

Direct Oral Anticoagulants (DOACs) for DVT and PE in adults

Prescribing criteria for Rivaroxaban (Xarelto®), Dabigatran, Apixaban or Edoxaban in the treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and prevention of recurrent DVT and PE in adults

Rivaroxaban (Xarelto®) is the first-line option

Hospital DVT treatment pathways

- The hospital treatment pathways found via the links below advise the GP how to deal with suspected DVTs according to which local hospital trust the patient is to be sent to for further investigation
- The treatment pathways should be used in conjunction with our documents about Rivaroxaban if that particular anticoagulant is being considered

RUH (Bath)

http://nww.ruh-bath.nhs.uk/For_Clinicians/clinical_guidelines/documents/medicine/ACUTE-027_Deep_Venous_Thrombosis.pdf

SFT (Salisbury)

- A large range of documents regarding VTE can be accessed via: <http://www.icid.salisbury.nhs.uk/CLINICALMANAGEMENT/THROMBOPROPHYLAXIS/Pages/IndexPage.aspx>
- The DVT pathway can be found here: <http://www.icid.salisbury.nhs.uk/ClinicalManagement/Thromboprophylaxis/Pages/SuspectedDVT>.

Please note that the anticoagulation service at Salisbury district hospital recommend rivaroxaban (off-label) for the treatment of extensive superficial thrombophlebitis for patients at high risk of DVT

GWH (Swindon)

- See treatment pathway overleaf

Pulmonary Embolism

- NICE recommends all of the DOACs as possible treatments for adults with pulmonary embolism and to prevent further deep vein thrombosis or pulmonary embolism as follows:
 - Rivaroxaban (2013): <http://www.nice.org.uk/guidance/ta287>
 - Dabigatran (2014): <http://www.nice.org.uk/guidance/ta327>
 - Apixaban (2015): <https://www.nice.org.uk/guidance/ta341>
 - Edoxaban (2015): <https://www.nice.org.uk/guidance/ta354>
- The above treatment pathways only discuss treatment of DVT. However, if a patient needs to have a DOAC for a PE, the pathways are applicable to that situation as well

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GWH OP DVT Treatment Flowchart

Patient (NHS Swindon or NHS Wiltshire) attends Community DVT team for initial assessment including FBC, Urea and electrolytes, eGFR, LFT's D-Dimer, Wells score and +/- Doppler ultrasound. If appropriate commence anticoagulation until result of Doppler scan known. Anti-coagulant options pre diagnosis are:

- LMWH
- Rivaroxaban (don't use this option if you think the patient would need to be on warfarin if the scan is positive).

Scan positive

Scan negative

Refer to anticoagulant clinic for on-going anticoagulation with either Rivaroxaban or warfarin. Continue anticoagulant until patient is seen by anticoagulant team

Community DVT team will liaise with patients GP to further investigate symptoms, anticoagulation discontinued

Rivaroxaban:

NICE [TA261](#) for DVT and NICE [TA287](#) for PE recommend:

Rivaroxaban is an option for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults.

Both rivaroxaban and warfarin are available as options for the treatment of all VTE patients.

Rivaroxaban will be considered first-line.

Anticoagulant team to consider rivaroxaban or warfarin for each patient:

1.) If Rivaroxaban is being considered, use the "[Rivaroxaban prescribing criteria for DVT & PE](#)" to ensure that it is prescribed safely & that the NICE criteria are fulfilled (See page 3)

2.) Use "[warfarin and rivaroxaban decision aid for DVT and PE](#)" to help decide the optimum treatment for the patient. (See page 5)

Considerations – warfarin may be more appropriate:

1.) For patients with a Cr CL below 30ml/min or eGFR below 30ml/min/1.73m³.

Refer to page 8 for further advice in any patient with renal impairment (or the SPC).

