



**Oxford University Hospitals**  
NHS Foundation Trust

## **OXFORD HAEMOPHILIA AND THROMBOSIS CENTRE OUT-PATIENT DVT SERVICE PROTOCOLS**

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It is available at

[Anticoagulation & Thrombosis Protocols & Guidance](#)

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## Referrals to the DVT Service

The DVT Service accepts adult patients suspected of having a lower limb DVT who are suitable for out-patient assessment and treatment. It operates seven days a week, 9-5 Mon-Fri, 9-1 Sat/Sun/Bank Holidays. On Christmas Day and New Year's Day the service is closed.

New patients need to arrive on time for their appointment to be guaranteed an ultrasound scan due to the availability of the sonographer staff.

Referrals are by telephone to the DVT nurse. They will take details and also ask for a brief letter to either accompany the patient or be emailed to [dvtservice@ouh.nhs.uk](mailto:dvtservice@ouh.nhs.uk)

Mon to Fri – telephone 01865 225629

Sat and Sun – telephone switchboard (01865 741841) and bleep 5165

### Exclusion criteria

- Pregnancy (patients  $\geq 16$  pregnant go to the maternity assessment unit (MAU) (20221) and patients  $< 16$  weeks pregnant go to the ambulatory assessment unit (part of acute general medicine) (21812; consultant bleep 4658).
- Patients under 16 years of age
- Suspected upper limb DVT
- In-patients (unless investigation complete and being discharged)
- Unable to transfer from chair to chair by self.
- Suspected pulmonary embolism
- $>180$  kg
- Active bleeding
- Known to be at increased risk of bleeding, e.g.
  - Active peptic ulceration
  - Liver disease (INR  $\geq 1.5$ )
  - Renal insufficiency: creatinine  $> 200$   $\mu\text{mol/L}$  with unknown eGFR or creatinine clearance  $< 20\text{ml/min}$ , found at: [Creatinine Clearance \(Cockcroft-Gault Equation\)](#)
  - Uncontrolled hypertension ( $>200/110$  mmHg)
  - Recent ( $<1/12$ ) eye or CNS surgery
  - Recent ( $<1/12$ ) haemorrhagic stroke

Patients with inherited bleeding disorders or thrombocytopenia (platelets  $<100 \times 10^9/\text{L}$ ) or with a Hb  $< 100$  g/L should be discussed with a doctor in the Haemophilia and Thrombosis Centre or with the on-call haematology registrar.

At the weekend (and on bank holidays) we cannot accept patients who require hospital transport.

## Mental health patients from Warneford & Littlemore Hospitals and Fulbrook & Fiennes Wards

### Warneford and Littlemore Hospitals

Patients can attend the DVT clinic on an outpatient basis if escorted by an appropriate member of staff. When discharged from the DVT service the patient's anticoagulant care will be the responsibility of these hospitals.

## **Fulbrook (Churchill) & Fiennes (Horton)**

These are inpatient wards and ward staff should be advised to refer to inpatient medical team for diagnosis and management of DVTs.

Mental health patients at the Fullbrook centre can attend the DVT clinic on an outpatient basis if escorted by an appropriate member of staff.

### **Out of Hours Referrals**

A GP seeing a patient with suspected DVT out of hours should decide whether they are suitable for out-patient assessment and treatment (see exclusion list above). If they are not suitable the patient should be referred to the on-call medical team at the JR (01865 741166).

If they are suitable for out-patient assessment and treatment a dose of either Low Molecular Weight Heparin (LMWH), apixaban or rivaroxaban should be given (dosing below) and an appointment arranged for the DVT Clinic the following day.

A blood sample for D-dimer testing should be taken before anticoagulation is given. This should be given to the patient to bring to their DVT appointment. D-dimers cannot be used as part of the diagnostic algorithm once patients have received a dose of anticoagulant so this sample is critical for effective diagnosis and use of resources.

### **Interim anticoagulation**

#### **Dose of dalteparin**

Weight (kg)	Dose by subcutaneous injection using a pre-filled syringe
Less than 46	7,500 once daily
46-56	10,000 once daily
57-68	12,500 once daily
69-82	15,000 once daily
83-98	18,000 once daily
99-112	10,000 twice daily
113-137	12,500 twice daily
138-165	15,000 twice daily
More than 166	18,000 twice daily

#### **Dose of apixaban**

10 mg bd - supply four 5 mg tablets in order to ensure a dose is not missed before review at DVT clinic (patient to take 10 mg stat and 10 mg 12 hours later).

#### **Dose of rivaroxaban**

15 mg bd - supply two 15 mg tablets in order to ensure a dose is not missed before review at DVT clinic (patient to take 15 mg stat and 15 mg 12 hours later).

Apixaban and rivaroxaban should not be used in pregnancy or breast feeding,

In patients weighing more than 98 kg therapeutic dalteparin doses are to be given twice daily and the GP should arrange for the appropriate dosing regimen. Please discuss with the clinical team, if this is practically difficult.

The GP should either email ([dvt-service@ouh.nhs.uk](mailto:dvt-service@ouh.nhs.uk)) or leave a message on the answerphone (01865 225629) to alert the clinic of the patient. A telephone number for the patient must be given so that the DVT clinic can phone the patient the following morning to arrange an appointment.

