249.5.1 ASSESSMENT OF DEEP VEIN THROMBOSIS (DVT) IN THE AMBULATORY SETTING AND ANTICOAGULATION MANAGEMENT OF DVT AND PULMONARY EMBOLISM (PE) IN ADULTS (aged 16 and over)

Content

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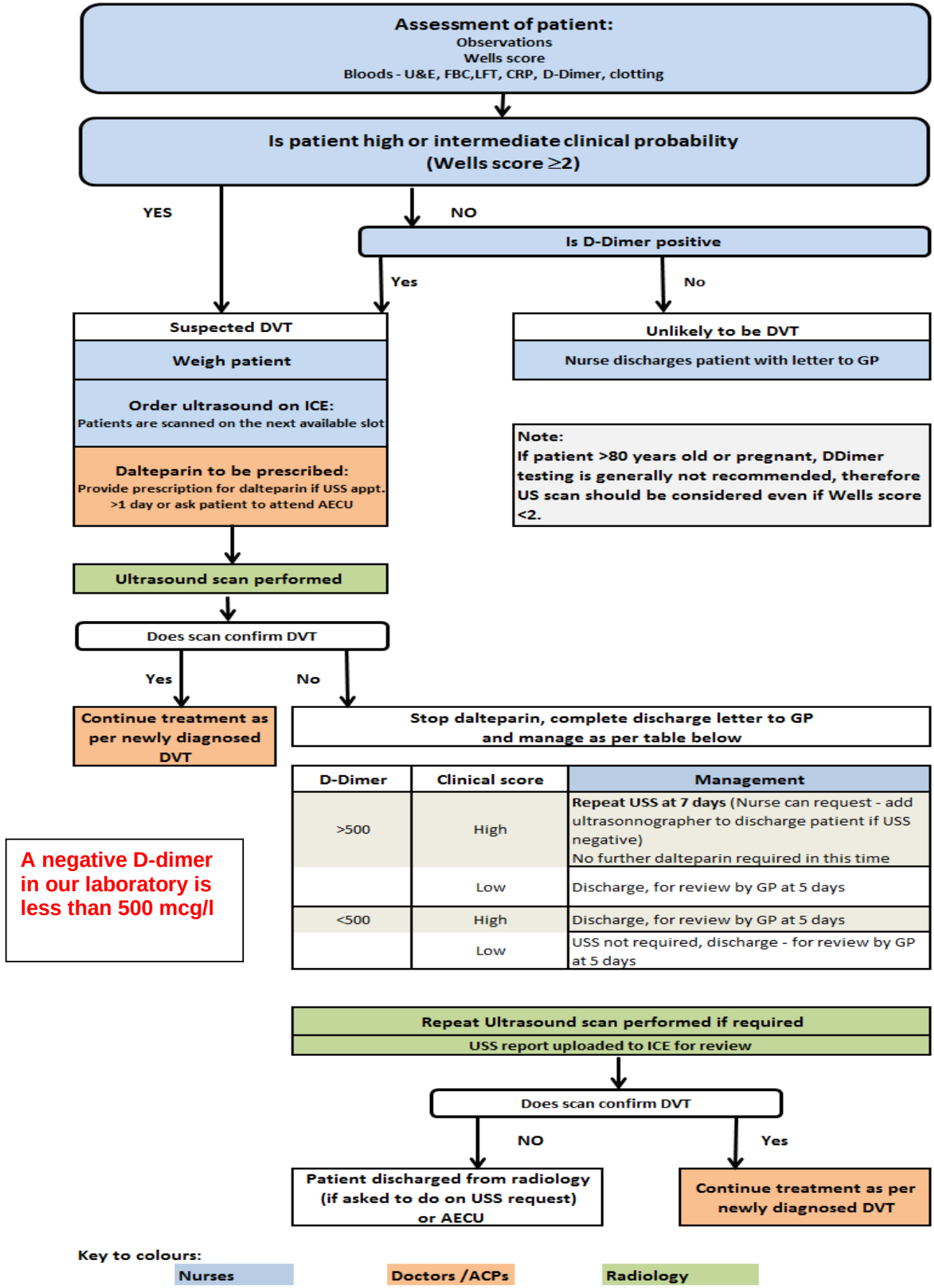
DVT Assessment Pathway



D-Dimer	Clinical score	Management
>500	High	**Repeat USS at 7 days** (Nurse can request - add ultrasonnographer to discharge patient if USS negative) No further dalteparin required in this time
	Low	Discharge, for review by GP at 5 days
<500	High	Discharge, for review by GP at 5 days
	Low	USS not required, discharge - for review by GP at 5 days

Buckinghamshire Healthcare NHS Trust

AECU DVT Clerking Proforma

History

Side (please circle)	RIGHT/ LEFT
Time of Onset (Days)	
Swelling	
Pain / Tenderness	
Erythema	
Hot	
Other Symptoms:	

Name:
DOB:
MRN:
NHS:

Referral Source:

Wells' Score (see overleaf)	

Past Medical History (if relevant)

Additional risk factors	
Pregnancy	
COCP/HRT	
Family history in 1st degree relative	
Known clotting abnormality	
Cancer	
Previous DVT/PE	
Smoking	

Medication

Observations	
RR	
Sats	
BP	
HR	
Temp	

Allergies

Examination

Blood Results	
Hb	
WCC	
Plt	
Creatinine	
Bilirubin/ALT	
CRP	
INR	
APPT	
D-dimer	

Ultrasound Scan indicated: Yes / No
Signature:
Name:

Time/Date: .....
Bleep/Ext:
Date & Time:

AECU DVT Clerking Proforma

DVT Scoring (Wells Score)

Buckinghamshire Healthcare NHS Trust

DOB:
MRN:
NHS:

Active cancer (on treatment, treatment in last 6 months, or palliative)	(1)	
Paralysis/ recent plaster immobilisation of lower limb	(1)	
Bedridden for ≥3 days OR Major surgery in last 12 weeks requiring general or regional anaesthesia	(1)	
Localised tenderness along deep venous system (i.e calf/popliteal area)	(1)	
Calf swelling >3 cm in affected leg (measured 10 cm below tibial tuberosity)	(1)	
Entire leg swollen	(1)	
Pitting oedema in affected leg only	(1)	
Dilated superficial veins (non-varicose) in affected leg	(1)	
Previous objectively documented DVT	(1)	
Alternative diagnosis more likely than DVT (e.g. muscle injury, Baker's cyst, cellulitis, chronic oedema, superficial phlebitis, arthritis, chronic venous insufficiency)	(-2)	
TOTAL		

Wells Score Guide:
0 – 1 = DVT unlikely
≥2 = DVT likely

Management following scoring:
The Wells score MUST be performed – <u>do not discharge patient purely on basis of negative D-dimer</u>

- If clinical score LOW and D-dimer <500: no ultrasound scan or anticoagulation.
  - Complete standard discharge letter and ask patient to see GP in 5 days
- **All** other patients (i.e. D-dimer >500 AND/OR Wells Score ≥2) should have ultrasound scanning of affected leg arranged and **given therapeutic-dose dalteparin (Fragmin®) (as per weight and renal function) until scan has been performed.**

Ultrasound Scan Results: Positive ⇒ Doctors informed
Negative ⇒ Alternate Diagnosis:

D-dimer >500 and Wells' Score ≥2 ⇓ Repeat USS in 5 - 7 days

D-dimer >500 and Wells' Score 0 - 1
OR
D-dimer <500 and Wells' Score ≥2 ⇓ Discharge with GP follow-up

Signature:
Name:

Bleep/Ext:
Date:

Calf Vein/Below Knee DVT/Distal DVT

All compression ultrasound (US) scans for suspected DVT are above knee only rather than whole leg scan, as per NICE NG158.

If an initial compression US does not show evidence of a DVT, follow the DVT assessment pathway. If the patient has a repeat compression US which again shows no evidence of DVT, but there is clinical suspicion of calf vein DVT, consider organising a duplex scan via a vascular sonographer.

Symptomatic calf vein DVT is treated with 3 months anticoagulation.

Mechanical Thrombectomy in Ileofemoral DVT

If a Doppler US is performed and there is evidence of thrombus in the common femoral vein or above, but the tip of the thrombus cannot be seen, an iliofemoral DVT/inferior vena caval (IVC) thrombus should be suspected and a computed tomography (CT) venogram considered. Patients with ilio-femoral DVT should be referred to interventional radiology for consideration of pharmacomechanical thrombectomy (AngioJet™) if:

- Symptoms of less than 14 days duration (consideration may be given to treating thrombus greater than 14 days old)
- Good functional status
- A life expectancy of >6 months
- A low bleeding risk

If a patient meets these criteria they should be referred for a CT venogram.
Liaise directly with the CT radiographers to arrange the scan and refer to interventional radiology to arrange the thrombectomy procedure.

Patients who are likely to undergo thrombectomy should remain on therapeutic dose dalteparin.

In urgent cases contact the vascular SpR on-call at the John Radcliffe Hospital.

Consider cautions

Risk of causing further PE should be considered in patients with PE and evidence of right heart strain on imaging or ECHO.

These patients as well as patients with large volume PE should be considered for temporary IVC filter prior to thrombectomy, with a plan for retrieval within 6 weeks of insertion.

In the case of massive or submassive PE, thrombectomy would be avoided in the acute phase.

Patients with extensive IVC thrombus should be referred to the vascular team in Oxford for management.

Pre-procedural anticoagulation

- If patient is on oral anticoagulation stop this and bridge with weight-based split therapeutic dose dalteparin 100 units/kg twice daily (rounded to the nearest syringe) unless already on this.
- Dalteparin in split doses can continue, and doses do not need to be omitted prior to the procedure and dalteparin dose on the morning of thrombectomy can be given to the patient.

Post thrombectomy treatment

If NO venous stent inserted

- Recommence weight-based split therapeutic dose dalteparin 100 units/kg twice daily 2 hours post procedure as long as no significant bleeding during procedure.
- Convert from dalteparin to oral anticoagulation and select either warfarin or DOAC as per guidance in this document and counsel patient about these options. See prescribing guidance in this document.

- If prescribing a direct oral anticoagulant (DOAC), this SHOULD NOT be given on the same day as dalteparin. Commence 24 hours after last dose of dalteparin if once daily dalteparin dosing or 12 hours post if on split dose dalteparin.
- Please prescribe the first 4 weeks of the DOAC and ask GP to continue the prescription.
- Refer patient to the anticoagulation clinic via an electronic referral on Evolve.
- If commencing warfarin, this can commence on the same day as the procedure and should continue along with dalteparin therapeutic dose until INR is 2 or more. See prescribing guidance in this document.
- Patients should be referred to Miss Wilton, vascular surgeon, for review at 6 weeks. An email referral should be sent to emma.wilton1@.nhs.net and copied to bht.vascularsurgerysecretaries@nhs.net.
- A referral should be made to the thrombosis clinic for review 3 months post diagnosis.
- Advise patient to return to the Ambulatory Emergency Care Unit (AECU) if recurrent swelling in treated leg.

