrointestinal and intracranial). See table 8 for the common adverse effects as listed in the individual SmPCs for NOACs. Overall, the NOACs are broadly similar in terms of adverse effects though these effects may occur to a lesser or greater extent depending on the particular NOAC. There is evidence to suggest that dabigatran and rivaroxaban are associated with an increased risk of gastrointestinal haemorrhage as compared to warfarin whereas apixaban has a similar risk to warfarin.39,43

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common adverse effects</td>
<td>Haemorrhage including eye, gastrointestinal and rectal haemorrhage, haematuria, contusion, epistaxis, haematoma</td>
<td>Anaemia, epistaxis, gastrointestinal haemorrhage, dyspepsia, skin and genito-urological haemorrhage</td>
<td>Anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, gastrointestinal haemorrhage, dyspepsia, subcutaneous and urogenital tract haemorrhage</td>
</tr>
</tbody>
</table>

Haemorrhagic complications at various sites are the predominant adverse effects of all NOAC therapies. There was a non-significant trend to a higher incidence of myocardial infarction with both doses of dabigatran compared with warfarin in the RE-LY study. Subsequent real-world studies did not show an increased risk of myocardial infarction for dabigatran versus warfarin.45 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.47 One meta-analysis suggests that apixaban was associated with a significantly lower incidence of myocardial infarction compared to dabigatran 150mg BD.42 Similarly, a lower rate of myocardial infarction with rivaroxaban as compared with dabigatran has been reported.48
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 110mg and 150mg groups and 5.8% of warfarin patients reporting the adverse event. There was also an increase in the rate of gastrointestinal bleeding with dabigatran 150mg 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.24

Treatment with anticoagulation 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 patients bleeding risk is significantly increased or significant bleeding has occurred. Table 9 highlights the percentage of patients discontinuing the study drug in the pivotal NVAF clinical trials.23,24,25 Of the patients who discontinued treatment, adverse events were responsible 30-40% of the time.

**Table 9: Discontinuation of study drug in clinical trials**

<table>
<thead>
<tr>
<th>Discontinued study drug early</th>
<th>Apixaban (N=9088)</th>
<th>Dabigatran 110mg (N=6015)</th>
<th>Dabigatran 150mg (N=6076)</th>
<th>Rivaroxaban (N=7111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discontinued</td>
<td>2310 (25.4%)</td>
<td>1161 (21%)</td>
<td>935 (16%)</td>
<td>1693 (23.9%)</td>
</tr>
<tr>
<td>% who discontinued due to adverse event</td>
<td>679 (30%)</td>
<td>355 (31%)</td>
<td>376 (40%)</td>
<td>594 (35%)</td>
</tr>
</tbody>
</table>

The trial data for the NOACs highlights that premature discontinuation of any oral anticoagulant increases the risk of thrombotic events and 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 with the new oral anticoagulants. 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 NOACs all exhibit a rapid onset of action and have relatively short half-lives when compared with warfarin. While onset and duration of the three agents is relatively consistent the modes of metabolism and elimination vary (see table 10). The direct thrombin inhibitor, dabigatran, is not metabolised by the CYP450 enzymes but both factor Xa inhibitors (apixaban and rivaroxaban) are metabolised by CYP3A4 and drug interactions may occur if they are co-administered with inducers or inhibitors of CYP3A4. Apixaban, dabigatran and rivaroxaban are all substrates for the efflux transporter P-glycoprotein (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 NOACs and may increase the risk of thrombosis or bleeding respectively (see table 11).
Table 10: Pharmacokinetic drug characteristics

<table>
<thead>
<tr>
<th>Drug Characteristics</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Oral direct factor Xa inhibitor</td>
<td>Oral direct thrombin inhibitor</td>
<td>Oral direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Bioavailability %</td>
<td>50%</td>
<td>Approximately 6.5%</td>
<td>60-80% (66% for 20mg dose fasting; increased to over 90% with food)</td>
</tr>
<tr>
<td>Time to peak levels (hours)</td>
<td>3-4 hours</td>
<td>0.5-2 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>Approximately 12 hours</td>
<td>12-14 hours</td>
<td>5-9 hours in younger patients 11-13 hours if older age</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4/3A5 (major pathway)</td>
<td>Conjugation, eliminated primarily unchanged in the urine</td>
<td>CYP3A4 (major pathway), CYP2J2, oxidative degradation and hydrolysis</td>
</tr>
<tr>
<td>Standard dose</td>
<td>5mg BD</td>
<td>150mg BD</td>
<td>20mg OD</td>
</tr>
<tr>
<td>Dose in renal impairment</td>
<td>2.5mg BD (and age/ weight considerations)</td>
<td>150mg BD or 110mg BD if high bleeding risk (or age considerations, 75-80 yrs. or &gt;80yrs)</td>
<td>15mg OD</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Do not open capsules – must be swallowed whole</td>
<td>15mg and 20mg must be taken with food</td>
<td>66% renal and faecal route; 36% unchanged eliminated via renal route</td>
</tr>
<tr>
<td>Excretion</td>
<td>27% renal; 25% faecal</td>
<td>85% renal</td>
<td>66% renal and faecal route; 36% unchanged eliminated via renal route</td>
</tr>
</tbody>
</table>
Table 11: Pharmacokinetic characteristics of NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Cytochrome P450 enzymes</th>
<th>Effect on P-glycoprotein</th>
<th>Onset of action</th>
<th>Elimination half-life (hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Partially metabolised by Cytochrome P450 3A4</td>
<td>Substrate for P-gp so interactions with inhibitors and inducers of P-gp</td>
<td>3-4 hours</td>
<td>Approximately 12 hours</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Not metabolised by Cytochrome P450 enzymes</td>
<td>Substrate for P-gp so interactions with inhibitors and inducers of P-gp</td>
<td>0.5-2 hours</td>
<td>12-14 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Partially metabolised by Cytochrome P450 3A4</td>
<td>Substrate for P-gp so interactions with inhibitors and inducers of P-gp</td>
<td>2-4 hours</td>
<td>5-12 hours</td>
</tr>
</tbody>
</table>

**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. 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. Dabigatran prolongs the thrombin clotting time (TT), ecarin clotting time (ECT) and the aPTT.

