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

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GUIDANCE ON THE USE OF RIVAROXABAN (*XARELTO*) FOR THE TREATMENT OF DEEP VEIN THROMBOSIS AND THE PREVENTION OF RECURRENT DVT AND PULMONARY EMBOLISM

Key points

- **NICE have recommended the use of rivaroxaban (*Xarelto*) as an option for the treatment of deep vein thrombosis (DVT) and the prevention of recurrent DVT and pulmonary embolism (PE) after a diagnosis of acute DVT in adults.**
- **Current management of venous thromboembolism (VTE) requires the initiation of a low molecular weight heparin (LMWH) (e.g. enoxaparin or tinzaparin) for rapid anticoagulation overlapped with warfarin until an effective dose of warfarin is reached (determined using INR monitoring).**
- **Rivaroxaban removes the need for initial treatment with LMWH, replaces a two stage therapy with a single oral component and removes the need for INR monitoring associated with warfarin.**
- **In new patients, rivaroxaban should be the preferred option in those with a suspected DVT (unless contraindicated) while awaiting and subject to Doppler confirmation. Rivaroxaban is also preferred in those with a clear provoking event requiring three months' treatment (e.g. combined oral contraceptive (COC), trauma, surgery, plaster cast, hormone replacement therapy). Patients should be reviewed at three months with a view to assessing the risks, benefits and need for a longer course where indicated (see *Duration of treatment* table below). Rivaroxaban is also preferred in those taking medicines known to interact with warfarin and those for whom regular INR monitoring is hard to access or problematic or where venapuncture is difficult.**
- **Rivaroxaban is contra-indicated in patients with active clinically significant bleeding and those with a lesion or condition at significant risk of major bleeding (e.g. recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage etc)) or severe renal impairment.**
- **In new patients, warfarin remains the preferred option in those requiring a longer duration of treatment (i.e. longer than three months). Warfarin is also preferred in those with severe renal impairment, those with a history of significant peptic ulcer disease, those with hypersensitivity to rivaroxaban or excipients and those with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.**
- **In existing patients, clinicians should consider rivaroxaban as a possible alternative to treatment with warfarin in patients with poor INR control despite evidence that they are fully compliant with treatment, in patients allergic to or intolerant of coumarin anticoagulants or in patients on long-term LMWH therapy.**

- **An informed discussion should take place between the clinician and the patient about the risks and benefits of warfarin compared with rivaroxaban prior to the initiation of therapy. Resources are provided to aid that discussion.**
- **The NICE Technology Appraisal confirms that there is no direct trial evidence demonstrating that rivaroxaban is superior to LMWH in patients with cancer. In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands (see NICE CG extract in Appendix 3).**

SUMMARY OF PACEF DECISIONS RELATING TO RIVAROXABAN (*XARELTO*)

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Rivaroxaban (Xarelto) tablets 15mg and 20mg	**For the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults.**	**GREEN subject to criteria (see below). Approved for Joint Formulary for this indication.**
Rivaroxaban (*Xarelto*) tablets 10mg	For the prevention of venous thromboembolism in patients undergoing hip or knee replacement surgery	RED Complete course provided from within ULH Approved for Joint Formulary for this indication.
Rivaroxaban (*Xarelto*) tablets 20mg	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor	GREEN (see *PACE Bulletin* Vol 6 No 13 (August 2012)). Approved for Joint Formulary for this indication.

Introduction

Venous thromboembolism (VTE) is a condition in which a blood clot (a thrombus) forms in a vein, most commonly in the deep veins of the legs or pelvis. This is known as deep vein thrombosis, or DVT. The thrombus can dislodge and travel in the blood, particularly to the pulmonary arteries. This is known as pulmonary embolism, or PE. The term 'VTE' includes both DVT and PE. Venous thromboembolic diseases cover a spectrum ranging from asymptomatic calf vein thrombosis to symptomatic DVT. They can be fatal if they lead to PE, in which the blood supply to the lungs is badly blocked by the thrombus. Non-fatal VTE can cause serious long-term conditions such as post-thrombotic syndrome. Failure to diagnose and treat VTE correctly can result in fatal PE. Major risk factors for VTE include thrombophilia, a history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility and pregnancy.