If venous stent inserted

- Patient should recommence weight-based split therapeutic dose dalteparin 100 units/kg twice daily 2 hours post procedure.
- Continue split therapeutic dose dalteparin 100 units/kg twice daily for 14 days then convert to once daily if appropriate.
- Please discharge patients with a 6 week supply of dalteparin and warfarin 'starter pack'. The patient should only commence warfarin once instructed to by the vascular surgeons or anticoagulation clinic.
- Refer patient to the anticoagulation clinic via an electronic referral on Evolve.
- Email vascular consultant, Miss Emma Wilton (emma.wilton1@.nhs.net), and copy in vascular secretaries (bht.vascularsurgerysecretaries@nhs.net) to arrange repeat duplex scan 2 weeks post procedure.
- If the 2 week scan shows stenosis or residual unresolved symptoms attributable to outflow obstruction, then repeat intervention will be considered by the vascular/IR team and patient should remain on dalteparin.
- At 2 weeks, duplex will be reviewed by vascular team and if no concerns the patient will be referred to the anticoagulation clinic to commence warfarin.
- Warfarin should be continued for at least 6 months - standard target International Normalised Ratio (INR) 2.5 (range 2 - 3).
- If after 6 months of anticoagulation the patient has not developed stent related thrombosis consider switching to a DOAC and continue for at least a further 6 months.
- DOACs should be avoided in the first 6 months following stent insertion.
- A referral should be made to the thrombosis clinic for review 3 months post diagnosis.
- Advise patient to return to AECU if recurrent swelling in treated leg.

Bilateral Leg Symptoms

In patients with bilateral leg swelling, consider a systemic condition such as heart failure, hypoalbuminaemia, renal failure or severe anaemia as these diagnoses are more likely than DVT.

If DVT is suspected however compression ultrasound is negative, consider the possibility of an IVC thrombus. The patient may need CT with contrast. Patients with high clinical suspicion, a grossly swollen leg, but a negative ultrasound scan should be considered for a CT venogram to look for iliac or pelvic vein thrombosis or pelvic pathology causing external compression of pelvic veins.

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
- DVT at a location that does not fit with the clinical signs

The scan, the clinical presentation and the D-dimers should be considered together.

The risk of recurrence whilst on anticoagulation is around 1% per annum.

Any new swelling may represent post thrombotic symptoms and the patient should be considered for duplex imaging for more accurate assessment.

Avoid switching anticoagulation or raising the target INR unless there is strong evidence of a new event.

This can be discussed with the on-call haematologist.

Patients with confirmed DVT should avoid vigorous exercise and air travel within two weeks of a new diagnosis of venous thromboembolism (VTE).

Investigating for Cancer in Patients with Unprovoked DVT or PE

All patients should have a full history and examination. Patients with any concerning signs and/or symptoms should have specific tests to investigate for an underlying cancer.

NICE (clinical guideline NG158) recommended that patients over 40 years with a first unprovoked VTE, but who do not have any concerning clinical symptoms or signs should be considered for further investigation with a CT scan of the abdomen and pelvis (and a mammogram for women).

More recent evidence from a large randomised controlled trial has however shown that routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

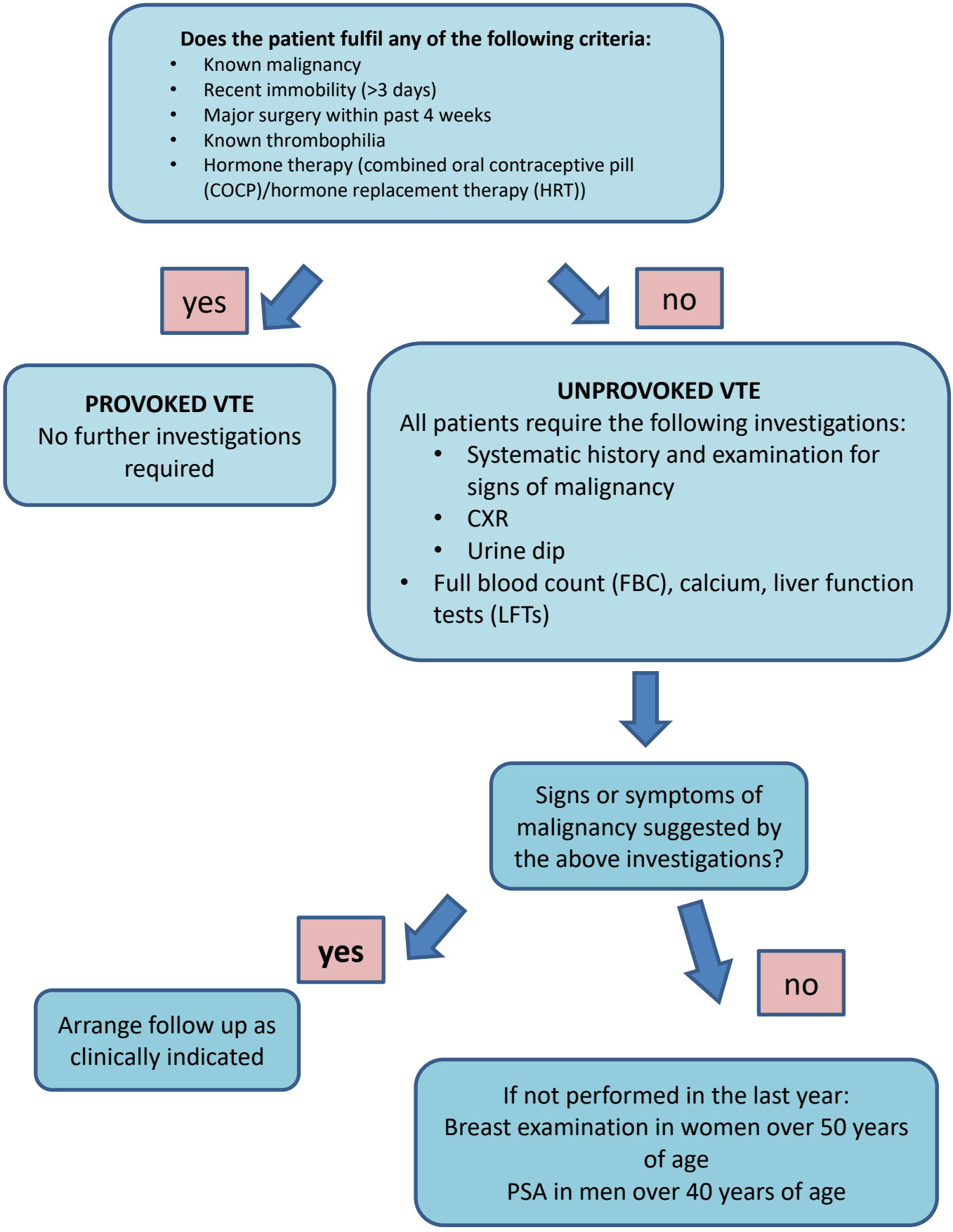
Based on this, the recommendation is that all patients with an unprovoked DVT should have:

- Chest X-ray (CXR)
- Urine dipstick

and if not performed in the last year:

- Breast examination in women over 50 years of age
- Prostate-specific antigen (PSA) in men over 40 years of age. *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.

Confirmed VTE Flowchart



Management of DVT or PE

People with suspected DVT are offered an interim therapeutic dose of anticoagulation therapy if diagnostic investigations are expected to take longer than 4 hours from the time of first clinical suspicion.

It is important that all diagnostic investigations for suspected DVT are completed within 24 hours to ensure prompt treatment if the diagnosis is confirmed, and to avoid unnecessary repeat doses of anticoagulants if the diagnosis is excluded.

Prior to commencing any anticoagulation, the following should be performed:

- The patient must be weighed to ensure correct dosing of anticoagulation.
- Ensure accurate weights are recorded on patient's drug chart and in the patient's notes.
- All patients should have: Full blood count (FBC), renal profile, liver profile and coagulation screen.
- Pregnancy test for women of child bearing potential.

Selecting an oral anticoagulant

We recommend that if an oral anticoagulant is started outside the anticoagulation clinic or haemostasis/thrombosis clinic, unless advised otherwise, the choice of oral anticoagulant should be limited to **apixaban** or **rivaroxaban**.

Although dabigatran (an oral thrombin inhibitor) and edoxaban (a factor Xa inhibitor) are also licensed for VTE, they are not considered within these guidelines because they require parenteral anticoagulation for at least five days before dabigatran or edoxaban can be initiated.

Patients should be referred to the anticoagulation service via the Evolve anticoagulant referral form.

In general, warfarin is favoured over a DOAC in the following situations:

1. Creatinine clearance (CrCl) <15 ml/min
2. Significant liver dysfunction, although warfarin control is likely to be affected
3. Weight greater than 120 kg
4. Patients under the age of 18 years - DOACs are not licensed

The patient should be counselled fully about the different options.

Some patients may prefer a drug with a longer history of use or use the same anticoagulant that they were previously using.

The efficacy of rivaroxaban, apixaban, edoxaban and dabigatran are similar to that of warfarin but the DOACs have not been directly compared with each other.

Compared to warfarin, rivaroxaban, apixaban and edoxaban 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) has an increased risk of gastrointestinal (GI) bleeding compared with warfarin.

The pivotal studies with dabigatran showed that there is a significant reduction in intracranial bleeding but non-significant risk reduction in major bleeding events compared with warfarin and an increased risk of GI haemorrhage compared with warfarin.

There is currently no reversal agent for the factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).

Patients should be fully counselled about the above, as well as the possible side-effects of DOACs.

Patients should be prescribed a 4 week supply of the DOAC and referred to their GP for ongoing prescribing. The patient should be provided with a DOAC information booklet and an anticoagulant alert card.

The anticoagulation service pharmacists can provide advice and can be contacted at Wycombe Hospital on 01494 425590.

DOACs and extremes of bodyweight

The International Society on Thrombosis and Haemostasis (ISTH) suggest that DOACs should not be used in patients with a weight of >120 kg due to limited clinical data available for patients at the extreme of weight.

There is evidence which raises concerns about under-dosing in the population at the extreme of weight.

There is also a lack of data on dosing in patients weighing below 50 kg and each DOAC manufacturer provides their own recommendations. This can be discussed with the anticoagulation service.

