

## **Direct Oral Anticoagulants (DOACs) for treatment of DVT or PE, or prevention against recurrent DVT or PE (in Adults)**

There are four DOACs available for the treatment of DVT or PE, and prevention of recurrent DVT or PE, these are:

- **Apixaban (Eliquis®)**
- **Dabigatran etexilate (Pradaxa®)**
- **Edoxaban (Lixiana®)**
- **Rivaroxaban (Xarelto®)**

Clinical trials have shown that DOACs are all non-inferior to vitamin K antagonists such as Warfarin for treatment of DVT and PE, as well as evidence for their long term use for protection against recurrent DVT or PE.

There are no clinical trials comparing the DOACs, so there is no evidence that one DOAC is superior to any other with respect to efficacy or side effects.

### **Secondary care will:**

- **Initiate anticoagulation for the treatment of DVT or PE** where the definitive investigations have been completed.
- **Guide the planned duration of anticoagulation.**

A switch between anticoagulants would be required in certain situations, such as:

- Intolerance of vitamin K antagonists or one of the DOACs,
- Poor INR control or time in therapeutic range with vitamin K antagonists,
- Patient choice.

### **This information sheet is intended to assist primary care clinicians in switching between anticoagulants.**

Full guidance about how to switch between parenteral anticoagulants or warfarin and DOACs can be found on the summary of product characteristics (SPC) of the DOAC being initiated. For DOAC to DOAC switches, initiate the new medicine when the next dose is due. See Appendix 1 on page 8.

There are scenarios where specific certain DOACs would be preferred:

- **Apixaban (Eliquis®)** or low dose **Rivaroxaban (Xarelto®)** if there are concerns about an individual's bleeding risk.
- High dose **Rivaroxaban (Xarelto®)**, **Dabigatran etexilate (Pradaxa®)** or **Edoxaban (Lixiana®)** if the patient suffered from an extensive thrombosis.

However, in most cases any of the DOACs would be a suitable option.

If advice about which DOACs to consider for an individual patient is required, please refer to Consultant Haematologist for review.

When starting or switching to a DOAC it is important to consider certain factors such as:

- **body weight** (initial clinical trials only included patients between 50kg and 120kg, but there is increasing evidence that these medications can safely be used up to 150kg<sup>1,2,3</sup>),
- **renal function** (see below prescribing information),
- **interacting medications** (see below prescribing information).

Reversibility may be an important consideration in certain cases (e.g. high risk of bleeding or patient choice).

There is a reversal agent available for:

- Warfarin,
- **Dabigatran etexilate (Pradaxa®)**.

But there is no specific reversal agent yet available for (and although there are strategies available to manage patients on these agents in the context of major bleeding, they are not fully effective):

- **Apixaban (Eliquis®)**,
- **Edoxaban (Lixiana®)**,
- **Rivaroxaban (Xarelto®)**.

