

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 (THIRD EDITION)

What's new in the Third Edition?

- The publication of NICE Clinical Guideline 180: *Atrial fibrillation: the management of atrial fibrillation* (June 2014) has necessitated a full review of existing PACEF guidance on stroke prevention in AF.
- These guidelines for anticoagulation apply to paroxysmal, persistent and permanent AF and atrial flutter.
- 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. NICE CG 180 recommends that manual pulse palpation should be used to identify an irregular pulse that may signify underlying AF in people presenting with breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, stroke or transient ischaemic attack (TIA).
- NICE CG 180 also recommends that an ECG is performed on all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.
- The Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF) tool can be run on GP clinical systems and used to identify patients with AF at risk of stroke.
- National data published as part of the GRASP-AF initiative reported 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. Anticoagulation is now the preferred treatment to reduce the risk of stroke in these patients.
- In accordance with NICE CG 180, the CHA₂DS₂-VASc score is the recommended stroke risk scoring system; the recommended threshold has also been reduced to greater than or equal to 1 in line with European Society of Cardiology recommendations. Patients with a CHA₂DS₂-VASc score ≥ 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.
- This guidance is designed to inform treatment selection for patients identified as at significant risk (i.e. CHA₂DS₂-VASc score ≥ 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 CHA₂DS₂-VASc assessment on the grounds of female gender.
- Use HAS-BLED in all AF patients to assess bleeding risk. Modifiable factors that reduce bleeding risk should be addressed. For most patients the benefit of anticoagulation outweighs the bleeding risk.
- Warfarin therapy should not be withheld solely due to the risk of falling. One study found that a person aged 65 or over anticoagulated with warfarin for stroke prevention in AF would need to fall 295 times in a year for warfarin not to be considered the optimum therapy.
- 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. As a result of this, NICE have recommended that aspirin monotherapy should not be used solely for stroke prevention in people with atrial fibrillation. All patients currently receiving aspirin monotherapy or dual antiplatelet therapy within this context should be reviewed. Patients taking antiplatelet therapy for another indication can continue as necessary.
- Apixaban, dabigatran and rivaroxaban have not been studied in patients with mechanical heart valves or in patients with valvular disease. As a result of this, warfarin is preferred in these patients.
- All of the NOACs have a restricted role in patients with renal failure, particularly dabigatran. For all patients being considered for NOAC therapy, renal function must be assessed and monitored. It is recommended that the Cockcroft and Gault formula should be used to calculate Creatinine Clearance to inform the decision around NOAC initiation, especially in patients with extreme BMI (see notes on eGFR and Creatinine Clearance calculation in the *Renal Impairment* section).
- Patients with a baseline eGFR of 30-40mL/min/1.73m² 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. Renal function can decline while on treatment; monitoring should be at least annually and every three months in high risk patients (i.e. those with existing renal impairment, those over 75 and those with declining renal function).

CONTENTS

Page 3	Summary of PACEF decisions and <i>Lincolnshire Joint Formulary</i> status: November 2014 update
Page 4	Introduction
Page 5	Considering or offering anticoagulation
Page 6	Treatment selection: <i>Newly diagnosed Atrial Fibrillation patients (CHA₂DS₂-VASc score ≥ 1) requiring oral anticoagulant stroke thromboprophylaxis</i>
Page 8	Treatment selection: <i>Existing patients diagnosed with AF (CHA₂DS₂-VASc score ≥ 1) currently taking a vitamin K antagonist</i>
Page 9	NICE Technology Appraisal 249: <i>Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation</i> (March 2012)
Page 9	NICE Technology Appraisal 256: <i>Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation</i> (May 2012)
Page 9	NICE Technology Appraisal 275: <i>Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation</i> (February 2013)
Page 10	NICE Clinical Guideline 180: <i>Atrial fibrillation: the management of atrial fibrillation</i> (June 2014)

