Arden and Greater East Midlands Commissioning Support Unit

Arden and Greater East Midlands Commissioning Support Unit in association with Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services, United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

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GUIDANCE ON THE USE OF WARFARIN AND NEWER ORAL ANTICOAGULANTS FOR THE TREATMENT AND SECONDARY PREVENTION OF DEEP VEIN THROMBOSIS AND/OR PULMONARY EMBOLISM (REVISED SECOND EDITION)

Key points

- **NICE have recommended all four of the newer oral anticoagulants, apixaban (*Eliquis*), dabigatran etexilate (Pradaxa), edoxaban (*Lixiana*) and rivaroxaban (*Xarelto*), as options for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or 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).**
- **Two of the newer oral anticoagulants, rivaroxaban and apixaban, remove the need for initial treatment with a LMWH, replacing two stage therapy with a single oral component and removing the need for the INR monitoring required with warfarin. By contrast, dabigatran and edoxaban can only be initiated for the treatment or prophylaxis of DVT or PE following at least 5 days treatment with a parenteral anticoagulant.**
- **In new patients, apixaban, dabigatran, edoxaban or rivaroxaban should be the preferred options in those with a suspected DVT (unless contraindicated) while awaiting and subject to Doppler confirmation. Apixaban, dabigatran, edoxaban or rivaroxaban are 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). Where a decision is taken to continue with anticoagulation, the anticoagulant originally prescribed should usually be continued unless there is good reason to change, for example due to poor tolerability or change in clinical circumstances.**
- **Increasingly newer oral anticoagulants are becoming the preferred option for these patients, unless contra-indicated.**
- **Apixaban, dabigatran, edoxaban or rivaroxaban are preferred in those taking medicines known to interact with warfarin and in those for whom regular INR monitoring is hard to access or problematic or where venapuncture is difficult.**
- **Apixaban, dabigatran, edoxaban and rivaroxaban are contra-indicated in patients with active clinically significant bleeding and those with a lesion or condition at significant risk of major bleeding (e.g. current or recent**

gastrointestinal 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), hepatic impairment or severe renal impairment (creatinine clearance < 30ml/min).

- **All four of the newer oral anticoagulants are broadly comparable in terms of cost with rivaroxaban emerging as the lowest cost agent following a recent price reduction.**
- **In new patients, warfarin remains the preferred option in those requiring a longer duration of treatment (i.e. longer than three months), although length of treatment is not always possible to predict from the outset.**
- **Warfarin is also preferred in those with severe renal impairment, those with a history of significant peptic ulcer disease, those with hypersensitivity to apixaban, dabigatran, edoxaban, rivaroxaban or their excipients and those with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.**
- **In existing patients, clinicians should consider apixaban, dabigatran, edoxaban or rivaroxaban as possible alternatives 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 newer oral anticoagulants prior to the initiation of therapy. Resources are provided to aid that discussion.**
- **NICE Technology Appraisals confirm that there is no direct trial evidence demonstrating that apixaban, dabigatran, edoxaban or rivaroxaban are 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 NEWER ORAL ANTICOAGULANTS JANUARY 2016

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Apixaban (*Eliquis*) 2.5mg tablet (BMS/Pfizer)	For the prevention of venous thromboembolism following elective hip or knee replacement surgery.	RED Complete course provided from within ULH Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Apixaban (*Eliquis*) 2.5mg and 5mg tablet (BMS/Pfizer)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor.	GREEN subject to criteria. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Apixaban (*Eliquis*) 2.5mg tablet (BMS/Pfizer)	For the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults.	GREEN subject to criteria. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Dabigatran (*Pradaxa*) 75mg and 110mg capsules (Boehringer Ingelheim)	For the prevention of venous thromboembolism following elective hip or knee replacement surgery.	RED Complete course provided from within ULH Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.