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. Prothrombin time is influenced by rivaroxaban and aPTT and HepTest are also prolonged.

For all NOACs 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 NOACs is not required.
Pharmacodynamic drug interactions

Factor Xa inhibitors (apixaban and rivaroxaban) have a common mechanism of action and pharmacodynamic interactions with other medications are likely to occur with all factor Xa inhibitors e.g. caution with other medications which will increase risk of bleeding (NSAIDS, anti-platelet drugs, 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). 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.

Pharmacokinetic drug interactions

Apixaban, dabigatran and rivaroxaban are all substrates for the efflux transporter P-glycoprotein (P-gp). Concomitant use of a medication that inhibits or induces P-gp may have an effect on plasma levels of the NOACs and care should be exercised. The factor Xa inhibitors apixaban and rivaroxaban are both partially metabolised by cytochrome P450 enzyme system and interactions may occur with co-administration of medications which induce or inhibit the Cytochrome P450 3A4 enzyme (tables 11-14).

Table 12: Apixaban drug interactions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Drug group</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated</td>
<td>Other anticoagulants (unless switching, then refer to individual SmPC)</td>
<td>Increased risk of bleeding, pharmacodynamic interaction</td>
</tr>
<tr>
<td>Avoid Concurrent Use</td>
<td>Ketoconazole, itraconazole, posaconazole, voriconazole, anti-retrovirals</td>
<td>Strong CYP3A4 and P-gp inhibitors - increased concentration of apixaban, increased bleeding risk</td>
</tr>
<tr>
<td>Caution</td>
<td>Carbamazepine, phenytoin, phenobarbitone, rifampicin, St Johns Wort</td>
<td>CYP3A4 and P-gp inducers-reduced apixaban concentration</td>
</tr>
<tr>
<td>Caution</td>
<td>NSAIDS including aspirin, platelet aggregation inhibitors</td>
<td>Increased bleeding risk, pharmacodynamic interaction</td>
</tr>
</tbody>
</table>
Table 13: Dabigatran drug interactions

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

Table 14: Rivaroxaban drug interactions

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

Favoured NOAC – Drug interactions: No preference

5.4 Safety
The use of anticoagulants is known to increase a patient’s risk of both significant and non-significant bleeding.\(^1\) Reduced renal function can increase bleeding risk and dose reduction is recommended for all NOAC therapies in patients with significant renal dysfunction. Patients should have renal function tests carried out at regular intervals. The 2012 update on the ESC guidelines for the management of atrial
fibrillation recommends annual renal function measurements in patients with normal (CrCl ≥ 80ml/min) or mild (50-79ml/min) renal dysfunction. For patients with moderate renal dysfunction (CrCl 30-49ml/min) renal function should be assessed 2-3 times per year.\textsuperscript{13} 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 relevant SmPCs for individual agents or access appropriate decision aids to ensure appropriate dose choice.\textsuperscript{9-11, 19}

It must also be noted that in all the studies of new oral anticoagulants 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.\textsuperscript{51} 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.\textsuperscript{26}

Over the last number of years the Health Products Regulatory Authority (HPRA) (formerly the IMB), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA) and the Medicines Management Programme (MMP) have issued warnings about the safety of anticoagulants including NOACs. While undertaking this review, we remained cognisant of these safety alerts.

**Regulatory agency alerts**

- **IMB Pradaxa\textsuperscript{®} (dabigatran etexilate) (Notice for MIMS December 2011):**
  
  Recommendations for assessment of renal function and monitoring in the elderly


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

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

• **MHRA Drug Safety Update (October 2013)**
  New oral anticoagulants apixaban, dabigatran and rivaroxaban: risk of serious haemorrhage – clarified contraindications apply to all three medicines

• **HPRA Drug Safety Newsletter (November 2014)**
  Oral anticoagulants – Update on National Monitoring Experience

**Special interest group alerts**

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

• **NOAC safety alert (IMB 9th September 2013):**
  The new oral anticoagulants Eliquis®, Pradaxa®, Xarelto®: Beware of the risk factors for bleeding, pay attention to posology, contraindications, and warnings and precautions for use to reduce the risk of bleeding

• **MMP letter to GPS (5th March 2014):**
  Re: Issues in relation to prescribing safety of New Oral Anticoagulants (NOACs)
5.5 Patient factors

5.5.1 Dosing

There are two standard dosing frequencies for NOACs in the treatment of AF. Apixaban and dabigatran are both administered twice daily while rivaroxaban is given once daily. 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 and this is stated in the EHRA guidelines on atrial fibrillation. 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 increased risk of thrombosis if abrupt discontinuation or missed doses occurs. 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.

A number of analyses looked specifically at the dosing frequency of NOACs and have found conflicting results. One meta-analysis carried out on behalf of Boehringer (twice daily dabigatran) looked at dosing frequency of NOACs and noted that twice daily dosing appears to offer a more balanced risk-benefit profile with respect to stroke prevention and intracranial haemorrhage. The potential for bias in analysis carried out on behalf of a particular product or manufacturer is recognised. Another recently published meta-analysis 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.

It is clear that whether a NOAC with once daily or twice daily dosing is chosen thorough patient education and counselling is 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.

**Favoured OAC – Dosing: Warfarin (once daily and long half-life)**

**Favoured NOAC – Dosing: No preference of NOAC**

### 5.5.2 Administration

There are a number of important administration considerations to take account of in relation to the NOACs (Table 14 and 15).

**Table 15: Administration with food**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration with Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No specific requirements for drug administration and can be taken with or without food.</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Food does not affect the bioavailability but delays the time to peak plasma concentrations by two hours.</td>
</tr>
<tr>
<td>Rivaroxaban (15mg and 20mg)</td>
<td>Food increases the bioavailability of the 15 and 20mg doses from 66% to 80% so they should be taken with food to ensure appropriate drug absorption.</td>
</tr>
</tbody>
</table>

**Table 16: Information on crushing medication**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Information on Crushing Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No specific information in the current SmPC. However evidence suggests that crushing the tablets for administration leads to comparable exposure of apixaban.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Capsules must not be opened and must be swallowed whole. Formulated in hydroxyl-propyl-methyl-cellulose (HPMC) capsules containing pellets of dabigatran coated with a tartaric acid core as low pH is required to enhance the absorption of dabigatran.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Can be crushed and mixed with water or apple puree immediately prior to use and dosing with 15mg or 20mg must be followed immediately by food. 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.</td>
</tr>
</tbody>
</table>

**Timing of doses**

- All NOACs 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.
**Considerations in relation to administration with other medications**

- For concomitant use of verapamil and dabigatran the lower dose of 110mg dabigatran twice daily should be used and both should be taken at the same time each day.  