Treat with Rivaroxaban

Treat with Warfarin

- Fully counsel patient re: anticoagulation
- Prescribe **Rivaroxaban 15mg b.d issuing a 21 day pack (42 tabs)**
- Issue patient with information leaflet and alert card
- **For Swindon patients: Arrange to review patient in the anticoagulant clinic in 3 weeks time to reduce the dose of Rivaroxaban to 20mg daily issuing a further 28 days prescription.**
- **For Wilts patients : Arrange appointment with GP in 3 weeks time to reduce dose and check compliance**
- Transfer care to GP for further supplies
- For all patients fax all details to patients GP

- Fully counsel patient re: anticoagulation, including information leaflet and alert card
- Prescribe warfarin and continue with anticoagulant initiated pre-diagnosis until INR>2 on two consecutive occasions.

Following this:

Either: Review patient in the anticoagulant clinic

Or: Arrange for follow up with patients GP and or D/N services to monitor INR's and review treatment.

Long-term LMWH may be an option for certain patient groups as advised by specialist anticoagulant services.

For patients that don't tolerate Rivaroxaban, Apixaban is the 2nd line and Edoxaban 3rd line DOAC alternative. See SPC for dosage details.

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Considerations when choosing the right anticoagulant to use

Should I admit or not?

- Do you have reason to suspect serious renal failure? *Patient not suitable for ambulatory treatment, refer for hospital assessment*
- Do you suspect serious (pelvic) DVT or PE? *Medical assessment in hospital required +/- consideration of catheter directed thrombolysis etc.*
- Does the patient have ongoing bleeding or serious anaemia? *Seek specialist advice*

Will a DOAC be ok for this patient?

- Do you think the patient has active cancer? *Use a LMWH until the situation is clear*
- Does the patient have significant mucosal bleeding? (eg. Heavy periods, frequent rectal bleeding / haematuria) *Apixaban preferred*
- Does the patient already suffer with dizziness / hypotension / troublesome headaches? *Apixaban preferred*
- Is the patient on any medications which might alter DOAC effectiveness (eg. Anti-epileptics, dronedarone)? *Use LMWH and then load with warfarin*

Allergies:

- Rash is an infrequent side effect of rivaroxaban but when it happens it can be severe / progressive – seek specialist advice
- Paradoxical thrombosis + a fall in platelet count can occur with LMWH – seek specialist advice
- Lactose intolerance / diarrhoea – rivaroxaban / apixaban may worsen symptoms – Use LMWH instead and seek specialist advice

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Use of rivaroxaban for suspected DVT & PE (pre-diagnosis) in adults

- Current management of venous thromboembolism (VTE) requires the initiation of a low molecular weight heparin (LMWH) (e.g. dalteparin) for rapid anticoagulation whilst awaiting diagnostic workup. Once diagnosis is confirmed, a DOAC such as rivaroxaban or a vitamin K antagonist such as warfarin is initiated to treat the DVT or PE
- Many CCG areas in England have started to use DOACs such as rivaroxaban pre-diagnosis as it is much more convenient for the patient and in terms of staff resource
- Rivaroxaban removes the need for initial treatment with LMWH, and so replaces a two stage therapy with a single oral component
- Local haematologists in the BaNES/Swindon/Wiltshire area support the use of rivaroxaban in this manner
- In new patients, rivaroxaban should be the preferred option in those with a suspected DVT (unless contraindicated- see SPC) while awaiting and subject to diagnostic confirmation. For suspected PE discuss anticoagulation options with the clinician on referral for advice
- If the patient in question has a known diagnosis of cancer they should be anticoagulated with a LMWH (e.g. dalteparin) rather than rivaroxaban
- An informed discussion should take place between the clinician and the patient about the risks and benefits of rivaroxaban compared with LMWHs pre-diagnosis of VTE prior to the initiation of therapy

Procedure to follow:

- Please refer to your local acute trusts diagnostic work up guidelines to ensure that the correct samples are done before initiating anticoagulation: **Ensure that baseline U&Es are done**
- **If DVT is likely** and ultrasound scan is **not** available within 4 hours, **prescribe rivaroxaban 15mg bd** for up to 7 days (depending on when the scan will take place) ie 14 x 15mg tablets . Check renal function. Remember to stop treatment if the diagnosis of DVT is disproved.
- **If DVT is unlikely** and ultrasound scan is not available within 4 hours, but a D-dimer test is positive, do as above in the “DVT is likely” statement.