NICE Technology Appraisal 261: *Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism* (July 2012)

In July 2012, NICE recommended the use of rivaroxaban as an option for treating DVT and preventing recurrent DVT and PE after a diagnosis of acute DVT in adults. It is the purpose of this special edition of the *PACE Bulletin* to clarify the role of rivaroxaban within the context of NICE guidance and to provide supporting information to enable clinicians and patients to hold an informed discussion on the risks and benefits of rivaroxaban use.

Licensed indication and dose

Rivaroxaban (*Xarelto*) 15mg and 20mg film coated tablets are licensed for the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults.

For the initial treatment of acute DVT, the recommended dose of rivaroxaban is 15mg twice daily for the first 21 days followed by 20mg once daily for continued treatment and prevention of recurrence.

A reduced dosage of 15mg twice daily for 21 days followed by 15mg once daily should be used in people with moderate (creatinine clearance 30-49ml/min) or severe (creatinine clearance 15-29ml/min) renal impairment.

Current Management

Current management of VTE is initiated with a low molecular weight heparin (LMWH) (e.g. enoxaparin or tinzaparin) for rapid anticoagulation overlapped with warfarin (a vitamin K antagonist (VKA) until an effective dose of warfarin is reached. Current UK practice indicates that the average treatment duration is 6 months.

Rivaroxaban removes the need for initial treatment with a LMWH, replaces a two stage therapy with a single oral component and removes the need for INR monitoring required with warfarin.

Role of LMWH and warfarin

For new patients

Warfarin should be the preferred option in those:

- **requiring a longer duration of treatment** (i.e. longer than three months).
- **with severe renal impairment** (creatinine clearance < 30mL/min). Rivaroxaban is contra-indicated in patients with a creatinine clearance of less than 15mL/min; caution is advised in those with a CrCl between 15mL/min and 30mL/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 rivaroxaban should be weighed on an individual basis.
- **with a history of significant peptic ulcer disease** (rates of major gastro-intestinal bleeding and GI symptoms are lower with warfarin than those reported with rivaroxaban).
- **with hypersensitivity to rivaroxaban or excipients**.
- **with hepatic disease associated with coagulopathy and clinically relevant bleeding risk** including cirrhotic patients with Child Pugh B and C.

Role of rivaroxaban

For new patients

Rivaroxaban should be the preferred option (unless contra-indicated) in those:

- **with a suspected DVT while awaiting and subject to Doppler confirmation.**
- **with a clear provoking event likely to require three months' treatment** (e.g. combined oral contraceptive (COC), trauma, surgery, plaster cast, hormone replacement therapy)
- **taking medicines known to interact with warfarin.** The potential for drug, food and alcohol interactions with warfarin is well documented with numerous 'black spot' drug interactions listed in the *BNF*; the range of interacting medicines with rivaroxaban is considerably narrower. A list of the drugs that are known to interact with rivaroxaban is provided below.
- **for whom regular INR monitoring is hard to access or problematic or where venapuncture is difficult.** It is emphasized that the decision to initiate a patient on rivaroxaban within this context must be based on sound clinical reasoning and should not simply reflect the convenience of the patient or the practice.

PACEF Comment:
Rivaroxaban is contra-indicated in patients with active clinically significant bleeding and those with a lesion or condition at significant risk of major bleeding (e.g. recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage etc)); it is also contra-indicated in severe renal impairment.

For existing patients

Warfarin remains the anticoagulant of clinical choice. Clinicians should consider rivaroxaban as a possible alternative to existing treatment with a VKA in patients with:

- **poor INR control despite evidence that they are fully compliant with treatment.** Poor INR control is defined as Time in Therapeutic Range (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 rivaroxaban. Poor compliers with warfarin are likely to be poor compliers with rivaroxaban.
- **allergy to or intolerable side effects with coumarin anticoagulants.**
- **on long-term LMWH therapy**.

In addition, conversion from warfarin (or alternative VKA) to rivaroxaban may also be considered for patients:

- with a history of significant bleeding on warfarin. Although significant bleeding is a contra-indication for both warfarin and rivaroxaban.
- with a history of stroke or transient ischaemic attack (TIA) while taking warfarin (providing there is no evidence of poor or non-compliance). Warfarin should be used with caution in recent ischaemic stroke and is contra-indicated in haemorrhagic stroke. Rivaroxaban is contra-indicated in recent intracranial haemorrhage.
- 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.