- Intestinal absorption of dabigatran is pH dependent and may be reduced in patients taking proton pump inhibitors - 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.

- Apixaban and rivaroxaban do not have any specific considerations in relation to administration with other medications except for documented interacting medications.

**5.5.3 Storage considerations**

- Apixaban and rivaroxaban do not have any special storage conditions

- Dabigatran capsules should be stored in their original packaging to protect against moisture and are therefore not suitable for blister packaging

**5.5.4 Reversibility**

There is currently no antidote or reversal agent for any of the NOACs. The availability of a reversal agent will be an important safety development for NOAC use and some early analysis of ongoing trials is available.
A study of the investigational Factor Xa inhibitor antidote andexanet alfa (apixaban, rivaroxaban or enoxaparin) was initiated in January 2015 to support its approval by the FDA under an Accelerated Approval pathway.\textsuperscript{57} Full results from the Phase III ANNEXA-R study demonstrated that andexanet alfa rapidly and significantly reversed the anticoagulant effect of the factor Xa inhibitor rivaroxaban shown as a reduction in anti-Factor Xa activity. A confirmatory study in patients receiving apixaban, rivaroxaban, edoxaban or enoxaparin who present with an acute major bleed is also ongoing.

Idarucizumab, a specific reversal agent for dabigatran is currently in clinical development and a phase III clinical trial in patients (REVERSE-AD) is in progress. REVERSE-AD is designed to evaluate idarucizumab in patients treated with dabigatran who are in need of emergency intervention, or experience an uncontrolled or life-threatening bleeding event. Idarucizumab is a humanised mouse monoclonal antibody fragment directed against 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.\textsuperscript{58} In March 2015, application for marketing authorisation of idarucizumab was submitted to the EMA and U.S. Food and Drug Administration (FDA). An interim analysis of the ongoing REVERSE-AD study was published online in the New England Journal of Medicine in June 2015.\textsuperscript{59} This analysis for 90 patients reported that the median maximum percentage reversal was 100% in 68 patients with an elevated dilute thrombin time and 81 patients with an elevated ecarin clotting time at baseline. The authors concluded that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes with no signal of a pro-coagulant effect and no safety concerns were identified.

### 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 NOACs were compared for treatment of atrial fibrillation.
The drug acquisition cost for warfarin (at a dose of 6mg per day by either 3mg x 2 or 5mg + 1mg) is €0.11 cent or €0.20 cent if 6 x 1mg tablets were used.

### Table 17: Cost of NOAC therapies per dose based on reimbursed price

<table>
<thead>
<tr>
<th></th>
<th>Apixaban 5mg</th>
<th>Apixaban 2.5mg</th>
<th>Dabigatran 150mg</th>
<th>Dabigatran 110mg</th>
<th>Rivaroxaban 20mg</th>
<th>Rivaroxaban 15mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Per day</td>
<td>€2.54</td>
<td>€2.54</td>
<td>€2.54</td>
<td>€2.54</td>
<td>€2.29</td>
<td>€2.29</td>
</tr>
</tbody>
</table>

*Based on reimbursed price on [www.PCRS.ie](http://www.PCRS.ie) 14/04/15

Licenses were granted for these medicines since 2008 (from 2011 for AF indication) and as such all products are currently under patent protection.

**Pharmacoeconomic Evaluations in Ireland**

The National Centre for Pharmacoeconomics reviewed the three NOACs for cost effectiveness for the indication of stroke prevention in NVAF. In August 2011 the NCPE recommended reimbursement of dabigatran only at a price significantly below €2.80 per day to ensure value for money for the HSE. The current price per day for dabigatran is €2.54.

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 non-valvular AF with one or more risk factors. 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 non-valvular AF. The evaluation found that apixaban 5mg BD could be considered cost effective for the prevention of stroke and systemic embolism and is currently reimbursed at a price of €2.54 per day.
Cost Summary

Significantly increased costs for anticoagulant therapy should correspond to significantly better clinical outcomes for more patients. Of the three NOACs currently available, rivaroxaban has the lowest acquisition cost (approximately €0.24 cheaper per day). The ROCKET-AF trial was a non-inferiority trial and superiority of rivaroxaban over warfarin (TTR 55%) was not demonstrated in clinical trials.

Favoured OAC – Cost: Warfarin

Favoured NOAC – Cost: Rivaroxaban

5.7 National Prescribing Trends

The MMP recognises that clinical experience is an important factor for prescribers when choosing a medication. In the case of the NOAC drugs, all three products under review came to market for stroke prevention in Atrial Fibrillation during the two years 2011 to 2013. While bearing in mind that it may take some time for prescribing trends to stabilise, the MMP performed an analysis of the PCRS data in order to provide an indication of the usage trends of the NOACs in Ireland to date.

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 Primary Care Reimbursement Service, 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, DP data is only available for patients whose monthly prescription drug expenditure exceeded the threshold beyond which the PCRS provides reimbursement (this threshold stood at €144 per month as of January 2013 onwards(1)). As such, the DP scheme is a less reliable 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 NOACs under the community drug schemes
PCRS data from January 2010 to October 2014 were analysed in order to determine new oral anticoagulant prescribing trends. Following the extension of the market authorisation of all three NOACs to include the indication of stroke prevention in NVAF, an increase in NOAC dispensing claims was observed. As of October 2014, rivaroxaban was the NOAC most frequently reimbursed under the community drug schemes.

Figure 1: Number of patients in receipt of each oral anticoagulant. GMS, DP and LTI drug scheme data, January 2013 - October 2014 inclusive.
Figure 2 presents data for the period January 2013 to October 2014 inclusive specifically for the GMS scheme this scheme being the subject of further analyses described below. Patients received apixaban from January 2013 onwards.