Do NOT use rivaroxaban if:

- **Patient already on DOACs/LMWHs or warfarin for other conditions**
- **Renal impairment:** Rivaroxaban should be used with caution in patients with severe renal impairment (15 to 30ml/min) and may need a dose adjustment *after* the initial BD dosing in the first 3 weeks. Rivaroxaban is not recommended in patients with a CrCL <15ml/min. See SPC for further information: (<http://www.medicines.org.uk/emc>) or discuss with medicines information or anticoagulant specialist
- **Rivaroxaban is not an option if there is a chance of pregnancy (or until negative pregnancy test) or if breastfeeding.** Seek advice for such patients from a specialist.

Ensure patient knows to ask their community pharmacist for an anticoagulant patient alert card

Once diagnosis is confirmed:

- **Dose:** **WEEK 1 TO 3: 15mg twice daily with food for 21 days**
- **WEEK 4 ONWARDS: followed by 20mg once daily with food** (total treatment of at least 3 months)
- **Duration of treatment** for confirmed DVT varies depending on clinical presentation. A shorter duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. If unprovoked, review at 3 months and consider lifelong anticoagulation.
- All patients who need to be considered for lifelong anticoagulation should be referred to / discussed with a haematologist

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Comparator	Warfarin (variable dosing od)	Rivaroxaban 15mg bd for 3/52 loading (provided by hospital), then 20mg od.		
Cost	£220 p.a. (inc. monitoring)	£657 p.a		
Licensed indication & NICE criteria	Prophylaxis & treatment of venous thrombosis & pulmonary embolism; Prophylaxis of systemic embolism in pts with rheumatic heart disease and AF; prophylaxis after insertion of prosthetic heart valves; transient attacks of cerebral ischaemia.	NICE TA261 and NICE TA287 for PE allow rivaroxaban to be used as an option in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults. Rivaroxaban is also licensed for prevention of stroke and systemic embolism in adult patients with non valvular AF, and prophylaxis of venous thromboembolism in adults after total hip or total knee replacement surgery.		
Clinical Experience	Has been used for >50yrs.	Long term safety data is limited to the duration of treatment exposure of up to 2 years in the clinical trials, EINSTEIN-DVT & EINSTEIN-EXT. EINSTEIN-PE had a mean study duration of 9 months. Available as an anticoagulant since Nov 2011.		
Monitoring	Regular INR tests are needed in order to ensure the correct dose is being taken.	No anticoagulation monitoring is needed (therefore unable to check adherence). No requirement in Summary of Product Characteristics (SPC) to do U&Es but it may be useful to monitor renal function as the dose needs adjusting if renal function declines.		
Dosage	Variable dose once daily dose according to INR.	15mg bd for 3/52, then reduce to 20mg once daily (duration depends on the type of DVT or PE).		
Efficacy	See Rivaroxaban information	Non-inferior to warfarin in EINSTEIN-DVT (n=3449 pts). 2.1% of rivaroxaban-treated pts had recurrent VTE compared with 3.0% of patients receiving standard treatment (hazard ratio: 0.68; 95% CI 0.44 to 1.04). Non-inferior to std therapy (p=0.003) in the treatment of PE in EINSTEIN-PE.		
Bleeding	See Rivaroxaban information		Rivaroxaban	Standard Treatment
		EINSTEIN-DVT: Primary safety outcome (major bleeding or clinically relevant non-major bleeding) (p=0.77)	8.1%	8.1%
		EINSTEIN-PE: Major or clinically relevant non-major bleeding (HR, 0.90; 95% CI, 0.76-1.07; p=0.23).	10.3%	11.4%
		EINSTEIN-PE: Major bleeding (HR, 0.49; 95% CI, 0.31 to 0.79; p=0.003).	1.1% (26pts)	2.2% (52pts)

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Warfarin versus Rivaroxaban Decision Aid for DVT and PE

