MIL

Oxford University Hospitals NHS
NHS Foundation Trust

Volume 8, No. 1 January 2026

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) in adults with anticoagulation (excluding pregnancy and the puerperium)

This guideline sets out the use of anticoagulation in acute treatment and secondary prevention of venous thromboembolism (VTE), both deep vein thrombosis (DVT) and pulmonary embolism (PE).

Choice of anticoagulant

Direct Oral Anticoagulants (DOACs) are the preferred treatment option with apixaban being our agent of choice. However, for some patients these medicines are not suitable and therefore alternatives are warfarin and/or Low Molecular Weight Heparin (LMWH).

1. Apixaban and Rivaroxaban

Apixaban or rivaroxaban should be considered as first line for treatment of the majority of acute VTE patients because of good efficacy, safety profile and ease of administration. Both oral anticoagulants are direct inhibitors of factor Xa.

The efficacy of apixaban and rivaroxaban is similar to warfarin for acute VTE and both are convenient to initiate because the quick onset of action negates the need for parenteral therapy. 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. However, 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.

2. Edoxaban and Dabigatran

Dabigatran and edoxaban are also licensed for VTE but are not considered within these guidelines because they are deemed a less practical option for acute VTE as parenteral anticoagulation for at least five days is required before dabigatran or edoxaban can be initiated.

3. 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 without coagulopathy, significant renal impairment, and those patients of high body weight (see section c in special patient groups). It can also be an advantage to have a monitored treatment in the poorly compliant. Warfarin is not recommended in the treatment of cancer associated VTE. For further information on starting warfarin refer to MIL Vol 5, No.8.

4. Low Molecular Weight Heparin (LMWH)

Enoxaparin sodium is the Low Molecular Weight Heparin (LMWH) of choice in OUH. Enoxaparin is a biological medicine and as such should be prescribed by brand; Inhixa® will be supplied for all enoxaparin prescriptions. Each reference to enoxaparin in this document relates to Inhixa®.
Enoxaparin is licensed for the treatment of VTE and further information is available in MIL Vol 2, No.2 for use in non-pregnant patients. If enoxaparin is not tolerated and DOACs or warfarin are not suitable, consider dalteparin and then fondaparinux as alternatives.

Special patient groups

a. Patients with antiphospholipid syndrome (APS)

DOACs should not be used in patients with triple positive APS, and instead warfarin should be used first line. '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 British Society of Haematology recommend the following:

1. New patients with an unprovoked VTE: patients deemed to be at higher risk of APS should be tested for APS. The testing can be done at a 3 month thrombosis review clinic, and the patient can be started on DOAC initially unless particularly concerned about risk of APS i.e. history of SLE or livedo reticularis.
The conditions in which testing is advocated are:

- history of SLE or other autoimmune disease
- presence of livedo reticularis
- prolonged APTT prior to starting anticoagulation
- recurrent thrombosis
- VTE at an unusual site
- history of arterial disease without a clear risk
- thrombocytopenia
- recurrent miscarriage/still birth/severe pre-eclampsia
- cardiac valve abnormalities in the absence of another cause

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 only if they fulfil the higher risk categories listed above. 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 little 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. See guideline for the management of VTE in pregnancy and the puerperium for treatment options. Women of child-bearing potential should be counselled appropriately.

c. Patients weighing more than 150kg or with a BMI over 50kg/m^2
There are limited data available for patients at the extreme of weight, and the available pharmacokinetic and pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing.

Our recommendation is that warfarin should be used first line particularly in the acute treatment of VTE (first 3 months) when risk of recurrent VTE is highest. Haematology would then consider a DOAC after the 3 month review for those continuing long term anticoagulation. However, if warfarin is deemed unsuitable, discuss with haematology about most appropriate anticoagulant. A thorough consultation should be carried out by the prescriber with the patient to guide them about the possible treatment options and potential risks and uncertainties around using a DOAC. This should be documented in the medical notes.

d. Patients who have undergone bariatric surgery or bowel resection, or have malabsorption
For these patients, absorption of a DOAC may be affected depending on several factors including site and type of surgery or disease, gastric pH and gut motility. Therefore, warfarin is recommended as this can be monitored and adjusted accordingly. If a DOAC is being considered, please discuss with Haematology (bleep 5529).

e. Patients with active cancer
Randomized controlled trials have evaluated the use of DOACs in patients with active cancer. When compared directly with LMWH, DOACs are as effective at treating VTE as LMWH and have a lower risk of recurrence. However, some can cause more clinically relevant non-major bleeding, particularly in patients with unresected luminal gastrointestinal or genitourinary cancers and caution should be applied when using DOACs for these patients. If a

DOAC is selected, apixaban would be the safest option.