**Figure 2: Number of patients in receipt of each oral anticoagulant. GMS scheme data, January 2013 - October 2014 inclusive.**
The emergence of NOACs has resulted in a fast moving and changing oral anticoagulation market in recent years, which is likely to continue to adjust with time and as further clinical evidence becomes available.

5.7.3 Prescribing patterns in new initiators of oral anticoagulants post January 2013

In order to consider patterns of prescribing of individual NOACs, particularly within the non-valvular atrial fibrillation (NVAF) indication, new initiators of NOACs were identified from the GMS data and patient characteristics and NOAC usage patterns were examined.

Analysis details

All patients who initiated a NOAC from January 2013 onwards under the GMS scheme were identified. Patients who did not have GMS scheme eligibility in 2012, or who received a NOAC in 2012, were excluded. January 2013 was chosen as the starting point for the analysis as no patients were dispensed apixaban under the GMS scheme prior to this time. As the present document focuses on the prescribing of NOACs for stroke prevention in patients with NVAF, the analysis excluded patients with fewer than 3 months of NOAC dispensing records. At the time of the analysis, data was available for the months up to and including June 2014; as such, only patients who initiated a NOAC between January 2013 and March 2014 inclusive were analysed to allow for a minimum of 3 months of dispensing records for all patients.

Characteristics of patients initiated on each NOAC

The total number of first-time initiators of NOACs between January 2013 and March 2014 inclusive amounted to 8,399 patients. The majority of these patients initiated on rivaroxaban (n=5,288, 63%). Just under one third of patients commenced therapy with dabigatran (n=2,642, approximately 31%) while approximately 6% of patients commenced therapy with the newest agent, apixaban (n=469). Among the 8,399 patients, switching between different NOACs was observed between initiation and the remainder of the follow-up time. The drug to which most patients switched was rivaroxaban; 7.6% of patients who initiated therapy with either dabigatran or
apixaban switched to rivaroxaban. Fewer patients switched to the other two drugs; 1.7% of patients initiated on a different NOAC switched to apixaban while just 1.4% of patients initiated on rivaroxaban/apixaban switched to dabigatran.

Age and gender characteristics for patients initiated on each drug are presented in Table 18. A higher proportion of patients who initiated NOAC therapy with apixaban were female (53% versus 47%). In contrast, the majority of dabigatran initiators were male (56% versus 44%). There was a higher proportion of patients in the 80+ age category in apixaban initiators (45% initiators aged 80 or above) than for dabigatran or rivaroxaban.

Table 18: Gender and age of patients initiated on NOACs - GMS scheme cohort of patients newly initiated on NOACs between January 2013 and March 2014 inclusive.

<table>
<thead>
<tr>
<th>N initiators</th>
<th>Dabigatran patients</th>
<th>Rivaroxaban patients</th>
<th>Apixaban patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>1,468 (~55.6%)</td>
<td>2,634 (~49.8%)</td>
<td>219 (~46.7%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1,174 (~44.4%)</td>
<td>2,654 (~50.2%)</td>
<td>250 (~53.3%)</td>
</tr>
<tr>
<td>Age &lt;80 years (%)</td>
<td>1,723 (~65.2%)</td>
<td>3,307 (~62.5%)</td>
<td>256 (~54.6%)</td>
</tr>
<tr>
<td>80+ years (%)</td>
<td>919 (~34.8%)</td>
<td>1,981 (~37.5%)</td>
<td>213 (~45.4%)</td>
</tr>
<tr>
<td>Mean age, years (S.D.)</td>
<td>75.5 (9.4)</td>
<td>75.0 (11.3)</td>
<td>77.5 (8.6)</td>
</tr>
</tbody>
</table>

NOAC doses received

Table 18 details statistics for the doses received by patients who initiated a NOAC, from January 2013 onwards. Dispensing claims for each patient were analysed where at least three pharmacy claims for the drug in question occurred per patient. Doses received were determined for pharmacy claims which represented a full month’s supply of treatment. Doses were inferred from the GMS data for all pharmacy claims.
and the highest and lowest daily dosage received by each patient was recorded. The maximum dose received by patients is presented in table 19.

### Table 19: Highest doses received in GMS patients who had at least three pharmacy claims for the drug in question

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran patients</th>
<th>Rivaroxaban patients</th>
<th>Apixaban patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75mg bd</td>
<td>36</td>
<td>1.4</td>
<td>10mg od</td>
</tr>
<tr>
<td>110mg bd</td>
<td>1,543</td>
<td>60.8</td>
<td>15mg od</td>
</tr>
<tr>
<td>150mg bd</td>
<td>959</td>
<td>37.8</td>
<td>20mg od</td>
</tr>
<tr>
<td>other/missing*</td>
<td>48</td>
<td></td>
<td>other/missing</td>
</tr>
<tr>
<td><strong>Age &lt;80</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75mg bd</td>
<td>11</td>
<td>0.7</td>
<td>10mg od</td>
</tr>
<tr>
<td>110mg bd</td>
<td>653</td>
<td>42.5</td>
<td>15mg od</td>
</tr>
<tr>
<td>150mg bd</td>
<td>873</td>
<td>56.8</td>
<td>20mg od</td>
</tr>
<tr>
<td>other/missing</td>
<td>37</td>
<td></td>
<td>other/missing</td>
</tr>
<tr>
<td><strong>Age 80+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75mg bd</td>
<td>25</td>
<td>2.5</td>
<td>10mg od</td>
</tr>
<tr>
<td>110mg bd</td>
<td>890</td>
<td>88.9</td>
<td>15mg od</td>
</tr>
<tr>
<td>150mg bd</td>
<td>86</td>
<td>8.6</td>
<td>20mg od</td>
</tr>
<tr>
<td>other/missing</td>
<td>11</td>
<td></td>
<td>other/missing</td>
</tr>
</tbody>
</table>

* ‘Other/missing’ values reflect patients whose doses were not calculated due to the quantity supplied falling outside that which would represent a single full month’s supply.