## Transport

If transport is needed for the first visit this will need to be arranged by the patient's own GP the following morning (a return journey should be booked with the patient arriving at the clinic at 12.00pm and being collected at 3.00pm). Please note that the DVT clinic is unable to accept patients requiring hospital transport at weekends. Patients requiring hospital transport should either be given an appointment on the next working day and provided with anticoagulation until this appointment or referred to the Ambulatory Assessment Unit at the John Radcliffe for investigation. Patients who do not have the return journey booked will have a taxi arranged by the DVT clinic and the GP surgery will be contacted for reimbursement.

Copies of our leaflet 'Welcome to the DVT Clinic' giving information to patients on how to get to the clinic and what to expect, can be downloaded from [our website](#).

## Diagnostic algorithm for suspected DVT

### Pre-test probability assessment

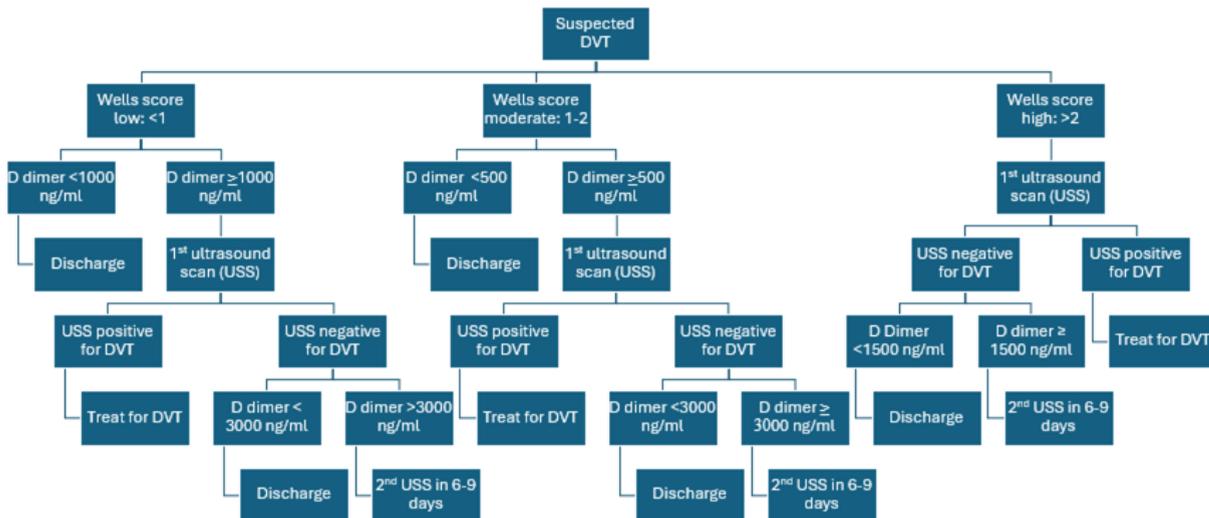
Patients will initially have a pre-test probability assessment (Keeling, et al 2004, Wells, et al 1997, Wells, et al 2003, Wells, et al 1995) by a DVT nurse and be classified as low, moderate, or high risk of DVT (see table below). The nurse will then follow the algorithm in the figure overleaf.

	Points
Active cancer (patient receiving treatment for cancer within the previous six months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within previous twelve weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than the asymptomatic leg (measured ten cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented venous thromboembolism	1
Alternative diagnosis at least as likely as deep vein thrombosis	-2

In cases in which it is unclear as to whether there is an alternative diagnosis the assumption of no alternative diagnosis will ensure the highest level of safety.

Score	Probability
<1	Low
1-2	Moderate
>2	High

## Diagnostic Algorithm



If proximal ultrasound positive: treat for DVT\*

Patients with a negative initial ultrasound scan may qualify for a repeat ultrasound scan in 6-9 days depending on the value of their D dimer.

This algorithm has recently been updated, following a prospective diagnostic and management study by Kearon et al (2022), which has been locally validated and adopted by OUH DVT service, in order to reduce the number of first and repeat ultrasound scans required in patients with clinically suspected DVT, while maintaining a very similar level of diagnostic accuracy (>99% negative predictive value)

Up to the age of 50 years and after this, a negative D-dimer is a result less than or equal to 10x the patient's age.

In patients who have already had an anticoagulant, D-dimers cannot be used as part of the diagnostic algorithm. Patients without a D-dimer result will follow the same path as if D-dimer were positive.

Patients on anticoagulation with a suspected recurrence will all get an initial ultrasound scan and a D-dimer. A doctor will use both of these plus clinical assessment to decide if a new clot has occurred.

## **Ultrasound**

This will be ordered by the DVT nurse in accordance with the diagnostic algorithm above. Patients in whom a DVT cannot be ruled out by clinical examination and D-dimers will be given LMWH, rivaroxaban or apixaban if scanning is delayed by 4 hours or more. The scan should take place within 24 hours.

If the initial ultrasound reveals an alternative diagnosis such as haematoma or a ruptured Baker's cyst then a second ultrasound is not required. For patients on anticoagulation or with a history of trauma we should ask ultrasound to look for a calf haematoma if a proximal DVT is not found.

## **Patients with bilateral symptoms**

Most patients with bilateral leg swelling will not have a DVT but will have a systemic condition such as heart failure, hypoalbuminaemia, renal failure or severe anaemia. However bilateral DVT was found in 4.4% (1 in 23) of DVT patients in the RIETE registry. During the week if a patient has bilateral symptoms ask the GP to speak with the DVT doctor. If the patient is accepted, the DVT doctor will decide if both legs need scanning (or if not which one to scan). If ultrasound negative, consider the possibility of IVC thrombus and therefore may need CT with contrast. At weekends suggest the patient should be reviewed at the Emergency Department.