Patients with active cancer can be offered DOACs (apixaban or rivaroxaban) first line or if not suitable, LMWH as treatment, and subsequent secondary prevention therapy. In making the choice of anticoagulant for a cancer patient the following points should be considered on an individual basis: site of cancer (counsel the patient carefully about increased risk of bleeding - **particularly** if a GU or GI cancer or has cerebral metastases and document discussion); ensure all cancer treatment regimens are checked for drug interactions with a DOAC, if using; consider reduced GI absorption of a DOAC with bowel resection/significant emesis (see section d); follow all other general good practice prescribing points set out in this MIL.

f. Patients with platelet counts which are less than 50 or expected to fall to less than 50

Therapeutic anticoagulation is not generally used in patients who have platelet counts less than 50 due to the risk of bleeding. If patients have an acute VTE then anticoagulation should be carefully considered. Please consider discussing with the Haemostasis SpR Bleep 5529 or Consultant.

g. Patients with Central Venous Catheter associated Thrombosis

These patients should have anticoagulation for at least 3 months. The line should not be removed if functional and needed for ongoing therapy. If the line is no longer required, anticoagulation for 3-5 days before removal can be considered if feasible to reduce the risk of clot embolisation upon removal.

Monitoring

Patients with poor adherence need careful assessment. INR monitoring enables assessment of adherence to warfarin and therefore is the preferred option in such patients. Given no monitoring is required for DOACs, assessment and reinforcement of adherence 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.

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 enoxaparin 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 enoxaparin even if the patient has received a prophylactic dose in the last 24 hours.

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.

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	Use with caution if CrCl 15-29ml/min*[3] Do not use if CrCl less than 15ml/min	Use with caution if CrCl 15-29ml/min*[3] 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 enoxaparin	Apixaban should be started instead of the next scheduled administration of enoxaparin (if a patient has received 7 days or more of enoxaparin, 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 enoxaparin
Switching to enoxaparin	Give the first dose of enoxaparin at the time the next apixaban dose would have been due	Give the first dose of enoxaparin 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.

*[3] Individual risk-benefit assessment is essential. Discuss suitability of DOAC vs warfarin with the patient. Factor in stability of renal function, bleeding risk and patient preference and adherence.

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), LMWH or fondaparinux is contraindicated (except when UFH is being used to maintain patency of a central venous or arterial catheter). For patients receiving chemotherapy, DOACs should be checked for potential drug-drug interactions..

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.

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 via EPR 'Consult Thrombosis Clinic'.

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.

Bleeding, overdose and emergency surgery

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

Guidelines regarding the reversal of warfarin can be found on MIL Vol. 5 No. 9

References

1. British National Formulary (BNF) 76th Edition *British Medical Association and the Royal Pharmaceutical Society of Great Britain* London, UK. September 2018- March 2019
2. Summary of Product Characteristics (SPC) for rivaroxaban (Xarelto®), *Bayer plc* accessed via www.medicines.org.uk.
3. Summary of Product Characteristics (SPC) for apixaban (Eliquis®), Bristol-Myers Squibb-Pfizer accessed via www.medicines.org.uk.
4. Bauersachs R et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism – The Einstein Investigators. NEJM 2010;**363:** 2499-2510
5. Agnelli G et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. NEJM 2013;**369**: 799-808
6. Weitz JI et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. NEJM 2017; **376**: 1211-1222
7. Arachchillage, D.R.J., Gomez, K., Anderson, J.A.M., Lester, W., Laffan, M., on behalf of British Society for Haemostasis and Thrombosis Taskforce.(2020) Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid syndrome, 2012 (Br.J.Haematol. 2012; 157: 47-58): use of direct acting oral anticoagulants. Br. J. Haematol, doi: 10.1111/bjh.16308
8. MHRA DSU. Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome accessed via www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-increased-risk-of-recurrent-thrombotic-events-in-patients-with-antiphospholipid-syndrome
9. Young et al. Comparison of an Oral Factor Xa Inhibitor with Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Onc 2018; 36(20):2017-2023.
10. Raskob et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism NEJM 2018; 378 615-624.
11. Agnelli G. et al Apixaban for the treatment of venous associated thromboembolism associated cancer. NEJM 2020; 382:1599-1607
12. Martin et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost 2021; 00:1-9
13. Speed V, Czuprynska J, Patel JP, Arya R. Use of direct oral anticoagulants for venous thromboembolism treatment at extremes of body weight, renal and liver function: an illustrated review. Res Pract Thromb Haemost. 2023 Oct 31;7(8):102240. doi: 10.1016/j.rpth.2023.102240.

Prepared by:

Vicki McDonnell Lead Anticoagulation and Thrombosis Pharmacist, Dr Dalia Khan Haematology Consultant and Dr Nicola Curry Haematology Consultant

Review date: *January 2028*