Comparator		Warfarin (variable dosing od)	Rivaroxaban 15mg bd for 3/52 loading, then 20mg od.
Renal Impairment	CKD 4 or 5 Cr Cl 0-29ml/min	If anticoagulation is needed, warfarin may be used in this group of patients with very careful monitoring & specialist advice.	Plasma levels may be significantly increased (1.6 fold in severe renal impairment) which may lead to an increased bleeding risk. A reduction of maintenance dose to 15mg once daily should be considered if assessed risk of bleeding outweighs risk of recurrent DVT and PE. Cr Cl 15-29ml/min - use with caution Cr Cl <15ml/min - use is not recommended
	CKD3 Cr Cl 30-49ml/min	Safe to use	If Cr Cl 30-49ml/min, a reduction of maintenance dose to 15mg once daily should be considered if assessed risk of bleeding outweighs risk of recurrent DVT and PE.
Administration & stability		Not suitable to go in a dosette box unless a risk assessment has been undertaken and a management plan is in place to manage dosage changes (NPSA guidance)	Suitable to go into a dosette box. Take with food.
Hepatic Impairment		Monitor INR more frequently	Contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C.
Antidote for haemorrhage		Vitamin K	Supportive care such as tranexamic acid and PCC can be used in severe bleeding. Potential problem where emergency surgery is needed.
Prescriber guides and patient alert cards		Yellow books available via SBS (stationary order)	Available from: http://www.xarelto-info.co.uk/hcp/
Contraindications		http://www.medicines.org.uk/emc/medicine/25626/SPC/Warfarin+0.5mg+Tablets/#CONTRAINDICATIONS	http://www.medicines.org.uk/emc/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/#CONTRAINDICATIONS
<p>NOTE : Drug Safety Update Oct 2013 - Revised contraindications for all NOACs http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con322740.pdf</p>			

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Prescribing criteria for Rivaroxaban (Xarelto®) in the treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism and prevention of recurrent DVT and PE in adults

- Rivaroxaban is licenced for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults. It has been approved by NICE TA261 as an option for treatment & prevention of DVT as per the licence and by NICE TA287 as an option for treating PE and preventing recurrent venous thromboembolism
- Rivaroxaban is also licenced for the prevention of stroke & systemic embolism in non-valvular AF: see separate guidance <https://prescribing.wiltshireccg.nhs.uk/prescribing-guidance-by-bnf-chapter/cardiovascular>

Rivaroxaban has been approved for use in Wiltshire as follows:

GREEN: A treatment option for acute DVT and PE and prevention of recurrent VTE in adults

AMBER: A treatment option for prevention of recurrent DVT & PE (following an acute DVT/PE) in cancer pts

Any potential use outside of NICE and/or license should be discussed with the specialist and/or Medicines Management

Before prescribing, please use the checklists overleaf to ensure safe and appropriate use of Rivaroxaban

- Once the decision to treat has been made, please follow guidance below

Dose and treatment schedule

- If a patient has been treated with a Low Molecular Weight Heparin (LWMH) until confirmed diagnosis initiate first dose of rivaroxaban 0 to 2 hours before the time of the next scheduled administration of LMWH

Initial Treatment of acute DVT or PE

- 15mg BD for the first three weeks (days 1-21)
- This is followed by 20mg once daily
- maintenance dose reduced to 15mg in moderate renal failure (see renal information overleaf)

Treatment Duration

- 3 months for distal (below knee) DVT
- Proximal (above knee) DVT or PE should be treated for 3 months then re-evaluated on treatment
- If proximal DVT/PE was provoked by transient risk factors, rivaroxaban may be stopped at this point
- If the risk factors persist, anticoagulation should continue for at least a total of 6 months
- The benefits of longer term anticoagulation following a single thrombosis are less clear
- Patients requiring individual risk/benefit evaluation for longer term anticoagulation should be referred to a consultant haematologist***

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Please use the following checklists before prescribing Rivaroxaban

•NOTE: These lists are not exhaustive and professional judgment should be used on an individual patient basis

1. Does the patient have any of the following contra-indications (from SPC)?

•Tick any that apply

<input type="checkbox"/>	Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C
<input type="checkbox"/>	Active clinically significant bleeding
<input type="checkbox"/>	Pregnancy & breastfeeding
<input type="checkbox"/>	Hypersensitivity to rivaroxaban or to any of the excipients
<input type="checkbox"/>	Lesion or condition at significant risk of major bleeding such as 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
<input type="checkbox"/>	Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives, oral anticoagulants except under the 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