## **Patients with high clinical suspicion, a grossly swollen leg, but a negative scan**

If a patient has a grossly swollen leg but a negative US scan consider a CT venogram to look for iliac or pelvic vein thrombosis or pelvic pathology causing external compression of pelvic veins.

To facilitate early scanning, contact the interventional radiology registrar on extension: 23484 at the JR. This must be done whilst the patient is still in DVT clinic so that the patient can be booked on to an in-patient list. (If it is not possible to make contact with the IR registrars, Dr Andy Wigham may be contacted via switchboard - please d/w the on call haemostasis Consultant first.

The purpose of the CT venogram is to: a) demonstrate the presence of a pelvic clot that has not been seen on US (to inform anticoagulation therapy) or b) demonstrate extension into the pelvic veins of a DVT that has been seen on US in patients who are eligible for thrombolysis. Do not refer a patient for a CT venogram when a DVT has been confirmed by US (and where the purpose of the scan would be to determine if the clot extends into the pelvis) if the patient is not a suitable candidate for thrombolysis (see below).

If a CT venogram shows external compression of the pelvic veins with no concomitant thrombosis do consider treating with prophylactic dose LMWH if the risk of future VTE due to the compression is deemed to be high until the cause for the external compression can

be treated.

## **Catheter directed thrombolysis and mechanical thrombectomy**

Consider referral to vascular surgeons for consideration of catheter-directed thrombolysis and/or mechanical thrombectomy therapy for patients with symptomatic iliofemoral DVT who have all of:

- symptoms of less than 14 days' duration
- good functional status
- a life expectancy of 1 year or more
- a low risk of bleeding

## **Diagnosis of a recurrence in the ipsilateral leg.**

If the scan is abnormal, but only in sites known to be abnormal on a previous scan (or no previous scan is available) it is often difficult to know whether there is new clot or residual vein thrombosis. Ultrasound findings suggestive of a prior DVT are non-occlusive DVT, disconnected DVT, echoes and signs of flow within the DVT, and DVT at a location that does not fit with the clinical signs. The scan, the clinical situation and the D-dimers should all be considered by the doctor in forming a management plan.

## **Second ultrasound**

In some patients proximal DVT will have been excluded by the first ultrasound but the patient could still have a distal DVT. They will be asked to re-attend for second ultrasound in one week. If this is a Saturday or Sunday they will be seen on Friday or Monday. If the ultrasound becomes positive they will be treated for proximal DVT. If it remains negative they will be discharged without treatment.

Those whose ultrasound remains negative will not be further investigated and will not see a doctor on the unit.

## **Patients who have a DVT excluded**

The patient will be referred back to their GP with this information. They will not be further investigated and will not see a doctor on the unit with the exception of patients found to have SVT adjacent to (within 3 cm of) the sapheno-femoral junction (SFJ)

It is not current OHTC policy to anticoagulate patients with SVT at the saphenopopliteal junction due to lack of supportive evidence.

## **Patients who have a DVT diagnosed**

These patients will be treated as out-patients and have a medical assessment by a doctor on the unit. Patients will be ambulant but we suggest it prudent to avoid vigorous exercise and air travel within two weeks of a new venous thromboembolism.

## **Investigations**

All patients should have:

- FBC
- UE/LFT
- PT/INR and APTT
- Pregnancy test for women of childbearing potential.

## Investigation for cancer in patients with unprovoked DVT

All patients should have a full history and examination. Attention needs to be paid to any concerning symptoms or signs that might suggest the presence of an underlying cancer. The NICE guideline NG 158 (2020) states: [\[Only\]](#) offer further investigations for cancer to people with unprovoked DVT or PE if they have relevant clinical symptoms or signs (for further information see the [NICE guideline on suspected cancer](#)). Patients should also be up to date with any age- and sex-appropriate routine cancer screening e.g. cervical smears, mammograms and FIT testing.

At OUH we would suggest the following:

CXR

and if not performed in the past year:

Breast examination in women over 50 years of age

PSA in men over 40 years of age\*.

We recommend the following thresholds for referring men for suspected prostate cancer:

For men aged:

40-49 years: refer if PSA level is 2.0 nanogram/mL or higher

50-59 years: refer if PSA level is 3.0 nanogram/mL or higher

60-69 years: refer if PSA level is 4.0 nanogram/mL or higher

70 years or older: refer if PSA level is 5.0 nanogram/mL or higher There are no age-specific reference limits for men older than 80 years of age.

## Out patient treatment of DVT

This can be either with A) apixaban, B) rivaroxaban or C) LMWH and warfarin or D) LMWH

### Treatment with apixaban

Apixaban, a direct inhibitor of factor Xa, is given orally for the treatment of DVT and PE and for the secondary prevention of recurrent DVT and PE (Agnelli, et al 2013a, Agnelli, et al 2013b). Apixaban does not require therapeutic monitoring (nor concurrent initial treatment with heparin). It should not be used in those less than 18 years of age.

### Dose

10 mg twice daily for 7 days, then 5 mg twice daily.

On the first day the second dose can be taken later that evening even if the first dose is given in the afternoon.

The licensed dose for secondary prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE is 2.5 mg twice a day (but see page 16 which considers this possibility after 3 months).

### Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. In patients with severe renal impairment (CrCL 15-29 mL/min) apixaban is to be used with caution. We will not routinely use apixaban if CrCL < 30 mL/minute but in selected patients it can be considered for use if the CrCL is 15-30 ml/min.

## **Pregnancy or breast feeding**

Avoid.