## Prescribing information for Direct Oral Anticoagulants (DOACs) for DVT or PE

See product SPCs for full prescribing information

Nottinghamshire Area Prescribing Committee

Medicine	Rivaroxaban (Xarelto® ▼)		Apixaban (Eliquis®)		Dabigatran etexilate (Pradaxa®)	Edoxaban (Lixiana® ▼)
<b>Licensed indication</b>	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Not recommended in PE patients who are haemodynamically unstable or may receive thrombolysis.					
<b>Standard Dosing for DVT / PE</b>	Day 1-21	15 mg <b>BD</b>	Day 1-7	10 mg <b>BD</b>	<b>After at least 5 days of parenteral anticoagulation:</b> 150mg <b>BD</b> Reduced to 110mg <b>BD</b> if: ->80yrs -taking verapamil -increased risk of bleeding (See <a href="#">SPC</a> )	<b>After at least 5 days of parenteral anticoagulation:</b> 60mg <b>OD</b> Reduced to 30mg <b>OD</b> if: -CrCl 15-50ml/min -low body weight (≤60kg) -concomitant use of potent P-gp inhibitors (eg Dronaderone, Erythromycin, Ketoconazole, Ciclosporin) (See <a href="#">SPC</a> )
	Day 22 +	20 mg <b>OD</b>	Day 8+	5mg <b>BD</b>		
	<b>After 6 months</b>	<b>10 mg OD or 20 mg OD if risk of recurrent DVT/PE is high</b> (See <a href="#">SPC</a> )	<b>After 6 months</b>	<b>2.5mg BD</b>  NB: 5mg <b>BD</b> is not a licenced long term dose for DVT/PE		
It is worth bearing in mind that <b>Apixaban (Eliquis®)</b> and <b>Rivaroxaban (Xarelto®)</b> drop to a lower dose after 6 months of treatment as the respective clinical trials highlighted a reduction in bleeding risk with this strategy (although <b>Rivaroxaban (Xarelto®)</b> has the option to remain on the higher dose for those deemed to be at high risk of recurrence), whereas <b>Dabigatran etexilate (Pradaxa®)</b> and <b>Edoxaban (Lixiana®)</b> have one dose throughout the duration of treatment.						
<b>Presentation</b>	10, 15 and 20mg film coated tablets		2.5 and 5mg film coated tablets		110mg and 150mg hard capsules  NB: 75mg capsules are not licensed for DVT/PE.	15, 30 and 60mg film coated tablets
<b>Administration</b>	The tablet is taken with food		Swallowed with water, with or without food		Take with or without food. Swallow whole with a glass of water, to facilitate delivery to the stomach	Take with or without food. Swallow whole with a glass of water, to facilitate delivery to the stomach
<b>Use in Renal Impairment</b>	<ul style="list-style-type: none"> <li>DOACs can be used in patients with renal impairment in line with the SPC of the specific agent (as below).</li> <li>Patients who develop acute renal failure should discontinue the DOAC and seek specialist advice</li> <li><b>Creatinine clearance must be calculated</b> (see <a href="#">here</a> for calculator), eGFR is NOT considered a suitable alternative.</li> </ul>					
<b>CrCl 30-50ml/min</b>	Limited clinical data: maintenance dose may be reduced to 15 mg <b>OD</b> based on bleeding risk and risk of recurrent VTE		No dosage adjustment		Consider 110mg <b>BD</b> in moderate renal impairment	<b>CrCl 15-50ml/min: 30mg OD</b>
<b>CrCl 15-30ml/min</b>			Use with caution		<b>CrCl &lt; 30ml/min: Contraindicated</b>	
<b>CrCl &lt;15ml/min</b>	<b>Contraindicated</b>		<b>Contraindicated</b>			<b>Contraindicated</b>

Medicine	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Dabigatran etexilate (Pradaxa®)	Edoxaban (Lixiana®)
<b>Use in Hepatic Impairment</b>	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.  Not recommended in patients with severe hepatic impairment. Caution in patients with mild or moderate hepatic impairment (Child Pugh A or B), but no dose adjustment is required.  Caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN as these patients were excluded in clinical trials.	Contraindicated in hepatic impairment or liver disease expected to have any impact on survival.  Not recommended in mild-moderate hepatic impairment with liver enzymes >2 ULN.	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.  Not recommended in patients with severe hepatic impairment. Use with caution in patients with mild/moderate hepatic impairment with liver enzymes >2 ULN or total bilirubin >1.5ULN.
<b>Suitability for patients with swallowing difficulties/ enteral tubes</b>	May be given via gastric tube or crushed and mixed with water or apple puree for patients with swallowing difficulties (licensed route of admin)	Tablets may be crushed and dispersed in dextrose 5% (unlicensed, info from personal communication with manufacturer)	<b>Capsules should not be opened- increased risk of bleeding</b> (oral bioavailability may be increased by 75% when the pellets are removed from the capsule shell)	Tablets may be crushed and administered either in apple puree and taken orally or as a water suspension via a nasogastric tube in patients who are unable to swallow solid oral dose formulations (unlicensed, from personal communication with manufacturer)
<b>Suitability for patients with compliance problems / multi-compartment compliance aids (MCAs)</b>	The shorter half-life of all DOACs may mean missed doses result in a lack of anticoagulation more quickly compared to warfarin. Also, as the therapeutic effect of DOACs is not easily measurable through routine clotting screens, it is difficult to objectively measure concordance in individuals suspected of poor adherence to therapy.			
	May be put in MCAs (no special storage conditions required)	May be put in MCAs (no special storage conditions required)	<b>Not suitable for use in MCAs (unstable out of original packaging)</b>	May be put in MCAs (no special storage conditions required).