### Dabigatran

A large proportion of patients receiving dabigatran were dispensed a dose of 110mg twice daily (>60% overall dabigatran patients) as opposed to the standard dose of 150mg twice daily. The 110mg twice daily dose is specifically recommended within the NVAF indication for patients over the age of 80 or where there is a high bleeding risk in patients with renal impairment (CrCl 30ml/min – 50ml/min). It is also recommended in patients with gastroesophageal reflux disease, patients receiving concomitant verapamil, or in other patients at increased risk of bleeding. Over 40% of patients under the age of 80 received 110mg twice daily while approximately 90% of patients aged 80 or above received this dose.
**Rivaroxaban**

In patients receiving rivaroxaban, 62% overall received the standard NVAF stroke prevention dose (20mg once daily) as the maximal dose received during their treatment. The 15mg rivaroxaban dose is recommended in patients with moderate renal impairment. Among patients under the age of 80, 20% received this as their maximal dose. In patients over the age of 80, just fewer than 50% of patients received 15mg once daily as their maximal dose.

Among patients receiving rivaroxaban for at least three pharmacy claim months, the data would suggest that a maximal dose of 10mg once daily appeared to have been received by a significant number of patients in this cohort (6.5%) during the time period examined in this analysis (January 2013-March 2014). As the information presented is derived from pharmacy claims data, as opposed to prescribers’ records, it is possible that the doses captured during the analysis do not necessarily reflect the dosage received by the patient in practice. However, the MMP wishes to highlight, as per the product SPC, that the 10mg once daily dose of rivaroxaban is indicated only for thromboprophylaxis post elective total knee replacement or total hip replacement, and is recommended for a duration of 14 days (knee replacement) or 35 days (hip replacement) only.

**Apixaban**

The standard stroke prevention in NVAF dose for apixaban, 5mg twice daily, was received by 48% of patients overall. The lower dose of 2.5mg twice daily is indicated in patients with two of the following: (i) age 80+ years; (ii) body weight ≤60kg; (iii) serum creatinine ≥133 micromole/L. This lower dose was received by 27% patients under the age of 80, and 79% of patients aged 80 or above, as their maximum dosage.

**Favoured OAC – Prescribing trends: Warfarin**

**Favoured NOAC – Prescribing trends: Rivaroxaban**
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 non-valvular atrial fibrillation. In general international recommendations do not choose one NOAC above another and this is often due to the current lack of clear evidence of superiority of both clinical and safety data for one NOAC 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 20 lists a number of American and European guidelines and their recommendations in relation to warfarin and NOAC use for NVAF.
<table>
<thead>
<tr>
<th>Group and Country</th>
<th>Year</th>
<th>Guideline</th>
<th>Recommended Drug (if applicable)</th>
<th>Excerpt/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irish Heart Foundation Ireland</td>
<td>2010</td>
<td>Council for Stroke National Clinical Guidelines and recommendations for the care of people with stroke and TIA</td>
<td>Warfarin (pre NOAC licenses)</td>
<td></td>
</tr>
<tr>
<td>NICE UK</td>
<td>2014</td>
<td>Clinical Guideline (CG 180) Atrial fibrillation: the management of atrial fibrillation</td>
<td>Warfarin or NOAC NOAC should be chosen based on results of patient TTR on warfarin</td>
<td></td>
</tr>
<tr>
<td>Royal College of Physicians UK</td>
<td>2012</td>
<td>National Clinical Guideline for diagnosis and initial management of acute stroke and TIA</td>
<td>None specified</td>
<td>Give consideration to: • The relative lack of experience of long term use of NOACs compared to VKA • The lack of a licensed product for rapid reversal of NOACs • The limited data on use in patients at the extremes of body weight and those with hepatic impairment</td>
</tr>
<tr>
<td>SIGN Scotland</td>
<td>2013</td>
<td>SIGN 129: Antithrombotics: indications and management. A national clinical guideline</td>
<td>Apixaban, dabigatran and rivaroxaban can be considered as alternatives to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>Prevention of stroke in patients with atrial fibrillation – a guide for primary care</td>
<td>None specified</td>
<td>Recommend if selecting a NOAC instead of warfarin consideration be given to the points raised in SIGN 129</td>
</tr>
<tr>
<td>All Wales Medicines Strategy Group Wales</td>
<td>2014</td>
<td>All Wales Advice on the Role of Oral Anticoagulants</td>
<td>Warfarin first line to support “managed entry” of newer agents No preference on newer agents</td>
<td>Ref. NICE CG180 and SIGN 129 Recommend use of NICE Patient Decision Aid</td>
</tr>
<tr>
<td>Source</td>
<td>Year</td>
<td>Title</td>
<td>Treatment Recommendations</td>
<td>Notes</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>-------</td>
<td>----------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>ESC Europe</td>
<td>2012</td>
<td>ESC Guidelines: 2012 focused update of the ESC Guidelines for management of atrial fibrillation</td>
<td>Either warfarin (INR 2-3 TTR &gt;70%) or NOAC (none specified) Dabigatran 150mg BD recommended in patients presenting with acute ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td>ASA/AHA USA</td>
<td>2014</td>
<td>Guideline for the primary prevention of stroke</td>
<td>NVAF with CHA₂DS₂-VASc ≥ 2 and low risk of haemorrhagic complications Warfarin (Class 1; level of evidence A) Apixaban, dabigatran, rivaroxaban (Class 1; level of evidence B)</td>
<td>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.</td>
</tr>
<tr>
<td>AHA/ACC/HRS USA</td>
<td>2014</td>
<td>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</td>
<td>No preference between NOACs</td>
<td></td>
</tr>
<tr>
<td>ASA/AHA USA</td>
<td>2014</td>
<td>Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals form the American Heart Association /American Stroke Association</td>
<td>Prevention of recurrent stroke in patients with NVAF (paroxysmal or permanent) Warfarin and apixaban (Class 1; level of evidence A)* Dabigatran (Class 1; level of evidence B)* Rivaroxaban is reasonable (Class IIa; Level of evidence B)*</td>
<td>The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, 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.</td>
</tr>
</tbody>
</table>

* 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 (2014) recommended warfarin therapy first line to support the managed entry of the newer anticoagulant agents. No preference is given by this group to which NOAC to use second line. The Scottish intercollegiate guidelines network considered the NOACs as alternatives to warfarin however 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.

