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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Contents

Referrals to the DVT Service

The Churchill Hospital 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 at least one hour before the clinic closes.

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 dvt.service@nhs.net

Mon to Fri – telephone 01865 225629

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

Exclusion criteria

- Pregnancy (patients ≥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 ≥ 1.5)
    - Renal insufficiency: creatinine > 200 µmol/L with unknown eGFR or creatinine clearance < 20ml/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 x 109/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.

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.

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, and are not recommended in patients who weigh more than 120kg.

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@nhs.net) 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 12.30pm and being collected at 3.30pm). 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 Churchill DVT Clinic' giving information to patients on how to get to the clinic and what to expect, can be downloaded from the Clinical Haematology website.

DIAGNOSTIC ALGORITHM FOR SUSPECTED DVT

Pre-test probability assessment

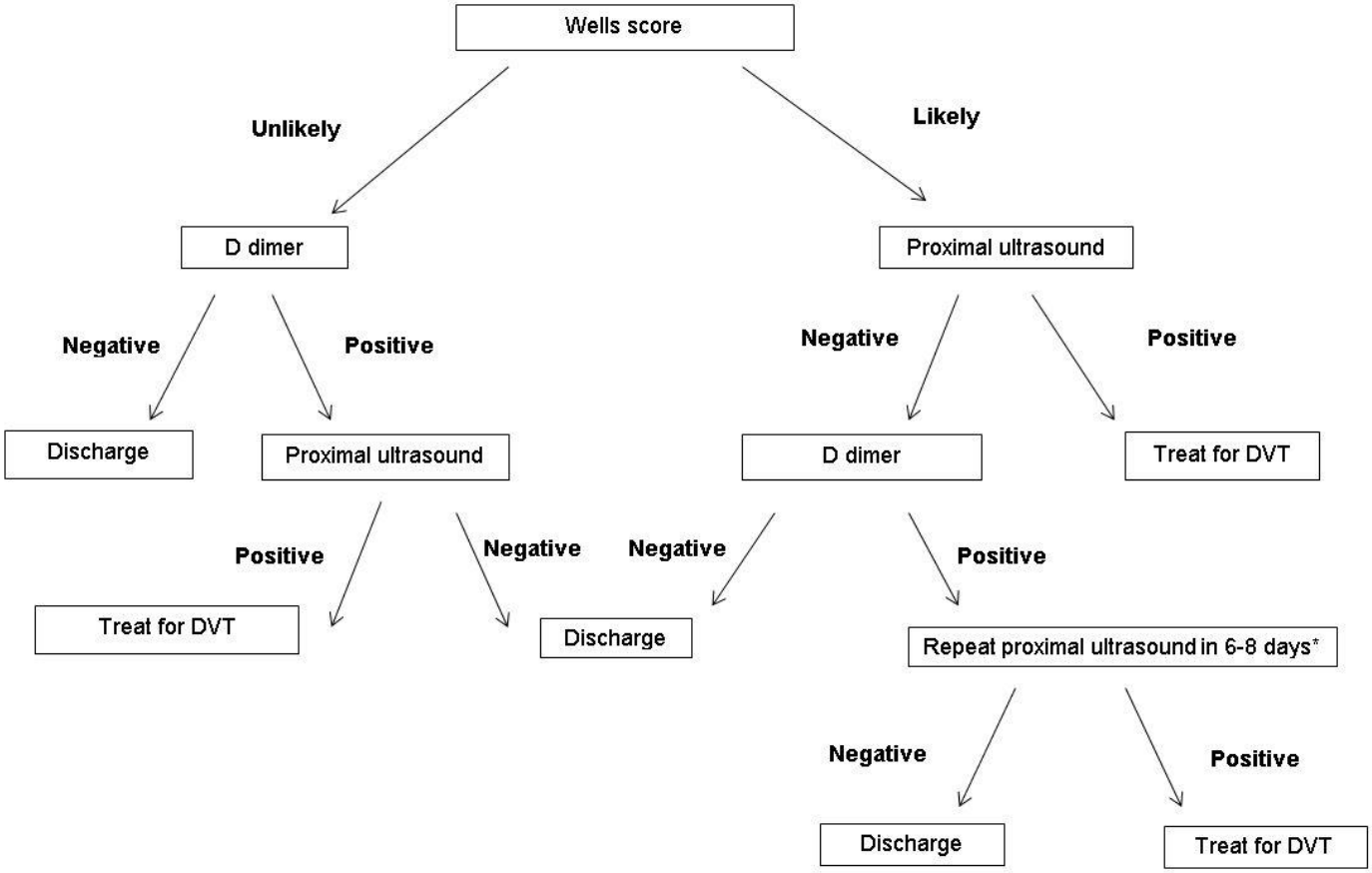
Patients will initially have a pre-test probability assessment (Keeling, et al 2004, Wells, et al 1997, Wells, et al 2003, Wells, et al 1995) by a DVT nurse and be classified as unlikely or likely to have a DVT (see table below). The nurse will then follow the algorithm in the figure overleaf.