## **Missed doses**

If a dose is missed the patient should take the missed dose immediately and take the next dose on time (if the next dose is due a double dose can be taken).

## **Interaction with other medicinal products**

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 active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban and apixaban plasma concentrations to a clinically relevant degree. Co-administration of factor Xa inhibitors with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, primidone or St. John's Wort, may lead to reduced rivaroxaban and apixaban plasma concentrations. We therefore recommend that strong CYP3A4 inducers should not be co-administered with factor Xa inhibitors when treating acute venous thromboembolism. Macrolide antibiotics, such as clarithromycin and erythromycin, may inhibit metabolism of factor Xa inhibitors and therefore caution should be applied if co-prescribed.

## **Prescription**

Initially three weeks treatment should be prescribed and the GP should then continue.

## **Treatment with rivaroxaban**

Rivaroxaban, a direct inhibitor of factor Xa, is given orally for the treatment of DVT and PE and for the secondary prevention of recurrent DVT and PE (Bauersachs, et al 2010). Rivaroxaban does not require therapeutic monitoring (nor concurrent initial treatment with heparin).

Children under the age of 18 may be treated with rivaroxaban. This is only after at least 5 days of initial parenteral anticoagulation (i.e. weight-adjusted dalteparin).

## **Dose**

Adults: 15 mg twice daily with food for 21 days, then 20 mg once daily with food.

Children: see BNF for Children drug monograph for weight-based dosing

## **Renal impairment**

If CrCL 15–49 mL/minute initially 15 mg twice daily for 21 days, thereafter, the recommended dose is the standard 20 mg once daily but 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. The SPC says use with caution if CrCL 15-29 mL/minute and avoid if CrCL less than 15 mL/minute.

We will not routinely use rivaroxaban if CrCL < 30 mL/minute.

## Hepatic impairment

Avoid in liver disease with coagulopathy.

## Pregnancy or breast feeding

Avoid in pregnancy. Use in breastfeeding is not routinely recommended but data suggests minimal transfer in breastmilk. This is reviewed on a case-by-case basis.

## Missed doses

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 on 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.

## Interaction with other medicinal products

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 active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban and apixaban plasma concentrations to a clinically relevant degree. Co-administration of factor Xa inhibitors with strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, primidone or St. John's Wort, may lead to reduced rivaroxaban and apixaban plasma concentrations. We therefore recommend that strong CYP3A4 inducers should not be co-administered with factor Xa inhibitors when treating acute venous thromboembolism. Macrolide antibiotics, such as 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.

## Prescription

Initially three weeks treatment should be prescribed and the GP should then continue.

## Treatment with low molecular weight heparin and warfarin

USE FIXED DOSE SYRINGES and give dalteparin subcutaneously once a day\*.

### Dose of dalteparin for initial treatment of VTE during month 1

Weight (kg)	Dose by subcutaneous injection using a pre-filled syringe	Colour Code
Less than 46	7,500 once daily	GREEN
46-56	10,000 once daily	RED
57-68	12,500 once daily	BROWN
69-82	15,000 once daily	PURPLE
83-98	18,000 once daily	GREY
99-112*	10,000 twice daily	RED
113-137*	12,500 twice daily	BROWN

138-165*	15,000 twice daily	PURPLE
More than 166*	18,000 twice daily	GREY

\*for patients >98 kg give bd dosing. Please discuss with the haematology doctors if this is practically difficult

There is no need to routinely monitor anti-Xa levels in patients who weigh less than 180 kg.

Dalteparin should be continued until the INR has been  $\geq 2$  for at least two consecutive days or for five days – whichever is the longer.

Monitoring the platelet count for heparin induced thrombocytopenia is not necessary.

## Warfarin

The usual recommended target INR is 2.5 (target range 2.0 – 3.0)

Our warfarin induction schedule is shown in the table. If the initial  $INR \leq 1.3$  the patient will receive 5mg of warfarin once daily on days 1 and 2. The INR is checked on days 3 and 4 and the warfarin dose is adjusted according to the schedule. After day 4, until the INR is  $\geq 2.0$  for two consecutive days, a senior thrombosis nurse or doctor will continue to amend the warfarin dose based on the INR result.

Days 1 & 2	Day 3 [INR / Dose]	Day 4 [INR / Dose]
Give 5 mg each day if baseline $INR \leq 1.3$	< 1.5 / <b>10 mg</b> 1.5-2.0 / <b>5 mg</b> 2.1-2.5 / <b>3 mg</b> 2.6-3.0 / <b>1 mg</b> > 3.0 / <b>0 mg*</b>	< 1.6 / <b>10 mg</b> 1.6-1.7 / <b>7 mg</b> 1.8-1.9 / <b>6 mg</b> 2.0-2.3 / <b>5 mg</b> 2.4-2.7 / <b>4 mg</b> 2.8-3.0 / <b>3 mg</b> 3.1-3.5 / <b>2 mg</b> 3.6-4.0 / <b>1mg</b> > 4.0 / <b>0mg*</b>

\*a senior thrombosis nurse or doctor should decide on further management.

## Selecting an oral anticoagulant

Warfarin will be favoured over a DOAC if CrCl < 15 ml/min, or if there is significant liver dysfunction. It is also favoured in patients with extremes of body weight (<40kg and >150kg), those on strong CYP3A4 enzyme inducers or inhibitors, and with unreliable GI absorption and recent (<4 weeks) bariatric surgery.

Choice of anticoagulant should be discussed with the patients considering the pros and cons of each option and considering any previous use.