Patients with active cancer

NICE TA 261 confirms that there is no direct trial evidence demonstrating that rivaroxaban is superior to LMWH in patients with cancer. The TA makes no specific recommendations in this regard, but recognizes the disadvantages of currently available treatment (e.g. regular injections which some patients choose to decline). In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands (see NICE CG extract in Appendix 3).

Patients who are pregnant or breast-feeding

Wherever possible, warfarin should be avoided in pregnancy, particularly in the first and third trimesters. Warfarin does not pass into breast milk in significant amounts and appears to be safe for the breast feeding infant, but there is a risk of haemorrhage particularly where there is vitamin K deficiency. Rivaroxaban (*Xarelto*) is contra-indicated during pregnancy and breast-feeding. Nonetheless, in women with a history of recurrent VTE or PE, anticoagulation may need to be considered and warfarin is preferred. After delivery, warfarin should be delayed until risk of haemorrhage is low, usually after 5 to 7 days. Warfarin is

contra-indicated within 48 hours postpartum. LMWHs are safe in breast feeding mothers and are preferred.

Discussing risks and benefits with the patient

An informed discussion should take place between the clinician and the patient about the risks and benefits of warfarin compared with rivaroxaban. A table summarizing the benefits and risks of each option is included in the text (see Appendix 2). Key topics for discussion between clinician and patient include:

- lack of long term safety data with rivaroxaban.
- issues concerning reversibility. There is currently no licensed product available to rapidly reverse rivaroxaban in the event of major bleeding.
- the principles used in patient selection (see above).
- the potential option to convert the patient to rivaroxaban (if appropriate), if TTR is < 60% after 4 months in the presence of compliance.
- the crucial importance of full compliance. Studies have revealed a gradual deterioration in compliance with therapy against time with an associated increase in VTE event rate.

PACEF Comment:
In the absence of INR monitoring, it is difficult to confirm objectively whether or not the patient is fully compliant with rivaroxaban therapy. Prescribers are reminded that each medication review should confirm that the patient is taking all of their medicines as prescribed, especially those like rivaroxaban where full compliance is so crucial. Requests for repeat prescriptions received earlier or later than expected may be a useful indicator of poor adherence.

Clinical Effectiveness
NICE have concluded that rivaroxaban is as effective as enoxaparin followed by a VKA for preventing VTE recurrence. Appendix 1 reviews the evidence base used by NICE to reach their conclusions.

Cost Effectiveness

NICE concluded that rivaroxaban represented a clinical and cost-effective option in patients for whom treatment is indicated for up to 12 months and beyond. The Incremental Cost Effectiveness Ratios per Quality of Life Year Gained are as follows:

- 3 month duration: rivaroxaban dominated LMWH/VKA (i.e. Cost per QALY lower than LMWH/VKA).
- 6 month duration: £3,200 per QALY.
- 12 month duration: £14,900 per QALY
- Longer than 12 months: £19,400 per QALY

The longer the duration of therapy, the less cost-effective rivaroxaban becomes culminating in the over 12 month ICER per QALY which comes close to but does not breach the NICE £20,000 to £30,000 threshold of cost-effectiveness.

PACEF Conclusion
The NICE cost model concludes that rivaroxaban is a cost-effective alternative to LMWH/warfarin in all scenarios. A short three month course of rivaroxaban was actually found to be more cost-effective that LMWH/warfarin. As a result of this, rivaroxaban is the preferred agent where there is a clear provoking event requiring three months' treatment. However, LMWH/warfarin is more cost-effective than rivaroxaban for those requiring a longer duration of treatment. Within this context,

LMWH/warfarin is preferred, although there are many scenarios detailed in the text in which rivaroxaban is the recommended choice. Within the NICE cost model, the cost-effectiveness of rivaroxaban declines as treatment duration increases.