	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	Unlikely
≥2	Likely

Diagnostic Algorithm



- <u>If wells score likely</u>: proximal ultrasound
  - If proximal ultrasound positive: treat for DVT
  - If proximal ultrasound negative: take D dimer.
  - If D dimer negative: discharge. If D dimer positive: repeat scan in 6-8 days
  - If repeat ultrasound in 6-8 days negative: discharge. If positive: treat for DVT
- <u>If wells score unlikely:</u> take D dimer.
  - If D dimer negative: discharge
  - If D dimer positive: proximal ultrasound
  - If proximal ultrasound negative: Discharge

If proximal ultrasound positive: treat for DVT*"Likely" patients who do not have a negative D-dimer need a repeat scan of the proximal veins one week later. They remain off anticoagulation whilst awaiting this. An alternative strategy for these patients would be to extend the initial scan to the whole leg (i.e. to also scan the calf veins).

A negative D-Dimer result is defined as < 500 □g/l FEU.

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 haemophilia 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.

Thrombolytic therapy

Consider referral to vascular surgeons for consideration of catheter-directed thrombolytic 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 (likely pre-test probability with a positive D- dimer) 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).

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 child bearing potential.

Investigation for cancer in patients with unprovoked DVT

All patients should have a full history and examination. Patients with any concerning symptoms or signs should have targeted further investigations to investigate for an

underlying cancer.

In patients over 40 years with a first unprovoked VTE, but who do not have any concerning clinical symptoms or signs, NICE (clinical guideline 144), based on a randomised trial (Piccioli, et al 2004), said consider the possibility of further investigation with an abdomino-pelvic CT scan (and a mammogram for women), though a non-randomised concurrent-controlled cohort study (Van Doormaal, et al 2011) did not support this. A recent large randomised controlled trial (Carrier, et al 2015) has however shown that routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit. This trial did offer targeted additional tests as part of a limited screen so following this trial we would suggest a:

- 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*.

Although women in this trial women were offered a cervical smear if they had not had one in the past year our cervical screening service advise that this is unlikely to have clinical utility.

*The Prostate Cancer Risk Management Programme recommends 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

DOACs and high body weight

The International society on Thrombosis and Haemostasis (ISTH) suggest that DOACs should not currently be used in patients with a weight of > 120 kg because there are limited clinical data available for patients at the extreme of weight, and the available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under- dosing in the population at the extreme of weight. As data accumulate this guidance may change, but as of 2019, DOACs should be used routinely only for patients less than 120kg.

A) 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 licenced dose for 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 (CrCL15-29 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.

Hepatic impairment

Avoid in liver disease with coagulopathy.

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.

B) 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).

It should not be used in those less than 18 years of age.

Dose

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

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 eGFR 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.

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.

C) Treatment with low molecular weight heparin and warfarin

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

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 ≥ 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≤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.

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

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

After day 4, until the INR is > 2.0 for two consecutive days, a senior thrombosis nurse or doctor will continue to amend the warfarin dose based on the INR result.

Selecting an oral anticoagulant

Warfarin will be favoured over a DOAC if eGFR < 30 ml/min, if there is significant liver dysfunction or if weight is greater than 120 kg.

Choice of anticoagulant should be discussed with the patient, some may prefer to opt for a drug with a longer history of use or have warfarin again if they've been on it before.

