NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 13 **August 2012**

GUIDANCE ON THE PRESCRIBING OF WARFARIN, DABIGATRAN OR RIVAROXABAN FOR THE PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN ATRIAL FIBRILLATION

CONTENTS

SUMMARY OF PACEF DECISIONS: JUNE/JULY 2012 UPDATE

Drug	Indication(s)	Traffic Light Status
Dabigatran etexilate capsules (Pradaxa)	Licensed 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%.	GREEN Subject to both NICE criteria and Lincolnshire *Guidance on the Prescribing of Warfarin, Dabigatran or Rivaroxaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation*

	• symptomatic heart failure (≥ NYHA class II). • ≥ 75 years. • ≥ 65 years with diabetes, coronary artery disease or hypertension (110mg and 150mg capsules only).	
Rivaroxaban tablets (Xarelto)	Licensed 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 or Rivaroxaban for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation*

Summary of Guidance

Newly diagnosed AF patients ($CHADS_2$ or CHA_2DS_2-VASc score greater than or equal to 2) 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 ($CHADS_2$ or CHA_2DS_2 –VASc score ≥ 2) with good INR control. It should be the preferred option in those with:

- **an estimated Glomerular Filtration Rate (eGFR) < 30mL/min/1.73m^2. Dabigatran should not be initiated in patients with severe renal impairment (creatinine clearance < 30mL/min) For rivaroxaban caution is required in patients with severe renal impairment (creatinine clearance < 30mL/min); it is 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 or rivaroxaban should be weighed on an individual basis.**
- **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).**
- **significant ischaemic heart disease in the absence of other determining considerations (rates of myocardial infarction are lower with warfarin than those reported with dabigatran).**

Recent MHRA guidance has also contra-indicated dabigatran in clinical conditions 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 use of dabigatran is also contraindicated with dronedarone and with other anticoagulants (except when switching treatment to or from dabigatran).

The newer oral anticoagulant drugs (OACs), dabigatran and rivaroxaban, 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. The range of interacting medicines with dabigatran and/or rivaroxaban is considerably narrower.**
- **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 and rivaroxaban. A table summarizing the benefits and risks of each option is included in the text. 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 or rivaroxaban in the event of major bleeding.**
- **the principles used in patient selection (see above)**
- **the potential option to convert the patient to dabigatran or rivaroxaban (if appropriate), if Time in Therapeutic Range (TTR) is < 60% after 4 months in the presence of compliance.**

Existing patients diagnosed with AF ($CHADS_2$ or CHA_2DS_2-VASc score greater than or equal to 2) 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 ($CHADS_2$ or CHA_2DS_2 –VASc score ≥ 2) with good INR control. Clinicians should consider dabigatran or rivaroxaban 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 or rivaroxaban. Poor compliers with warfarin are likely to be poor compliers with dabigatran or rivaroxaban.**
- **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 or rivaroxaban 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.**
- **with a history of stroke or transient ischaemic attack (TIA) while taking warfarin (providing there is no evidence of poor or non compliance). 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 or rivaroxaban please refer to the guidance on switching that appears in this *Bulletin* (see below) and in the Summaries of Product Characteristics for dabigatran and rivaroxaban. Similarly, guidance on switching from dabigatran/rivaroxaban to warfarin is also provided.

Introduction to Supporting Information

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. Both drugs have recently 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). Both 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 both of these drugs. Local criteria have been agreed, closely based on East Midlands Cardiac and Stroke Network Guidance, which provide answers to questions raised by the NICE guidance, namely:

- **When can dabigatran or rivaroxaban be considered to be appropriate alternatives to warfarin for this indication?**
- **What is the role of warfarin now that both of these drugs have been approved by NICE?**
- **What are the risks and benefits of either drug in comparison to warfarin?**
- **Which, if any, of the newer oral anticoagulants should be preferred?**

NICE Technology Appraisals 249 and 256: *Dabigatran and rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation*

What have NICE said about dabigatran?

