Greater East Midlands Commissioning Support Unit

Greater East Midlands Commissioning Support Unit in association with
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Prescribing and Clinical Effectiveness Bulletin

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GUIDANCE ON THE PRESCRIBING OF WARFARIN, DABIGATRAN, RIVAROXABAN AND APIXABAN FOR THE PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN ATRIAL FIBRILLATION (SECOND EDITION)

What's new in the Second Edition?

- **All three of the newer oral anticoagulants are now licensed for the prevention of stroke and systemic embolism in people with atrial fibrillation (AF) and have all been approved by NICE for this indication. Within this context dabigatran (*Pradaxa*), rivaroxaban (*Xarelto*) and apixaban (*Eliquis*) are all designated GREEN.**
- **Epidemiological studies identify AF as the cause of between 15 and 20% of thromboembolic strokes. The East Midlands Cardiovascular Network *Pathway for the Management of AF in Primary Care* recommends that all patients aged 65 and older should have a manual pulse palpation at least annually with any irregularity followed up with a 12 lead ECG. Opportunistic screening is crucial to enable detection of AF before the first stroke and to ensure the effective deployment of stroke prevention therapy, such as oral anticoagulation.**
- **Recent national data published as part of the Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF) initiative reports that 8.5% of AF patients at high risk of stroke are receiving no treatment, 35% are on aspirin and 56.9% are receiving an oral anticoagulant.**
- **In accordance with European Society of Cardiology (ESC) guidance, the CHA_2DS_2-VASc score is now the recommended stroke risk scoring system; the recommended threshold has also been reduced to greater than or equal to 1 in line with ESC recommendations. Patients with a CHA_2DS_2-VASc score $\geq$ 1 should be considered for oral anticoagulant stroke prophylaxis (i.e. warfarin or one of the newer oral anticoagulants) subject to an assessment of bleeding risk and patient preference. The $CHADS_2$ system is still recommended where there are problems accessing CHA_2DS_2-VASc.**
- **This guidance is designed to inform treatment selection for patients identified as at significant risk (i.e. CHA_2DS_2-VASc score $\geq$ 1).**
- **Stroke rates in both male and female patients that fulfil the 'age<65 and lone AF' criteria are so low that antithrombotic therapy is not recommended in this group; this means that female patients meeting this criteria are not appropriate**

for oral anticoagulant therapy even though they will score 1 on the CHA_2DS_2-VASc assessment on the grounds of female gender.

- **The evidence for effective stroke prevention with aspirin in AF is weak, with a potential for harm; data suggests that the risk of major bleeding or intra-cranial haemorrhage (ICH) with aspirin is not significantly different to oral anticoagulants, especially in the elderly. Aspirin or dual antiplatelet therapy must not be used routinely as an alternative to oral anticoagulants in patients with a CHA_2DS_2–VASc score of $\geq$ 1. If, after an informed discussion, the patient refuses treatment with any oral anticoagulant, dual antiplatelet therapy should be considered using aspirin 75mg plus clopidogrel 75mg daily (where bleeding risk is low). Alternatively, and less effectively, aspirin 75 to 300mg daily monotherapy can be used.**

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SUMMARY OF PACEF DECISIONS: SEPTEMBER 2013 UPDATE

Drug	Indication(s)	Traffic Light Status
Dabigatran etexilate 110mg and 150mg capsules (*Pradaxa*)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more of the following: • previous stroke, transient ischaemic attack or systemic embolism. • LVEF <40%. • symptomatic heart failure (≥ NYHA class II). • ≥ 75 years. • ≥ 65 years with diabetes, coronary artery disease or hypertension (110mg and 150mg capsules only).	GREEN Subject to both NICE criteria and Lincolnshire *Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation* (Second Edition) Approved for inclusion in the *Joint Formulary* for this indication
Rivaroxaban 20mg tablets (*Xarelto*)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors: • congestive heart failure. • hypertension. • ≥ 75 years. • diabetes mellitus. • previous stroke or transient ischaemic attack.	GREEN Subject to both NICE criteria and Lincolnshire *Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation* (Second Edition) Approved for inclusion in the *Joint Formulary* for this indication
Apixaban tablets 2.5mg and 5mg (*Eliquis*)	For the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors: • symptomatic heart failure (≥ NYHA class II). • hypertension. • ≥ 75 years. • diabetes mellitus. • prior stroke or transient ischaemic attack.	GREEN Subject to both NICE criteria and Lincolnshire *Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation* (Second Edition) Approved for inclusion in the *Joint Formulary* for this indication

Summary of Guidance

Newly diagnosed AF patients (CHA_2DS_2-VASc score greater than or equal to 1) requiring oral anticoagulant stroke thromboprophylaxis

On balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk AF patients (CHA_2DS_2–VASc score ≥ 1) with good INR control. It should be the preferred option in those with:

- **an estimated Glomerular Filtration Rate (eGFR) < 30mL/min/1.73m^2 (see section on *Renal Impairment*).**

- **a history of significant peptic ulcer disease (rates of major gastro-intestinal bleeding and GI symptoms are lower with warfarin than those reported with dabigatran and rivaroxaban; apixaban seems to be better tolerated than this with no statistically significant difference between warfarin and apixaban in terms of major GI bleeding in the key trial).**
- **significant ischaemic heart disease in the absence of other determining considerations (rates of myocardial infarction are lower with warfarin than those reported with dabigatran).**

The newer oral anticoagulant drugs (OACs), dabigatran, rivaroxaban or apixaban may be the preferred option in those:

- **predicted to have variable interacting medications (e.g. recurrent antibiotics). The potential for drug, food and alcohol interactions with warfarin is well documented and detailed in *BNF* Appendix 1; there are far fewer interactions with other medicines documented with dabigatran, rivaroxaban or apixaban.**
- **for whom regular INR monitoring is hard to access. It is emphasized that the decision to initiate a patient on a new OAC within this context must be based on sound clinical reasoning as defined in this guidance and should not simply reflect the convenience of the patient or the practice.**
- **with a high HAS-BLED score where dabigatran 110mg twice daily should be considered. Further information on the HAS-BLED score is included in Appendix 2. Low dose dabigatran (110mg twice daily) has been shown to reduce the risk of major bleeding compared with warfarin.**

In all other patients, warfarin is recommended as the preferred first line treatment. NICE recommend an informed discussion between the clinician and the patient about the risks and benefits of warfarin compared with the newer drugs, dabigatran, rivaroxaban and apixaban. A table summarizing the benefits and risks of each option is included in the text (see Appendix 3). A frequently asked questions sheet is also provided as Appendix 4. Key topics for discussion between clinician and patient include:

- **lack of long term safety data with the new OACs.**
- **issues concerning reversibility. There is currently no product available to rapidly reverse dabigatran, rivaroxaban or apixaban in the event of major bleeding.**
- **the principles used in patient selection (see above)**
- **the potential option to convert the patient to dabigatran, rivaroxaban or apixaban (if appropriate), if Time in Therapeutic Range (TTR) is < 60% after 4 months in the presence of compliance.**

The evidence for effective stroke prevention with aspirin in AF is weak, with a potential for harm; data suggests that the risk of major bleeding or intra-cranial haemorrhage (ICH) with aspirin is not significantly different to oral anticoagulants, especially in the elderly. Aspirin or dual antiplatelet therapy must not be used routinely as an alternative to oral anticoagulants in patients with a CHA_2DS_2–VASc score of $\geq$ 1. If, after an informed discussion, the patient refuses treatment with any oral anticoagulant, dual antiplatelet therapy should be considered using aspirin 75mg

plus clopidogrel 75mg daily (where bleeding risk is low). Alternatively, and less effectively, aspirin 75 to 300mg daily monotherapy can be used.