The efficacy of rivaroxaban and apixaban are similar to that of warfarin. If there is no medical reason to favour warfarin and if there is no patient preference for warfarin we will use a Xa inhibitor. Compared to warfarin, both are significantly less likely to cause major bleeding (including a 50% reduction in risk of intracranial haemorrhage). 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 compared with placebo for long-term secondary prevention rivaroxaban had a significantly increased risk of bleeding but apixaban did not. Apixaban is our current Xa inhibitor of choice.

## Continuing LMWH (in those unable to take oral anticoagulation)

For patients in whom a DOAC or warfarin is contraindicated or not suitable, ongoing treatment solely with dalteparin will be necessary. Full dose LMWH is given for the first month (see above). We give a prescription for the first 4 weeks supply of dalteparin, and after that time the GP should prescribe it. After the first month the dose is most commonly reduced to the pre-filled syringe in the band below (see table below). Please give clear instructions to the GP. If continuing LMWH the patient will need to be able to administer their own LMWH or have a carer do it.

### Dose of dalteparin after month 1 (please reweigh the patient to determine the correct dose)

Body weight (kg)	Dose of dalteparin by subcutaneous injection using a pre-filled syringe (units)
Less than 57	7,500 once daily
57-68	10,000 once daily
69-82	12,500 once daily
83-98	15,000 once daily
99-112	18,000 once daily
113-137	10,000 twice daily
138-165	12,500 twice daily
More than 166	15,000 twice daily

At three months, review the patient to decide on subsequent management.

## Other factors to consider when deciding on anticoagulation

### **Body weight <40kg or >150kg or with a BMI over 50kg/m<sup>2</sup>**

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 as there is limited evidence on the effectiveness of fixed dose DOACs in this group of patients 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 on long term anticoagulation. If DOACs are used in patients with BMI >40, consideration should be given to monitoring of DOAC plasma concentrations to ensure reliable absorption. Beyond 150kg, extreme caution should be applied. 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.

### ***Cancer-related VTE***

Randomised controlled trials have recently evaluated the use of DOACs in patients with active cancer. When compared directly with LMWH, DOACs are as effective at treating VTE as LMWH. However, they 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 DOAC with lowest risk of bleeding compared to LMWH, based on data from CARVAGGIO and ADAM VTE trials.

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 an unresected GU or GI cancer 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. Patients with cerebral metastases require careful evaluation as they are at substantial bleeding risk with anticoagulation.

At six months, review the patient to decide on subsequent management. If cancer is not cured or there is ongoing cancer-directed therapy, continuing anticoagulation is usually recommended. If using apixaban, we suggest considering 5 mg bd for continuing anticoagulation rather than 2.5 mg bd in this **high-risk** group unless there is high bleeding risk, pending further clinical trials.

### ***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. For the first 4 weeks, warfarin or LMWH is preferred as this can be monitored and adjusted accordingly. Subsequent use of DOACs depends on whether the patient has any persistent risk factors for malabsorption such as large small bowel resections, high output stomas, biochemical evidence of malabsorption or small intestinal bacterial overgrowth. If used, DOAC peak levels should be checked at steady state to ensure adequate absorption.

### ***Antiplatelet medication***

For patients with stable coronary artery disease patients (> 12 months from ACS, NSTEMI, STEMI, CABG or stent) antiplatelet therapy can be stopped when anticoagulated unless there is a high risk of future coronary events (prior stenting of the left main, proximal LAD, proximal bifurcation, recurrent MIs), in which case cardiology advice should be sought. Patients with more recent coronary artery disease should have their antiplatelet and anticoagulant regimen discussed with the relevant interventional cardiologist.

### **Duration of treatment and follow up**

Patients with proximal DVT or PE should be treated for at least 3 months. An analysis of

data from seven trials (Boutitie, et al 2011) concluded that three months of treatment achieves a similar risk of recurrent venous thromboembolism after stopping anticoagulation as a longer course of treatment. This was also found in a British study (Campbell, et al 2007).

**Isolated calf DVT:** As the diagnostic strategy used will not identify isolated calf DVTs we will usually be treating proximal DVT. If a first isolated calf veing DVT is identified the option is serial scanning (ACCP suggest scanning at on and two weeks) or treatment for three months (Kearon et al 2012).

For a **first proximal DVT or a PE associated with major transient risk factors** treatment will stop at three months.

Major transient risk factors (TRF):

- Major surgery (defined as surgery with anaesthetic time >45min or with breach of body cavity, orthopaedic, abdominopelvic and curative cancer surgery) within 90 days
- Significant trauma e.g. fracture, pregnancy/puerperium
- Hospitalisation (lasting >48 hours) with pneumonia, stroke, COVID, and critical care within 90 days
- For cancer associated DVT or PE, where cancer is considered in complete remission and all cancer directed therapy (chemotherapy, radiation, and hormonal therapy excluding aromatase inhibitors) – note that 6 months of anticoagulation is recommended for this group, rather than 3 months of anticoagulation.

Patients who have had a DVT or PE whilst taking the COCP should be offered a 3 month appointment

Weaker transient risk factors include is temporary immobility in previous 4 weeks e.g. confined to bed  $\geq 3$  days at home, community acquired infections, minor lower limb injuries not requiring immobilization, COVID as outpatient, or a flight > 4 hours. In this case a three month review is appropriate.

Long-term treatment will be *considered* for:

- Recurrent thrombosis
- patients with an on-going risk factor such as cancer
- a first unprovoked and minimally provoked proximal DVT (or PE).