Dabigatran (*Pradaxa*) 150mg capsules (Boehringer Ingelheim)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor.	GREEN subject to criteria. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Dabigatran (*Pradaxa*) 110mg and 150mg capsules (Boehringer Ingelheim)	For the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults.	GREEN subject to criteria. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Edoxaban (*Lixiana*) 60mg tablets (Dalichi Sankyo)	For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor.	RED-RED pending NICE and PACEF approval. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication.
Edoxaban (*Lixiana*) 60mg tablets (Dalichi Sankyo)	For the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults.	GREEN subject to criteria. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
Rivaroxaban (Xarelto) tablets 2.5mg	For use in combination with aspirin plus clopidogrel or aspirin alone for prevention of atherothrombotic events after acute coronary syndrome s in patients with elevated cardiac biomarkers.	GREEN Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved for this indication.
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. Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved 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 inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved 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 subject to criteria Approved for inclusion in *Lincolnshire Joint Formulary* for this indication. NICE approved 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.

It is the purpose of this special edition of the *PACE Bulletin* to update clinicians on recently published NICE guidance on the use of all four of the newer oral anticoagulant drugs for the treatment of DVT and prevention of recurrent DVT and PE and to provide supporting information to enable clinicians to hold informed discussion with patients on the risks and benefits of the different treatment options.

NICE guidance

Which of the newer oral anticoagulant drugs are now approved by NICE for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism?

Drug	NICE Technology Appraisal	NICE recommendation	Authorised indication and dose
Apixaban (*Eliquis*)	NICE TA 341: *Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism* (June 2015)	NICE recommend the use of apixaban within its marketing authorisation as an option for treating and for preventing recurrent DVT and PE in adults.	Apixaban (*Eliquis*) 2.5mg, 5mg and 10mg tablets are licensed for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults. For the treatment of acute DVT and treatment of PE the recommended dose is 10mg twice daily for the first 7 days followed by 5mg twice daily. Short duration therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) For the prevention of recurrent DVT and PE the recommended dose is 2.5mg twice daily should be initiated after completion of 6 months treatment on 5mg twice daily (or with an alternative anticoagulant). No dose adjustment is necessary in patients with mild or moderate renal impairment. In severe renal impairment (creatinine clearance 15-29mL/ min) apixaban should be used with caution. In patients with creatinine clearance < 15mL/min or in patients undergoing dialysis, apixaban is not recommended.
Dabigatran (*Pradaxa*)	NICE TA327: *Dabigatran etexilate for*	NICE recommend dabigatran as an option	Dabigatran (*Pradaxa*) 110mg and 150mg

	the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (December 2014)	for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism in adults.	capsules are licensed for the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults. The recommended dose is 150mg twice daily following initial use of parenteral anticoagulant for at least 5 days. The duration of therapy should be based on individualised risk-benefit assessment. Short duration of therapy should be based on transient risk factors (e.g. recent surgery, trauma, imobilisation); longer durations should be based on permanent risk factors or idiopathic DVT or PE. For patients aged 80 years or over, 110mg twice daily is recommended. No dose adjustment is necessary in patients with mild renal impairment (CrCL 50 - < 80mL/min) In moderate renal impairment (creatinine clearance 30-50mL/min) dose is 150mg twice daily. In patients at high risk of bleeding reduce to 110mg twice daily. Treatment with dabigatran is contra-indicated in patients with severe renal impairment (creatinine clearance < 30mL/min).
Edoxaban (*Lixiana*)	NICE TA354: *Edoxaban for treating and preventing deep vein thrombosis and pulmonary embolism*	NICE recommend the use of edoxaban as an option for treating and for preventing DVT and PE.	Edoxaban (*Lixiana*) 60mg tablets are licensed for the treatment of DVT and PE and prevention of

	(August 2015)		recurrent DVT and PE in adults. The recommended dose is 60mg once daily following initial use of parenteral anticoagulant for at least 5 days. Edoxaban and initial parenteral anticoagulant should not be administered simultaneously. The duration of therapy should be based on individualised risk-benefit assessment. Short duration of therapy should be based on transient risk factors (e.g. recent surgery, trauma, imobilisation); longer durations should be based on permanent risk factors or idiopathic DVT or PE. In moderate to severe renal impairment (creatinine clearance 15-50mL/min) dose should be reduced to 30mg once daily. In patients with creatinine clearance < 15mL/min or in patients undergoing dialysis, edoxaban is not recommended.
Rivaroxaban (*Xarelto*)	NICE TA 261: *Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism* (July 2012)	NICE recommend the use of rivaroxaban as an option for treating DVT and preventing recurrent DVT and PE after a diagnosis of acute DVT in adults.	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.