Anticoagulation for VTE in renal impairment or established renal failure

Patients with CrCl <15 ml/min or deteriorating renal function, commence one of the following:

- Unfractionated heparin if this can be managed appropriately
- Renal dose subcutaneous dalteparin see section below on dalteparin in renal impairment
- Renal dose subcutaneous dalteparin concurrently with warfarin for at least 5 days or until INR at least 2.0 for two consecutive readings followed by warfarin alone

Patients with CrCl 15 – 30 ml/min commence one of the following:

- Apixaban
- Therapeutic dose dalteparin with warfarin, continue dalteparin for at least 5 days or until INR is at least 2.0 for 2 consecutive readings followed by warfarin alone

Patients with CrCl 30 – 50 ml/min:

Recommend one of the following:

- Apixaban
- Rivaroxaban

See Table 4 for dalteparin dosing in renal impairment
See relevant sections below for apixaban and rivaroxaban dosing

Warfarin

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

Table 1 **Warfarin dosing regimen for initial 4 days (target INR 2.5)**

Day	INR	Dose	Day	INR		Dose	
1.	<1.4	10.0 mg	4.	<1.4		>8 mg	Always
				=1.4		8.0 mg	check INR
2.	<1.8	10.0 mg		=1.5		7.5 mg	on day 4.
	=1.8	1.0 mg		1.6 - 1.7		7.0 mg	
	>1.8	0.5 mg		=1.8		6.5 mg	
				=1.9		6.0 mg	
3.	<2.0	10.0 mg		2.0 - 2.1		5.5 mg	
	2.0 - 2.1	5.0 mg		2.2 - 2.3		5.0 mg	
	2.2 - 2.3	4.5 mg		2.4 - 2.6		4.5 mg	
	2.4 - 2.5	4.0 mg		2.7 - 3.0		4.0 mg	
	2.6 - 2.7	3.5 mg		3.1 - 3.5		3.5 mg	
	2.8 - 2.9	3.0 mg		3.6 - 4.0		3.0 mg	
	3.0 - 3.1	2.5 mg		4.1 - 4.5	miss one day then	2.0 mg	
	3.2 - 3.3	2.0 mg		>4.5	miss two days then	1.0 mg	
	= 3.4	1.5 mg					
	= 3.5	1.0 mg	5.	For acutely admitted patients: Monitor INR daily until in range and stable (at least 2 INR tests are required in the second week and subsequently).			
	3.6 - 4.0	0.5 mg					
	>4.0	Zero					

Please refer to Standard Operating Procedure for Oral Anticoagulation with Vitamin K Antagonists.

Prescribe warfarin 'starter pack' (consisting of 1 mg, 3 mg, 5 mg tablets and an oral anticoagulant therapy wallet) and a 7 day supply of treatment dose dalteparin.

Counsel the patient on warfarin and dalteparin use.

Complete Evolve referral form to anticoagulation clinic with all necessary clinical information.

Contact the anticoagulation clinic (SMH ext 5510 or Bleep 776, WH ext 6270 or Bleep 3670) to confirm receipt of referral and book appointment for within 3 - 4 days of discharge.

The anticoagulation team will contact the patient with an appointment time.

Patients should be prescribed dalteparin subcutaneously until the INR is 2 or more for two consecutive readings and for a minimum of 5 days.

Seek advice from the on-call haematologist for dalteparin prescription for patients with a CrCl less than 30 ml/min.

Dalteparin

Table 2: Dalteparin subcutaneous (SC) dosing chart for month 1 where CrCl >20 ml/min (excluding pregnancy and the puerperium)

Weight	Dose (units)	Colour Code
≤40 kg	**Discuss with haematology**	
41 - 45 kg	7,500 once daily*	Green
46 – 56 kg	10,000 once daily	Red
57 – 68 kg	12,500 once daily	Brown
69 – 82 kg	15,000 once daily	Purple
83 – 98 kg	18,000 once daily	Grey/white
99 – 112 kg	10,000 twice daily*	X
113 – 137 kg	12,500 twice daily*	X
138 – 165 kg	15,000 twice daily*	X
166 - 179 kg	18,000 twice daily*	X
≥180 kg	**Discuss with haematology**	

Single doses should not excess 18,000 units.
NB: Doses of dalteparin differ from BNF in patients >98 kg in line with American Society of Hematology (ASH) guidance.
*Unlicensed dosing

In patients who might be at increased risk of bleeding, it may be safer to administer dalteparin in divided doses of 100 units/kg subcutaneously twice daily.

If patient requires ongoing anticoagulation with dalteparin, they should be reweighed and the dose reduced as per Table 3.

GPs in Buckinghamshire are currently not prescribing dalteparin, however, this is likely to change in the near future. Until then, the responsibility for prescribing dalteparin remains with the team initiating this.

Patients must be told how long they are likely to stay on the dalteparin for, and should be notified of how they will receive further prescriptions. The haematology and anticoagulation teams should not be expected to prescribe dalteparin, this includes for patients who have been referred to the thrombosis clinic.

Table 3: Dose after the first month of treatment (excluding pregnancy and puerperium) i.e. month 2 onwards - ensure patient is reweighed

Weight (kg)	Dalteparin subcutaneous (SC)dose after month 1
≤57	7,500 units once daily s/c
57 - 68	10,000 units once daily s/c
69 - 82	12,500 units once daily s/c
83 - 98	15,000 units once daily s/c
99 - 112	18,000 units once daily s/c
113 - 137	10,000 units twice daily s/c
138 - 165	12,500 units twice daily s/c
≥166	15,000 units twice daily s/c

Dalteparin dosing in renal impairment

Dalteparin is renally cleared and should be used with caution in patients with severe renal impairment (CrCl <20 ml/min).

Low molecular weight heparin (LMWH) is likely to accumulate when the CrCl falls below 20 ml/min.