If any of the contra-indications apply to your patient do not prescribe Rivaroxaban and seek advice

2. Further restrictions on use:

•Safety & efficacy of rivaroxaban has not been studied in patients with prosthetic heart valves therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with rivaroxaban is therefore not recommended for these patients

3. Assess your patient's bleeding risk.

•It might be worth considering co-prescription of a PPI to add gastroprotection in certain patient groups on concomitant medications which increase bleeding risk

Renal Function (Rivaroxaban) - as renal function declines, drug clearance is reduced

Creatinine Cl (ml/min)	Recommended dose
Normal or Mild CrCl >50ml/ min	No dose adjustment is necessary
Moderate to Severe CrCl 15-49ml/ min	Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Use with caution in these patients. Moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply: For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks (NOTE this is prescribed and supplied by the hospital). Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting
Severe CrCl <15ml/ min	NOT recommended

There are no requirements in the Summary of Product Characteristics to monitor urea & creatinine routinely. U&Es must be checked if there is any clinical suspicion of renal deterioration as the dose may need adjusting.

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Weight of Patient

- No dose adjustment is necessary

Drug Interactions

- See Summary of Product Characteristics for full details (this list is not exhaustive)

Drug Interactions (See SPC for full details, this list is not exhaustive)	
Interacting Drug	Management
Anti-platelets (e.g. aspirin, clopidogrel)	May increase the haemorrhagic risk. Careful monitoring for bleeds and anaemia would be essential.
NSAIDs	May increase the haemorrhagic risk. Careful monitoring for bleeds and anaemia would be essential.
P-gp inhibitors: e.g. Itraconazole & Ketoconazole	Combination thought to result in increased Rivaroxaban plasma concentrations. Concomitant use not recommended.
P-gp inducers: e.g. Rifampicin, St. John's wort, Phenobarbital, Carbamazepine, or Phenytoin	Expected to result in decreased Rivaroxaban concentrations. Concomitant use should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.
Dronedarone	Due to limited clinical data, concomitant use not recommended
Protease Inhibitors e.g. Ritonavir	Not recommended for concomitant treatment with Rivaroxaban

Mechanical prophylaxis for DVT

- **Proximal deep vein thrombosis**
- NICE now state that **below-knee** graduated compression stockings should only be offered to patients if clinically indicated.

Alert Cards (Rivaroxaban)

- Ensure that the patient is given an alert card by the pharmacy and that the patient knows to carry it around with them at all times and present it to every health care provider that they see. The alert card can be found in the patient booklet "A patient's guide to deep vein thrombosis treatment" which is available from the manufacturer <http://www.xarelto-info.co.uk/hcp/> or pharmacy

Counselling Checklist and Patient Alert Card (Rivaroxaban)

- **Go through each point, keep at hand:**
 - Dose and duration of treatment
 - Possible side effects and what to do (see SPC and/or FAQ document)
 - Advice on planning pregnancy or becoming pregnant (see SPC)
 - Impact on dental treatment (see FAQ document)
 - Take with food
 - Effect on sports and travel
 - When and how to seek medical help
 - Importance of compliance
 - Non-reversibility of rivaroxaban and bleeding risk
 - Missed dose advice (see FAQ or SPC)
 - Avoid OTC aspirin/ibuprofen where possible
 - Expect dose change from 15mg twice daily to 20mg once daily after 3 week loading phase (if not completed already)

Other important considerations (Rivaroxaban)

- A bleeding risk that would lead to a contra-indication to warfarin would also contra-indicate rivaroxaban
- Sub-optimal compliance with warfarin may not be improved by switching to rivaroxaban as many of the causes of non-compliance with warfarin may also result in non-compliance with rivaroxaban (e.g. alcoholism, chaotic lifestyle, wilful non-compliance)
- Rivaroxaban is stable in monitored dosage systems (e.g. dosette) (unlike warfarin and Dabigatran)
- Rivaroxaban has no antidote, therefore cessation of treatment and general haemostatic measures are used
- For patients with swallowing difficulties or PEG tubes etc, please contact the Medicines Management Team for specific advice
- Experience with rivaroxaban in this indication for more than 12 months is limited