Amber with Guidance= To be recommended or initiated by a specialist with follow up prescribing and monitoring by primary care clinicians.*
**Specialist is defined by the APC as a clinician who has undertaken an appropriate formal qualification or recognised training programme within the described area of practice*

Barnsley Hospital NHS Foundation Trust | South West Yorkshire Partnership NHS Foundation Trust | NHS Barnsley Clinical Commissioning Group

The use of DOACs (Direct Oral Anticoagulants) for the treatment and prevention of DVT and PE:

Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®), Rivaroxaban (Xarelto®)

Please see the full Summary of Product Characteristics for more information http://www.medicines.org.uk/emc/

<table>
<tr><td>Background Information</td><td colspan="4">NICE have approved the following DOACs for the treatment and prevention of venous thromboembolism:
Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (TA341)
Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and or/pulmonary embolism (TA327)
Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism (TA 354)
Pulmonary embolism and recurrent venous thromboembolism - rivaroxaban (TA287)</td></tr>
<tr><td>BNF therapeutic class</td><td colspan="4">2.8.2 Oral anticoagulants</td></tr>
<tr><td>Indication</td><td colspan="4">Treatment and prevention of deep vein thrombosis or pulmonary embolism</td></tr>
<tr><td>Dosage and administration</td><td colspan="4">Patients should be provided with a patient held alert card and be advised to carry the card with them in case of emergency.</td></tr>
<tr><td></td><td>Apixaban
<u>Treatment of DVT or PE:</u> 10mg twice a day for 7 days, followed by 5mg twice a day for at least 3 months.

<u>Prevention of recurrent DVT or PE:</u> 2.5mg twice a day for patients having completed 6 months treatment for DVT or PE.</td><td>Dabigatran
<u>Treatment and prevention of DVT or PE:</u>
150 mg twice daily for at least 3 months, following treatment with a parenteral anticoagulant for at least 5 days.

Dose reduction recommended
110 mg twice daily for the following groups –
• Aged 80 years and over
• Those receiving concomitant verapamil

Dose reduction for consideration
Either dose of 150mg twice daily or 110mg twice daily should be selected based on an individual assessment of the</td><td>Edoxaban
<u>Treatment and prevention of DVT or PE:</u>
60mg once daily for at least 3 months, following treatment with a parenteral anticoagulant for at least 5 days.

Dose reduction recommended
30 mg once daily in specific patient groups:
• People with moderate or severe renal impairment (CrCL 15 - 50 mL/min)
• Low body weight (60 kg or less)
• Concomitant use of potent P−glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)</td><td>Rivaroxaban
<u>For initial treatment and prevention of DVT or PE:</u>
15 mg twice daily for the first 21 days followed by 20 mg once daily for at least 3 months for the continued treatment and prevention of recurrent DVT and PE.

<u>For extended prevention of DVT or PE:</u>
10 mg once daily following completion of at least 6 months treatment. Consider 20mg once daily in patients at high risk of recurrent DVT or PE, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban 10 mg once daily.</td></tr>
</table>

		thromboembolic risk and the risk of bleeding, for the following groups – • Aged 75–79 years • Moderately reduced kidney function (CrCL 30-50mL/min) • People with gastritis, esophagitis or gastroesophageal reflux •People at increased risk of bleeding		***Dose reduction recommended*** For people with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment, the treatment dose is 15 mg twice daily for 21 days. Thereafter when 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. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary. Due to a reduced absorption under fasting conditions, Rivaroxaban 15mg and 20mg need to be taken with food.
Contraindications	• Hypersensitivity to the active substance or to any of the excipients • Active clinically significant bleeding • Lesion or condition if considered a significant risk factor for major bleeding. This may include 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 • Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, apixaban, edoxaban) except under specific circumstances of switching anticoagulant or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Pregnancy and breast feeding • Patients with prosthetic heart valves • Antiphospholipid syndrome			
Precautions	• Haemorrhage risk – observe for signs of bleeding • Surgery and invasive procedures • Temporary discontinuation places the patient at an increased risk of thrombosis • Active cancer • Renal impairment • Elderly patients due to increased bleeding risk • Body weight less than 50kg or more than 120kg - Limited data is available on the use of DOACs in patients weighing less than 50kg			