Existing patients diagnosed with AF (CHA_2DS_2-VASc score greater than or equal to 1) currently taking a vitamin K antagonist (e.g. warfarin)

On balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk AF patients (CHA_2DS_2 –VASc score ≥ 1) with good INR control. Clinicians should consider dabigatran, rivaroxaban or apixaban as possible alternatives to existing treatment with a vitamin K antagonist (i.e. warfarin, acenocoumarol, phenindione) in patients with:

- **poor INR control despite evidence that they are fully compliant with treatment. Poor INR control is defined as TTR of < 60% after 4 months in the presence of compliance. Poor INR control as a result of poor compliance is not considered to be sufficient reason to move to an alternative oral anticoagulant. INR monitoring enables assessment of compliance with warfarin; there is no comparable way to assess compliance with dabigatran, rivaroxaban or apixaban. Poor compliers with warfarin are likely to be poor compliers with dabigatran, rivaroxaban or apixaban.**
- **allergy to or intolerable side effects with coumarin anticoagulants.**
- **continuing supply difficulties with phenindione.**

In addition, conversion from warfarin (or alternative vitamin K antagonist) to dabigatran, rivaroxaban or apixaban may also be considered for patients:

- **with a history of significant bleeding on warfarin. Low dose dabigatran (110mg twice daily) has been shown to reduce the risk of major bleeding compared with warfarin. Apixaban may also present a useful option within this context.**
- **with a history of stroke or transient ischaemic attack (TIA) while taking warfarin (providing there is no evidence of poor or non-compliance). Apixaban is associated with a lower incidence of stroke (both ischaemic and haemorrhagic) than warfarin. The MHRA have specifically contraindicated the use of dabigatran following recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage or major intraspinal or intracerebral vascular abnormalities.**
- **for whom regular INR monitoring is hard to access. It is emphasized that the decision to initiate a patient on a new OAC within this context must be based on sound clinical reasoning as defined in this guidance and should not simply reflect the convenience of the patient or practice.**

All other patients who are well controlled and tolerant of warfarin (or another vitamin K antagonist) are not recommended to change.

When switching from warfarin (or alternative vitamin K antagonist) to dabigatran, rivaroxaban or apixaban please refer to the guidance on switching that appears in this *Bulletin* (see below) and in the Summaries of Product Characteristics for the products. Similarly, guidance on switching from dabigatran/rivaroxaban/apixaban to warfarin is also provided.

Introduction

It has been estimated that the prevalence of atrial fibrillation (AF) in the developed world is approximately 1.5 to 2% with the average age of patients falling between 75 and 85 years. AF is associated with a five-fold increase in stroke risk and three-fold incidence of congestive heart failure; it is also associated with higher mortality. Epidemiological studies identify AF as the cause of between 15 and 20% of thromboembolic strokes. Recent national data published as part of the Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF) initiative reports that 8.5% of AF patients at high risk of stroke are receiving no treatment, 35% are on aspirin and 56.9% are receiving an oral anticoagulant. With this in mind the importance of opportunistic screening for atrial fibrillation to detect the condition before the first stroke and the need for active and effective treatment to prevent stroke have been emphasized by the European Society of Cardiology, the All Party Parliamentary Group on AF and the East Midlands Cardiac Network among many others. The East Midlands Cardiovascular Network *Pathway for the Management of AF in Primary Care* recommends that all patients aged 65 and older should have a manual pulse palpation at least annually and any irregularity should be followed up with a 12 lead ECG.

Following diagnosis, it is important to undertake a stroke and bleeding risk assessment. Stroke risk is normally assessed using either the $CHADS_2$ score or the CHA_2DS_2-VASc score (see Appendix 1). CHA_2DS_2-VASc takes into account a wider range of risk factors than $CHADS_2$ and evidence suggests that it is better at identifying truly low risk patients and those most at risk from future stroke and thromboembolism. As a result of this, the European Society of Cardiology guidelines recommend CHA_2DS_2-VASc as the preferred risk assessment tool. This has been endorsed by the local cardiologists and stroke physicians who have peer reviewed this text. In addition, it has been agreed as part of the update to this guidance that the threshold for initiation of oral anticoagulant therapy should be lowered to $CHADS_2$ or CHA_2DS_2–VASc score $\geq$ 1 with CHA_2DS_2-VASc assessment preferred. Stroke rates in both male and female patients that fulfil the 'age<65 and lone AF' criteria are so low that antithrombotic therapy is not recommended in this group; this means that female patients meeting this criteria are not appropriate for oral anticoagulant therapy even though they will score 1 on the CHA_2DS_2-VASc assessment on the grounds of female gender.

In addition to an assessment of stroke risk, patients will also need to be assessed against the risk of major bleeding, especially intra-cranial haemorrhage (ICH), which is the most feared complication of anticoagulant therapy and can result in disability or death. More details on the HAS-BLED score are provided in Appendix 2. The HAS-BLED score has been validated in several independent cohorts and correlates well with ICH risk. In patients with a HAS-BLED score of $\geq$ 3, caution and regular review are recommended, as well as efforts to correct potentially reversible risk factors for bleeding wherever possible (see Appendix 2)..

Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (male and female) who are at low risk (aged <65 and lone AF) or in those that have contra-indications (NB female patients in this category will have a CHA_2DS_2 –VASc score of 1 based on gender alone). Patients with a CHA_2DS_2–VASc score of $\geq$ 1

should be considered for oral anticoagulant therapy, either adjusted dose vitamin K antagonist therapy (warfarin) or direct thrombin inhibitor therapy (dabigatran) or oral factor Xa inhibitor therapy (rivaroxaban or apixaban) subject to an assessment of bleeding risk and patient preference. Where patients refuse any oral anticoagulant therapy, dual antiplatelet therapy should be considered using aspirin 75mg plus clopidogrel 75mg daily (where bleeding risk is low) or less effectively, aspirin 75 to 300mg daily. The evidence for effective stroke prevention with aspirin in AF is weak, with a potential for harm; data suggests that the risk of major bleeding or ICH with aspirin is not significantly different to oral anticoagulants, especially in the elderly. Aspirin or dual antiplatelet therapy must not be used routinely as an alternative to oral anticoagulants in patients with a CHA_2DS_2–VASc score of $\geq$ 1.