Cost

	Dose	***Cost of treatment***
Rivaroxaban (*Xarelto*) 15mg tabs	15mg twice daily	£88.20 (21 days)
Rivaroxaban (*Xarelto*) 15mg tabs	15mg once daily	£58.80 (28 days) £189 (3 months) £378 (6 months) £756 (12 months)
Rivaroxaban (*Xarelto*) 20mg tabs	20mg once daily	£58.80 (28 days) £189 (3 months) £378 (6 months) £756 (12 months)

Drug interactions

Rivaroxaban interacts with the following drugs:

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

Care should be taken if patients are treated concurrently with rivaroxaban and other drugs that affect haemostasis (e.g. NSAIDs, aspirin or other antiplatelet drugs). Rivaroxaban should not be given concurrently with any other anticoagulant agent (e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), oral anticoagulants (warfarin, apixaban, dabigatran)) except under circumstances of switching therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

Duration of treatment

Indication	**Duration**
Isolated calf-vein DVT	If calf-vein DVT suspected re-scan at or within 7days to exclude proximal extension. Treat for 3 months if proven to be a symptomatic calf-vein clot.
Venous thromboembolism provoked by surgery or other transient risk factor (e.g. combined oral contraceptive, pregnancy, trauma, plaster cast, hormone replacement therapy)	3 months
Confirmed proximal DVT or PE	3 months. At 3 months, assess the risks and benefits of continuing treatment.
Unprovoked PE	At least 3 months, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Long-term anticoagulation may be required.
Unprovoked proximal DVT	At least 3 months, if risk of VTE recurrence is high and there is no additional risk of major

	bleeding. Long-term anticoagulation may be required.
Active cancer and confirmed proximal DVT or PE	Continue LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation.

Treatment duration is based on the benefit of anticoagulation compared with the risk of bleeding. The main concerns with long-term anticoagulation with warfarin are:

- impact on people's lifestyle (e.g. dietary restrictions, INR monitoring, drug interactions, anxiety over monitoring and dosage adjustment).
- resource use associated with regular INR monitoring

Treating superficial vein thrombosis/thrombophlebitis near a deep vein

14 to 28% of patients with superficial vein thrombosis/thrombophlebitis near a deep vein will have co-existing DVT or PE. Unless it is a short segment in association with varicose veins, patients should have a Doppler ultrasound scan. If the clot is found to be within or at 3cm from a junction with DVT, treat as DVT (see above). If the clot is more than 3cm from a junction with DVT and extensive, a prophylactic dose of a LMWH (e.g. enoxaparin 40mg by SC injection every 24 hours for 6 weeks) is recommended. If the clot is between 3cm and 5cm from a junction with DVT, manage with a non-steroidal anti-inflammatory (ibuprofen or naproxen) with or without topical heparinoid 0.3% cream (*Hirudoid*) for one week.

Safety concerns

The long-term safety and tolerability of rivaroxaban is not yet known. The most common adverse events reported with rivaroxaban in EINSTEIN-DVT and EINSTEIN-Ext were headache, pain in extremity, nasopharyngitis and nosebleed. Approximately 4% of patients in the rivaroxaban group experienced side effects. Rivaroxaban is associated with comparable rates of clinically relevant bleeding to enoxaparin and a VKA; unsurprisingly, rivaroxaban is associated with higher numbers of bleeding events than placebo. Other common side effects include anaemia, GI haemorrhage, abdominal pain, diarrhoea, dyspepsia and hepatic dysfunction. 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.

Monitoring

Renal function should be assessed by calculating the CrCl prior to initiation of treatment with 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 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.

Guidance on switching: *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.

Laboratory results in patients on rivaroxaban

1. The INR is not a valid or useful test for rivaroxaban.
2. The Activated Partial Thromboplastin Time (APTT) is not 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.
4. Neither of these laboratory tests can be used to determine the drug level. Where this is required, contact the Haematology Consultant for further advice.
5. Effect on other clotting tests:
    - D-dimer results are low (as with all anticoagulants).
    - these agents **do not** cause thrombocytopenia (HIT)

Reversal of rivaroxaban

There is no known method for reversing 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. ULH have developed a hospital policy for dealing with rivaroxaban related bleeding problems that includes use of PCC.

