The use of 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:

- **Rivaroxaban** (tablets, NOT capsules, due to cost)
- **Apixaban**
- **Edoxaban**
- **Dabigatran etexilate**

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.

The updated NICE guideline published in March 2020 (NG158) recommends that patients with a suspected DVT or PE should receive interim anticoagulation that can be continued if DVT or PE is subsequently confirmed. This means that it is now acceptable to use either **Apixaban** or **Rivaroxaban** as an alternative to Low Molecular Weight Heparin (LMWH) injections (e.g. Enoxaparin) for suspected DVT or PE whilst investigations are being carried out. Although it is imperative that baseline blood tests including FBC, UE, LFT and clotting screen are taken, the results do not need to be known prior to starting anticoagulation, as long as they are reviewed within 24 hours.

Secondary care will:

- **Ensure that patient continues an appropriate anticoagulant** if subsequently confirmed to have a DVT or PE.
- **Guide the planned duration of anticoagulation (include in the discharge letter).**

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,
- Change in other medication meaning that current anticoagulant no longer suitable,
- Patient choice.

This information sheet is intended to assist primary care clinicians in initiating interim anticoagulation for suspected DVT or PE, or when 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. This is all summarised in Appendix 1 on page 9.

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), *there is increasing evidence to support the use of DOACs in patients weighing above 120kg, and recent ISTH guidance suggests that **Rivaroxaban** or **Apixaban** can be used for the management of DVT or PE in patients with obesity irrespective of weight (although this guidance does not cover the use of these agents in the context of Atrial Fibrillation); this ISTH guidance has been adopted locally by the NUH Anticoagulation Service for patients coming through the DVT pathway.*
- **renal function** (see below prescribing information),
- **interacting medications** (see below prescribing information),
- **the differences between dosing regimens** (e.g. once daily or twice daily, whether taken with food or not; 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 specific reversal agent available for:

- Warfarin,
- **Dabigatran etexilate,**
- **Apixaban** – although only approved for use in the context of major bleeding related to gastrointestinal tract,
- **Rivaroxaban** – although only approved for use in the context of major bleeding related to gastrointestinal tract.

Although the risk of bleeding is lower than Warfarin, there is no specific reversal agent yet available for **Edoxaban**, although there are strategies available to manage patients in the context of major bleeding (which would also be adopted in patients on **Apixaban** or **Rivaroxaban** in the context of major bleeding not related to the gastrointestinal tract).

With respect to anticoagulation used long term as prevention against recurrent DVT or PE, the updated NICE guidance published in March 2020 (NG158) recommends that patients are offered continued treatment with the anticoagulant they started when DVT or PE was confirmed or consider switching to **Apixaban** if the current anticoagulant isn't well tolerated. This assessment of choice of anticoagulant for those patients continuing long term anticoagulation will usually be made in secondary care as part of a follow up appointment.

When switching from Warfarin onto a DOAC in a patient where the plan for long term anticoagulation was made historically, the above considerations (i.e. body weight, renal function, interacting medications and the differences between dosing regimens) apply, and there are scenarios where specific DOACs may be preferred to **Apixaban**:

- Once a day dosing regimen: **Rivaroxaban 10mg od**
- Concerns related to high thrombotic risk: **Rivaroxaban 20mg od**, **Dabigatran etexilate** or **Edoxaban**

If advice about which DOACs to consider for an individual patient is required, please liaise with Consultant Haematologist (e.g. via Advice and Guidance service).

There are certain scenarios where anticoagulation for prevention against recurrent DVT or PE should not be changed without consultation with secondary care:

- Renal impairment (i.e. creatinine clearance below 30ml/min)
- Active cancer
- Established triple positive antiphospholipid syndrome
- Extremes of body weight (i.e. body weight less than 50kg, or greater than 150kg)

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

See product SPCs for full prescribing information

Nottinghamshire Area Prescribing Committee

Medicine	Rivaroxaban		Apixaban		Dabigatran etexilate	Edoxaban
Licensed indication	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.					
Standard Dosing for DVT / PE	Day 1-21	15 mg **BD**	Day 1-7	10 mg **BD**	**After at least 5 days of parenteral anticoagulation:** 150mg BD Reduced to 110mg BD if: ->80yrs -taking verapamil -increased risk of bleeding (See SPC)	**After at least 5 days of parenteral anticoagulation:** 60mg OD Reduced to 30mg OD if: -CrCl 15-50ml/min -low body weight (≤60kg) -concomitant use of potent P-gp inhibitors (e.g. Dronedarone, Erythromycin, Ketoconazole, Ciclosporin) (See SPC)
	Day 22 +	20 mg **OD**	Day 8+	5mg **BD**		
	After 6 months review and if treatment still required	**10 mg OD or 20 mg OD if risk of recurrent DVT/PE is high** (See SPC)	**After 6 months** review and if treatment still required	**2.5mg BD** NB: 5mg BD is not a licenced long-term dose for DVT/PE		
It is worth bearing in mind that **Apixaban** and **Rivaroxaban** 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 **Rivaroxaban** has the option to remain on the higher dose for those deemed to be at high risk of recurrence), whereas **Dabigatran etexilate** and **Edoxaban** have one dose throughout the duration of treatment.						
Presentation	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
Administration	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
Use in Renal Impairment	• DOACs can be used in patients with renal impairment in line with the SPC of the specific agent (as below). • Patients who develop acute renal failure should discontinue the DOAC and seek specialist advice • **Creatinine clearance must be calculated** (see here for calculator), eGFR is NOT considered a suitable alternative.					
CrCL 30-50ml/min	Limited clinical data: maintenance dose may be reduced to 15 mg OD based on bleeding risk and risk of recurrent VTE		No dosage adjustment		Consider 110mg BD in moderate renal impairment	**CrCl 15-50ml/min: 30mg OD**
CrCL 15-30ml/min			Use with caution		**CrCl < 30ml/min: Contraindicated**	
CrCL <15ml/min	**Contraindicated**		**Contraindicated**			**Contraindicated**