Page 11	NICE Diagnostic Guidance 14: <i>Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point of care coagulometers (CoaguChek XS system and INRatio 2 PT/INR monitor)</i> (September 2014)
Page 12	Licensed doses for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation
Page 12	Safety concerns
Page 14	Contra-indications
Page 15	Renal impairment
Page 16	Interactions
Page 16	Guidance on switching: <i>Warfarin to dabigatran, rivaroxaban or apixaban</i>
Page 17	Guidance on switching: <i>Dabigatran, rivaroxaban or apixaban to warfarin</i>
Page 17	Laboratory results in patients on dabigatran, rivaroxaban or apixaban
Page 18	Reversal of dabigatran, rivaroxaban and apixaban
Page 18	Dabigatran vs Rivaroxaban vs Apixaban: How they compare
Page 20	Dabigatran vs Rivaroxaban vs Apixaban: Comparative Cost
Page 20	References
Page 21	Acknowledgements
Page 21	Appendix 1: CHA₂DS₂-VASc score
Page 22	Appendix 2: HAS-BLED score
Page 24	Appendix 3: <i>Summary of Benefits and Risks: Warfarin vs Dabigatran, rivaroxaban and apixaban</i>
Page 26	Appendix 4: <i>Frequently asked questions about new oral anticoagulants</i>
Page 29	Appendix 5: <i>Considerations for anticoagulation in NVAF in primary care (East Midlands Strategic Cardiac Network Algorithm)</i>

SUMMARY OF PACEF DECISIONS AND LINCOLNSHIRE JOINT FORMULARY STATUS: DECEMBER 2014 UPDATE

Drug	Indication(s)	Traffic Light Status
Dabigatran etexilate 110mg and 150mg capsules (<i>Pradaxa</i>)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more of the following: <ul style="list-style-type: none"> • 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 <i>Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation</i> (Third Edition) Approved for inclusion in the <i>Joint Formulary</i> for this indication
Rivaroxaban 20mg tablets (<i>Xarelto</i>)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors: <ul style="list-style-type: none"> • congestive heart failure. • hypertension. • ≥ 75 years. • diabetes mellitus. • previous stroke or transient ischaemic attack. 	GREEN Subject to both NICE criteria and Lincolnshire <i>Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation</i> (Third Edition) Approved for inclusion in the <i>Joint Formulary</i> for this indication
Apixaban tablets 2.5mg and 5mg (<i>Eliquis</i>)	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: <ul style="list-style-type: none"> • 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 <i>Guidance on the Prescribing of Warfarin, Dabigatran, Rivaroxaban or Apixaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation</i> (Third Edition) Approved for inclusion in the <i>Joint Formulary</i> for this indication

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. AF is the most common sustained cardiac arrhythmia; it affects men more commonly than women with prevalence increasing steeply with age from 0.5% in those aged 50 to 59 to 10% in those over 80.

National data published as part of the Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF) initiative reported that 8.5% of AF patients at high risk of stroke were receiving no treatment, 35% were on aspirin and 56.9% were 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, the East Midlands Cardiac Network and most recently NICE in Clinical Guideline 180: *Atrial fibrillation: the management of atrial fibrillation* (June 2014). 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. NICE CG 180 recommends that manual pulse palpation should be used to identify an irregular pulse that may signify underlying AF in people presenting with breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, stroke or transient ischaemic attack (TIA). NICE also recommend that an ECG should be performed on all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.

Following diagnosis, it is important to undertake a stroke and bleeding risk assessment. NICE recommend that the CHA₂DS₂-VASc stroke risk score should be used to assess stroke risk in people with: (1) symptomatic or asymptomatic paroxysmal, persistent or permanent AF; (2) atrial flutter, or (3) a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm (for more information on CHA₂DS₂-VASc see Appendix 1). CHA₂DS₂-VASc takes into account a wider range of risk factors than CHADS₂ 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, and in accordance with the NICE CG, the CHA₂DS₂-VASc score is the recommended stroke risk scoring system in Lincolnshire. Patients with a CHA₂DS₂-VASc score ≥ 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. 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 CHA₂DS₂-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. The HAS-BLED score should be used in all AF patients to assess bleeding risk (see 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 ≥ 3 , caution and regular review are recommended, as well as efforts to correct potentially reversible risk factors for

bleeding wherever possible. For most patients the benefit of anticoagulation outweighs the bleeding risk. Warfarin therapy should not be withheld solely due to the risk of falling.