Peri-operative Management of the Novel Oral Anticoagulants (NOACs)

Rivaroxaban

Pre-procedure

1. Pre-operative bridging with parenteral anticoagulation is not needed in the majority of patients receiving rivaroxaban
2. Renal function should be considered as impairment may significantly increase plasma levels

Renal function: When to stop Rivaroxaban before elective surgery

	Standard Bleeding Risk	**High Bleeding Risk**
≥ 30ml/min	Stop 24 hrs before surgical procedure	Stop 48 hrs before procedure
≤ 30ml/min	Stop 48 hrs before surgical procedure	Stop 72 hrs before procedure

Post procedure

1. Onset of therapeutic anticoagulation with rivaroxaban occurs within 2-4 hrs.
2. Rivaroxaban should be resumed as soon as possible after a procedure:

a) **Minor surgery or procedure with low bleeding risk**: Resume 24 hours post surgery at patient's normal dose.If patient has a high VTE risk consider prescribing enoxaparin 40mg on the evening post surgery and then restarting rivaroxaban the next day.

b) **Major surgery or high bleeding risk surgery/procedure**: Prescribe thromboprophylaxis as per VTE risk assessment then convert to full anticoagulation with rivaroxaban at patient's normal dose 48-72 hrs if approved by surgeon

Appendix 1: Evidence Base

EINSTEIN-DVT

This was an open-label non-inferiority study comparing rivaroxaban 15mg twice daily for 3 weeks then 20mg once daily for 3, 6 or 12 months) with enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for patients with acute symptomatic DVT without any symptoms of PE and for the prevention of recurrent DVT and PE. Enoxaparin was given until a vitamin K antagonist had brought the INR into the target range; then the enoxaparin was stopped. Based on individual patient risk factors the patients were assigned to 3, 6 or 12 months of treatment.

The primary efficacy endpoint of symptomatic recurrent venous thromboembolism (a composite of DVT or PE) occurred in 2.1% of patients in the rivaroxaban group and 3.0% of patients in the enoxaparin/VKA group (Hazard Ratio: 0.68). Recurrent DVT occurred less frequently in patients treated with rivaroxaban than with enoxaparin/VKA. Fatal and non-fatal PE did not differ between treatment groups.

The primary safety endpoint was a composite of major bleeding and other clinically relevant non-major bleeding. The HR for rivaroxaban for clinically relevant bleeding was 0.97; the HR for death from all causes was 0.67.

The manufacturer report a time in therapeutic range for enoxaparin/VKA of 57.7% across all centres; the NPSA recommend a TTR of at least 60%.

PACEF Comment:
EINSTEIN-DVT sets rivaroxaban up as an alternative to enoxaparin followed by VKA (e.g. warfarin) in patients with acute symptomatic DVT without any symptoms of PE and for the prevention of recurrent DVT and PE. Rivaroxaban emerges as non-inferior to enoxaparin/VKA in terms of preventing recurrent DVT or PE. It may even be superior to enoxaparin/VKA in preventing recurrent DVT. It is non-inferior in terms of causing clinically relevant bleeding and may actually reduce deaths from all causes. Improvements in INR control with warfarin measured in terms of TTR could have improved warfarin performance in this study.

EINSTEIN-Ext

This was a randomised placebo-controlled superiority trial comparing rivaroxaban 20mg once daily) with placebo once daily in patients with confirmed symptomatic DVT or PE that had been treated for 6 or 12 months with a VKA (warfarin or acenocoumarol) or rivaroxaban up to the moment of randomisation. Patients were recruited if the risks and benefits of further anticoagulation were finely balanced.

Patients taking rivaroxaban experienced fewer recurrences of VTE (1.3%) than placebo (7.1%). The incidence of non-major bleeding events was significantly higher in the rivaroxaban arm than in the placebo arm. There were more major bleeding events in the rivaroxaban arm.

PACEF Comment
EINSTEIN-Ext looks at patients with confirmed symptomatic DVT or PE and determines the benefit or disbenefit of continuing rivaroxaban 20mg daily beyond 6 or 12 months in patients previously treated with a VKA or rivaroxaban. Rivaroxaban reduces recurrence of VTE but increases the risk of non-major bleeding and major bleeding events compared to placebo.