**Favoured OAC – Clinical guidelines: No preference**

**Favoured NOAC – 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 over the NOACs for first line use:
✓ Many years of experience using warfarin as an anticoagulant
✓ Multiple indications including use with prosthetic heart valves and valvular AF
✓ 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
✓ Long half-life ensures a level of underlying anticoagulant cover if a dose is missed

✓ NOACs

✓ There is little difference in terms of efficacy for the three NOACs, apixaban, dabigatran and rivaroxaban.
✓ Apixaban and dabigatran 150mg dose were superior to warfarin for the primary efficacy endpoint of stroke or systemic embolism
✓ Dabigatran 150mg twice daily demonstrated superiority to warfarin in preventing ischaemic stroke
✓ Apixaban appears to have an advantage in terms of safety and reduced bleeding
✓ Major bleeding seems to be reduced with apixaban and dabigatran 110mg twice daily.
✓ Apixaban and rivaroxaban have favourable evidence in terms of patient factors such as administration and storage however rivaroxaban 15mg and 20mg doses must be taken with food to ensure appropriate absorption.
✓ There is evidence that rivaroxaban and apixaban can be crushed for administration
✓ Rivaroxaban is licensed for once daily administration while apixaban and dabigatran are twice daily Rivaroxaban has an advantage in terms of daily cost of treatment
7. Conclusion

Having reviewed the available evidence, considering pivotal clinical trials, international guidelines and patient factors such as dosing, administration and safety issues the Medicines Management Programme recommends warfarin therapy for first line therapy in stroke prevention in atrial fibrillation. In cases where warfarin is unsuitable due to an allergy or labile INR levels the MMP recommends the use of a NOAC with APIXABAN as the first line option.

Preferred OAC for stroke prevention with Atrial Fibrillation:  
WARFARIN with TTR >70%

Preferred NOAC for stroke prevention with Atrial Fibrillation:  
APIXABAN

Where there are issues of tolerability and/or suitability with both WARFARIN and APIXABAN, an alternative oral anticoagulant may be considered third line. Patients should be provided with sufficient information on ALL AVAILABLE THERAPIES when anticoagulation is being commenced*

Care should be taken at times where anticoagulation therapy is being changed
References

1. NMIC bulletin 2012, Update on Oral Anticoagulation Therapy volume 18 Number 6 (available on www.nmic.ie)


4. PCRS database – number of patients on warfarin ~(Oct 14), GMS and DPS combined


8. NICE patient decision aid, Atrial fibrillation medicines to help your risk of a stroke – what are the options? June 2014


12. Irish Heart Foundation available on: http://www.irishheart.ie/iopen24/atrial-fibrillation-t-7_19_53.html


14. NICE CG92 2010 Venous thromboembolism: reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary
embolism) in patients admitted to hospital. Available on: 
www.nice.org.uk/guidance/cg92/chapter/introduction


18. Issues in relation to prescribing safety of New Oral Anticoagulants, HSE communication sent to prescribers. 2014 Available on: 
http://www.hse.ie/eng/about/Who/clinical/natclinprog/medicinemanagementprogramme/NOACs.pdf

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Bibliography


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

### Table 21: Trial design information for Aristotle, RE-LY and ROCKET-AF

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomised Double-blind, double dummy</td>
<td>Randomised Open label</td>
<td>Randomised Double-blind, double dummy</td>
</tr>
</tbody>
</table>
| Study population            | AF or flutter and at least one of the following risk factors:  
  • ≥75  
  • Previous stroke, TIA or SE  
  • Symptomatic heart failure (previous 3 months or LVEF≤40%)  
  • Diabetes  
  • Hypertension  
  Atrial fibrillation documented on ECG at screening or within 6 months beforehand and at least one of:  
  • 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  
  Non-valvular atrial fibrillation with moderate-high risk of stroke indicated by:  
  • 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<=35%, hypertension, age >=75, diabetes mellitus |
<p>| Number of patients          | 18,201                                        | 18,113                                        | 14,264                                          |
| Follow-up period (years)    | 1.8 (median)                                  | 2.0 (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. rivaroxaban 20mg OD   |
| TTR for warfarin            | 62.2% (mean) 66% (median)                     | 64% (mean)                                    | 55% (mean) 58% (median; interquartile range 43-71) |
| Primary efficacy endpoint   | Ischaemic or haemorrhagic stroke or systemic embolism | Stroke or systemic embolism                  | Composite of stroke (ischaemic or haemorrhagic) and systemic embolism |
| Secondary efficacy endpoint | Death from any cause                          | Death from any cause                          | Stroke, systemic embolism or death               |
|                            | Rate of MI                                    |                                               |                                                  |</p>
<table>
<thead>
<tr>
<th>Rate of MI</th>
<th>from cardiovascular causes</th>
<th>A composite of stroke, systemic embolism, death from cardiovascular causes or MI</th>
<th>Individual components of the composite end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety endpoints</td>
<td>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</td>
<td>Major bleeding Life-threatening bleeding Intracranial bleeding Major and minor GI bleeding</td>
<td>Composite of major and non-major clinically relevant bleeding events</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>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</td>
<td>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 a. Major surgery within the previous month. b. Planned surgery or intervention</td>
<td>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</td>
</tr>
<tr>
<td>Cardiac-related conditions</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
≤100,000/mm³;
7. Uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg)
8. Planned AF ablation procedure
9. Treatment with aspirin > 165 mg a day or for both aspirin and clopidogrel or investigational drug within 30 days
10. Severe renal insufficiency (serum creatinine 221 micromol/L or > 2.5 mg/dL) or calculated creatinine clearance of < 25 ml/min
11. ALT or AST > 2 ULN;
12. Total bilirubin > 1.5 ULN;
13. Haemoglobin level < 9 g/dL; Pregnancy
14. Severe comorbid condition with life expectancy ≤ 1 year
15. Substance abuse disorder
16. Inability to comply with INR monitoring

within the next 3 months.