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 CHA₂DS₂-VASc score of 1 based on gender alone). Patients with a CHA₂DS₂-VASc score of ≥ 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. The evidence for effective stroke prevention in AF with aspirin 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. As a result of this, NICE have recommended that aspirin monotherapy should not be used solely for stroke prevention in people with AF. All patients currently receiving aspirin monotherapy or dual antiplatelet therapy within this context should be reviewed. Aspirin or dual antiplatelet therapy must not be used routinely as an alternative to oral anticoagulants in patients with a CHA₂DS₂-VASc score of ≥ 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 within the context of NICE CG180 and other local, national and European guidance.

Considering or offering anticoagulation

CHA₂DS₂-VASc score	Action
CHA ₂ DS ₂ -VASc = 0 (Men) or CHA ₂ DS ₂ -VASc =1 (Women)	No antithrombotics. Reassess stroke risk and bleeding risk annually. Do not offer aspirin, clopidogrel or dual antiplatelet therapy (or any other drug) for stroke prevention. Existing patients at this level of risk should not be taking antiplatelet therapy for stroke prevention in AF. Reassess stroke and bleeding risk annually. Review patients not taking any anticoagulants when they reach the age of 65 or if they develop any of the following at any age: (1) diabetes; (2) heart failure; (3) peripheral arterial disease; (4) coronary heart disease; (5) stroke, TIA or systemic thromboembolism.
CHA ₂ DS ₂ -VASc = 1 (Men)	Consider anticoagulation either warfarin or a new oral anticoagulant bearing in mind bleeding risk. Do not offer aspirin, clopidogrel or dual antiplatelet therapy (or any other drug) for stroke prevention. Existing patients at this level of risk should not be taking antiplatelet therapy for stroke prevention in AF. If anticoagulation is not indicated do not offer antithrombotic therapy.

	<p>Discuss the options for anticoagulation with the patient and base treatment selection on their clinical features and preferences.</p> <p>Reassess stroke and bleeding risk annually. If on warfarin assess time in therapeutic range; if on a NOAC assess compliance.</p> <p>This intervention will do more good than harm for most patients and is cost-effective; other options may be similarly cost effective.</p>
CHA ₂ DS ₂ -VASc ≥ 2 (men and women)	<p>Offer anticoagulants either warfarin or a new oral anticoagulant bearing in mind bleeding risk.</p> <p>Do not offer aspirin, clopidogrel or dual antiplatelet therapy (or any other drug) for stroke prevention. Existing patients at this level of risk should not be taking antiplatelet therapy for stroke prevention in AF.</p> <p>Discuss the options for anticoagulation with the patient and base treatment selection on their clinical features and preferences.</p> <p>Reassess stroke and bleeding risk annually. If on warfarin assess time in therapeutic range; if on a NOAC assess compliance.</p> <p>This intervention will do more good than harm and is cost-effective</p>

Treatment selection

Newly diagnosed AF patients (CHA₂DS₂-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 (CHA₂DS₂-VASc score ≥ 1) with good INR control. It should be the preferred option in those with:

- an estimated Glomerular Filtration Rate (eGFR) < 30mL/min/1.73m² as clearance of warfarin is not affected by renal function (see notes on eGFR and Creatinine Clearance calculation in the *Renal Impairment* section).
- a history of significant peptic ulcer disease (rates of major gastrointestinal 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).
- concomitant valve disease, including valve replacement or valvular AF (where treatment should be with warfarin, not a NOAC).