Dabigatran etexilate (*Pradaxa*) is a direct thrombin inhibitor licensed for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation. Rivaroxaban (*Xarelto*) is a direct inhibitor of activated factor X also licensed for the same indication. Apixaban (*Eliquis*) is a direct and highly selective inhibitor of factor Xa. All three drugs have been approved by NICE as options for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (subject to criteria detailed below). All three have the potential advantage over warfarin of not requiring blood monitoring and may have fewer clinically important drug interactions. It is the purpose of this special edition of the *PACE Bulletin* to detail local guidance on the use of all three of these drugs. Local criteria have been agreed, closely based on East Midlands Cardiac and Stroke Network Guidance and European Society of Cardiology Guidelines which provide answers to many questions which arise from the NICE guidance, specifically:

- **When can dabigatran, rivaroxaban or apixaban be considered to be appropriate alternatives to warfarin for this indication?**
- **What is the role of warfarin now that the newer oral anticoagulants have been approved by NICE?**
- **What are the risks and benefits of each drug in comparison to warfarin?**
- **What is the role of dual antiplatelet therapy or aspirin monotherapy in these patients?**

NICE Technology Appraisal 249: *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation* (March 2012)

Dabigatran etexilate is recommended by NICE *as an option* for the prevention of stroke and systemic embolism, within licensed indications, that is in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism.
- left ventricular ejection fraction below 40%.
- symptomatic heart failure of NYHA class 2 or above.
- $\geq$ 75 years.
- $\geq$ 65 years with one of the following diabetes, coronary artery disease or hypertension.

NICE Technology Appraisal 256: *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation* (May 2012)

Rivaroxaban is recommended by NICE *as an option* for the prevention of stroke and systemic embolism, within its licensed indication, that is in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- congestive heart failure.
- hypertension.
- ≥ 75 years.
- diabetes mellitus.
- previous stroke or transient ischaemic attack.

NICE Technology Appraisal 275: *Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation* (February 2013)

Apixaban is recommended by NICE *as an option* for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:

- prior stroke or transient ischaemic attack.
- age 75 years or older.
- hypertension.
- diabetes mellitus.
- symptomatic heart failure.

PACEF Comment:
NICE have approved all three of these new OACs as an option for this indication. In conjunction with the East Midlands Cardiovascular and Stroke Network, PACEF and ULH Drug and Therapeutics Committee have worked to clarify the remaining role for warfarin and the criteria within which dabigatran or rivaroxaban or apixaban can be considered for these patients. This guidance closely follows the East Midlands Cardiovascular Network guidance entitled *Implementation of NICE TA249 and NICE TA 256: Dabigatran and rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation* (June 2012). It now incorporates additional information from NICE TA275 *Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation* (February 2013) and information from the apixaban (*Eliquis*) Summary of Product Characteristics. European Society of Cardiology guidelines have also been highly influential on the text.

The decision about whether to start treatment with dabigatran, rivaroxaban or apixaban should be made after informed discussion between the clinician and the person about the risks and benefits of dabigatran, rivaroxaban or apixaban compared with warfarin. For people taking warfarin, the potential risks and benefits of switching to dabigatran or

rivaroxaban or apixaban should be considered in light if their level of international normalised ratio (INR) control.

PACEF Comment:
It is crucial that patients fully understand the risks and benefits of both warfarin and dabigatran/rivaroxaban/apixaban as part of the initial consultation. A table is provided as part of this *Bulletin* that summarizes these risks and benefits. The risks of warfarin therapy are well known and fully documented after many years of exposure to a large population of patients. Dabigatran, rivaroxaban and apixaban are new drugs associated with serious emerging safety concerns that have to date been largely initiated in hospitals and used in a much smaller patient population. Patients need to be fully aware of the not inconsiderable risks with either warfarin or the newer anticoagulant drugs.

Trial evidence: *Dabigatran vs warfarin - Randomised Evaluation of Long-term Anticoagulant Therapy (RE-LY) Study and Long-Term Multi-Centre Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) Study*

RE-LY was a multicenter, prospective randomised controlled trial (RCT) with 18,113 participants which sought to show that dabigatran was non-inferior to warfarin for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation and at least one additional risk factor for stroke. The additional risk factors were:

- history of stroke, transient ischaemic attack (TIA) or systemic embolism.
- left ventricular ejection fraction of less than 40%.
- symptomatic heart failure.
- age 75 years or older.
- age 65 years or older with diabetes mellitus, documented coronary artery disease or hypertension.

The average age of participants was 71 years; 64.3% were male; 50% were naïve to anticoagulants. The risk of stroke at baseline was classified according to the $CHADS_2$ score, which is used to estimate the risk of stroke in people with AF and to determine whether there is a need for anticoagulant treatment (see below). Eligibility criteria for inclusion in the study meant by definition that all patients had a $CHADS_2$ score of at least one, although 68% had a $CHADS_2$ score of 2 or more. People were excluded from RE-LY if they had had a severe, disabling stroke in the previous 6 months or any stroke within the previous14 days or any condition associated with increased risk of bleeding or a contra-indication to warfarin treatment.

The primary efficacy outcome in the study was incidence of all types of stroke (including haemorrhagic) and systemic embolism; the primary safety endpoint was major bleeding. There was a relative risk reduction of stroke or systemic embolism which favoured dabigatran over warfarin at both the 110mg and 150mg doses. However, there were no statistically significant differences between dabigatran and warfarin in the incidence of stroke or systemic embolism, ischaemic stroke or vascular mortality at the lower dose. NICE concluded that dabigatran 150mg twice daily was more effective than warfarin in reducing

the risk of stroke or systemic embolism, ischaemic stroke and vascular mortality; dabigatran 110mg twice daily was judged to be non-inferior to warfarin. At the higher dose, the National Prescribing Centre estimated the Number Needed to Treat (NNT) at 1 year of 172 (i.e. you would have to treat 172 people for 1 year with dabigatran rather than warfarin to prevent an additional stroke or systemic embolism).

In terms of adverse effects compared to warfarin, dabigatran was associated with:

- a statistically significant reduction in the incidence of haemorrhagic stroke.
- fewer life-threatening bleeds.
- a significantly higher incidence of major gastro-intestinal bleeding and life-threatening GI bleeding.
- a higher incidence of dyspepsia (indigestion and abdominal pain/discomfort)
- a higher risk of MI.

The RE-LY study in isolation has been criticised for not providing sufficient assurance of long-term efficacy and safety. A follow-up study (RELY-ABLE- *Long-Term Multi-Centre Extension of Dabigatran Treatment in Patients with Atrial Fibrillation*) continued to observe dabigatran treated RE-LY patients beyond the trial's follow-up period. RELY-ABLE suggests no significant difference between dabigatran 110mg twice daily and 150mg twice daily in terms of incidence of stroke and systemic embolism. Predictably, the 150mg twice daily dosage of dabigatran was associated with a higher incidence of major bleeding events than the lower dose.