<b>Contraindications</b>	<ul style="list-style-type: none"> <li>• Hypersensitivity to drug or excipients</li> <li>• Active clinically significant bleeding</li> <li>• Risk factors for 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, uncontrolled severe hypertension</li> <li>• Hepatic disease associated with coagulopathy and clinically relevant bleeding risk</li> <li>• Dabigatran is contraindicated and neither rivaroxaban, apixaban nor edoxaban are not recommended in patients with prosthetic heart valves</li> <li>• Pregnancy or breast feeding</li> </ul>
<b>Drug interactions</b>	<p>Interactions with common medicines listed below (See SPC or specialist source for more detailed list)</p> <ul style="list-style-type: none"> <li>• <b>Anticoagulants</b> – all DOACs contraindicated with other anticoagulants</li> <li>• <b>Antiplatelets</b> (e.g. aspirin, clopidogrel, prasugrel, ticagrelor etc) and <b>NSAIDs</b> – caution, increase bleeding risk</li> <li>• <b>Azole antimycotics</b> (e.g. <b>ketconazole, itraconazole, voriconazole</b>) - contraindicated with dabigatran, not recommended with rivaroxaban or apixaban (increased plasma levels and bleeding risk), dose adjustment required with edoxaban (see above)</li> <li>• <b>HIV protease inhibitors</b> (e.g. <b>ritonavir</b>) - contraindicated with dabigatran, not recommended with rivaroxaban or apixaban (increased plasma levels and bleeding risk)</li> <li>• <b>Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort</b> - should be avoided with rivaroxaban and dabigatran, use with caution with apixaban or edoxaban</li> <li>• <b>Dronedarone</b> - contraindicated with dabigatran, avoid with rivaroxaban, dose adjustment with edoxaban (see above)</li> <li>• <b>Posaconazole</b> – not recommended with apixaban and rivaroxaban, use with caution with dabigatran (dose reduction required)</li> <li>• <b>Ciclosporin</b> – contraindicated with dabigatran (increased plasma levels of dabigatran expected), use with caution with rivaroxaban or apixaban (possible increased plasma levels and bleeding risk), dose adjustment with edoxaban (see above)</li> <li>• <b>Tacrolimus</b> – contraindicated with dabigatran (increased plasma levels of dabigatran expected), use with caution with rivaroxaban or apixaban (possible increased plasma levels and bleeding risk)</li> <li>• <b>SSRIs / SNRIs</b> – caution</li> <li>• <b>Clarithromycin</b> – caution with dabigatran especially in renal impairment, caution with rivaroxaban in renal impairment</li> <li>• <b>Erythromycin</b> – caution with rivaroxaban if renal impairment, dose adjustment with edoxaban (see above)</li> <li>• <b>Verapamil</b> – reduce dabigatran dose (see above)</li> <li>• <b>Amiodarone and quinidine</b> – caution with dabigatran, monitor for signs of bleeding / anaemia</li> <li>• <b>Fluconazole</b> - caution if renal impairment and concomitant rivaroxaban</li> </ul>

## Monitoring of DOACs

Baseline blood tests				
Patient group	U + Es (Creatinine clearance)	Full blood count	Coagulation screen	Liver function tests
All	✓	✓	✓	✓
Follow up tests				
Patient group	U + Es (Creatinine clearance)	Full blood count	Coagulation screen	Liver function tests
Creatine Clearance > 60ml/min	Annually ✓	Annually ✓	X Inappropriate without correct reagent	Annually ✓
Creatine Clearance 30-60ml/min	Six Monthly ✓			
* In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate				

- Clinical trials have demonstrated that the therapeutic anticoagulation effect of DOACs does not require routine monitoring.
- Unlike warfarin, a prothrombin time may not be sensitive to their anticoagulant effect. Likewise an INR **will not** demonstrate the level of anticoagulation.
- As DOACs are predominantly eliminated by the renal route, it is prudent to monitor the renal function of a patient taking a DOAC. The following regimen is broadly in line with NICE guidance on Chronic Kidney Disease and based on consensus clinician opinion. This may recommend more frequent monitoring than that advised in the manufacturer's summary of product characteristics .
- Initial clinical trials only included patients between 50kg and 120kg, but there is increasing evidence that these medications can safely be used up to 150kg<sup>1,2,3,4</sup>

### Local consensus is that:

- Creatinine clearance must be used for calculating renal function** using the Cockcroft and Gault equation (see below). eGFR is **not** a suitable alternative:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/l)}} \times 1.04 \text{ (female) or } 1.23 \text{ (male)}$$

**NB The clinical systems used in Nottinghamshire in primary care (SystemOne and EMIS) have an inbuilt Cockcroft-Gault based renal function calculator which can be used to dose DOACs. Both systems use ideal body weight (IBW) if actual body weight is greater than 120% IBW. The most up to date values for the patient's actual body weight and height will have to be inserted. These calculators make adjustments for a body mass index that is outside normal ranges and may produce a slightly different result to the equation provided. Controversy exists over which form of weight to use (actual BW, ideal BW, lean BW or adjusted BW).**

- If your built in creatinine clearance calculator does not work, then you can use the [MD+ CALC Creatinine Clearance calculator](#) (it can be downloaded as an app to an apple or android device). Always use the most up to date values and check the default units are correct when entering weight, serum creatinine and height. It would be good practice for the clinician reviewing the patient to document what method was used.
- If you have concerns about dose adjustments for DOACs based on estimating renal function using Cockcroft Gault, please seek advice from your local specialists.