For patients with CrCl <20 ml/min use one of the following:

- Intravenous unfractionated heparin with APTT monitoring
- Dalteparin with 2/3 of the normal weight adjusted dosage and monitor anti-Xa plasma concentration

Table 4: Dalteparin dose recommendations for treatment of VTE in patients with significant renal impairment (CrCl less than 20 ml/min) in month 1
(Aligned with Medicines Information Leaflet OUH)

Weight	Dose (units) by subcutaneous injection
<46 kg	5,000 once daily
46 – 56 kg	6,500 once daily*
57 – 68 kg	8,500 once daily*
69 – 82 kg	10,000 once daily
83 – 98 kg	12,500 once daily
99 – 112 kg	15,000 once daily
113 – 137 kg	18,000 once daily
138 – 165 kg	10,000 twice daily
≥166 kg	12,500 twice daily

Graduated syringes containing 10,000 units in 1 ml of dalteparin are available to administer these doses.

Apixaban and rivaroxaban (see Table 5 and Table 6 overleaf for more information)

Apixaban and rivaroxaban are oral direct inhibitors of factor Xa, and given orally for the treatment of DVT and PE and for the secondary prevention of recurrent DVT and PE. Apixaban and rivaroxaban do not require therapeutic monitoring (or concurrent initial treatment with heparin).

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

See Guideline 295FM Dabigatran, Rivaroxaban, Apixaban and Edoxaban for Deep Vein Thrombosis and Pulmonary Embolism.

Table 5: Apixaban

Standard dose	10 mg orally twice daily days 1 – 7. 5 mg orally twice daily day 8 onwards. The patient should be prescribed the first month of treatment, including the loading dose. 2.5 mg orally twice daily after 3 or 6 months (only after haematology input).
Renal impairment	Do not use if CrCl less than15 ml/min.
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.
Pregnancy or breastfeeding	AVOID
Interaction with other medicinal products	Avoid azole-antimycotics (such as ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase apixaban plasma concentrations to a clinically relevant degree. Avoid strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort, may lead to reduced apixaban plasma concentrations. We therefore recommend that strong CYP3A4 inducers should not be co-administered with factor Xa inhibitors. Macrolide antibiotics, such as clarithromycin and erythromycin, may inhibit metabolism of factor Xa inhibitors and therefore caution should be applied if co-prescribed.
Switching from dalteparin	Apixaban should be started instead of the next scheduled administration of dalteparin (if a patient has received 7 days or more of dalteparin, then apixaban can be started at 5 mg twice daily (as for day 8 onwards).
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).

Table 6: Rivaroxaban

Standard dose	15 mg orally twice daily with food for 21 days. Then 20 mg orally once daily day 22 onwards. The patient should be prescribed the first month of treatment.
Renal impairment	Avoid if CrCl less than 30 ml/min. Warfarin preferred if CrCl less than 30 ml/min. SPC states use with caution if CRCl 15 – 29 ml/min. CrCl 15 – 49 ml/min initially 15 mg twice daily for 21 days, thereafter, the recommended dose is the standard 20 mg once daily. 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.
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.
Pregnancy or breastfeeding	AVOID
Interaction with other medicinal products	Avoid azole-antimycotics (such as ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree. Avoid strong CYP3A4 inducers e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort, may lead to reduced rivaroxaban plasma concentrations. We therefore recommend that strong CYP3A4 inducers should not be co-administered with factor Xa inhibitors. Macrolide antibiotics, such as clarithromycin and erythromycin, may inhibit metabolism of factor Xa inhibitors and therefore caution should be applied if co-prescribed.
Switching from dalteparin	Rivaroxaban should be started instead of the next scheduled administration of dalteparin (if a patient has received dalteparin, then the number of doses of dalteparin plus days of rivaroxaban 15 mg twice daily should total 21 days and rivaroxaban 20 mg once daily starts from day 22).
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.

Anticoagulation in Cancer Patients

For DVT or PE in cancer patients, current guidelines continue to recommend LMWH monotherapy for at least 3 – 6 months although there is now evidence from clinical trials demonstrating that DOACs can also be used in cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy.

Apixaban and rivaroxaban have been compared with LMWH in randomised control trials (RCTs) in cancer populations. Both agents have been found to be non-inferior to LMWH but associated with an increased risk of clinically relevant non-major bleeding. In particular, patients with gastrointestinal and genitourinary cancers.

Where suitable, consider starting a DOAC first line - see above for choice of anticoagulant.

Dalteparin should be used for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, oesophagitis, or colitis.

Patients commenced on LMWH should be referred to their oncologist/palliative care specialist to continue the prescribing.

The choice of anticoagulant in cancer patients with VTE under an oncologist should be discussed with the patient and the oncology team.

If a patient is not under an oncologist or other specialist, the patient should be referred to the anticoagulation team to continue to prescribe LMWH.

All cancer patients should be referred to the haemostasis/thrombosis clinic for review 3 months post VTE diagnosis.

Continuing dalteparin in patients with cancer

If continuing dalteparin the patient will need to be able to self-administer this or have a friend/carer do it. Compared to warfarin, dalteparin carries a similar risk of bleeding but halves the recurrence of VTE in patients with cancer (Lee, et al 2003). Therapeutic dalteparin is given for the first month, thereafter the dose is approximately 75 - 80% of full therapeutic dose, see Table 2 for dosing.