Trial evidence: Rivaroxaban vs warfarin - *The Rivaroxaban Once daily Compared with Vitamin K antagonism for prevention of stroke and Embolism Trail in Atrial Fibrillation (ROCKET AF)*

The ROCKET AF study was a large scale RCT which sought to show non-inferiority of rivaroxaban to dose adjusted warfarin (target INR of 2.0 -3.0) in the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation. Rivaroxaban was shown to be non-inferior to warfarin, both in terms of prevention of strokes and systemic embolism in those with AF at moderate to high risk for a stroke; it was also shown to have a comparable risk to warfarin of major and non-major clinically significant bleeding. Major bleeding from a gastrointestinal site was more common in the rivaroxaban group than the warfarin group. Intracranial haemorrhage occurred less frequently with rivaroxaban than with warfarin.

Trial evidence: Apixaban vs warfarin – Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)

The ARISTOTLE study was a large scale RCT (18,201 patients) comparing apixaban 2.5mg to 5mg twice daily with warfarin (in patients with an INR target range of 2.0 to 3.0). The primary objective was to determine if apixaban was non-inferior to warfarin for the combined end point of stroke (both ischaemic and haemorrhagic) and systemic embolism.
Appoximately 65% of patients enrolled had a CHADS2 score of 2 or more. Apixaban met the non-inferiority criteria and was actually found to be superior to warfarin in some scenarios:
(1) Apixaban was associated with a significantly lower rate of stroke and systemic thromboembolism than warfarin.

(2) The rate of fatal or disabling stroke was significantly lower in the apixaban group.
(3) Apixaban was associated with a significant reduction in haemorrhagic stroke compared with warfarin.
(4) The rates of myocardial infarction (MI), pulmonary embolism and deep vein thrombosis were lower with apixaban but not statistically significant.
(5) Apixaban was associated with fewer all cause deaths than warfarin.

In terms of adverse events and safety, apixaban resulted in significantly fewer bleeding events than warfarin for all of the major bleed types (e.g. intracranial) and clinically relevant non-major bleeding events (apart from gastrointestinal bleeding where there was no statistically significant difference). Serious adverse events occurred in 35% of patients treated with apixaban and 36.5% with warfarin.

There is no direct head-to-head comparative data between apixaban, dabigatran and rivaroxaban, although NICE have reviewed a meta-analysis undertaken by Bristol Myers Squibb, the manufacturers of apixaban (*Eliquis*). The conclusions are as follows:

- There are no statistically significant differences between apixaban and rivaroxaban and dabigatran in the incidence of stroke, systemic embolism and all-cause mortality.
- Apixaban is associated with a significantly lower incidence of MI compared to dabigatran (150mg or 110mg twice daily).
- Apixaban is associated with a significantly lower incidence of all bleeding outcomes compared with rivaroxaban (intracranial haemorrhage, major bleeding, GI bleeding, clinically relevant non-major bleeding).
- Apixaban is associated with a significantly lower incidence of all bleeding events except intracranial haemorrhage and clinically relevant non-major bleeding than dabigatran 150mg. it has a significantly lower incidence of any bleeding with dabigatran 110mg.
- Apixaban was associated with significantly fewer discontinuations compared with dabigatran and rivaroxaban.

Licensed doses for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation

Drug	**Licensed dose for prevention of stroke and systemic embolism in non-valvular AF**
Apixaban (*Eliquis*)	5mg twice daily; for the elderly over 80 with body weight less than 60kg 2.5mg twice daily.
Dabigatran (*Pradaxa*)	150mg twice daily long-term (provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding). For patients aged 75 to 80, 110mg twice daily can be considered for those considered to have a low thromboembolic risk and a high bleeding risk. Patients aged 80 or older should be treated with a daily dose of 110mg twice daily because of increased bleeding risk in this population. **Low dose dabigatran (110mg twice daily) has been shown to reduce the risk of major bleeding compared with warfarin**
Rivaroxaban (*Xarelto*)	20mg once daily long-term (provided the benefit of prevention of stroke and systemic embolism

	outweighs the risk of bleeding).

Safety concerns including MHRA and EMA guidance

The long-term safety and tolerability of dabigatran, rivaroxaban and apixaban are not yet known. All three drugs are commonly associated with anaemia, epistaxis and GI haemorrhage. In the RE-LY study more people experienced dyspepsia (indigestion, abdominal pain or discomfort) with dabigatran than with warfarin. In addition, more people dropped out of the study due to serious adverse events with dabigatran than with warfarin. In the ROCKET AF study major bleeding from a gastrointestinal site was more common in the rivaroxaban group than the warfarin group. In ARISTOTLE, apixaban was associated with fewer bleeding events than warfarin for all of the major bleed types (e.g. intracranial) and clinically relevant non-major bleeding events (apart from gastrointestinal bleeding where there was no statistically significant difference). Serious adverse events occurred in 35% of patients treated with apixaban and 36.5% with warfarin. Prescribers are referred to the SPCs for all three products for further information.

In the RE-LY study, both doses of dabigatran were associated with higher overall rates of myocardial infarction and increased relative risk of MI compared to warfarin. The highest absolute risk of MI was seen in patients with previous MI, patients $\geq$ 65 years with either diabetes or coronary artery disease, patients with a left ventricular ejection fraction < 40%, patients with moderate renal dysfunction and patients taking aspirin plus clopidogrel or clopidogrel alone. In ARISTOTLE, apixaban was associated with a lower rate of MI than warfarin, although this was not statistically significant. The meta-analysis from BMS utilized by NICE concluded that apixaban is associated with a significantly lower incidence of MI than dabigatran (150mg or 110mg twice daily).

Both the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) have recently published on dabigatran. In the December 2011 edition of the MHRA *Drug Safety Update* (reported in *PACE Bulletin* Vol 6 No 4 (February 2012), the MHRA highlighted a number of cases of serious and fatal haemorrhage reported in elderly patients with renal impairment who were receiving dabigatran. A subsequent *Drug Safety Update* published in July 2012 clarified existing MHRA guidance still further as follows:

Dabigatran is contraindicated in clinical conditions associated with a significant risk of bleeding such as:

- current or recent gastrointestinal ulceration.
- malignant neoplasms.
- recent brain or spinal injury.
- recent brain, spinal or ophthalmic surgery.
- recent intracranial haemorrhage.
- oesophageal varices.
- arteriovenous malformations.
- vascular aneurysms.
- major intraspinal or intracerebral vascular abnormalities.