<table>
<tr><td>Precautions cont…</td><td colspan="4">or more than 120kg and there may be a risk of over or under-anticoagulation respectively. Use of DOACs in these patient groups should be based on discussion with the patient taking into account individual bleeding risk and other patient specific factors. Where uncertainty remains, individual patients may be discussed with the relevant specialists.
• Hepatic impairment
• Interaction with other medicinal products affecting haemostasis – NSAIDs including acetylsalicylic acid, platelet aggregation inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs).
• Use of Thrombolytic agents for the treatment of acute ischemic stroke
• Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp). (E.g. ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir).
• Interaction with inducers of both CYP3A4 and P-gp. E.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort
• Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
• History of Myocardial Infarction</td></tr>
<tr><td>Adverse Drug Reactions</td><td>Apixaban:

Common (1 in 10 – 1 in 100): Bleeding, bruising, thrombocytopenia, nausea, haematuria, gamma-glutamyltransferase increase, alanine aminotransferase increase, skin rash and anaemia.

Uncommon (1 in 100- 1 in 1000): Hypotension, haemoptysis, liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, alopecia, pruritus hypersensitivity, allergic oedema.</td><td>Dabigatran:

Common (1 in 10- 1 in 100): Bleeding, dyspepsia.

Uncommon (1 in 100- 1 in 1000): Anaemia, diarrhoea, nausea, vomiting, hepatobiliary disorders, gastro-intestinal discomfort, gastrointestinal disorders and ulcers, hepatic function abnormal, rash, pruritus.

Rare (1 in 1000 – 1 in 10000): Angioedema, anaphylactic reaction dysphagia, urticaria, thrombocytopenia.</td><td>Edoxaban:

Common (1 in 10- 1 in 100): Bleeding, anaemia, nausea, rash, dizziness headache, abdominal pain, pruritus, hepatobiliary disorders (increased blood bilirubin and gamma−glutamyl transferase) and abnormal liver function test.

Uncommon (1 in 100- 1 in 1000): Hypersensitivity, thrombocytopenia, blood alkaline phosphatase increased, transaminases increased, urticaria

Rare(1 in 1000 – 1 in 10000): Allergic oedema, anaphylactic reaction.</td><td colspan="2">Rivaroxaban:

Common (1 in 10- 1 in 100): Anaemia, asthenia, gastrointestinal discomfort, bleeding, dizziness, headache, hypotension, wound complications, dyspepsia, rash, haematoma, nausea, constipation, diarrhoea, vomiting, pruritus, bruising, renal impairment, fever, pain in the extremities, increase in transaminases, peripheral oedema.

Uncommon (1 in 100- 1 in 1000): Angioedema, dry mouth, hepatic impairment, increased bilirubin, increased blood alkaline phosphatase, increased GGT, malaise, syncope, tachycardia, thrombocytopenia, thrombocytosis, urticaria, malaise, increased LDH, increased lipase, increased amylase.

Rare or very rare (1 in 1000 – less than 1 in 10000): Severe cutaneous adverse reaction, jaundice, vascular pseudoaneurysm,</td></tr>
</table>

				bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis, Stevens Johnson syndrome, localised oedema, anaphylactic reactions.

<table>
<tr><th>Monitoring</th><th colspan="4">All DOACs</th></tr>
<tr><td>Early monitoring until patient stabilised</td><td colspan="4">Monitoring/follow-up to be undertaken by GP.
• No routine anticoagulation monitoring is needed
• For all forms of anticoagulation please consider performing an early FBC within 2-6 weeks to confirm stable haemoglobin levels.
• Ideally assess patient every 3 months to:
○ Assess compliance and reinforce advice regarding regular dosing schedule.
○ Enquire about adverse effects such as bleeding.
○ Assess for the presence of thromboembolic events
○ Enquire about other medicines, including OTC medicines</td></tr>
<tr><td rowspan="3">Long term monitoring</td><td colspan="4">• 3 monthly follow-up / assessment as above.
• U&E, LFT and FBC at least annually.
• More frequent U&Es / LFTs advised if intercurrent illness that may impact on renal or liver function.
• If calculated CrCl <60ml/min, or patient >75yrs on dabigatran, monitor U&E more frequently as below:</td></tr>
<tr><th>Apixaban</th><th>Rivaroxaban</th><th>Edoxaban</th><th>Dabigatran</th></tr>
<tr><td>U&E:
• CrCl >60ml/min - annually
• CrCl 36 – 60ml/min – every 6 months
• CrCl 15 – 35ml/min – every 3 months
• CrCl <15ml/min – do not use</td><td>U&E:
• CrCl >60ml/min - annually
• CrCl 36 – 60ml/min – every 6 months
• CrCl 15 – 35ml/min – every 3 months
• CrCl <15ml/min – do not use</td><td>U&E:
• CrCl >60ml/min - annually
• CrCl 36 – 60ml/min – every 6 months
• CrCl 15 – 35ml/min – every 3 months
• CrCl <15ml/min – do not use</td><td>U&E:
• Aged <75 years and CrCl >60ml/min - annually
• Age >75 years or fragile, and CrCl > 60ml/min – every 6 months