The hospital will provide a prescription for the first 4 weeks supply of dalteparin, and after that time the patient's oncologist or palliative care team should be requested to prescribe it. A discharge summary and referral should be sent to the relevant clinician informing them of the new VTE diagnosis and the requirement for ongoing dalteparin prescriptions.

It is not the responsibility of the anticoagulation clinic or ambulatory care to prescribe dalteparin.

Management of cancer patients after 3 months

Following a cancer associated DVT or PE, the decision for ongoing anticoagulation should be reviewed. This review process should involve a haematologist and an oncologist. Guidelines recommend continuing anticoagulation for a minimum of 6 months.

If cancer is not in remission and the patient remains on active treatment, it is advisable to continue with anticoagulation and review anticoagulation once treatment plan is complete.

For patients with ongoing cancer, a decision for ongoing anticoagulation should be made and a suitable oral anticoagulant initiated after counseling the patient.

Anticoagulation Treatment for DVT or PE with Triple Positive Antiphospholipid Syndrome

Offer people with confirmed proximal DVT or PE and an established diagnosis of triple positive antiphospholipid syndrome dalteparin concurrently with warfarin for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a warfarin alone.

Do not give a DOAC

Antiplatelet Medication

Patients with stable coronary artery disease (more than 12 months from acute coronary syndrome (ACS), non-ST-elevation myocardial infarction (NSTEMI), STEMI, coronary artery bypass graft (CABG) or stent) can stop antiplatelet therapy when anticoagulated unless there is a high risk of future coronary events (prior stenting of the left main, proximal left anterior descending (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

Patients with **proximal DVT** should be treated for at least 3 months. This can be extended to 6 months if the DVT was extensive i.e. ilio-femoral or if lower limb symptoms persist beyond 3 months.

For **isolated calf DVT**, we suggest anticoagulation for 3 months.

For a **first proximal DVT associated with a major transient risk factors** treatment can stop at 3 months and does not require review in the haemostasis/thrombosis clinic.

Major transient provoking risk factors are as follows:

- Surgery up to 3 months prior
- Significant trauma e.g. fracture, plaster cast
- Significantly reduced mobility compared to baseline
- Pregnancy/puerperium
- COCP/HRT

Minor transient risk factors are as follows:

- Temporary immobility in previous 4 weeks e.g. confined to bed for 3 or more days
- Flight of more than 4 hours

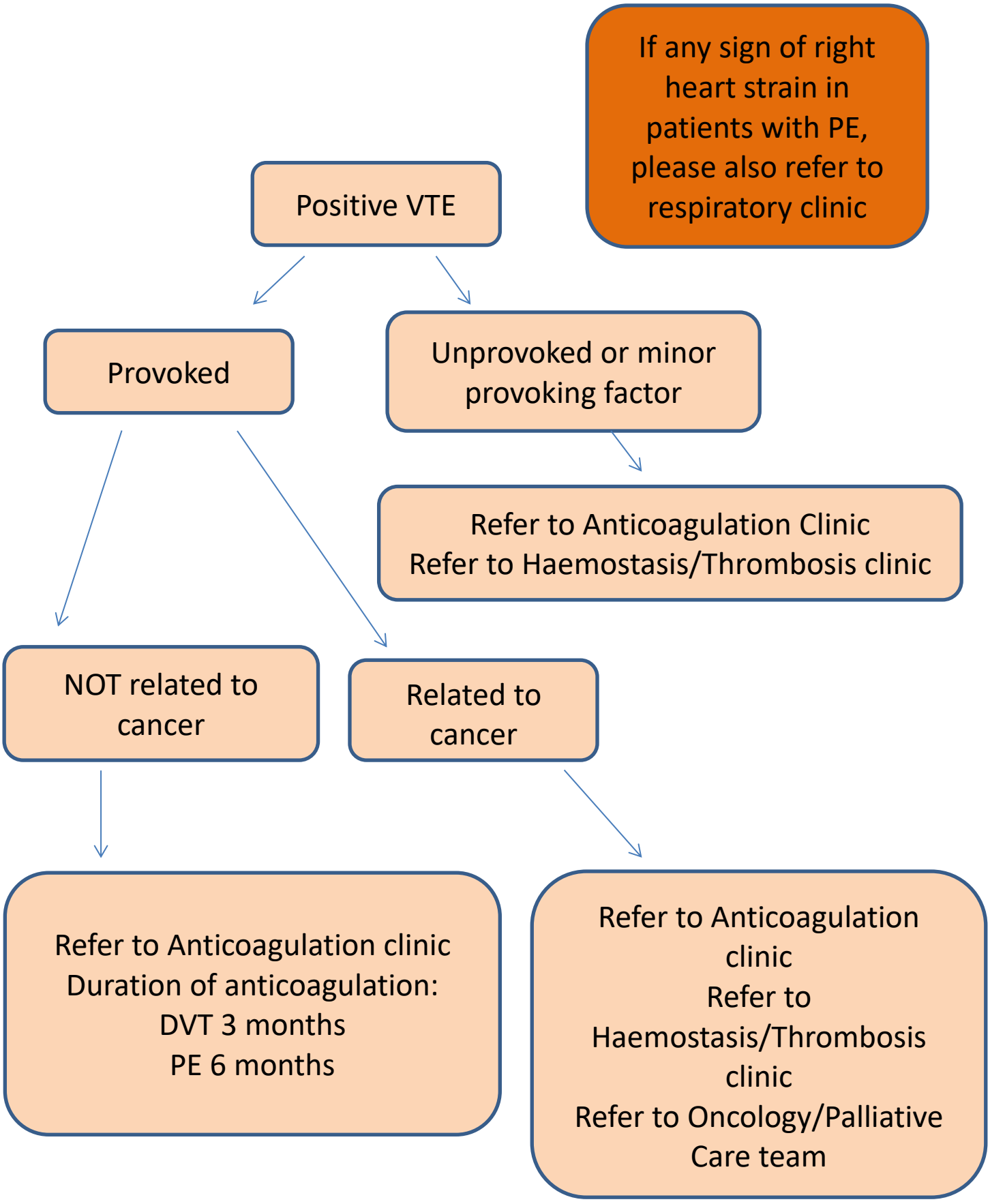
For patients with unprovoked VTE or VTE after a minor provoking factor a 3 month review in the haemostasis/thrombosis clinic is recommended and anticoagulation continued until review.