Exclusions from EINSTEIN-DVT and EINSTEIN-Ext

The following people were excluded from both trials:
- those with a creatinine clearance of less than 30ml/min.
- those with clinically significant liver disease.
- those with high BP (systolic > 180mm/Hg; diastolic > 110mm/Hg)
- those with active bleeding or a high risk of bleeding.

PACEF Comment:
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 rivaroxaban should be weighed on an individual basis. While rivaroxaban interacts with other medicines, these are far fewer than the medicines that potentially interact with warfarin and other coumarin anticoagulants. This means that rivaroxaban represents a viable alternative for patients requiring warfarin but taking potentially interacting concurrent therapy.

Adverse events in EINSTEIN-DVT and EINSTEIN-Ext

The most common adverse events reported with rivaroxaban in EINSTEIN-DVT and EINSTEIN-Ext were headache, pain in extremity, nasopharyngitis and nosebleed. Approximately 4% of patients in the rivaroxaban group experienced side effects. Rivaroxaban is associated with comparable rates of clinically relevant bleeding to enoxaparin and a VKA; unsurprisingly, rivaroxaban is associated with higher numbers of bleeding events than placebo.

Appendix 2: Summary of Benefits and Risks - *Warfarin vs Rivaroxaban*

	Benefits	***Risks***
Effectiveness	*LMWH followed by warfarin remains a well-proven first line therapy. There is no evidence that patients with good INR control will not achieve comparable outcomes to those using rivaroxaban.* *In EINSTEIN-DVT, rivaroxaban emerges as non-inferior to enoxaparin/VKA in terms of preventing recurrent DVT or PE. It may even be superior to enoxaparin/VKA in preventing recurrent DVT. Improvements in INR control with warfarin measured in terms of TTR could have improved warfarin performance in this study.*	

	EINSTEIN-Ext looks at patients with confirmed symptomatic DVT or PE and determines the benefit or disbenefit of continuing rivaroxaban 20mg daily beyond 6 or 12 months in patients previously treated with a VKA or rivaroxaban. Rivaroxaban reduces recurrence of VTE compared to placebo.	
INR Monitoring	*INR monitoring enables assessment of compliance with warfarin.* *Rivaroxaban does not require INR monitoring. A more stable level of anticoagulation is achieved.*	*Patients can be inconvenienced by the demands of routine INR monitoring.* *As rivaroxaban does 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 rivaroxaban as the shorter half-life 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 rivaroxaban is difficult. There is currently no licensed product available to rapidly reverse rivaroxaban although prothrombin complex has been used successfully.*
Major GI bleeding and GI symptoms	*In EINSTEIN-DVT rivaroxaban was non-inferior to warfarin in terms of causing clinically relevant bleeding and may actually reduce deaths from all causes.* *In EINSTEIN-Ext, rivaroxaban increased the risk of non-major bleeding and major bleeding events compared to placebo.*	*In other studies related to stroke prevention in AF, rates of major GI bleeding and GI symptoms are greater with rivaroxaban than 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 profile of rivaroxaban is still not fully understood. There are significant risks in exposing a wider population to rivaroxaban before long-term safety has been fully evaluated. Safety concerns have been raised around rivaroxaban and more safety data is continuing to emerge as levels of prescribing increase worldwide.*
Interactions	*There are fewer potential interactions with other medication, alcohol and diet with 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 rivaroxaban. .*	*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*	*Rivaroxaban has a half-life of 5 to 9 hours in young patients and 11 to 13 hours in elderly*

	rivaroxaban.	*patients. Poor compliance could be potentially disastrous exposing the patient to a greater risk of thromboembolic complications*

Appendix 3: NICE Clinical Guideline: *Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing* (June 2012)

Annotated Extract
Please note that this CG predates the publication of NICE Technology Appraisal 261: *Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism* (July 2012) and provides no specific guidance on the use of rivaroxaban within this context. The text of this Bulletin provides guidance on when LMWH/ warfarin or rivaroxaban should be the preferred option.

Pharmacological interventions
Deep vein thrombosis or pulmonary embolism
1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT (i.e. above knee DVT) or PE, taking into account co-morbidities, contraindications and drug costs, with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy.

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until INR is 2 or above for at least 24 hours, whichever is longer.