## Follow-up

Patients who may require long-term anticoagulation will be reviewed at three months to decide whether to stop or whether to continue indefinitely.

If it is decided to continue apixaban although the SPC recommends that the 2.5 mg bd dose should be used after six months of treatment at 5 mg bd it might be best to reduce to this prophylactic dose after three months of full dose anticoagulation. Dose reduction is not routinely advocated in those >120kg/BMI >35 as they were not well represented in the clinical trials, and risks underdosing unless high bleeding risk. It is also not recommended in patients with cancer associated thrombosis unless high bleeding risk.

Patients who are definitely stopping at three months do not have a routine follow-up.

<b>3 months</b>	<b>3 months then consider for long-term</b>
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1st proximal DVT or PE with major TRF* PE with TRF* 1st isolated calf vein DVT High risk saphenous thrombophlebitis	Recurrent thrombosis Proximal DVT or PE with on-going risk factors 1st unprovoked or minimally provoked proximal DVT or PE
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\*If minor transient risk factor (see above), the patient should have a three months review.

Patients with unprovoked proximal DVT or PE are at a higher risk of recurrence than those with a transient precipitating factor (Iorio, et al 2010) and it is therefore recommended that they should be considered for long-term anticoagulation (Kearon, et al 2012). We should take into account information that may help predict risk of recurrence in the individual patient.

Recurrences after unprovoked VTE are more likely in:

- males
- those with raised D-dimers (>500g/l FEU) after completing anticoagulation. Note that D-dimer prognostic data is mainly derived from the warfarin literature and its validity in the DOAC era is not known (see the Apidulcis study).

Prediction scores such as HER DOO2 (Rodger, et al 2008) and DASH (Tosetto, et al 2012) have been proposed.

It is important to take into account that patients with an initial symptomatic PE are 3 to 4 times more likely to suffer recurrence as PE rather than DVT as compared with patients who present with an initial DVT (Baglin, et al 2010, Murin, et al 2002).

Each patient should be counselled as to the risk of recurrence if anticoagulation is stopped and the risk of bleeding if it is continued. Bleeding risk increases in those > 75 years old and in those patients on warfarin who have a low time in therapeutic range (TTR).

The following figure from the European Respiratory society 2019 guidelines helps inform the risk-benefit discussion

Estimated risk for long-term recurrence <sup>a</sup>	Risk factor category for index PE <sup>b</sup>	Examples <sup>b</sup>
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	<ul style="list-style-type: none"> <li>• Surgery with general anaesthesia for &gt;30 min</li> <li>• Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness</li> <li>• Trauma with fractures</li> </ul>
Intermediate (3-8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	<ul style="list-style-type: none"> <li>• Minor surgery (general anaesthesia for &lt;30 min)</li> <li>• Admission to hospital for &lt;3 days with an acute illness</li> <li>• Oestrogen therapy/contraception</li> <li>• Pregnancy or puerperium</li> <li>• Confined to bed out of hospital for ≥3 days with an acute illness</li> <li>• Leg injury (without fracture) associated with reduced mobility ≥3 days</li> <li>• Long-haul flight</li> </ul>
	Non-malignant persistent risk factors	<ul style="list-style-type: none"> <li>• Inflammatory bowel disease</li> <li>• Active autoimmune disease</li> </ul>
	No identifiable risk factor	
High (>8% per year)		<ul style="list-style-type: none"> <li>• Active cancer</li> <li>• One or more previous episodes of VTE in the absence of a major transient or reversible factor</li> <li>• Antiphospholipid antibody syndrome</li> </ul>

PE: pulmonary embolism; VTE: venous thromboembolism. <sup>a</sup>If anticoagulation is discontinued after the first 3 months (based on data from Baglin *et al.* [340] and Iorio *et al.* [341]). <sup>b</sup>The categorization of risk factors for the index VTE event is in line with that proposed by the International Society on Thrombosis and Haemostasis [338]. The present Guidelines avoid terms such as "provoked", "unprovoked", or "idiopathic" VTE.

It is also worth noting that recurrence risk is elevated in males compared to females, and in those with a persistent known positive lupus anticoagulant. The presence of a high risk thrombophilia (protein C deficiency, protein S deficiency, Antithrombin deficiency or compound heterozygosity or homozygosity for factor V Leiden/prothrombin gene mutation) increase the recurrence risk (HR 1.5-2x) but are a relatively small contributor.

In general, patients in the green category should have anticoagulation ceased after 3 months, and those in the red category should have anticoagulation continued long-term. Those in the yellow category require a risk-benefit discussion, with continuation being favoured in males and those with minimal provoking factors such as long-haul flights. Patients who have a first hormonal VTE (pregnancy, puerperium, and in the first 12 months after the combine oral contraceptive pill or HRT) can generally be discontinued after 3-6 months as the recurrence risk is estimated at 2-3%.

## Testing for thrombophilia

Do not offer routine thrombophilia testing to patients who are continuing anticoagulation treatment. However, it is important to test patients who are deemed to have an increased likelihood of antiphospholipid syndrome as the results may potentially change anticoagulation medication.

The BSH guidance (Arachchillage, 2020) recommends testing in the following situations:

- 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

Consider testing for hereditary thrombophilia in patients under the age of 50 who have had unprovoked DVT or PE and who have a first-degree relative who has had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.

Do not routinely offer thrombophilia testing to patients who have had provoked DVT or PE.

Consider testing for hereditary thrombophilia in patients under 50 years who have an unprovoked or oestrogen-provoked VTE and have a first-degree relative who might get pregnant.