Conventional Management

Conventional 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.

Two of the newer oral anticoagulants, rivaroxaban and apixaban, remove the need for initial treatment with a LMWH, replacing two stage therapy with a single oral component and removing the need for the INR monitoring required with warfarin. By contrast, dabigatran and edoxaban can only be initiated for the treatment or prophylaxis of DVT or PE following at least 5 days treatment with a parenteral anticoagulant.

Role of LMWH and warfarin

For new patients

Warfarin should be the preferred option in those:

- **with severe renal impairment** (creatinine clearance < 30mL/min). All four of the newer anticoagulants are potentially problematic in patients with renal impairment. Specific information on cautions, contra-indications and recommended dosage adjustments are tabulated above. NICE guidance on Chronic Kidney Disease states that for creatinine clearance between 30 and 50mL/min, apixaban is preferable to warfarin. Dosage adjustments for all four of the newer oral anticoagulants in patients with renal impairment are tabulated above.
- **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 apixaban, dabigatran, edoxaban, rivaroxaban or excipients**.
- **with hepatic disease associated with coagulopathy and clinically relevant bleeding risk** including cirrhotic patients with Child Pugh B and C (all four of the newer anticoagulants are contra-indicated in this patient group).

Role of newer anticoagulants

For new patients

Newer oral anticoagulants 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 newer oral anticoagulants is considerably narrower. A list of the drugs that are known to interact with newer oral anticoagulants 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 a newer oral anticoagulant within this context must be based on sound clinical reasoning and should not simply reflect the convenience of the patient or the practice.

For existing patients

Warfarin remains the anticoagulant of clinical choice. Clinicians should consider a newer oral anticoagulant as a possible alternative to existing treatment with a vitamin K antagonist (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 a NOAC. Poor compliers with warfarin are likely to be poor compliers with a NOAC.
- **allergy to or intolerable side effects with coumarin anticoagulants.**
- **on long-term LMWH therapy**.

In addition, conversion from warfarin (or alternative VKA) to a NOAC 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 newer oral anticoagulants.
- 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 and in acute coronary syndrome with prior stroke or TIA.
- 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.

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	3 months

surgery or other transient risk factor (e.g. combined oral contraceptive, pregnancy, trauma, plaster cast, hormone replacement therapy)	
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

Clinical Effectiveness

NICE have concluded that:

- Apixaban is effective at treating VTE and is associated with fewer bleeds than warfarin.
- There is no demonstrable difference between dabigatran etexilate, warfarin and rivaroxaban in treating VTE and preventing recurrent evants.
- Edoxaban is non-inferior to warfarin for VTE recurrence.
- Rivaroxaban is as effective as enoxaparin followed by a VKA for preventing VTE recurrence.

Adverse Events

	Major bleeding	**Any bleeding**	**Intracranial haemorrhage**	**Notes**
Apixaban	Fewer people taking apixaban in the AMPLIFY trial had a major bleed compared to enoxaparin/warfarin.	Fewer people taking apixaban in the AMPLIFY trial had a clinically relevant non-major bleed compared to enoxaparin/warfarin.	Lower incidence with apixaban compared to enoxaparin/warfarin.	
Dabigatran	Fewer people taking dabigatran in the RE-COVER and RE-MEDY trials had a major bleeding event compared to warfarin.	Lower incidence with dabigatran compared to warfarin	Lower incidence with dabigatran compared to warfarin	In RE-MEDY, more people had an acute coronary syndrome event with dabigatran compared with warfarin. This is now thought to be due to a protective effect of warfarin,

				rather than an adverse effect of dabigatran etexilate.
Edoxaban	Fewer people taking edoxaban had a major bleeding event compared to warfarin.	Lower incidence with edoxaban compared to warfarin	Lower incidence with edoxaban compared to warfarin	
Rivaroxaban	*In EINSTEIN-DVT rivaroxaban was non-inferior to warfarin in terms of causing clinically relevant bleeding and may actually reduce deaths from all causes.*			

The long-term safety and tolerability of NOACs is not yet known. Commonly reported adverse events with each of the NOACs are as follows:

Apixaban

The most commonly reported adverse event with apixaban is bleeding. In the VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study. Clinical experience locally suggests that these bleeding rates are higher than those observed in practice. Common adverse reactions reported from the VTEt studies were: haemorrhage, haematoma, epistaxis, GI haemorrhage, rectal haemorrhage, gingival bleeding, haematuria and contusion.