1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation.

PACEF Comment:
NICE TA 261 confirms that there is no direct trial evidence demonstrating that rivaroxaban is superior to LMWH in patients with cancer. The TA makes no specific recommendations in this regard, but recognizes the disadvantages of currently available treatment (e.g. regular injections which some patients choose to decline). In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits probably still stands.

1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment.

PACEF Comment:
A sub-group analysis provided to NICE by the manufacturer appears to suggest that rivaroxaban is less effective than LMWH/VKA in those for whom 3 months treatment is clinically indicated. NICE have dismissed this as biologically implausible and have not given specific advice against rivaroxaban within this context.

1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.
1.2.5 Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

Appendix 4: Patient information on Rivaroxaban (*Xarelto*)

What is rivaroxaban?
Rivaroxaban is an anticoagulant drug. This means it prevents your blood from clotting as quickly or effectively, so it makes you less likely to develop blood clots.

Why have I been prescribed rivaroxaban?
You have been prescribed rivaroxaban either:

1. to treat blood clots and prevent them from happening again in the: veins of your legs (deep vein thrombosis); or blood vessels in your lungs (pulmonary embolism).
2. to reduce the risk of stroke if you have an irregular heart beat (atrial fibrillation)

What are the benefits of taking rivaroxaban?

- It cuts your risk of developing deep vein thrombosis or pulmonary embolism again
- it reduces the risk of stroke at least as well as warfarin.
- You need fewer blood tests than if you are taking other anticoagulants such as warfarin.
- Compared with warfarin, it is not affected by changes in your diet, the amount of alcohol you drink and other medicines you take.

What are the risks?
Rivaroxaban may cause dizziness and headaches in between 1-10 users in every 100. If you have any of these symptoms, please tell your haematology doctor, nurse or pharmacist. We may prescribe you another type of anticoagulant instead.
If you feel dizzy or have headaches do **not** drive or use machinery.
You are at a greater risk of bleeding when taking rivaroxaban. It is a possible side effect of taking any anticoagulant and it can be serious. You should seek medical help straight away if you have bleeding, especially if you have any of the following:

- unexpected or uncontrollable bleeding
- coughing or vomiting blood
- black stools or blood in your stools
- a severe headache that will not go away, dizziness or weakness
- a fall or injury to your head or face
- blood in your urine
- unexplained or severe bruising.

Your doctor, nurse or pharmacist will discuss these risks with you in more detail if you have any concerns or questions.

Are there any alternatives?
Warfarin is the main alternative drug that you are likely to be offered. It has been used to treat pulmonary embolism and deep vein thrombosis for a many years.
If you take warfarin you need frequent blood tests to know what dose you should be on. This is because changes in your diet, the amount of alcohol you drink and other medicines can interfere with it. What you eat or drink or the other medicines you take are much less likely to interfere with rivaroxaban, so you need fewer blood tests. If you get bleeding, it is easy to reverse warfarin's effects.

Rivaroxaban's effects are not currently reversible, but they do wear off in about 24 hours.

How long will I need to take rivaroxaban?
How long you need to take rivaroxaban depends on your individual condition. Your clinic doctor will discuss this with you and agree with you how long you need to continue your treatment.

How do I take rivaroxaban?

- Your doctor, nurse or pharmacist will let you know how much rivaroxaban you should take.
- It comes in two doses: 15mg and 20mg.
- At first you need to take **15mg twice a day** about 12 hours apart if you have recently had a DVT or PE. Take each dose at the same times each day for **three** weeks. After this you take a smaller dose of **20mg once a day**. If you are taking it for stroke prevention, then you will take 20mg a day.
- It is very important that you take your rivaroxaban as advised.
- During the **first three weeks**, when you are taking 15mg twice a day, if you miss a dose, take it as soon as you remember. For example, you can take two 15mg tablets at the same time on one day if you need to. The next day, you should go back to taking one **15mg tablet twice a day**.
- When you are taking rivaroxaban 20mg once a day, if you miss a dose, take it as soon as you remember it. But if you do not remember until the next day, take the tablet when it is next due – do **not** take two tablets at the same time.
- Take rivaroxaban tablets **with** food.
- Store rivaroxaban at room temperature.