- The benefits and risks of starting dabigatran should also be considered carefully for patients who may have other conditions that put them at an increased risk of major bleeding (but in whom treatment with dabigatran is not contraindicated).
- Use of dabigatran is contraindicated with dronedarone, and with other anticoagulants, except when switching treatment to or from dabigatran , or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency.
- Concomitant use of antiplatelet agents increases the risk of major bleeding with dabigatran approximately two-fold, therefore a careful benefit-risk assessment should be made prior to initiation of treatment.
- Renal function should be assessed: (1) in all patients before starting dabigatran; (2) when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration or with some co-medications); (3) at least annually in patients over 75; (4) at least annually in patients with renal impairment.
- To minimise the risk of bleeding, dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30mL/min).
- In moderate renal impairment (creatinine clearance 30 - 50mL/min), a dose reduction and close clinical surveillance should be considered, particularly in those at increased risk of bleeding. Similar precautions are advocated in those over 75.
- For warfarin, a dose reduction in elderly people should be considered and increased frequency of INR monitoring in patients at high risk of bleeding, including those with renal insufficiency.
- For rivaroxaban caution is required in patients with severe renal impairment (creatinine clearance < 30mL/min) or moderate hepatic impairment. It is not recommended in patients with a creatinine clearance of less than 15mL/min.

Most recently, the EMA have updated their guidance as follows:

- Prescribers are reminded of the need to follow all the necessary precautions with regard to the risk of bleeding with dabigatran, including the assessment of kidney function before treatment in all patients and during treatment if a deterioration is suspected, as well as dose reductions in certain patients.
- Dabigatran must not be used in patients with a lesion or condition putting them at significant risk of major bleeding.
- Dabigatran must not be used in patients using any other anticoagulant, unless the patient is being switched to or from dabigatran.

In March 2013, the MHRA published further guidance on dabigatran, contra-indicating its use in patients with prosthetic heart valve(s) requiring anticoagulant treatment related to their valve surgery, regardless of the length of time that has elapsed since valve replacement took place.

Contra-indications: *Dabigatran*

Dabigatran is contra-indicated in people with:

- hypersensitivity to the active substance or any of the excipients

- severe renal impairment (creatinine clearance < 30ml/min).
- active clinically significant bleeding.
- organic lesion at risk of bleeding.
- impairment of haemostasis.
- hepatic impairment or liver disease expected to have an impact on survival.
- concomitant treatment with systemic ketoconazole, quinidine, ciclosporin, itraconazole, tacrolimus or dronedarone
- concomitant treatment with other anticoagulants (except when switching treatment to or from dabigatran).
- prosthetic heart valve(s) requiring anticoagulant treatment related to their valve surgery, regardless of the length of time that has elapsed since valve replacement took place.

As reported under safety concerns, the MHRA have recently widened this list to include:

- current or recent gastrointestinal ulceration.
- malignant neoplasms.
- recent brain or spinal injury.
- recent brain, spinal or ophthalmic surgery.
- recent intracranial haemorrhage.
- oesophageal varices.
- arteriovenous malformations.
- vascular aneurysms.
- major intraspinal or intracerebral vascular abnormalities.
- prosthetic heart valve(s) requiring anticoagulant treatment related to their valve surgery

Dabigatran should also be used with caution with other p glycoprotein substrates (e.g. verapamil, amiodarone, clarithromycin). A reduced dose of dabigatran is required in patients on verapamil.

Contra-indications: *Rivaroxaban*

Rivaroxaban is contra-indicated in people with:

- hypersensitivity to the active substance or any of the excipients
- severe renal impairment (creatinine clearance < 15ml/min).
- active clinically significant bleeding.
- hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- pregnancy and breast feeding.

Rivaroxaban interacts with the following drugs: any other anticoagulants, azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), HIV protease inhibitors, dronedarone, ciclosporin, tacrolimus, phenytoin, carbamazepine, phenobarbital and St John's wort.

Contra-indications: *Apixaban*

- hypersensitivity to the active substance or any of the excipients.
- clinically significant active bleeding.
- hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- lesion or condition at significant risk of major bleeding such as current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- concomitant treatment with any other anticoagulant agent (e.g. unfractionated heparin, low molecular weight heparins, heparin derivatives, oral anticoagulants)

Apixaban interacts with the following drugs: any other anticoagulants, antiplatelet agents, NSAIDs, acetyl salicylic acid (ASA), ketoconazole, itraconazole, voriconazole, posoconazole, HIV protease inhibitors (e.g. ritonavir), rifampicin, phenytoin, carbamazepine, phenobarbital and St.John's wort.

PACEF Comment: *Drug Interactions*
Whilst dabigatran, rivaroxaban and apixaban interact with other medicines, these are far fewer than the medicines that potentially interact with warfarin and other coumarin anticoagulants. This means that dabigatran, rivaroxaban and apixaban represent viable alternatives for patients requiring warfarin but taking potentially interacting concurrent therapy. The MHRA have recently issued guidance contra-indicating the concurrent use of dabigatran with dronedarone or other anticoagulants (except when switching treatment to or from dabigatran).

Renal Impairment

Drug	Restrictions in patients with renal failure
Apixaban	Reduce dose to 2.5mg twice daily if the eGFR is between 15 and 29mL/minute/1.**73m^2; a**lso reduce to 2.5mg twice daily if serum creatinine $\geq$ 133micromol/litre and age $\geq$80 years or body weight $\leq$ 60kg; apixaban should be avoided if eGFR is less than 15mL/minute/1.73m^2
Dabigatran	Should not be initiated in patients with severe renal impairment (creatinine clearance < 30mL/min).
Rivaroxaban	Caution is required in patients with severe renal impairment (creatinine clearance < 30mL/min); not recommended in patients with a creatinine clearance of less than 15mL/min.

Patients with a baseline eGFR of 30-40mL/min/1.73m^2 are at risk of progressive/acute renal dysfunction and the potential risks of bleeding with dabigatran, rivaroxaban or apixaban

should be weighed on an individual basis. Whilst dabigatran, rivaroxaban or apixaban interact with other medicines, these are far fewer than the medicines that potentially interact with warfarin and other coumarin anticoagulants. This means that dabigatran, rivaroxaban and apixaban represent viable alternatives for patients requiring warfarin but taking potentially interacting concurrent therapy. The MHRA have recently issued guidance contra-indicating the concurrent use of dabigatran with dronedarone or other anticoagulants (except when switching treatment to or from dabigatran).

Monitoring

Renal function should be assessed by calculating the CrCl prior to initiation of treatment with dabigatran, rivaroxaban or apixaban to exclude patients with severe renal impairment. While on treatment, renal function should be assessed at least once a year.

Guidance on switching: *Warfarin to dabigatran or rivaroxaban or apixaban*

When switching warfarin (or another vitamin K antagonist (VKA)) to dabigatran, the VKA should be stopped and the dabigatran initiated as soon as the INR is < 2.0. When switching to dabigatran, the first dose of dabigatran should be given 0-2 hours prior to the time that the next dose of the alternate medicine is due or at the time that continuous alternate treatment is discontinued

When switching warfarin (or another VKA) to rivaroxaban, the VKA should be stopped and the rivaroxaban initiated as soon as the INR is < 3.0. When converting from warfarin to rivaroxaban, INR levels are likely to be falsely elevated after initiation of rivaroxaban. The INR is not a valid measurement of the anticoagulant activity of rivaroxaban and should not be used for this purpose.

When switching warfarin (or another VKA) to apixaban, the VKA should be discontinued and the apixaban initiated as soon as the INR is < 2.0.

