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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Treatment of venous thromboembolism (VTE) with apixaban or rivaroxaban in adults

This guideline sets out the use of apixaban and rivaroxaban in the acute treatment and secondary prevention of venous thromboembolism (VTE), both deep vein thrombosis (DVT) and pulmonary embolism (PE). Both oral anticoagulants are direct inhibitors of factor Xa with apixaban being our agent of choice.

Choice of anticoagulant

Treatment of DVT and PE can be with one of the following options:

1. Warfarin

Warfarin is a well-established drug. There is considerable experience with its use including long-term safety data and direct reversal agents are readily available. It is preferred in patients with liver dysfunction or significant renal impairment. It can also be an advantage to have a monitored treatment in the poorly compliant. For further information see MIL volume 5, number 8.

2. Factor Xa inhibitors

Apixaban and rivaroxaban are convenient for initiation of treatment as the quick onset of action negates the need for parenteral therapy.

The efficacy of apixaban and rivaroxaban are similar to that of warfarin for acute VTE. However, compared to warfarin, both are significantly less likely to cause major bleeding. Additionally, apixaban is significantly less likely to cause clinically relevant non-major bleeding. Rivaroxaban (but not apixaban) had an increased risk of GI bleeding compared with warfarin. When used for long-term secondary prevention the 2.5mg dose of apixaban had no more bleeding than placebo. The 10mg rivaroxaban dose has been shown to be as effective as the 20mg dose in preventing recurrent VTE. The 20 mg dose had a significantly increased risk of bleeding over placebo but the 10 mg dose has a bleeding risk similar to aspirin. Although the Summary of Product Characteristics (SPCs) do not have an upper limit for body weight, the International Society on Thrombosis and Haemostasis (ISTH) currently suggest that DOACs should not be used in patients with a weight of more than 120kg. This is because there are limited clinical data available for patients at the extreme of weight, and the available pharmacokinetic/pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing. (If a DOAC is being considered in a patient more than 120kg, this should be discussed with the haematology SpR on bleep 5529, as monitoring is advised).

3. Dalteparin

Dalteparin remains the gold standard treatment for cancer-related VTE and further information is available in MIL volume 7, number 10. (Clinical trial data are emerging and this guidance may change soon (as of July 2019)).

Whilst it is recognised that dabigatran (an oral thrombin inhibitor) and edoxaban (a factor Xa inhibitor) are also licensed for VTE they are not considered within these guidelines because they are deemed a less practical option for acute management; parenteral anticoagulation for at least five days is required before dabigatran or edoxaban can be initiated.

Special patient groups

a. Patients with antiphospholipid syndrome (APS)

Following the results of a randomised clinical trial of patients with triple positive APS, the EMA and MHRA have recently issued a warning about the use of DOACs in patients who are known to have

APS. 'Triple positive APS' refers to a patient who fulfils the clinical criteria for APS and who is also positive for all three of the laboratory tests used to diagnose APS (lupus anticoagulant, anticardiolipin antibody and anti-beta2-glycoprotein 1 antibody). The following is recommended:

1. New patients with an unprovoked VTE: it is recommended that all new patients with an unprovoked VTE who are considered for long-term anticoagulation are tested for APS. This can be done at a 3 month thrombosis review clinic.

2. Switching from warfarin to a DOAC in patients on long-term anticoagulation for VTE prevention: for patients already taking long-term anticoagulation for unprovoked VTE, who are being considered for a switch from warfarin to a DOAC, the doctor should test the patient for APS prior to switching. If the initial test is positive, a repeat test should be conducted after 3 months (12 weeks) and reviewed before switching.

3. *Triple positive APS patients with a VTE:* warfarin should be offered as first line therapy.

4. *Non-triple positive APS patients with a VTE:* there is no evidence to support the choice of anticoagulant. A discussion should be had with the patient about the clinical uncertainty around whether a DOAC is as effective at preventing thrombotic events as warfarin. A shared decision, taking the patient's wishes into consideration, should be made and documented. It is recognised that if a patient has been stable and has not developed a further thrombotic event whilst on a DOAC, that it is reasonable to continue that medication.

b. Pregnancy and Breastfeeding

Apixaban and rivaroxaban should be avoided in pregnancy and in those who are breast feeding. Women of child-bearing potential should be counselled appropriately.