Do I need blood tests when taking rivaroxaban?
You need to have blood tests to make sure your kidneys are working well during the first stage of your treatment with rivaroxaban. You then usually have these tests once a year, if you continue to take the rivaroxaban long-term. Sometimes your doctor may decide you need to have specialist blood tests.

Can I take other medicines with rivaroxaban?
It is important to let the doctor or pharmacist who prescribes rivaroxaban know all the other medicines you are currently taking. This includes any medicines you buy over the counter, because they might interfere with rivaroxaban and affect how it works. If you start a new medicine, please tell the doctor that you are taking rivaroxaban. If you are unsure about whether you can take a particular medicine with rivaroxaban, please ask your doctor, nurse or pharmacist for advice.

What else do I need to know when taking rivaroxaban?

- Your risk of bleeding is greater – please take this into account before taking part in activities with a high risk of injury.
- If you become pregnant or plan to become pregnant, tell your doctor straight away because we do not know the affects of rivaroxaban during pregnancy.
- To reduce your risks of bleeding during surgery, minor procedures or dental work, please tell your doctor that you are on rivaroxaban. You may need to stop taking it for a short time.
- The anticoagulation clinic will give you an alert card. Carry this in your wallet or purse to make sure people know you are taking an anticoagulant.

How do I find out more about rivaroxaban?
Please ask your doctor, pharmacist, nurse or the anticoagulation clinic for more information

Appendix 5: Frequently asked questions for new oral anticoagulants (NOACs) dabigatran, (Pradaxa®) rivaroxaban, (Xarelto®) apixaban (Eliquis®)

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

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

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 long term safety data available.

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 at all.

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

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

What happens if I miss a dose of an 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?
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 the medication packaging until it is taken, but it can be placed in its blister pack within the dosette.

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, dental or medical procedure. Do not stop taking NOACs without first talking to the doctor who prescribes it for you.

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

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

What if I develop heartburn or stomach upset after starting a NOAC?
Many new drugs can cause stomach upset. This problem occurs in up to 10% of patients who start dabigatran and is less common with rivaroxaban or apixaban. Taking the medication with meals can reduce the risk of stomach upset and the problem often improves on its own after a few days. Antacids may help. If the problem persists, contact your doctor.
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Can I take a nonsteroidal 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, 3-5day 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 if you are uncertain.

Appendix 6: Anticoagulation Therapy Checklist for New Patients Rivaroxaban

Diagnosis :

Seen by :

Date:

Dose 20mg/15mg

Please tick each point once patient has been informed of the following:

1. Clinical need for anticoagulation therapy ❑y
2. Mode of action of Rivaroxaban (xarelto)- ; ensure not contraindicated ❑y
NB associated with less intracranial bleeding than wearfarin but ↑GI bleeding

3. Duration of treatment ❑y
4. Need for (at least) yearly Kidney function monitoring ❑y

5. Using a phone/alarm/calendar to remember dose ❑y
6. Obtaining supply of medication from:
Hospital initially ; repeat prescriptions from GP ❑y

7. Discuss over the counter and herbal remedies
Avoid: aspirin, nurofen, ibuprofen,health shop remedies (St John's wort) ❑y

8. Ask local pharmacist for advice on possible interactions
↑effect: HIV protease inhibitors; azole antifungals (ketoconizole,etc; verapamil; amiodarone; quinine
↓effect: CPY3A4 inducers rifampicin, phenytoin, carbamezipine; phenobarb; St John's wort ❑y

9. Aware of possible side effects of therapy,
- e.g. bleeding, bruising
- recurrence of VTE ❑y

10. For women only, contraception, periods, pregnancy and HRT ❑ y

11. Surgical procedures, dental work ❑y
12. Injections (immunisations) ❑y

13. Hobbies/leisure activities ❑y
14. Lifestyle issues discussed: smoking, exercise, weight control, work ❑y

15. Information leaflet & rivaroxaban card given ❑y
16. Contact numbers given ❑y

FOR PATIENTS WITH DVT:
17. Need for leg care, wearing compression stockings, rest and moderate exercise ❑N/A
18. What to do if experiencing worsening pain / leg swollen / discoloration / dsypnoea ❑N/A