The newer oral anticoagulant drugs (NOACs), 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 medicines or foods 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 NOAC 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. Prescribers should note that NICE have recently published a piece of diagnostic guidance (DG14) that supports self-monitoring of coagulation status in adults and children on long-term vitamin antagonist therapy who have AF or heart valve disease using either the *CoaguChek XS* system or *INRatio 2* PT/INR monitoring. Only people who are considered physically and cognitively able to self-monitor in this way should be supported to do this. Patients must be trained in the use of the self-monitoring system prescribed and must be monitored regularly to ensure that they continue to test regularly and reliably. Where self-monitoring is supported, the patient's equipment should be regularly recalibrated and checked for accuracy. Where self-monitoring is supported, the *CoaguChek XS* system is preferred.
- 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. As a result of this, NICE have recommended that aspirin monotherapy should not be used solely for stroke prevention in people with atrial fibrillation. All patients currently receiving aspirin monotherapy or dual antiplatelet therapy within this context should be reviewed. Patients taking antiplatelet therapy for another indication can continue as necessary. An algorithm to inform decision making around the potential for dual or triple therapy with antiplatelet agents and anticoagulants is under development in collaboration with cardiologists at United Lincolnshire Hospital Trust and will be published separately in 2015.

Existing patients diagnosed with AF (CHA₂DS₂-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 (CHA₂DS₂-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. Prescribers should note that NICE have recently published a piece of diagnostic guidance (DG14) that supports self-monitoring of coagulation status in adults and children on long-term vitamin antagonist therapy who have AF or heart valve disease using either the *CoaguChek XS* system or *INRatio 2 PT/INR* monitoring. Only people who are considered physically and cognitively able to self-monitor in this way should be supported to do this. Patients must be trained in the use of the self-monitoring system prescribed and must be monitored regularly to ensure that they continue to test regularly and reliably. Where self-monitoring is supported, the patient's equipment should be regularly recalibrated and checked for accuracy. Where self-monitoring is supported, the *CoaguChek XS* system is preferred.

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.

All of the NOACs have a restricted role in patients with renal failure, especially dabigatran. For all patients being considered for NOAC therapy, renal function must be assessed and monitored. It is recommended that the Cockcroft and Gault formula should be used to calculate Creatinine Clearance to inform the decision around NOAC initiation, especially in patients with extreme BMI.

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.
- ≥ 75 years.
- ≥ 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.

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 of their level of international normalised ratio (INR) control.

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 used in a relatively small patient population. Patients need to be fully aware of the not inconsiderable risks with either warfarin or the newer anticoagulant drugs.

NICE Clinical Guideline 180: Atrial fibrillation: the management of atrial fibrillation (June 2014)

Key points are as follows:

Diagnosis and assessment

- Perform manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying AF in people presenting with breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, stroke/TIA.
- Perform an ECG on all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.

Assessment of stroke and bleeding risks

Stroke risk

- Use the CHA₂DS₂-VASc stroke risk score to assess stroke risk in people with: (1) symptomatic or asymptomatic paroxysmal, persistent or permanent AF; (2) atrial flutter, or (3) a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Bleeding risk

- Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:
 - uncontrolled hypertension.
 - poor control of international normalised ratio (INR)
 - concurrent medication (e.g. aspirin, NSAID etc)
 - harmful alcohol consumption.
- For most people the benefit of anticoagulation outweighs the bleeding risk.
- Do not withhold anticoagulation solely because the person is at risk of having a fall.

Interventions to prevent stroke

- Do not offer stroke prevention therapy to people aged under 65 with AF and no risk factors other than their sex (i.e. CHA₂DS₂-VASc score of 0 for men and 1 for women).

Anticoagulation

- Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist.
- Consider anticoagulation to men with CHA₂DS₂-VASc stroke risk score of 1. Take the bleeding risk into account.
- Offer anticoagulation to people with a CHA₂DS₂-VASc stroke risk score of 2 or above, taking bleeding into account.

Assessing anticoagulation control with vitamin K antagonists

- Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR: (1) use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual

dosing; (2) exclude measurements taken during the first 6 weeks of treatment; (3) calculate TTR over a maintenance period of at least 6 months.

- Reassess anticoagulation for a person with poor anticoagulation control shown by: (1) 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months; (2) 2 INR values less than 1.5 within the past 6 months; (3) TTR less than 65%.
- When reassessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control: (1) cognitive function; (2) adherence to prescribed therapy; (3) illness; (4) interacting drug therapy; (5) lifestyle factors including diet and alcohol consumption.
- If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person.