Dabigatran

The most commonly reported adverse event with dabigatran is bleeding. Bleeding was reported in 19.4% of patients in the DVT/PE prevention trial RE-MEDY and 10.5% of patients in the DVT/PE trial RE-SONATE. Other common adverse reactions in DVT/PE treatment and prevention with dabigatran include epistaxis, gastrointestinal haemorrhage, dyspepsia, rectal haemorrhage, skin haemorrhage and genitourological haemorrhage including haematuria. In moderate renal impairment (creatinine clearance 30-50mL/min) the dose of dabigatran is 150mg twice daily. In patients at high risk of bleeding the dose should be reduced to 110mg twice daily. Treatment with dabigatran is contra-indicated in patients with severe renal impairment (creatinine clearance < 30mL/min).

Edoxaban

The most commonly reported adverse events associated with edoxaban relate to bleeding. Commonly reported adverse events in the Hokusai-VTE study include anaemia, epistaxis, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increase, gammaglutamyltransferase increase, skin haemorrhage, rash, pruritis, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage and abnormal liver function tests.

Rivaroxaban

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. Clinical experience locally suggests that these bleeding rates are lower than those observed in practice. 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.

Contra-indications to NOACs

- Severe hepatic impairment or liver disease expected to affect survival.
- Prosthetic heart valves.
- Moderate to severe mitral stenosis.
- Severe renal impairment, end stage renal disease or dialysis.
- Active clinically significant bleeding.
- Impaired haemostasis.
- Condition at significant risk of major bleeding (including hepatic disease associated with coagulopathy).
- Haemodynamically unstable pulmonary embolism.
- Pulmonary embolism requiring thrombolysis or embolectomy.
- Uncontrolled severe hypertension.
- Acute coronary syndrome with prior stroke or transient ischaemic attack.
- Hip fracture surgery.
- Pregnancy and lactation.

Patients with active cancer

NICE TA	Evidence in patients with active cancer	Recommendation
NICE TA 341: *Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism* (June 2015)	There are insufficient data to assess the effectiveness and safety of apixaban in people with active cancer who have DVT or PE.	Standard treatment for VTE in people with cancer is LMWH. In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands
NICE TA327: *Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism* (December 2014)	There are insufficient data to assess the effectiveness and safety of dabigatran etexilate in people with active cancer who have DVT or PE.	Standard treatment for VTE in people with cancer is LMWH. In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands
NICE TA354: *Edoxaban for treating and preventing deep vein thrombosis and pulmonary embolism* (August 2015)	A small number of people with cancer were included in the pivotal trial, but no subgroup analysis was presented to NICE. There is no comparative evidence between edoxaban and current best practice available. Existing trial evidence does not provide relevant data for people with cancer who experienced VTE.	Standard treatment for VTE in people with cancer is LMWH. In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands
NICE TA 261: *Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism* (July 2012)	Confirms that there is no direct trial evidence demonstrating that rivaroxaban is superior to LMWH in patients with cancer. Makes no specific recommendations, but recognizes the disadvantages of	Standard treatment for VTE in people with cancer is LMWH. In the absence of evidence, existing NICE guidance to use LMWH for 6 months then assess risks and benefits still stands

	currently available treatment (e.g. regular injections which some patients choose to decline).	

There is no direct trial evidence demonstrating that any of the newer oral anticoagulant drugs are 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.

Patients who are pregnant or breast-feeding

Warfarin should be avoided in pregnancy wherever possible. It does not pass into breast milk in significant amounts and appears to be safe for the breast feeding infant. However, there is a risk of haemorrhage, particularly where there is vitamin K deficiency. 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. All four of the newer oral anticoagulants are contraindicated during breast feeding (see table).