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. 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.

D) Continuing LMWH in patients with cancer

Patients with an underlying malignancy will be considered for continuing LMWH rather than oral anticoagulation. However, in those who do not want to inject, an oral Xa inhibitor (that is apixaban or rivaroxaban) is a reasonable alternative. If continuing LMWH the patient will need to be able to administer their own LMWH or have a carer do it. Compared to warfarin, LMWH carries a similar risk of bleeding but halves recurrences in patients with cancer (Lee, et al 2003). Full dose LMWH is given for the first month (see page 12). 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.

Dose after the first month (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. If cancer is not cured some form of continuing anticoagulation is usually recommended. If this is with LMWH we suggest continuing the same dose rather than reducing to a prophylactic dose. If switching to (or already taking) apixaban we suggest considering 5 mg bd for continuing anticoagulation rather than 2.5 mg bd in this high risk group.

Continuing LMWH in patients without cancer

We suggest a dose reduction after one month as in the above regimen could be considered.

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).

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

Transient risk factors (TRF):

- surgery (the various studies used within 6 weeks/8 weeks/3 months)
- significant trauma e.g. fracture, plaster castpregnancy/puerperium

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

A weaker TRF is temporary immobility in previous 4 weeks e.g. confined to bed ≥ 3 days or a flight > 6 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 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.

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

3 months	3 months then consider for long-term
1st proximal DVT with TRF* 1st PE with TRF* 1st isolated calf vein DVT	Recurrent thrombosis Proximal DVT or PE with on-going risk factors 1st unprovoked proximal DVT 1st unprovoked PE

*If temporary immobility e.g. confined to bed ≥ 3 days or a flight > 6 hours is the only transient risk factor 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 (> 500 □g/l FEU) after completing anticoagulation

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 most important initial considerations are male v female and PE v DVT. Patients may express a clear preference for stopping or continuing but for those in whom the best course of action is not clear a D-dimer one month after stopping treatment may be the best way to decide.

The table below summarises the approximate risk of recurrence after a first unprovoked VTE:

	DD+		DD not done		DD-	
	1 yr	**5 yr**	**1 yr**	**5 yr**	**1 yr**	**5 yr**
M	15 %	50-60 %	7.5-10 %	30-40 %	5 %	20-25 %
F	7.5 %	30-35 %	3-5 %	15-25 %	2.5 %	10-15 %

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 who have had unprovoked DVT or PE and who have a first-degree relative who has had 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 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

Testing may be helpful to assist counselling regarding COC and HRT in asymptomatic female relatives in selected thrombosis-prone families with high risk thrombophilia

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 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). A three month review is not required.

Otherwise STPhas 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 Vein Thrombosis (SVT). Patients with mild SVT (eg less than 5 cm in length) can be treated with NSAIDs but patients with more severe disease (eg more than 5 cm in length) may be better treated with an intermediate dose of LMWH for six weeks (Cosmi, et al 2012, Scott, et al 2015) as this has been shown to provide better symptomatic relief. If you wish to do this we suggest dalteparin at approximately 125 units/kg od (rounding to the nearest syringe). Prophylactic dose of fondaparinux (2.5 mg od) is an alternative (Decousus, et al 2010), although at present fondaparinux is not prescribed by GPs and therefore is not easily accessible. Although DOACs are not licenced for this indication a recent study (Beyer-Westendorf, et al 2017) suggested prophylactic dose rivaroxaban (10 mg od) was non-inferior to prophylactic dose fondaparinux (2.5 mg od).

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.

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.

DVT patients who when reviewed are suspected to have 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 ≥ 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 OF PATIENTS WITH VTE TREATED WITH LMWH/WARFARIN

DVT

If a DVT inpatient has been started on LMWH and warfarin they can attend the DVT Clinic (at either the Churchill or Horton site) for daily LMWH injections until they are no longer required. If a DVT inpatient has completed transfer to warfarin (heparin for ≥ 5 days and INR ≥ 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 ≥ 5 days and INR ≥ 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 (dvt.service@nhs.net) 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 VTE patients 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, if so please write a referral letter on discharge. For further details see Anticoagulation & Thrombosis > Referral forms and notes on the OUH intranet.

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