Medicine	Rivaroxaban	Apixaban	Dabigatran etexilate	Edoxaban
Use in Hepatic Impairment	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 >1.5 ULN.
Suitability for patients with swallowing difficulties/ enteral tubes	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)	**Capsules should not be opened- increased risk of bleeding** (oral bioavailability may be increased by 75% when the pellets are removed from the capsule shell)	Tablets may be crushed and mixed with water/apple puree and immediately administered. Alternatively, tablets may be crushed and suspended in water and immediately delivered through a gastric tube followed by flushing with water.
Suitability for patients with compliance problems / multi-compartment compliance aids (MCAs)	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)	**Not suitable for use in MCAs (unstable out of original packaging)**	May be put in MCAs (no special storage conditions required).

Contraindications		• Hypersensitivity to drug or excipients • Active clinically significant bleeding • 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 • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Dabigatran is contraindicated and neither rivaroxaban, apixaban nor edoxaban are not recommended in patients with prosthetic heart valves • Pregnancy or breast feeding			
Drug interactions - refer to SPC for more information.		• Dabigatran and edoxaban are substrates for P-glycoprotein (P-gp) • Apixaban and rivaroxaban are metabolised by cytochrome P450 enzyme CYP3A4 and are substrates for P-gp. The table below outlines main DOAC drug interactions (drugs in bold font recommend not be used with DOACs – except those marked with * can be used with edoxaban): **N.B. This is not an exhaustive list and if in doubt check for interactions using BNF, SmPC or online tool.**			
Class	**Medicine**	**Rivaroxaban**	**Apixaban**	**Dabigatran**	**Edoxaban**
Strong P-gp inhibitors (also CYP3A4 inhibitors)	***Ciclosporin** ***Dronedarone** **Itraconazole** ***Ketoconazole** **Posaconazole** **Tacrolimus** **Voriconazole** **Imatinib** **Crizotinib** **Vandetanib** **Sunitinib** **Abiraterone**	Strong recommendation not to use.	Strong recommendation not to use.	Combination contraindicated.	Reduce dose to 30mg daily if on ciclosporin, dronedarone, erythromycin or ketoconazole. Recommend not use with others listed.
Other strong P-gp inhibitors (also CYP3A4 inhibitors)	Amiodarone Clarithromycin Quinidine Verapamil	Caution.	Caution.	Caution. If on verapamil give 110mg twice daily.	Caution.

HIV Protease inhibitors (P-gp inhibitors and CYP3A4 inhibitors)	**Ritonavir** **Telaprevir** **Lopinavir** **Darunavir** **Cobicistat**	Strong recommendation not to use.	Strong recommendation not to use.	Concomitant use not recommended.	Not recommended to use.
Strong P-gp and CYP3A4 inducers	**Carbamazepine** **Phenobarbital** **Phenytoin** **Primidone** **Rifampicin** **St John's Wort** **Vinblastine** **Doxorubicin** **Enzalutamide**	Combination should be avoided.			
Other anticoagulants	E.g. **LMWH, warfarin, UFH, fondaparinux**	Combination contraindicated except when switching therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.			
Others	Aspirin Clopidogrel NSAID's	Caution. Combination not recommended. A careful risk-benefit assessment should be made prior to initiation if required.			
	Prasugrel **Ticagrelor**	Combination not recommended.			
	SSRI's and SNRI's	Caution. Monitor for signs of bleeding.			

Monitoring of DOACs

Baseline blood tests				
Patient group	**U + Es (Creatinine clearance)**	**Full blood count**	**Coagulation screen**	**Liver function tests**
All	✔	✔	✔	✔
The current national recommendations, once DOAC treatment is started, are to review patients after 1 month, and at least 3 monthly thereafter. Follow up intervals may vary depending on the individual patient's characteristics, comorbidities, and co-medications.[27] **Please see below for frequency on blood monitoring during the first year and ongoing**.				
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
If the person is frail or older than 75 years[28]	6 monthly	6 monthly	**X** Inappropriate without correct reagent	6 monthly
Creatine Clearance **30-60ml/min****	Minimum 6 monthly**	Minimum 6 monthly **	**X** Inappropriate without correct reagent	Minimum 6 monthly**
Creatinine Clearance **15-30ml/min**	3 monthly***	3 monthly***	**X** Inappropriate without correct reagent	3 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

** NICE CKS and SPS recommend that if CrCl < 60 mL/min, the frequency of monitoring (in months) can be guided by the CrCl divided by 10. For example, every 3 months if CrCl is 30 mL/min.

*** PCCS and UKCPA recommend routine surveillance every 6 months in patients over 75 years of age and/or frail and routine surveillance 3 monthly in CrCl 15-30mls/min.

- Clinical trials have demonstrated that the therapeutic anticoagulation effect of DOACs does not require routine monitoring and may be beneficial in patients on interacting medicines that do not want to take warfarin.
- 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 (SPC).

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

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

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

Event	Action
Haemorrhage	Refer patient immediately to Emergency Department if serious bleeding occurs e.g. 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 CrCl calculation). If renal function continues to worsen consider alternative anticoagulant.
Fall in creatinine clearance 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
From Apixaban	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
From Dabigatran	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
From Edoxaban	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.
From Enoxaparin	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
From Rivaroxaban	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
From Warfarin	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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