Drug	**Advice in pregnancy**	**Advice in breast-feeding mothers**
Apixaban (*Eliquis*)	Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is no data on use in pregnant women. **Apixaban is not recommended in pregnancy.**	It is unkown whether apixaban or its metabolites are excreted in human milk. Available data in animals has shown excretion of apixaban in breast milk. **Where apixaban is indicated, a decision must be made to either discontinue breast-feeding or discontinue/abstain from apixaban therapy.**
Dabigatran (*Pradaxa*)	Associated with reproductive toxicity in animals and **should not be used during pregnancy unless clearly necessary.**	There is no clinical data on the effect of dabigatran on infants during breast-feeding; **in the interests of safety, breast-feeding should be discontinued during treatment with dabigatran.**
Edoxaban (*Lixiana*)	Studies in animals have shown reproductive toxicity. Safety and efficacy have not been established in pregnant women. **Edoxaban is contra-indicated during pregnancy.**	Safety and efficacy have not been established in breast-feeding women. **Edoxaban is contra-indicated during breast-feeding.**
Rivaroxaban (*Xarelto*)	Studies in animals have shown reproductive toxicity. Safety and efficacy have not been established in pregnant women. **Rivaroxaban is contra-indicated during pregnancy.**	Safety and efficacy have not been established in breast-feeding women. **Rivaroxaban is contra-indicated during breast-feeding.**

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 newer oral anticoagulants. Key topics for discussion between clinician and patient include:

- lack of long term safety data with newer oral anticoagulants.
- issues concerning reversibility. There is currently no *licensed* product available to rapidly reverse the effects of NOACs in the event of major bleeding. Idarucizumab

(*Praxbind*) was recently licensed in the EU for reversal of bleeding associated with dabigatran and is expected to be launched in the UK shortly. Other agents are in development and are set to follow.

- the principles used in patient selection (see above).
- the potential option to convert the patient to a newer oral anticoagulant (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 NOAC therapy. Prescribers are reminded that each medication review should confirm that the patient is taking all of their medicines as prescribed, especially those like NOACs where full compliance is so crucial. Requests for repeat prescriptions received earlier or later than expected may be a useful indicator of poor adherence.

Cost

	Dose	Cost of treatment
Apixaban (*Eliquis*) tablets	10mg twice daily for 7 days followed by 5mg twice daily (acute DVT/PE)	£26.60 (7 days) £159.60 (3 months) £319.20 (6 months)
Apixaban (*Eliquis*) 2.5mg and 5mg tablets	After completion of 6 month regime detailed above, 2.5mg twice daily (prevention of recurrent DVT and PE)	£478.80 (9 months) £638.40 (12 months)
Dabigatran (*Pradaxa*) 110mg capsules	110mg twice daily (treatment or prevention of DVT and PE in patients aged 80 and over)	£61.50 (28 days) £199.87 (3 months) £399.75 (6 months) £799.50 (12 months)
Dabigatran (*Pradaxa*) 150mg capsules	150mg twice daily (treatment or prevention of DVT and PE)	£61.50 (28 days) £199.87 (3 months) £399.75 (6 months) £799.50 (12 months)
Edoxaban (*Lixiana*) 60mg tablets	60mg once daily	£58.80 (28 days) £191.10 (3 months) £382.20 (6 months) £764.40 (12 months)
Rivaroxaban (*Xarelto*) 15mg and 20mg tablets	15mg twice daily for the first 21 days followed by 20mg once daily for continued treatment and prevention of recurrence.	£75.60 (21 days) £190.00 (3 months) £341.20 (6 months) £694.00 (12 months)

PACEF Comment
Recent price reductions mean that apixaban and rivaroxaban are emerging as the lowest cost agents with apixaban currently lowest cost. Both of these drugs are preferred at ULH and are widely prescribed in county. Further price changes may be announced over the coming months.

Cost Effectiveness

NICE have concluded that apixaban, dabigatran, edoxaban and rivaroxaban represent a clinical and cost-effective option in patients for whom treatment is indicated for up to 12 months and beyond. The NICE cost model takes into account INR costs, but NICE acknowledge that this is difficult to model due to variation in INR costs across the country.