Self-monitoring and self-management of vitamin K antagonists

- NICE has developed diagnostics guidance on self-monitoring of VKAs using point of care coagulometers (e.g. *CoaguChek XS* system and *INRatio2 PT/INR monitor*) (see below)

Antiplatelets

- Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation.

Review of people with AF

- For people who are taking an anticoagulant, review stroke risk when they reach 65 or if they develop any of the following at any age: diabetes, heart failure, peripheral arterial disease, coronary heart disease, stroke, TIA or systemic thromboembolism.
- For people who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks annually and ensure that all reviews and decisions are documented.
- For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk.

NICE Diagnostic Guidance 14: Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point of care coagulometers (CoaguChek XS system and INRatio 2 PT/INR monitor) (September 2014)

NICE recommend the *CoaguChek XS* system and the *InRatio2* PT/INR monitor for self-monitoring coagulation status in adults and children on long-term VKA therapy who have AF or heart valve disease if:

- the person prefers this form of testing and
- the person or carer is both physically and cognitively able to self-monitor effectively.

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

<u>Drug</u>	<u>Licensed dose for prevention of stroke and systemic embolism in non-valvular AF</u>
Apixaban (<i>Eliquis</i>)	5mg twice daily; for the elderly over 80 with body weight less than 60kg 2.5mg twice daily.
Dabigatran (<i>Pradaxa</i>)	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. Dabigatran capsules must be swallowed whole and not chewed or crushed.
Rivaroxaban (<i>Xarelto</i>)	20mg once daily long-term (provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding).

Safety concerns

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 ≥ 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. Local specialist guidance recommends quarterly re-assessment of CrCl in patients particularly at risk of declining renal function. Patients with a baseline eGFR of 30-40mL/min/1.73m² 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. Renal function can decline while on treatment; monitoring should be at least annually and every three months in high risk patients (i.e. those with existing renal impairment, those over 75 and those with declining renal function).
- 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

Drug	Contra-indications
Apixaban (<i>Eliquis</i>)	<p>Hypersensitivity to the active substance or any of the excipients.</p> <p>Clinically significant active bleeding.</p> <p>Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.</p> <p>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.</p> <p>Concomitant treatment with any other anticoagulant agent (e.g. unfractionated heparin, low molecular weight heparins, heparin derivatives, oral anticoagulants)</p> <p>Apixaban interacts with the following drugs: any other anticoagulants, antiplatelet agents, NSAIDs, acetyl salicylic acid (ASA), ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (e.g. ritonavir), rifampicin, phenytoin, carbamazepine, phenobarbital and St.John's wort.</p>
Dabigatran (<i>Pradaxa</i>)	<p>Hypersensitivity to the active substance or any of the excipients</p> <p>Severe renal impairment (creatinine clearance < 30ml/min).</p> <p>Active clinically significant bleeding.</p> <p>Organic lesion at risk of bleeding.</p> <p>Impairment of haemostasis.</p> <p>Hepatic impairment or liver disease expected to have an impact on survival.</p> <p>Concomitant treatment with systemic ketoconazole, quinidine, ciclosporin, itraconazole, tacrolimus or dronedarone</p> <p>Concomitant treatment with other anticoagulants (except when switching treatment to or from dabigatran).</p> <p>Pprosthetic 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.</p> <p>The MHRA have recently widened this list to include:</p> <ul style="list-style-type: none"> ○ current or recent gastrointestinal ulceration. ○ malignant neoplasms. ○ recent brain or spinal injury. ○ recent brain, spinal or ophthalmic

	<p>surgery.</p> <ul style="list-style-type: none"> ○ 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 <p>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.</p>
Rivaroxaban (<i>Xarelto</i>)	<p>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.</p> <p>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.</p>

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 ; also reduce to 2.5mg twice daily if serum creatinine ≥ 133micromol/litre and age ≥80 years or body weight ≤ 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); contra-indicated in patients with a creatinine clearance of less than 15mL/min.
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All of the NOACs have a restricted role in patients with renal failure (see table above). For all patients being considered for NOAC therapy, renal function must be assessed and monitored. It is recommended that the Cockcroft and Gault formula should be used to calculate Creatinine Clearance to inform the decision around NOAC initiation, especially in patients with extreme BMI:

$$\text{Estimated Creatinine Clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{Weight} \times \text{Constant}}{\text{Serum Creatinine}}$$