Haemorrhage risk-related criteria
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 atraumatic intra-articular bleed, chronic haemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation or aneurysm.
10. Platelet count < 90,000/microliter at screening
11. Sustained uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 100 mmHg)

Concomitant conditions and therapies
12. Severe disabling stroke within 3 months or any stroke within 14 days before randomization
13. TIA within 3 days of
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5. Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism).</td>
<td></td>
<td></td>
<td>randomisation.</td>
</tr>
<tr>
<td></td>
<td>6. Plan to perform a pulmonary vein ablation or surgery for cure of the AF.</td>
<td></td>
<td>14. Indication for anticoagulation other than AF (e.g. VTE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Severe renal impairment (estimated creatinine clearance (&lt;=30 \text{ mL/min}))</td>
<td></td>
<td>15. Treatment with aspirin (&gt;100\text{mg/day}), aspirin in combination with thienopyridines within 5 days of randomisation, IV antiplatelets within 5 days, fibrinolytics within 10 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Active infective endocarditis</td>
<td></td>
<td>16. Anticipated need for chronic NSAID therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
<td>17. Systemic treatment with strong inhibitors of CYP3A4 (ketoconazole or protease inhibitors) within 4 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10. Women who are pregnant, lactating, or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study.</td>
<td></td>
<td>18. Treatment with strong inducers of CYP3A4 (rifampicin) within 4 days before randomization.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11. Anaemia (haemoglobin &lt;100g/L) or thrombocytopenia (platelet count &lt;100 x 10^9/L)</td>
<td></td>
<td>19. Anaemia (haemoglobin &lt;10g/dL).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12. Patients who have developed transaminase elevations upon exposure to ximelagatran.</td>
<td></td>
<td>20. Pregnant or breast feeding.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13. Patients who have received an investigational drug in the past 30 days or are participating in another drug study.</td>
<td></td>
<td>21. Any other contraindication to warfarin.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14. Patients considered unreliable by randomisation.</td>
<td></td>
<td>22. Known HIV at screening.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23. CrCl&lt; 30ml/min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24. Known significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis, of ALT &gt; 3 x the ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25. Serious concomitant illness</td>
<td></td>
</tr>
</tbody>
</table>
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) 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

<table>
<thead>
<tr>
<th>Baseline patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 (median) (63-76 interquartile range)</td>
</tr>
<tr>
<td>Female</td>
<td>35% (warf) 35.5% (apix)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82kg (median) (70-96) interquartile range</td>
</tr>
<tr>
<td>CHADS² scores</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>34%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

Baseline patient characteristics

Age (years)
- 70 (median) (63-76 interquartile range)
- 71.5 (150mg) (mean) ±SD (8.7)
- 73 (median) (65-78 interquartile range)

Female
- 35% (warf) 35.5% (apix)
- 36.4% (average of 3 groups)
- 39.7%

Weight (kg)
- 82kg (median) (70-96) interquartile range
- 82.7kg (mean) ±19.7 (average SD?)
- BMI median and interquartile 28.3 and 28.1 (w) 25.2-32.1, 25.1-31.8

CHADS² scores
- 0
- 1
- 2
- 3
- 4
- 5
- 6
Renal Function proportions

<table>
<thead>
<tr>
<th>Renal Function proportions</th>
<th>% (excluded &lt;25ml/min)</th>
<th>(excluded &lt;30ml/min)</th>
<th>67 (median) interquartile range 52-88(86) (excluded &lt; 30ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt;80ml/min)</td>
<td>41.3</td>
<td>Dabigatran dose was not stratified by CrCl in RE-LY</td>
<td>32.2%</td>
</tr>
<tr>
<td>Mild impair (&gt;50-80ml/min)</td>
<td>41.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate impair (&gt;30-50ml/min)</td>
<td>15.1 (4.7% and 4.4% in active and control groups received renal dose of 2.5mg)</td>
<td></td>
<td>21.1%</td>
</tr>
<tr>
<td>Severe (≤30ml/min)</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes (% per year intention to treat)

<table>
<thead>
<tr>
<th>Trial</th>
<th>ARISTOTLE</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (n=9,081)</td>
<td>Apixaban (n=9,120)</td>
<td>Warfarin (n=6022)</td>
<td>Dabigatran 150mg (n= 6076)</td>
</tr>
<tr>
<td>% outcome</td>
<td>% outcome (HR; 95% CI; P value)</td>
<td>% outcome</td>
<td>% outcome (RR;95%CI;P value)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Stroke/systemic embolism (% per year based on intention to treat population)</td>
<td>1.6%</td>
<td>1.27% (0.79:0.66-0.95; P=0.01 for superiority)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1.05%</td>
<td>0.97% (0.92; 0.74-1.13; P=0.42)</td>
<td>1.20%</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.47%</td>
<td>0.24% (0.51; 0.35-0.75; P&lt;0.001)</td>
<td>0.38%</td>
</tr>
<tr>
<td>Primary Safety endpoint (Aristotle and RE-LY)</td>
<td>3.09%</td>
<td>2.13% (0.69;0.60-0.80; P&lt;0.001)</td>
<td>3.36%</td>
</tr>
</tbody>
</table>
## Major bleeding

<table>
<thead>
<tr>
<th>Major bleeding</th>
<th>rivaroxaban</th>
<th>warfarin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Safety endpoint (ROCKET AF) Major and non-major clinically relevant bleeding</td>
<td>0.80%</td>
<td>0.74%</td>
<td>0.74%</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.80%</td>
<td>0.74%</td>
<td>0.74%</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>2.67%</td>
<td>2.84% (1.07; 0.92-1.25; P=0.38)</td>
<td>2.51% (0.94; 0.80-1.10; P=0.45)</td>
</tr>
<tr>
<td>Other location bleeding</td>
<td>2.27%</td>
<td>1.79% (0.79; 0.68-0.93; P=0.004)</td>
<td>1.1%</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.86%</td>
<td>0.76% (0.89; 0.70-1.15; P=0.37)</td>
<td>1.02%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.61%</td>
<td>0.53% (0.88; 0.66-1.17; P=0.37)</td>
<td>0.64%</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.94%</td>
<td>3.52% (0.89; 0.80-0.99; P=0.047)</td>
<td>4.13%</td>
</tr>
<tr>
<td>% discontinuation at end of follow-up</td>
<td>27.5%</td>
<td>25.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>% discontinuation/yr.</td>
<td>15.3%</td>
<td>14.1%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>
Appendix 2: Anticoagulation Prescribing Tips – Warfarin and NOACs