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.

What have NICE said about rivaroxaban?

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.

PACEF Comment:
NICE have approved these two new OACs as an option for this indication. In conjunction with the East Midlands Cardiovascular and Stroke Networks, PACEF and ULH Drug and Therapeutics Committee have been striving to clarify the remaining role for warfarin and the criteria within which dabigatran or rivaroxaban 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).

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

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 previous 14 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. An ongoing follow-up study (RELY-ABLE) is designed to rectify this.

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.

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

The recommended dose of dabigatran for this indication is 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.

PACEF Comment:
Low dose dabigatran (110mg twice daily) has been shown to reduce the risk of major bleeding compared with warfarin.

The recommended dose of rivaroxaban for this indication is 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 and rivaroxaban are not yet known. Both drugs are commonly associated with anaemia, epistaxis, GI haemorrhage, abdominal pain, diarrhoea, dyspepsia and hepatic dysfunction. In the RE-LY study more people experienced dyspepsia (indigestion, abdominal pain or discomfort) 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. Prescribers are referred to the SPCs for both 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.

PACEF Comment:
The increased risk of MI with dabigatran compared to warfarin justifies the preference for warfarin in patients with significant ischaemic heart disease as detailed earlier in this guidance.

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.

Contra-indications

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).

As reported under safety concerns, the MHRA have recently widened this list to include:
- o current or recent gastrointestinal ulceration.
- o malignant neoplasms.
- o recent brain or spinal injury.
- o recent brain, spinal or ophthalmic surgery.
- o recent intracranial haemorrhage.
- o oesophageal varices.
- o arteriovenous malformations.
- o vascular aneurysms.
- o major intraspinal or intracerebral vascular abnormalities.

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.

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: azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole), HIV protease inhibitors, dronedarone, ciclosporin, tacrolimus. phenytoin, carbamazepine, phenobarbital and St John's wort.

PACEF Comment:
Dabigatran should not be initiated in patients with severe renal impairment (creatinine clearance < 30mL/min) For rivaroxaban caution is required in patients with severe renal impairment (creatinine clearance < 30mL/min); it is 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 or rivaroxaban should be weighed on an individual basis. Whilst dabigatran and rivaroxaban interact with other medicines, these are far fewer than the medicines that potentially interact with warfarin and other coumarin anticoagulants. This means that dabigatran and rivaroxaban 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 creatinine clearance (CrCl) prior to initiation of treatment with dabigatran or rivaroxaban 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*

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.

Guidance on switching: *Dabigatran or rivaroxaban 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.

Laboratory results in patients on dabigatran or rivaroxaban

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 and rivaroxaban

There is no known method for reversing either dabigatran or rivaroxaban. 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: 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**
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)
Reduced risk of bleeding compared to warfarin	Evidence for reduced risk of major bleeding at lower dose	Equivalent to warfarin (except reduced ICH)

	(110mg bd). Increased risk of GI bleeding compared to warfarin at higher dose (150mg bd dose) Overall reduced risk of intra cranial haemorrhage (ICH)	Increased risk of GI bleeding compared to warfarin
Reversibility	Uncertain.	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)
Dialysable	Yes, but will need to be carried out for at least 6 hours in order to ensure adequate drug clearance	No
Dosing	Twice daily	Once daily
Drug cautions (increased bleeding risk)	Antiplatelet agents, NSAIDs, SSRIs or SNRIs	Antiplatelet agents, NSAIDs
Use in patients with swallowing difficulties	Cannot be crushed	May be crushed and put through NG tube
Suitability for Monitored Dosage System	Not suitable	Suitable
Cost / year (Costs may vary in different settings because of negotiated procurement discounts)	£799.63	£764.40
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. Licensed for treatment of DVT, and the prevention of recurrent DVT and PE following an acute DVT in adults. DVT NICE FAD issued on 1st June 2012.