Age (years), Weight (kg), Serum Creatinine (micromole/litre), Constant 1.23 for men; 1.04 for women. For web based calculation <http://nephron.com/cgi-bin/CGSI.cgi>

Patients with a baseline eGFR of 30-40mL/min/1.73m² 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. Renal function can decline while on treatment; monitoring should be at least annually and every three months in high risk patients (i.e. those with existing renal impairment, those over 75 and those with declining renal function).

Interactions

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).

Guidance on switching: Warfarin to dabigatran or rivaroxaban or apixaban

	Action
Warfarin to dabigatran	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. Caution: INR values will be falsely elevated when taking dabigatran.
Warfarin to rivaroxaban	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. Caution: INR values will be falsely elevated when taking rivaroxaban.
Warfarin to apixaban	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.
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Guidance on switching: Dabigatran or rivaroxaban or apixaban to warfarin

	Action
Dabigatran 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 \geq 50ml/min, start warfarin 3 days before discontinuing dabigatran. If the CrCl is \geq 30 to < 50ml/min, start warfarin 2 days before discontinuing dabigatran. Caution: INR values will be falsely elevated. INR testing should not be performed until dabigatran has been stopped for at least 2 days.
Rivaroxaban to warfarin	Switching rivaroxaban to warfarin requires the rivaroxaban and the warfarin to be given concurrently until the INR is \geq 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.
Apixaban to warfarin	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 co-administration of apixaban with VKA therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and VKA therapy until the INR is \geq 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

<i>(Note that the trials compared different levels of INR rates –TTR was 64% in RE-LY and 55% in ROCKET AF)</i>	Dabigatran	Rivaroxaban	Apixaban
Efficacy in stroke prevention compared to warfarin	Overall no difference Slightly superior to warfarin (150mg bd dose) Non-inferior (110mg bd dose) (RE-LY)	Overall no difference Non inferior to warfarin (ROCKET-AF)	Overall superior to warfarin (ARISTOTLE) Apixaban is associated with a significantly lower rate of stroke, fatal or disabling stroke, and haemorrhagic stroke than warfarin.
Risk of bleeding compared to warfarin	Evidence for reduced risk of major bleeding at lower dose (110mg bd) (RE-LY); 150mg bd similar risk Increased risk of GI bleeding compared to warfarin at higher dose (150mg bd)	Similar risk of major bleeding to warfarin (ROCKET-AF) Reduced risk of intracranial bleeding (ROCKET-AF) Increased risk of GI	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) (ARISTOTLE).

	dose) Overall reduced risk of intra cranial haemorrhage (ICH)	bleeding compared to warfarin (ROCKET-AF)	
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	Only suitable for use in pre-packaged MDS produced by the manufacturer	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	NICE approved for orthopaedic prophylaxis.

Dabigatran vs Rivaroxaban vs Apixaban: Comparative cost

	Dose	Cost of 12 months treatment
Apixaban 2.5mg tablets (<i>Eliquis</i>)	2.5mg twice daily	£799.50 (28 day cost £61.50)
Apixaban 5mg tablets (<i>Eliquis</i>)	5mg twice daily	£799.50 (28 day cost £61.50)
Dabigatran 150mg capsules (<i>Pradaxa</i>)	150mg twice daily	£799.63 (28 day cost £61.51)
Dabigatran 110mg capsules (<i>Pradaxa</i>)	110mg twice daily	£799.63 (28 day cost £61.51)
Rivaroxaban 20mg tablets (<i>Xarelto</i>)	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; all three are included in the *Lincolnshire Joint Formulary*. There is a financial 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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NICE Technology Appraisal 256: *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation* (May 2012)

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Appendix 1

CHA₂DS₂ –VASc score

CHA₂DS₂ –VASc is a mnemonic device which incorporates a wide range of stroke risk factors that can help to determine stroke risk. CHA₂DS₂ –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 (A₂), a previous stroke, TIA or thromboembolism (S₂).