• CrCl 36 – 60ml/min – every 6 months
• CrCl 30 – 35ml/min – every 3 months
• CrCl <30ml/min – do not use</td></tr>
<tr><td>Risk assessment for long term treatment.</td><td colspan="4"><u>The duration of treatment for patients with DVT or PE will be specified by the referring Consultant Physician following assessment of their bleeding/thrombosis risk</u>, and in general the thrombosis risk in the first 3-6 months of treatment outweighs the bleeding risk. Any changes in the bleeding/thrombosis risk of the patient within the first 6 months of treatment (such as a cancer diagnosis or GI bleed) should be referred back to the initial prescriber for reassessment.

Patients with a confirmed proximal DVT or PE should be offered anticoagulation treatment for at least 3 months (3 to 6 months for those with active cancer).

Assess and discuss the benefits and risks of continuing, stopping or changing the anticoagulant with people who have had anticoagulation treatment for 3 months (3 to 6 months for people with active cancer) after a proximal DVT or PE.

Consider stopping anticoagulation treatment 3 months (3 to 6 months for those with active cancer) after a provoked DVT or PE if the provoking factor is no longer present and the clinical course has been uncomplicated. Patient should be advised on the risk of recurrence including signs and symptoms to look out for.

For patients with an unprovoked DVT or PE, consider continuing anticoagulation beyond 3 months (beyond 6 months for those with active cancer).
Base the decision on the balance between the person's risk of venous thromboembolism (VTE) recurrence and their risk of bleeding.

For patients deemed to require long term prophylaxis for recurrent proximal DVT or PE (e.g. those with unprovoked VTE) bleeding risk may be assessed using the HASBLED scoring tool used in AF patients.</td></tr>
</table>

	Consider stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified. Please note it is not recommended to rely solely on HASBLED to assess the need for long term anticoagulation as there is very limited evidence of use in VTE recurrence. Ongoing thrombosis risk should be assessed clinically with consideration of the following known VTE risk factors: • Active cancer or cancer treatment • Aged over 60 years • Known thrombophilias • Obesity (BMI>30kg/m2) • Significant medical comorbidities including heart disease, respiratory disease, endocrine or metabolic pathologies, neurological disability, acute infectious disease and inflammatory disease. • Varicose veins with phlebitis • Women who are pregnant or have given birth in the last 6 weeks • Previous DVT/PE • Recent surgery or trauma • Significant immobility • Hormonal therapy (combined oral contraceptive pill or hormone replacement therapy) (adapted from NICE VTE assessment tool for adults admitted to Hospital, 2010)
Interactions	• Inhibitors of CYP3A4 and P-gp – ketoconazole, itraconazole, voriconazole and posaconazole, HIV protease inhibitors (e.g. ritonavir), erythromycin, diltiazem, naproxen, verapamil, amiodarone, quinidine, dronedarone, clarithromycin, ticagrelor, tacrolimus, fluconazole, ciclosporin, glecaprevir, pibrentasvir. • Inducers of CYP3A4 and P-gp – rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort • Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs • Medications known to increase the risk of bleeding

Contact names and details

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Development Process

This guideline was developed following an AMBER-G (Amber with guidance) classification status of Apixaban, Dabigatran, Edoxaban and Rivaroxaban for the treatment and prevention of VTE, by the Barnsley Area Prescribing Committee. This information has been subject to consultation by the Consultants at BHNFT and was ratified at the Area Prescribing Committee on 12th May 2021.