Guidance on switching: *Dabigatran or rivaroxaban or apixaban to warfarin*

When switching from dabigatran to warfarin in patients with AF, the starting time of warfarin should be adjusted according to the patient's CrCl. If the patient has a CrCl ≥ 50ml/min, start warfarin 3 days before discontinuing dabigatran. If the CrCl is ≥ 30 to < 50ml/min, start warfarin 2 days before discontinuing dabigatran.

Switching rivaroxaban to warfarin requires the rivaroxaban and the warfarin to be given concurrently until the INR is ≥ 2. For the first two days of the conversion period, give standard initial dosing of warfarin, followed by guidance from INR testing. While patients are on both drugs, the INR should not be tested earlier than 24 hrs after the warfarin dose BUT prior to next dose of rivaroxaban (as stated above rivaroxaban may contribute to an elevated INR). There is a risk of underdosing if this procedure is not followed.

When converting patients from apixaban to VKA therapy, continue administration of apixaban for at least 2 days after beginning VKA therapy. After 2 days of coadministration of

apixaban with VKA therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue coadministration of apixaban and VKA therapy until the INR is ≥ 2.0.

Laboratory results in patients on dabigatran or rivaroxaban or apixaban

1. The INR is not a valid or useful test for dabigatran or rivaroxaban.
2. The Activated Partial Thromboplastin Time (APTT) is sensitive to **dabigatran**. At peak concentration the ratio is 1.5-1.8. High levels may still UNDER-estimate the anticoagulant effect. A normal APTT ratio is likely to exclude therapeutic level of anticoagulation in dabigatran, but cannot exclude a prophylactic-dose anticoagulant effect. The APTT is less sensitive to **rivaroxaban** and cannot be used to assess anticoagulant effect.
3. The Prothrombin Time (PT) is sensitive to **rivaroxaban.** For most laboratories, a normal level of PT excludes a therapeutic intensity of anticoagulation, but cannot exclude a prophylactic level effect.
For both drugs, these laboratory tests cannot be used to determine the drug level. Where this is required, contact the Haematology Consultant for further advice.
4. Effect on other clotting tests:
    - fibrinogen level may be falsely low;
    - D-dimer results are low (as with all anticoagulants).
    - these agents **do not** cause thrombocytopenia (HIT)

Reversal of dabigatran, rivaroxaban and apixaban

There is no known method for reversing dabigatran, rivaroxaban or apixaban. Studies in human volunteers have shown that Prothrombin Complex Concentrate (PCC) can reverse the laboratory abnormalities caused by rivaroxaban, but not dabigatran. However both drugs are associated with a non-linear relationship between prolongation of coagulation tests and bleeding tendency and drug levels, and it remains uncertain whether PCC is a clinically effective method of reversing these drugs. rVIIa and PCC (Beriplex/Octaplex) have been found to be ineffective in dabigatran reversal and rVIIa has been associated with an increased incidence of arterial events. This may be explained by the fact that dabigatran inhibits the last enzymatic step of the coagulation cascade. Any agent that replaces coagulation factors proximal to thrombin will not compensate for the profound terminal defect in haemostasis. Activated PCC (FEIBA) may improve haemostasis by providing small amounts of thrombin, however clinical data to date is lacking.

The MHRA have recently issued advice on reversal and the management of haemorrhagic complications as follows:

- There is no specific antidote to dabigatran and excessive anticoagulation may require interruption of treatment.
- In the event of haemorrhagic complications, dabigatran must be discontinued and the source of the bleeding investigated. Adequate diuresis must be maintained and surgical haemostasis and blood volume replacement should be undertaken at the clinician's discretion.
- Additional measures may be considered in the treatment of serious haemorrhage including: activated prothrombin complex concentrates,

recombinant factor VIIa, or concentrates of coagulation factors II, IX and X and platelet concentrates where appropriate. Coagulation tests may become unreliable following administration of reversing agents and measurements may remain elevated despite administration. Caution must be exercised when interpreting these results.

Dabigatran vs Rivaroxaban vs Apixaban: How they compare

(Note that the trials compared different levels of INR rates –TTR was 64% in RE-LY and 55% in ROCKET AF)	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Efficacy in stroke prevention compared to warfarin	Overall no difference Superior (150mg bd dose) Non-inferior (110mg bd dose)	Overall no difference Non inferior (ITT analysis)	Overall superior. Apixaban is associated with a significantly lower rate of stroke, fatal or disabling stroke, and haemorrhagic stroke than warfarin.
Reduced risk of bleeding compared to warfarin	Evidence for reduced risk of major bleeding at lower dose (110mg bd). Increased risk of GI bleeding compared to warfarin at higher dose (150mg bd dose) Overall reduced risk of intra cranial haemorrhage (ICH)	Equivalent to warfarin (except reduced ICH) Increased risk of GI bleeding compared to warfarin	Apixaban is associated with significantly fewer bleeding events than warfarin for all of the major bleed types (e.g. intracranial) and clinically relevant non-major bleeding events (apart from gastrointestinal bleeding where there was no statistically significant difference).
Reversibility	Uncertain. If last dose taken in last 2 hours consider oral activated charcoal. PCC, rVII or activated PCC can be considered after risk vs benefit assessment	Uncertain (possible data supports use PCC which may reverse the laboratory abnormalities of clotting but this may not translate into stopping the actual bleeding event). PCC, rVII or activated PCC can be considered after risk vs benefit assessment	Uncertain Area Under the Curve may be reduced using activated charcoal. PCC, rVII or activated PCC can be considered after risk vs benefit assessment

Dialysable	Yes, but will need to be carried out for at least 6 hours in order to ensure adequate drug clearance	No	No.
Dosing	Twice daily	Once daily	Twice daily
Drug cautions (increased bleeding risk)	Other anticoagulants. Antiplatelet agents, NSAIDs, SSRIs or SNRIs	Other anticoagulants. Antiplatelet agents, NSAIDs	Other anticoagulants. Antiplatelet agents NSAIDs Acetyl salicylic acid (ASA)
Use in patients with swallowing difficulties	Cannot be crushed	May be crushed and put through NG tube but this is outside of license.	May be crushed and put through NG tube but this is outside of license.
Suitability for Monitored Dosage System	Not suitable	Suitable	suitable
Cost / year (Costs may vary in different settings because of negotiated procurement discounts)	£799.63	£764.40	£799.50
Possibility of using in other conditions	NICE approved for orthopaedic prophylaxis. Phase III data shows efficacy in DVT but no NICE appraisal currently planned	NICE approved for orthopaedic prophylaxis, prevention and treatment of deep vein thrombosis and pulmonary embolism. Licensed for treatment of DVT and PE and prevention of recurrent DVT and PE in adults.	NICE approved for orthopaedic prophylaxis.