	CHA₂DS₂ –VASc Risk Criteria	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A ₂	Age ≥ 75	2
D	Diabetes mellitus	1
S ₂	Stroke or TIA or	2

	thromboembolism	
V	Vascular disease (prior MI, PAD or aortic plaque)	1
A	Age 65-74	1
S	Sex category (i.e. female)	1

CHA₂DS₂-VASc Score and stroke risk

CHA ₂ DS ₂ -VASc Score	n	Ischaemic stroke (events per 100 patients/year)	Stroke/TIA/peripheral emboli (events per 100 patients/year)
0	5343	0.2	0.3
1	6770	0.6	1.0
2	11,240	2.5	3.3
3	17,689	3.7	5.3
4	19,091	5.5	7.8
5	14,488	8.4	11.7
6	9577	11.4	15.9
7	4465	13.1	18.4
8	1559	12.6	17.9
9	268	14.4	20.3

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Friberg L et al., Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal* (2012) 33 (12): 1500-1510.

NICE recommend the use of CHA₂DS₂-VASc to assess the risk of stroke in people with:

- symptomatic or asymptomatic paroxysmal, persistent or permanent AF.
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Any patient with a CHA₂DS₂-VASc score of ≥ 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 CHADS₂ or CHA₂DS₂-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 \geq 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 phosphatase >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 and risk of major bleeding

HAS-BLED Score	Major bleeding events per 100 patient/year in anticoagulant users (N=48,599)
0	-
1	0.7
2	1.9
3	2.4
4	3.4
5	5.7
6	15.5

Reference

Friberg L et al., Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal* (2012) 33 (12): 1500-1510.

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 \geq 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, harmful alcohol consumption etc. For most patients the benefit of anticoagulation outweighs the bleeding risk. Warfarin therapy should not be withheld solely due to the risk of falling.

Appendix 3

Summary of Benefits and Risks: Warfarin vs Dabigatran and rivaroxaban

	Benefits	Risks
Effectiveness	<p><i>Warfarin remains a well-proven first line therapy. Patients with good INR control using warfarin may achieve slightly better outcomes than those using dabigatran.</i></p> <p><i>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.</i></p> <p><i>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.</i></p> <p><i>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.</i></p>	
INR Monitoring	<p><i>INR monitoring enables assessment of compliance with warfarin.</i></p> <p><i>Dabigatran, rivaroxaban and apixaban do not require INR monitoring. A more stable level of anticoagulation is achieved.</i></p>	<p><i>Patients can feel inconvenienced by the demands of routine INR monitoring. Some people may have difficulty complying with or accessing INR monitoring.</i></p> <p><i>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</i></p>

		<i>thromboembolic complications as the shorter half-lives will potentially result in more time with insufficient levels of anticoagulation..</i>
Management of major bleeding	<i>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.</i>	<i>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)</i>
Major GI bleeding and GI symptoms	<i>Rates of major GI bleeding and GI symptoms are lower with warfarin than those reported with dabigatran and rivaroxaban.</i> <i>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).</i>	<i>Rates of major GI bleeding and GI symptoms <u>are</u> greater with dabigatran and rivaroxaban compared to warfarin.</i> <i>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).</i>
Long-term safety	<i>Warfarin has been in clinical use for over 60 years and long term safety risk is well understood.</i>	<i>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.</i>
Interactions	<i>There are fewer potential interactions with other medication, alcohol and diet with dabigatran, rivaroxaban and apixaban.</i>	<i>Warfarin is known to interact with certain foods (e.g. cranberry, alcohol and other foods containing high amounts of vitamin K).</i>
Onset of action	<i>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.</i> <i>For warfarin, the time to peak effect ranges from 3 to 5 days with a half-life averaging 40 hours. For patients with poor adherence, the long time to onset and offset of action may be advantageous as the anticoagulant effect of warfarin will persist for days after the last dose.</i>	<i>Dabigatran and rivaroxaban should be used with caution post- surgery.</i>
Offset of action	<i>Therapeutic effect is lost within 24-48 hours post-dose with both</i>	<i>Dabigatran has a half life of 12-14 hours in the presence of</i>