Monitoring

Patients with poor compliance need careful assessment. INR monitoring enables assessment of compliance with warfarin and therefore is the preferred option in such patients. Given no monitoring is required for DOACs, assessment and reinforcement of compliance do not take place. In addition, the anticoagulant effects from DOACs wears off much quicker than those of warfarin due to a much shorter half-life.

Contraindications to anticoagulation

The following substantially increase the risk of major bleeding:

- Current or recent gastrointestinal ulceration
- Presence of malignant neoplasm 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 malformation
- Vascular aneurysms, major intraspinal or intracerebral vascular abnormalities
- Acute stroke (contact stroke team)

If anticoagulation is felt to be contraindicated, the patient should be discussed with Haematology (bleep 5529) and in the acute setting an IVC filter may be considered.

Starting apixaban and rivaroxaban therapy

Prior to starting treatment, a baseline coagulation screen, full blood count, U&Es (including renal function) and liver function must be performed. Table 1 provides guidance on the recommended doses. **Patients should be started on a therapeutic dose of anticoagulation if diagnostic investigations are suspected to take longer than 1 hour (PE) or 4 hours (DVT).** It will usually be simplest to give a treatment dose of dalteparin to provide 24 hours of cover. If the risk of therapy is felt to outweigh the benefit, this should be documented in the medical notes. Standard advice is to give a full treatment dose of dalteparin even if the patient has received a prophylactic dose in the last 24 hours.

Table 1: Dosing advice for apixaban and rivaroxaban

	Apixaban	Rivaroxaban
Standard Dose	Days 1-7: 10mg bd Days 8 onwards: 5mg bd After 3 - 6 months: 5mg bd or 2.5mg bd*[2] (see below)	Days 1-21: 15mg bd with food*[1] Day 22 onwards: 20mg od with food*[1] After 3 - 6 months: 20mg od or 10mg od*[2] (see below)
Renal impairment	Warfarin preferred if CrCl less than 30ml/min Do not use if CrCl less than15ml/min	Warfarin preferred if CrCl less than 30ml/min Do not use if CrCl less than 15ml/min
		Day 22 onwards if CrCl 30-49ml/min; consider reducing to 15mg od with food if the patient's risk of bleeding outweighs the risk of recurrence
Hepatic impairment	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Use with caution in mild and moderate hepatic impairment (Child Pugh A or B). Not recommended in severe 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
Switching from dalteparin	Apixaban should be started instead of the next scheduled administration of dalteparin (if a patient has received 7 days or more of dalteparin, then apixaban should be started at 5mg bd (as for day 8 onwards) and if a patient has received less than 7 days apixaban should be started at 10mg bd for 7 days then reduced to 5mg bd).	Rivaroxaban should be started instead of the next scheduled administration of dalteparin
Switching to dalteparin	Give the first dose of dalteparin at the time the next apixaban dose would have been due	Give the first dose of dalteparin at the time the next rivaroxaban dose would have been due
Switching from warfarin	Stop warfarin and start apixaban once INR is less than 2	Stop warfarin and start rivaroxaban once INR 2.5 or less (not forgetting higher initial dosing when within three weeks of an acute event)
Switching to warfarin	Co-administer apixaban and warfarin for 2 days. After 2 days, check INR prior to next apixaban dose and continue until INR 2 or greater.	Co-administer rivaroxaban and warfarin until INR 2 or greater

*[1] Evidence has shown a significant reduction in absorption and efficacy if this is taken on an empty stomach.

*[2] For patients taking long-term apixaban or rivaroxaban as secondary prevention a risk-benefit assessment should be made to decide on the appropriate long-term dose. This assessment may take place between 3 and 6 months from the initial diagnosis of VTE. For patients deemed to be at higher risk of recurrent VTE, continuation of apixaban at 5mg bd or rivaroxaban 20mg od, should be considered.