Dabigatran vs Rivaroxaban: Comparative cost

	Dose	***Cost of 12 months treatment***
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 (Xarelto) 20mg tabs	20mg once daily	£764.40 (28 day cost £58.80)

PACEF Comment

Following the recent reduction in NHS reimbursement price for dabigatran (Pradaxa), dabigatran and rivaroxaban are now broadly comparable in cost (rivaroxaban is only marginally less costly than dabigatran). The comparative information provided above demonstrates a role for both drugs in different patient groups. As a result of this, both drugs are approved for use for this indication subject both to NICE criteria and the guidance for new and existing AF patients detailed above. Both 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 or rivaroxaban 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 three by a considerable margin. Clinicians are urged to prescribe the new oral anticoagulants solely within the criteria detailed in this guidance. PACEF are acutely aware that an additional new oral anticoagulant, apixaban (Eliquis), is now available and that additional licensed indications for all three of the newer agents are continuing to emerge. As a result of this, it is expected that this guidance will be subject to regular review.

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Acknowledgements

Many thanks to Sharon Verne, Assistant Director, East Midlands Cardiovascular Network and Dr Richard Andrews, Cardiac Clinical Lead, East Midlands Cardiovascular Network. Also thanks to Sue Smith, Head of Prescribing and Medicines Management, Nene and Corby Clinical Commissioning Groups for regular updates on progress as the East Midlands guidance developed. Also many thanks to Dr Bethan Myers, Consultant Haematologist at ULH, for her significant contribution to the guidance on switching and the text on laboratory results in patients on dabigatran or rivaroxaban. Many thanks to all members of Lincolnshire PACEF for regularly reviewing the various drafts of the text. Many thanks to the wider stakeholder group within United Lincolnshire Hospitals Trust including all members of the ULH Drug and Therapeutics Committee and specialists in cardiology and stroke medicine.

Appendix 1

$CHADS_2$ score

$CHADS_2$ is a simple mnemonic device to help recall the major stroke risk factors in people who have AF. $CHADS_2$ assigns one point each for congestive heart failure (C), high blood pressure (H), age 75 or older (A), and diabetes (D), and two points for a previous stroke (S) or TIA. The $CHADS_2$ scoring system determines stroke risk as follows:

	$CHADS_2$ Risk Criteria	Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age $\geq$ 75	1
D	Diabetes mellitus	1
S_2	Stroke or TIA	2

Points from the table are converted into a score and used to estimate risk as detailed below:

$CHADS_2$ Score	Adjusted stroke rate (%/ Year)
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

Any patient with a $CHADS_2$ or CHA_2DS_2 –VASc score of $\geq$ 2 is appropriate for consideration for warfarin, dabigatran or rivaroxaban within the context of this guidance.

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 $CHADS_2$ or CHA_2DS_2 –VASc score of $\geq$ 2 is appropriate for consideration for warfarin, dabigatran or rivaroxaban within the context of this guidance.

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

Hypertension is defined as systolic BP > 160mmHg.
Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200micromol/L
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).
Bleeding refers to previous bleeding history or predisposition to bleeding (e.g. bleeding diathesis, anaemia).
Labile INRs refers to unstable/high international normalized ratios or poor time in therapeutic range (e.g. <60%).
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

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.*	
INR Monitoring	*INR monitoring enables assessment of compliance with warfarin.* *Dabigatran and rivaroxaban 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 and rivaroxaban 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 with dabigatran and rivaroxaban 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 or rivaroxaban is difficult. There is currently no licensed product available to rapidly reverse dabigatran or rivaroxaban.(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.*

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 and rivaroxaban are still not fully understood. There are significant risks in exposing a wider population to dabigatran and rivaroxaban before long-term safety has been fully evaluated. Safety concerns have been raised around both of these drugs 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 and rivaroxaban.*	*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. .*	*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. For both agents, poor compliance could be potentially disastrous exposing the patient to a greater risk of thromboembolic complications*