<table>
<thead>
<tr>
<th><strong>ANTICOAGULATION PRESCRIBING TIPS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>These prescribing tips are intended to assist prescribers, and advise of appropriate dosing, when a new oral anticoagulant (NOAC) is selected for treatment. The dosing recommendations in this document are based on the Summary of Product Characteristics (SmPC) for each product (available on <a href="http://www.hpa.ie">www.hpa.ie</a> and <a href="http://www.medicines.ie">www.medicines.ie</a>).</td>
</tr>
</tbody>
</table>

The Medicines Management Programme considers WARFARIN to be the agent of choice and the first line anticoagulant for most patients with Atrial Fibrillation. The following points should be noted prior to choosing an anticoagulant:

1) **Warfarin is the established anticoagulant of choice for many patients including those with:**
   - Mechanical heart valves
   - Valvular Atrial Fibrillation (AF)
   - Severe renal impairment
   - Cancer related venous thromboembolism (VTE)
   - Complicated VTE such as patients with recurrent VTE
   - Patients with antiphospholipid syndrome (APS)

2) **Clinical trials: considerations regarding trial evidence for NOACs:**
   - The NOACs were not shown to be superior to optimal warfarin therapy in clinical trials for stroke prevention in Atrial Fibrillation i.e. where time in therapeutic range (TTR) for warfarin is over 70% (2,4). RE-LY: mean TTR = 64% (5), ARISTOTLE: mean TTR = 65% (6).
   - The pivotal clinical trial for rivaroxaban for stroke prevention in AF was a non-inferiority trial (ROCKET-AF) with a TTR of 55% (4).
   - Patients with severe renal dysfunction were excluded from pivotal clinical trials in AF i.e exclusion criteria for rivaroxaban in ROCKET-AF: Creatinine Clearance (CrCl) <30ml/min, for dabigatran in RE-LY was <30ml/min (5), and for apixaban in ARISTOTLE was <25ml/min (6). Therefore the Medicines Management Programme advises extreme caution when using NOACs in patients with CrCl of 15-30ml/min. Apixaban and rivaroxaban are contraindicated at <30ml/min.

   **Patients on NOAC therapy should have regular assessment of their renal function and have 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 trials (7,8,9,10,11,12,13,14).
   - The trials for treatment of DVT/PE with dabigatran and rivaroxaban studied the standard treatment doses only (150mg BD and 20mg once daily respectively). The lower doses of 110mg BD dabigatran and 15mg once daily rivaroxaban to treat DVT/PE have not been studied in a clinical setting (11,13,15).
   - Trials for the treatment of DVT and PE (for rivaroxaban and dabigatran) were also non-inferiority trials (11,12,13).

3) **Significant drug interactions may also occur with NOAC therapy and the most common of these are highlighted in the prescribing add (15,16,17).**

4) **Poor compliance with NOAC therapies carries a risk of thrombotic events due to the short half-life of these agents (15,16,17).**

5) **There are currently no antidotes available for the haemorrhagic complications associated with the NOACs (15,16,17).**

**WARFARIN DOSING AND MONITORING**


References:
1. Reference: [Text](https://example.com)
2. Reference: [Text](https://example.com)
3. Reference: [Text](https://example.com)
4. Reference: [Text](https://example.com)
5. Reference: [Text](https://example.com)
6. Reference: [Text](https://example.com)
7. Reference: [Text](https://example.com)
8. Reference: [Text](https://example.com)

Contact: [Email](mailto:example@email.com) for more details
# Non-Valvular Atrial Fibrillation (NVAF)

**General Information**
- CRRT should be considered in patients who are at increased risk of bleeding.
- Interactions: this list is not exhaustive, for full list of interacting drugs and for management of interactions see Summary of Product Characteristics (SmPC) [www.medicines.org.uk or www.hpa.org.uk]

## Apixaban

- **Adjust dose for AGE, BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS**

### Dosing

<table>
<thead>
<tr>
<th>Standard dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg twice daily (BD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CONTRAINDICATED in CrCl < 15 ml/min

### Dabigatran

- **Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS**

### Dosing

<table>
<thead>
<tr>
<th>Less than 75 years (see also options below)</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg twice daily (BD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CONTRAINDICATED in CrCl < 30 ml/min

### Rivaroxaban

- **Adjust dose for RENAL FUNCTION and consider INTERACTIONS**

### Dosing

<table>
<thead>
<tr>
<th>Standard dose</th>
<th>Stroke prevention in NVAF</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CONTRAINDICATED in CrCl < 15 ml/min

**Important information:** 15 mg and 20 mg tablets should be taken WITH FOOD.

**References:**
  Clinical Knowledge Summaries: Anticoagulants. Updated 27th May 2014
Appendix 3: Preferred NOAC for stroke prevention in AF prescribing tips

Preferred NOAC (second line to warfarin): APIXABAN

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

<table>
<thead>
<tr>
<th>Onset of Action</th>
<th>Apixaban has a very fast onset of action (3-4 hours after first dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>MUST be taken TWICE DAILY every 12 hours</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 and administration of Apixaban

<table>
<thead>
<tr>
<th>DOSING</th>
<th>Stroke prevention in NVAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose</td>
<td>5 mg twice daily (BD)</td>
</tr>
<tr>
<td>Serum creatinine &gt; 133micromol/L (measured) \ AND \ ≥80yrs OR weight ≤60kg (or any two of three above i.e. serum creatinine, age ≥80, weight ≤60kg)</td>
<td>2.5mg BD</td>
</tr>
<tr>
<td>CrCl 15-29ml/min [use Cockroft-Gault equation (SI units)] (regardless of age or weight)</td>
<td>2.5mg BD – EXTREME CAUTION, consider alternative (review HAS-BLED and other risk factors)</td>
</tr>
</tbody>
</table>

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 as azole-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.