	<p><i>dabigatran and rivaroxaban.</i></p> <p><i>For warfarin, the time to peak effect ranges from 3 to 5 days with a half-life averaging 40 hours. For patients with poor adherence, the long time to onset and offset of action may be advantageous as the anticoagulant effect of warfarin will persist for days after the last dose.</i></p>	<p><i>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</i></p>
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Appendix 4: Frequently asked questions about new oral anticoagulants (NOACs) dabigatran (Pradaxa), rivaroxaban (Xarelto) and 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 a once or twice daily dose without the need for regular monitoring. They are used

- a) to reduce the risk of blood clot formation in people 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 medicine wear off. It is easier to manage major bleeding in patients on warfarin.

Do NOACs need to be monitored?

No. This can be an advantage as long as you reliably take the NOAC as prescribed. Traditional anticoagulants like warfarin are regularly monitored by your doctor, with blood monitoring providing confirmation that you are taking your warfarin as prescribed. There is no similar way of checking your continued compliance with NOAC therapy.

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; they must be swallowed whole and not chewed. 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.

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.

Considerations for Anticoagulation in NVAF for Primary Care

The EMSCN has produced the NVAF anticoagulation algorithm as an aid to clinicians to decide upon the most appropriate anticoagulation option for a patient **once the decision to anticoagulate has been made.**

The algorithm is being shared with CCGs and medicines management groups in the East Midlands as an aid to support the updating of local prescribing guidelines following publication of the NICE Guidelines for Atrial Fibrillation in June 2014.

Clinicians who view this algorithm should be aware that it is not a replacement of their local published guidelines.

Table 1 (adapted from NICE: Patient Decision Aid –Atrial Fibrillation: medicines to help reduce your risk of a stroke – what are the options; June 2014?)

Patients should be encouraged to consider how important the following issues are to them and to discuss them with their GP prior to the initiation of an anticoagulant whether that be warfarin or a NOAC

1. What tablets or capsules I'd have to take and how often

Warfarin dosing is variable whereas NOAC dosing is fixed. Warfarin is prescribed once daily whereas NOACs are either once daily (rivaroxaban) or twice daily (dabigatran or apixaban)

2. The effect on my risk of having an AF-related ischaemic stroke

Warfarin reduces the stroke risk in AF patients by approximately 65%. The NOACs have been shown to be at least as good as warfarin at reducing ischaemic stroke in AF patients and dabigatran 150mg bd has actually been shown to be better than warfarin at reducing ischaemic stroke in a large clinical trial.

3. The effect on my risk of having major bleeding

All anticoagulants significantly increase the risk of major bleeding. The NOACs in general cause no more major bleeding than warfarin and dabigatran 110mg and apixaban 5mg are both actually associated with less overall major bleeding when compared to warfarin. All NOACs are associated with significantly less bleeding within the brain compared to warfarin. Dabigatran 150mg and rivaroxaban 20mg are both associated with more gastrointestinal bleeding than warfarin.

4. The need for regular blood tests

Unlike with warfarin, the NOACs do not require anticoagulation monitoring. However, renal function, full blood count and liver function should be periodically assessed.

5. What would happen if I forget to take a dose?

It is potentially more dangerous if the odd dose of a NOAC is missed compared to missing the odd dose of warfarin as the NOACs have much shorter half lives (~ 12 hrs).

6. The need to change what I eat or drink

The NOACs have no known food or drink interactions (unlike warfarin- eg green leafy vegetables). The NOACs are also likely to be safer than warfarin in patients who have a high and variable alcohol intake

7. Whether the medicine will interact with other medicines I take

The NOACs have far fewer drug interactions compared to warfarin. Use of anti-inflammatory painkillers (eg ibuprofen) should be with caution with all anticoagulants.

8. What would happen if the effects need to be reversed in an emergency

Warfarin has a known antidote but it is not always possible to reverse its effects quickly. The NOACs do not have known antidotes but their effects wear off more quickly than warfarin and there are strategies that can be used to help reduce the anticoagulant effects