Drug interactions

Apixaban, dabigatran, edoxaban and rivaroxaban interact with the following drugs:

- strong inhibitors of CYP3A4 and P-gp such as azole antifungals (ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir).
- weaker inhibitors of CYP3A4 and P-gp (e.g. diltiazem, naproxen, amiodarone, verapamil, quinidine)
- P-gp inhibitors (e.g.amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor).
- ciclosporin and tacrolimus.
- inducers of CYP3A4 and P-gp (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and St John's wort).

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

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 LMWH is recommended (e.g. enoxaparin 40mg by SC injection every 24 hours for 6 weeks). 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. A treatment algorithm is provided as an Appendix to aid decision making.

Monitoring

Renal function should be assessed by calculating the CrCl prior to initiation of treatment 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 apixaban	When converting patients from warfarin (or another VKA) to apixaban, discontinue warfarin/other VKA and start apixaban when the INR is < 2.0.
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 two days of co-administration of apixaban with VKA therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue to co-administer apixaban and VKA therapy until the INR is $\geq$ 2.0.

Warfarin to dabigatran	The VKA should be stopped and dabigatran given as soon as the INR is ≤ 2.0.
Dabigatran to warfarin	Adjust the starting time of the VKA based on CrCL. If CrCL is ≥ 50mL/min, start VKA three days before discontinuing dabigatran. If CrCL ≥ 30 - < 50mL/min start VKA two days before discontinuing dabigatran. Interpret INR values with caution as the INR will better reflect the VKAs effect only after dabigatran has been stopped for at least 2 days.
Warfarin to edoxaban	Discontinue the VKA and start edoxaban when the INR is ≤ 2.5.
Edoxaban to warfarin	For patients on a 60mg dose of edoxaban, give 30mg once daily together with an appropriate VKA dose. For patients on a 30mg dose, give 15mg once daily together with an appropriate VKA dose. Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued.
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.
Rivaroxaban to warfarin	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 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. Apixaban does not affect APTT or PT; a patient may have therapeutic levels associated with a normal clotting screen.
5. Neither of these laboratory tests can be used to determine the drug level. Where this is required, contact the Haematology Consultant for further advice.

6. Effect on other clotting tests:
   - D-dimer results are low (as with all anticoagulants).
   - these agents **do not** cause thrombocytopenia (HIT)

Reversal of NOACs

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. New reversal agents are in various stages of development with idarucizumab (*Praxbind*) for reversal of dabigatran recently licensed in the EU and due for launch shortly.

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

(Further updated guidance will be published soon).

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Appendix 1: Summary of Benefits and Risks - *Warfarin vs Newer Oral Anticoagulants*

	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 newer oral anticoagulants.* NICE have concluded that: apixaban is effective at treating VTE and is associated with fewer bleeds than warfarin. There is no demonstrable difference between dabigatran etexilate, warfarin and rivaroxaban in treating VTE and preventing recurrent evants. Edoxaban is non-inferior to warfarin for VTE recurrence. Rivaroxaban is as effective as enoxaparin followed by a VKA for preventing VTE recurrence.	
INR Monitoring	*INR monitoring enables assessment of compliance with*	*Patients can be inconvenienced by the demands of routine INR*

	warfarin. *Newer oral anticoagulants do not require INR monitoring. A more stable level of anticoagulation is achieved.*	*monitoring.* *As NOACs 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 NOACs 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 NOACs is more difficult. There is currently no licensed product available to rapidly reverse NOACs although prothrombin complex has been used successfully.*
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 NOACs is still not fully understood. There are significant risks in exposing a wider population to NOACs before long-term safety has been fully evaluated. Safety concerns have been raised around dabigatran and rivaroxaban and more safety data is continuing to emerge as levels of prescribing increase worldwide.*
Interactions	*There are fewer potential interactions with other medication, alcohol and diet with NOACs.*	*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.*	*Rivaroxaban has a half-life of 5 to 9 hours in young patients and 11 to 13 hours in elderly patients. Poor compliance could be potentially disastrous exposing the patient to a greater risk of thromboembolic complications*

Appendix 2: 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 Appraisals of the newer oral anticoagulants and provides no specific guidance on the use of the newer agents within this context. The text of this *Bulletin* provides guidance on when LMWH/ warfarin or a NOAC 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.

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.

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 3: *Treating superficial vein thrombosis/thrombophlebitis near a deep vein*