Dabigatran vs Rivaroxaban vs Apixaban: Comparative cost

	Dose	***Cost of 12 months treatment***
Apixaban 2.5mg tablets (*Eliquis*)	2.5mg twice daily	£799.50 (28 day cost £61.50)
Apixaban 5mg tablets (*Eliquis*)	5mg twice daily	£799.50 (28 day cost £61.50)
Dabigatran 150mg capsules (*Pradaxa)*	150mg twice daily	£799.63 (28 day cost £61.51)
Dabigatran 110mg capsules (*Pradaxa*)	110mg twice daily	£799.63 (28 day cost £61.51)
Rivaroxaban 20mg tablets (*Xarelto*)	20mg once daily	£764.40 (28 day cost £58.80)

PACEF Comment

All three agents are broadly comparable in terms of NHS cost. The comparative information provided above demonstrates a potential role for all three drugs in different patient groups. As a result of this, all three drugs are approved for use for this indication subject both to NICE criteria and the guidance for new and existing AF patients detailed above. All three drugs are designated GREEN and can be initiated in both primary and secondary care within guidance. There is a considerable financial risk and safety risk associated with inappropriate initiation of dabigatran, rivaroxaban or apixaban in patients that would be more appropriately managed on warfarin. In the NICE TAs referred to above, NICE assumed a reference cost of INR monitoring plus warfarin to be £414.90 per patient per annum. This means that, even with the cost of INR monitoring included, warfarin still emerges as the lowest cost option of the four by a considerable margin. Clinicians are urged to prescribe the new oral anticoagulants solely within the criteria detailed in this guidance.

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Appendix 1

CHA_2DS_2 –VASc score

CHA_2DS_2 –VASc is a further mnemonic device which incorporates a wider range of stroke risk factors that can help to determine stroke risk. CHA_2DS_2 –VASc assigns one point each for congestive heart failure/LV dysfunction (C), hypertension (H), diabetes mellitus (D), vascular disease (prior MI, PAD or aortic plaque), age 65-74 (A), sex (i.e. female) and two points for age 75 or older (A_2), a previous stroke, TIA or thromboembolism (S_2).

	CHA_2DS_2 –VASc Risk Criteria	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age $\geq$ 75	2
D	Diabetes mellitus	1
S_2	Stroke or TIA or thromboembolism	2
V	Vascular disease (prior MI, PAD or aortic plaque)	1
A	Age 65-74	1
S	Sex category (i.e. female)	1

CHA_2DS_2 VASc Score	Adjusted stroke rate (%/ Year)
0	0
1	0.7%

2	1.9%
3	4.7%
4	2.3%
5	3.9%
6	4.5%
7	10.1%
8	14.2%

Any patient with a CHA_2DS_2 –VASc score of $\geq$ 1 is appropriate for consideration for warfarin, dabigatran, rivaroxaban or apixaban within the context of this guidance.

Notes

C A history of any heart failure is not consistently defined as a risk factor. The C in $CHADS_2$ or CHA_2DS_2 –VASc refers to documented moderate-to-severe systolic dysfunction or patients with recent decompensated heart failure requiring hospitalization irrespective of ejection fraction.

Sc Female gender independently increases the risk of stroke overall unless the criteria of 'age <65 and lone AF' is clearly fulfilled whereby female gender does not independently increase stroke risk.

Stroke rates in both male and female patients that fulfil the 'age<65 and lone AF' criteria are so low that antithrombotic therapy is not recommended in this group.

Appendix 2

HAS-BLED Score

Letter	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Definitions

H Hypertension is defined as systolic BP > 160mmHg.

A Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200micromol/L

A Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 times the upper limit of normal, in association with aspartate transaminase /alanine transaminase/alkaline phosphatise >3 times the upper limit of normal).

B Bleeding refers to previous bleeding history or predisposition to bleeding (e.g. bleeding diathesis, anaemia).

L Labile INRs refers to unstable/high international normalized ratios or poor time in therapeutic range (e.g. <60%).

D Drug/alcohol use refers to concomitant use of drugs (e.g. antiplatelet agents, non-steroidal anti-inflammatory drugs).

HAS-BLED Score	**Bleeds per 100 patient years**
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70

The HAS-BLED score has been validated in several independent cohorts and correlates well with intracranial haemorrhage risk. In patients with a HAS-BLED score of ≥ 3, caution and regular review are recommended, as well as efforts to correct potentially reversible risk factors for bleeding wherever possible.

The HAS-BLED score alone should not be used to exclude patients from oral anticoagulant therapy, but can enable clinicians, in conjunction with their patients, to make much more informed decisions. It can also help to identify correctable risk factors such as uncontrolled hypertension, concomitant use of aspirin or NSAIDs, labile INR etc.

Appendix 3

Summary of Benefits and Risks: *Warfarin vs Dabigatran and rivaroxaban*

	Benefits	***Risks***
Effectiveness	*Warfarin remains a well-proven first line therapy. Patients with good INR control using warfarin may achieve slightly better outcomes than those using dabigatran.* *In the RE-LY study, high dose dabigatran (150mg twice daily) has been shown to reduce the risk of stroke compared with warfarin with similar rates of major bleeding. Low dose dabigatran (110mg twice daily) has been shown to reduce risk of major bleeding compared with*	

	warfarin, but there was no difference in risk of stroke. The relative risk of major bleeding with dabigatran, compared to warfarin, increases with age. *In the ROCKET AF trial, rivaroxaban was non-inferior to warfarin for the prevention of stroke, whilst the rates of major bleeding compared with warfarin were similar.* *In the ARISTOTLE trial, apixaban was found to be non-inferior to warfarin and was actually found to be superior to warfarin in some scenarios. It was associated with a significantly lower rate of stroke, both ischaemic and haemorrhagic and systemic thromboembolism than warfarin. The rates of myocardial infarction (MI), pulmonary embolism and deep vein thrombosis were also lower with apixaban compared to warfarin, but differences were not statistically significant.*	
INR Monitoring	*INR monitoring enables assessment of compliance with warfarin.* *Dabigatran, rivaroxaban and apixaban do not require INR monitoring. A more stable level of anticoagulation is achieved.*	*Patients can feel inconvenienced by the demands of routine INR monitoring.* *As dabigatran, rivaroxaban and apixaban do not require INR monitoring, assessment of compliance will have to be undertaken by other means. Patients with poor compliance may be at greater risk of thromboembolic complications as the shorter half-lives will potentially result in more time with insufficient levels of anticoagulation..*
Management of major bleeding	*It is easier to manage major bleeding with patients on warfarin. The anticoagulant effect is easier to measure and rapid reversal can be achieved with vitamin K and prothrombin complex concentrates.*	*Managing major bleeding in patients on dabigatran , rivaroxaban or apixaban is difficult. There is currently no licensed product available to rapidly reverse dabigatran, rivaroxaban or apixaban.(see below)*
Major GI bleeding and GI symptoms	*Rates of major GI bleeding and GI symptoms are lower with warfarin than those reported with dabigatran and rivaroxaban.*	*Rates of major GI bleeding and GI symptoms are greater with dabigatran and rivaroxaban compared to warfarin.*