Interactions

The use of factor Xa inhibitors is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (such as ritonavir). These medicines are strong inhibitors of both CYP3A4 and P-gp and therefore may significantly increase apixaban/rivaroxaban plasma concentrations. Co-administration of factor Xa inhibitors with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, primidone or St. John's Wort, may reduce apixaban and rivaroxaban plasma concentrations. We therefore recommend that strong CYP3A4 inducers should not be co-administered with factor Xa inhibitors. Macrolide antibiotics e.g. clarithromycin and erythromycin, may inhibit metabolism of factor Xa inhibitors and therefore caution should be applied if co-prescribed. Co-administration of rivaroxaban with dronedarone should be avoided given limited clinical data. Care should also be taken if patients are treated concomitantly with medicinal products affecting haemostasis (e.g. NSAIDS, SSRIs and antithrombotics). Further information for cardiac patients, can be found in MIL Vol 8, No 5. Concomitant treatment with unfractionated heparin (UFH), dalteparin or fondaparinux is contraindicated (except when UFH is being used to maintain patency of a central venous or arterial catheter).

Missed doses

1. Apixaban

If a dose is missed, the patient should take the apixaban immediately and then continue with twice daily intake as before.

2. Rivaroxaban

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take the missed dose immediately and take the next dose on time (if the next dose is due two 15 mg tablets can be taken together). The patient should then continue with 15 mg twice daily.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take the missed dose immediately, and continue the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Duration of therapy

Patients with proximal DVT or PE should be treated for at least 3 months. For a first proximal DVT or a PE associated with transient risk factors treatment will usually stop at 3 months. Long term treatment will be considered for recurrent thrombosis, patients with an on-going risk factor, or unprovoked proximal DVT or PE. It may be possible to decide on finite (3 months) or indefinite anticoagulation when treatment is started but many patients (e.g. those with a first unprovoked proximal DVT or PE) will need to be reviewed at 3 months to decide whether to stop anticoagulation or whether to continue indefinitely.

Patient or carer education

It is vital that all patients newly started on anticoagulation therapy receive written and verbal information from a healthcare professional before discharge. Patient booklets are available from pharmacy to all staff for both apixaban and rivaroxaban. Patients should be encouraged to carry the alert cards with them at all times. Further counselling advice can be found on the Anticoagulation & Thrombosis website.

Discharge arrangements

Patients should be provided with enough supply of apixaban or rivaroxaban to complete the first 3 weeks of treatment. GPs will then take over the prescribing to provide further supplies. It should be stated on the discharge summary how long the patient should be anticoagulated for; this will usually be 3 months or to continue indefinitely. Many patients will need a 3 month review to make this decision. Patients can be referred to the thrombosis consultants at the Oxford Haemophilia and Thrombosis Centre for this 3 month review if required.

Reversal

There is currently no specific antidote to apixaban or rivaroxaban.

Effect on coagulation tests

If the PT and/or APTT are prolonged, levels are likely to be significant but a normal PT and APTT do not exclude significant drug levels (especially with apixaban). If necessary, drug levels can be measured with a specific assay (based on Xa inhibition). Further information is available on the Anticoagulation & Thrombosis website.

Elective surgery

For patients undergoing elective surgery, apixaban and rivaroxaban should be discontinued at least 24 hours before the surgery is planned and for high bleeding risk surgery this should be 48-72 hours, see MIL Vol 10, No 5 for further details. In patients undergoing a procedure which carries a low bleeding risk, full dose anticoagulation is commonly restarted 24 hours after the procedure assuming adequate haemostasis was achieved at surgery (discuss with operating surgeon). In patients undergoing a procedure which carries a high bleeding risk, full dose anticoagulation should not be restarted until **at least** 48 hours after the procedure. The decision on when to reinstate therapeutic anticoagulation post-operatively should be made by the operating surgeon.

Bleeding, overdose and emergency surgery

Please refer to MIL Vol 10, No 6 on apixaban and rivaroxaban.

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