Do not routinely offer thrombophilia testing to asymptomatic first-degree relatives of patients with thromboembolic disease and thrombophilia.

Consider testing asymptomatic female relatives planning a pregnancy who have a first degree relative with unprovoked (or hormone-related) VTE age under 50 years for antithrombin deficiency.

Patients with unexplained/unprovoked venous thrombosis at unusual sites (splanchnic vein thrombosis, cerebral vein thrombosis) should be tested for antiphospholipid syndrome, JAK2 and PNH even in the absence of abnormal full blood count. JAK2 and PNH testing should otherwise be reserved to those with concordant FBC abnormalities or other concerning symptoms.

Women with a family history in a first degree relative of unprovoked venous thrombosis should not be offered routine testing, but should avoid the combined oral contraceptive pill and oral estrogen-containing HRT.

Testing is not usually offered in the acute setting following a DVT or PE but is considered in certain patients at the 3 month clinic appointment (as set out above).

## Compression stockings

Initial studies suggested that stockings with 40 mm Hg (Brandjes, et al 1997) or 30-40 mm Hg (Prandoni, et al 2004) compression at the ankle can halve the incidence of post-thrombotic syndrome. However, the randomised SOX Trial (Kahn, et al 2013) which was much larger and which blinded doctors and patients by comparing stockings with 30-40 mmHg pressure with placebo stockings gave negative results.

Stockings should no longer be prescribed routinely but only used selectively in patients to treat post-thrombotic symptoms.

Absolute contra-indications are advanced peripheral arterial occlusive disease, decompensated heart failure, septic phlebitis, and phlegmasia caerulea dolens (DVT leading to severe swelling of the whole leg). Relative contra-indications are suppurative dermatoses, intolerance of compression stocking fabric, advanced neuropathy, and chronic arthritis.

## Superficial Thrombophlebitis (STP)

The most commonly affected superficial veins are the long (great) and short saphenous veins of the leg. Referral for investigation should not normally be necessary for a short segment of below knee STP unless concomitant DVT is suspected. Patients who are referred with suspected concomitant DVT are assessed for DVT. If during this investigation it is found that STP is adjacent to (within 3 cm of) the sapheno-femoral junction (SFJ) we will treat with therapeutic anticoagulation for three months as there is a high risk of progression to DVT (Tait, et al 2012).

It is not current OHTC policy to anticoagulate patients with SVT at the saphenopopliteal junction due to lack of supportive evidence.

Otherwise STP has been considered to be a benign and self-limiting condition and in the past was treated exclusively with non-steroidal anti-inflammatory drugs (NSAIDs). Although this is reasonable for mild cases (STP less than 5cm in length and not within 3cm of the SFJ) it has become recognised that more severe cases (more than 5cm in length and not within 3cm of the SFJ) have a better symptomatic response to anticoagulation.

[There is a MIL which covers options for treatment found here](#)

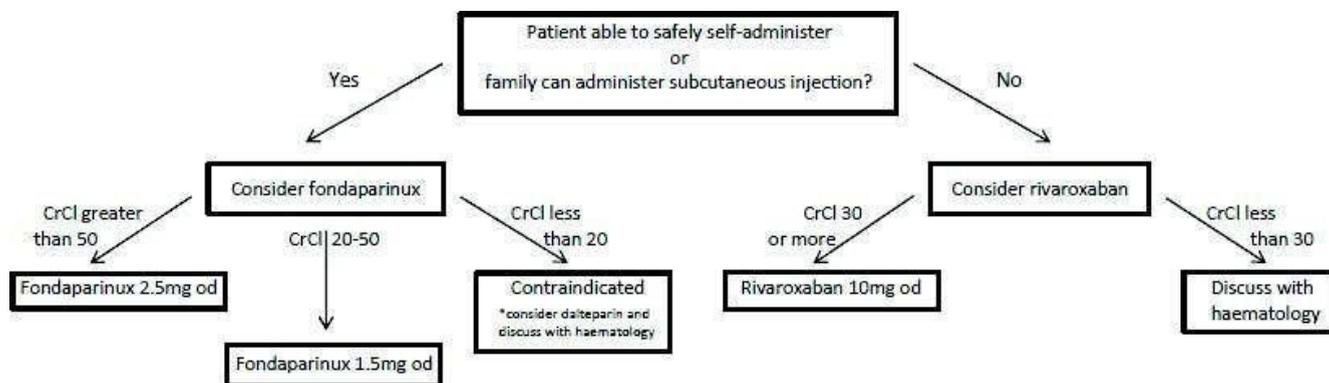
Our "STP letter" to GPs says:

"Your patient has Superficial Thrombophlebitis (STP) - please refer to scan report for more details. This has been deemed to be low risk for DVT progression.

1. Patients with mild STP (less than 5 cm in length) can be treated with NSAIDs
2. Patients with more severe disease (more than 5 cm in length) may be better treated with 45 days of one of the following:
  - fondaparinux 2.5 mg once daily
  - rivaroxaban 10mg once daily
  - dalteparin 125 units/kg once daily

Fondaparinux is the only licensed medicine for superficial thrombophlebitis and should be considered as first-line treatment. The prescribing of dalteparin and rivaroxaban in this setting are off-label. Please refer to the following algorithm for more advice:

## Flow diagram to aid decision making for patients with superficial thrombophlebitis



### If patient or family can safely administer a subcutaneous injection: consider fondaparinux:

- Creatinine clearance greater than 50 – give fondaparinux 2.5mg once daily
- Creatinine clearance 20-50 – given fondaparinux 1.5mg once daily
- Creatinine Clearance less than 20 – contraindicated, consider dalteparin and discuss with haematology

### If patient or family **cannot** safely administer a subcutaneous injection or strong preference for oral agent: consider rivaroxaban

- Creatinine clearance 30 or more – give rivaroxaban 10mg once daily with food
- Creatinine clearance less than 30 – discuss with haematology (cautious use is recommended with CrCL 15-29mL/min, it is contraindicated with CrCL <15mL/min).