	In ARISTOTLE, apixaban was associated with fewer bleeding events than warfarin for all of the major bleed types (e.g. intracranial) and clinically relevant non-major bleeding events (apart from gastrointestinal bleeding where there was no statistically significant difference).	In ARISTOTLE, apixaban was associated with fewer bleeding events than warfarin for all of the major bleed types (e.g. intracranial) and clinically relevant non-major bleeding events (apart from gastrointestinal bleeding where there was no statistically significant difference).
Long-term safety	*Warfarin has been in clinical use for over 60 years and long term safety risk is well understood..*	*The long-term safety profiles of dabigatran, rivaroxaban and apixaban are still not fully understood. There are significant risks in exposing a wider population to these drugs before long-term safety has been fully evaluated. Safety concerns have been raised around dabigatran and rivaroxaban and more safety data is continuing to emerge as levels of prescribing increase worldwide.*
Interactions	*There are fewer potential interactions with other medication, alcohol and diet with dabigatran, rivaroxaban and apixaban.*	*There are many complicating interactions with other medication, alcohol and diet with warfarin.*
Onset of action	*There is a rapid onset of action (2-4 hours after first dose) with both dabigatran and rivaroxaban. Apixaban is rapidly absorbed with maximum concentrations appearing 3 to 4 hours after ingestion.*	*Dabigatran and rivaroxaban should be used with caution post surgery.*
Offset of action	*There is a rapid offset of action. Therapeutic effect is lost within 24-48 hours post-dose with both dabigatran and rivaroxaban.*	*Dabigatran has a half life of 12-14 hours in the presence of normal renal function. Rivaroxaban has a half life of 5 to 9 hours in young patients and 11 to 13 hours in elderly patients. Apixaban has a half-life of approximately 12 hours. For all three agents, poor compliance could be potentially disastrous exposing the patient to a greater risk of thromboembolic complications*

Appendix 4: Frequently asked questions about new oral anticoagulants (NOACs) dabigatran, (Pradaxa®) rivaroxaban, (Xarelto®) apixaban (Eliquis®)

Your doctor has assessed you as possibly suitable for one of the new oral anticoagulants. Here are some of the questions you may have about them:

What are NOACs and what are they used for?
NOACs are anticoagulants (blood thinning medicines) which have the advantage of once or twice daily dose without the need for regular monitoring**.** They are used
a) to reduce the risk of blood clot formation in patients with atrial fibrillation (abnormal heart beat). A blood clot in an artery is called an embolism. If the embolism occurs in the arteries of the brain it can cause a stroke.
b) to treat clots in veins (deep vein thrombosis) or the blood vessels of the lungs (pulmonary embolism) and prevent of recurrence of these clots.

Are NOACs associated with any side effects?
All anticoagulants may be associated with side effects. In clinical trials, dabigatran caused more gastrointestinal symptoms than warfarin (e.g., indigestion, stomach ache), whereas rivaroxaban caused more nose-bleeds and haematuria (blood in urine) than warfarin. As these are new drugs, there is no information available about long term safety.

Do NOACs cause less bleeding than warfarin?
NOACs are anticoagulants, and all anticoagulants may cause bruising and bleeding, but serious bleeding is rare. However, the most serious type of bleeding, intracranial bleeding (bleeding into the brain) is rare with the NOACs, but gastrointestinal (stomach and bowel) bleeding is more common, particularly in those over 75 years of age. If you are over 75, or have an increased bleeding risk your doctor may only prescribe dabigatran at a reduced dose or may not prescribe it at all.

If I have excessive bleeding, can the effect of NOACs be reversed?
Unlike warfarin, there is not a licensed product currently available to reverse the effect of NOACs. However, if urgent treatment is required, there are treatments that can be given whilst the effects of the medicines wear off. It is easier to manage major bleeding in patients on warfarin.

Do NOACs need to be monitored?
No. This is an advantage, however if the medication is not taken as prescribed, there is no way of checking the effectiveness of NOACs. It may also be a problem in the elderly as reduced kidney function can increase the risk of bleeding. The dose of NOACs has to be reduced in certain patient groups, for example, the elderly, those with kidney disease and those on some other medicines.

What happens if I miss a dose of a NOAC?
Do not ‘double the dose’ to make up for the missed dose(s). If you have an irregular heartbeat (atrial fibrillation) and 1 or 2 days doses of these drugs are missed, simply continue at the usual dose starting with the next scheduled dose. However, if you are taking rivaroxaban twice daily during the first 3 weeks after a blood clot in the leg or lungs, you should take a missed morning dose as soon as possible and make sure you take 2 of the 15 mg tablets that day.

Can I place my NOAC medication in a Dosette box or other compliance aid?
Rivaroxaban and apixaban, which come in a pill form, can be placed in a Dosette. This is not the case with dabigatran, which is a capsule. Dabigatran needs to be kept in its original

packaging until it is taken, but it can be placed into the Dosette if still within a sealed blister pack.

Should I stop taking NOACs if I have a dental or medical procedure?
NOACs, like warfarin, are anticoagulants and will increase the risk of bleeding. They may need to be stopped a few days prior to surgery or a dental or medical procedure. Do not stop taking NOACs without first talking to the doctor who prescribes it for you.

Will NOACs interact with my other medicines, food or alcohol?
These drugs have fewer potential interactions with other medicines compared with warfarin, and at present there are no known interactions with specific foods or alcohol. There are, however, some medicines that these drugs do interact with. Tell your prescriber the names of all the medicines you are taking (including over-the-counter medicines, vitamins and herbal supplements) so that they can consider all potential interactions.

Can I take my NOAC medication with meals?
Dabigatran capsules should be taken with food to reduce the risk of stomach upset. Rivaroxaban should be taken with a meal to enhance absorption; the pill can also be crushed and taken with soft food such as apple sauce. Apixaban can be taken with a meal but does not need to be.

What if I develop heartburn or stomach upset after starting a NOAC?
Many new drugs can cause stomach upset. This problem occurs in up to 10% of patients who start dabigatran and is less common with rivaroxaban or apixaban. Taking the medication with meals can reduce the risk of stomach upset and the problem often improves on its own after a few days. Antacids may help. If the problem persists, contact your doctor.
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Can I take a non-steroidal drug anti-inflammatory drug (NSAID) if I am taking a NOAC?
In general, long-term use of a NOAC combined with a NSAID such as ibuprofen should be avoided. However, it is probably safe to combine a NOAC with an NSAID for short, 3 to 5 day periods, for example, to treat acute joint pain. Paracetamol is preferred over an NSAID for joint pain, headache or if you have cold or flu-like symptoms. If there is a need for longer periods of treatment with an NSAID, contact your doctor.

Are there other medications that should be avoided when taking a NOAC?
There are certain medications that should be avoided when taking a NOAC. Your doctor or anticoagulant team will advise you.

Can I take herbal medications if I am taking a NOAC?
You should avoid taking St.John's Wort (used to treat symptoms of depression) if you are taking a NOAC. There are no restrictions for other herbal medications. Check with your doctor or pharmacist if you are uncertain.