**Should the individual patient be deemed at a greater risk of developing renal dysfunction, more frequent monitoring may be warranted.** The frequency of testing will need to be increased if there is rapid progression, or during intercurrent illness and perioperatively in all patients with CKD.

### **Criteria for review and discontinuation of DOACs**

<b>Event</b>	<b>Action</b>
Haemorrhage	Refer patient immediately to Emergency Department if serious bleeding occurs eg GI bleeding, epistaxis lasting more than 1 hr.
Dyspepsia	Common with dabigatran. Consider a proton pump inhibitor. If persists consider alternative anticoagulant.
Unexplained acute fall in haemoglobin or blood pressure	Refer patient immediately to the Emergency Department for investigation.
Trauma (especially to the head)	Consider referral to Emergency Department.
Excessive bruising	Check FBC and U+Es. Consider discussion with Haematologist.
Any acute illness that MAY affect renal function	Measure U+Es and calculate creatinine clearance. Reduce dose or withhold treatment if required.
Significant reduction in renal function (and see below)	Reduce dose as appropriate according to the medicine's recommended dosing schedule in renal impairment (see above for <a href="#">CrCl calculation</a> ). If renal function continues to worsen consider alternative anticoagulant.
Fall in <a href="#">creatinine clearance</a> to <30ml/min with dabigatran or <15ml/min with rivaroxaban, apixaban or edoxaban	Stop DOAC, assess for bleeding and seek advice as to whether specific assays are indicated / alternative anticoagulant required.

## Appendix 1: Switching between anticoagulants

Drug switch	To Apixaban	To Dabigatran	To Edoxaban	To Enoxaparin	To Rivaroxaban	To Warfarin
<b>From Apixaban</b>	X	Stop apixaban and commence dabigatran at same time as next scheduled apixaban dose	Stop apixaban and commence edoxaban at same time as next scheduled apixaban dose	Stop apixaban and give enoxaparin at same time as next scheduled apixaban dose	Stop apixaban and commence rivaroxaban at same time as next scheduled apixaban dose	Load with warfarin as per loading guide, take INR prior to next dose of apixaban, continue apixaban until INR in range
<b>From Dabigatran</b>	Stop dabigatran and commence apixaban at same time as next scheduled dabigatran dose	X	Stop dabigatran and commence edoxaban at same time as next scheduled dabigatran dose	Stop dabigatran and commence enoxaparin at same time as next scheduled dabigatran dose	Stop dabigatran and commence rivaroxaban at same time as next scheduled dabigatran dose	Load with warfarin as per loading guide, take INR prior to next dose of dabigatran, continue dabigatran until INR in range
<b>From Edoxaban</b>	Stop edoxaban and commence apixaban at same time as next scheduled edoxaban dose	Stop edoxaban and commence dabigatran at same time as next scheduled dabigatran dose	X	Stop edoxaban and commence enoxaparin at same time as next scheduled edoxaban dose	Stop edoxaban and commence rivaroxaban at same time as next scheduled edoxaban dose	Load with warfarin as per loading guide, take INR prior to next dose of edoxaban, continue edoxaban at half of usual daily dose until INR in range.
<b>From Enoxaparin</b>	Stop enoxaparin and commence apixaban at same time as next scheduled enoxaparin dose	Stop enoxaparin and commence dabigatran at same time as next scheduled enoxaparin dose	Stop enoxaparin and commence edoxaban at same time as next scheduled enoxaparin dose	X	Stop enoxaparin and commence rivaroxaban at same time as next scheduled enoxaparin dose	Load with warfarin as per loading dose guide and continue enoxaparin until INR in range
<b>From Rivaroxaban</b>	Stop rivaroxaban and commence apixaban at same time as next scheduled rivaroxaban dose	Stop rivaroxaban and commence dabigatran at same time as next scheduled rivaroxaban dose	Stop rivaroxaban and commence edoxaban at same time as next scheduled rivaroxaban dose	Stop rivaroxaban and give enoxaparin at same time as next scheduled rivaroxaban dose	X	Load with warfarin as per loading guide, take INR prior to next dose of rivaroxaban, continue rivaroxaban until INR in range
<b>From Warfarin</b>	Stop warfarin and start apixaban when INR<2	Stop warfarin and start dabigatran when INR<2	Stop warfarin and start edoxaban when INR<2.5	Stop warfarin and commence enoxaparin when INR<2 (or below usual range)	Stop warfarin and start rivaroxaban when INR<3 (AF) or <2.5 (DVT/PE)	X



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