## Foam sclerotherapy

Occasionally patients who have been treated for their varicose veins with foam sclerotherapy may be referred to the DVT clinic. If a DVT is ruled out, it is an expected finding for the superficial veins to look as though they are affected by ‘superficial vein thrombosis’ – this is because the foam that has been injected occludes the superficial veins. In time, it is expected that the foam will lead to scarring and collapse of the veins – however this may take 6 - 8 weeks post-procedure. There is no need to treat patients with anticoagulation for this routine finding.

The only time that foam sclerotherapy may warrant anticoagulation is if there is evidence of ‘thrombus’ within 3 cm of the SFJ – however it is advised in this circumstance to discuss this finding with the vascular surgeons prior to anticoagulation.

## Incidentally discovered asymptomatic DVTs and PEs

In patients who are unexpectedly found to have asymptomatic DVT or PE, the ACCP recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic VTE (Kearon, et al 2012).

## Upper limb DVT

These patients are not normally seen for diagnosis as pre-test probability assessment and

D-dimers are not used but rather all suspected cases have an ultrasound examination (At the JR)

When referred to the DVT clinic the initial treatment is the same as for lower limb DVT. Recurrence rates for upper limb DVT after treatment for three to six months are low and it is likely that prolonged anticoagulation is not required for most patients.

For most patients with upper limb DVT in association with an indwelling central venous catheter, the catheter should not be removed if it is functional and there is an on-going need for the catheter. If the catheter is removed anticoagulant treatment should not be shortened to less than 3 months. Young patients with idiopathic upper limb DVT may have 'effort thrombosis' caused by thoracic outlet syndrome and this group of patients would benefit from thoracic outlet imaging and cardiothoracic surgery assessment.

Elastic compression is not used routinely but is reserved for patients who have persistent oedema and pain.

### **Women on the combined oral contraceptive pill (COCP)**

The COCP should be stopped at least one month before anticoagulation is discontinued and an alternative form of contraception should be organised. The patient should be warned of the risks of pregnancy on warfarin, apixaban or rivaroxaban.

It is important the COCP should not be stopped in the acute setting as significant withdrawal bleeds may occur, and there is a risk of undesired pregnancy. There is no evidence that continuation of the COCP in women with acute DVT/PE along with concomitant anticoagulation results in inferior outcomes or increased recurrence.

### **DVT patients with suspected concomitant symptomatic PE**

These patients do not necessarily need to be investigated for PE as the treatment is the same. However, consider whether they should be referred to the medics for consideration of admission.

They should if they have any of:

- Age > 80 years
- Pulse  $\geq$  110 bpm
- Systolic bp < 100 mm Hg
- Sat < 90%
- Cancer
- Chronic cardiopulmonary disease (i.e. a positive sPESI), as this indicates a higher early mortality.

### **Referral to DVT service on discharge for patient with VTE treated with LMWH/warfarin**

#### **DVT**

If a DVT inpatient has been started on LMWH and warfarin they can attend the DVT Clinic for daily LMWH injections until they are no longer required. If a DVT inpatient has completed transfer to warfarin (heparin for  $\geq$  5 days and INR  $\geq$  2 for two consecutive days) they should be discharged and referred not to the DVT Service but to the anticoagulation service.

## PE

The DVT Service may accept PE patients who are ready for discharge before being fully anticoagulated with warfarin if they have been on treatment with full dose heparin for > 24 hours (if on once daily dalteparin the medical team must give the first two doses) and their consultant has confirmed their suitability for discharge. If a PE inpatient has completed transfer to warfarin (heparin for  $\geq 5$  days and INR  $\geq 2$  for two consecutive days) they should be discharged and referred not to the DVT Service but to the anticoagulation service.

The normal exclusion criteria apply and in addition PE patients must not have hypotension or hypoxia

The in-patient team should:

- Check patient is suitable for referral (see exclusion criteria)
- Phone the DVT clinic on 25629 (Sat & Sun bleep 5165)
- Email ([dvtservice@ouh.nhs.uk](mailto:dvtservice@ouh.nhs.uk)) with the [referral form available on the intranet](#) (the following details will be required):
  - details of current event
  - any predisposing factors and diagnostic imaging results
  - past Medical History including current medication
  - desired duration of anticoagulation
  - target INR (please discuss if other than 2.5, i.e. range 2.0 – 3.0) Daily INR results whilst in hospital
  - daily warfarin and dalteparin doses whilst in hospital
  - duration of treatment/plan for review at the end of treatment
- On receipt of the completed referral form the DVT nurse will phone the ward to arrange the first appointment. If transport is required the ward will need to arrange this.
- The patient will need TTOs
- A discharge summary should be sent to the GP in the normal way.

## Referral for three month review of VTE patients

For all patients with unprovoked or weakly provoked proximal VTE, it needs to be determined whether treatment is to stop at three months or to continue indefinitely. Patients can be referred to the thrombosis consultants for a three month review if required via EPR 'Consult Thrombosis Clinic' using the template (~R-ThrombosisClinic)



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