Long-term treatment will be considered for:

- Recurrent thrombosis
- Patients with an ongoing risk factor such as cancer
- A first proximal DVT or PE either unprovoked or after a minor provoking factor

Patients where long-term anticoagulation is considered should be referred to the haemostasis/thrombosis clinic for follow up. A referral can be made via email to the haematology secretaries (SMH BHT.haemsecssmh@nhs.net, WH BHT.haemsecswh@nhs.net) or via referral letter to the haematology department.

Referral and Follow Up Flowchart for VTE



Counselling

All patients should be counselled on complications and side effects of anticoagulation medications, the signs and symptoms of recurrent VTE, and the duration of anticoagulation.
Provide relevant patient information leaflets - see below.

Provide contact information and where they can seek advice should they have specific related concerns.

Inform patients regarding whether or not they will be reviewed in the haemostasis/thrombosis clinic at 3 months post diagnosis or whether they have been referred to the respiratory clinic.

Advise patients of the duration of their anticoagulation as outlined below.

Follow-up

Patients who may require long-term anticoagulation should be referred to the haemostasis/thrombosis clinic to be reviewed at 3 months to decide whether to stop or whether to continue indefinitely. Patients who are definitely stopping at three months do not need routine follow-up.

Duration of Anticoagulation

3 months	3 months then consider long-term
1st proximal DVT with major transient risk factor	Recurrent VTE Proximal DVT with ongoing risk factors 1st unprovoked DVT or PE
1st isolated calf vein DVT	

Patients with unprovoked proximal DVT or PE are at a higher risk of recurrence than those with a transient precipitating factor. It is therefore recommended that they are considered for long-term anticoagulation.

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) after completing anticoagulation.

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** vs female and **PE** vs 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.

	D-dimer positive		D-dimer not done		D-dimer negative	
	1 y	5 y	1 y	5 y	1 y	5 y
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%

In patients who are unexpectedly found to have asymptomatic DVT or PE, the recommended duration is the same for initial and long-term anticoagulation as for similar patients with symptomatic VTE.

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.

Thrombophilia Testing

This has a very limited role and should be considered carefully before expediting.

Patients continuing anticoagulation should not be offered routine thrombophilia testing.

It is advisable to avoid thrombophilia testing in the acute setting.

However, in light of recent studies on patients with triple antibody positive antiphospholipid antibody syndrome showing an increased risk of thrombotic events when anticoagulated with rivaroxaban, we would advise testing for antiphospholipid antibodies in patients with the following:

- Unprovoked VTE and <50 years old
- History of systemic lupus erythematosus (SLE) or autoimmune diseases
- Prolonged APTT prior to anticoagulation
- Recurrent thrombosis
- VTE at unusual sites
- Arterial thrombosis with no vascular risk factors
- Recurrent miscarriages/stillbirth
- Persistent thrombocytopenia

Antiphospholipid antibody testing includes lupus anticoagulant, anticardiolipin IgG/IgM antibody and anti-beta2-glycoprotein IgG/IgM antibody tests. Lupus anticoagulant ideally should be tested prior to any anticoagulation as this will cause false positive results.

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

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

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 COCP and HRT in asymptomatic female relatives in selected thrombosis-prone families with high risk thrombophilia.

Testing is usually performed one month after discontinuing anticoagulation and the doctor should clearly indicate which of the following are required:

- Testing for heritable thrombophilia
- Testing for antiphospholipid antibodies
- D-dimers

Compression Stockings

In light of the most recent evidence from the SOX trial, compression stockings should no longer be prescribed routinely but only used selectively in patients to treat symptoms.

Absolute contraindications are:

- Advanced peripheral arterial occlusive disease
- Decompensated heart failure
- Septic phlebitis
- Phlegmasia caerulea dolens (DVT leading to severe swelling of the whole leg)

Relative contraindications are:

- Suppurative dermatoses
- Intolerance of compression stocking fabric
- Advanced peripheral neuropathy
- Chronic arthritis

The patient should be referred for class II compression hosiery by the anticoagulation service or GP 1 month post DVT diagnosis if there are ongoing symptoms in the affected leg.

Superficial Thrombophlebitis/Superficial Vein Thrombosis (SVT)

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 SVT unless concomitant DVT is suspected. Patients who are referred with suspected concomitant DVT should undergo compression US.

If US shows SVT is within 3 cm of the sapheno-femoral junction (SFJ) treat with therapeutic anticoagulation for 3 months as there is a high risk of progression to DVT. A three month review in the haemostasis/thrombosis clinic is not required.

Otherwise SVT 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 it has become recognised that more severe cases have a better symptomatic response to anticoagulation.

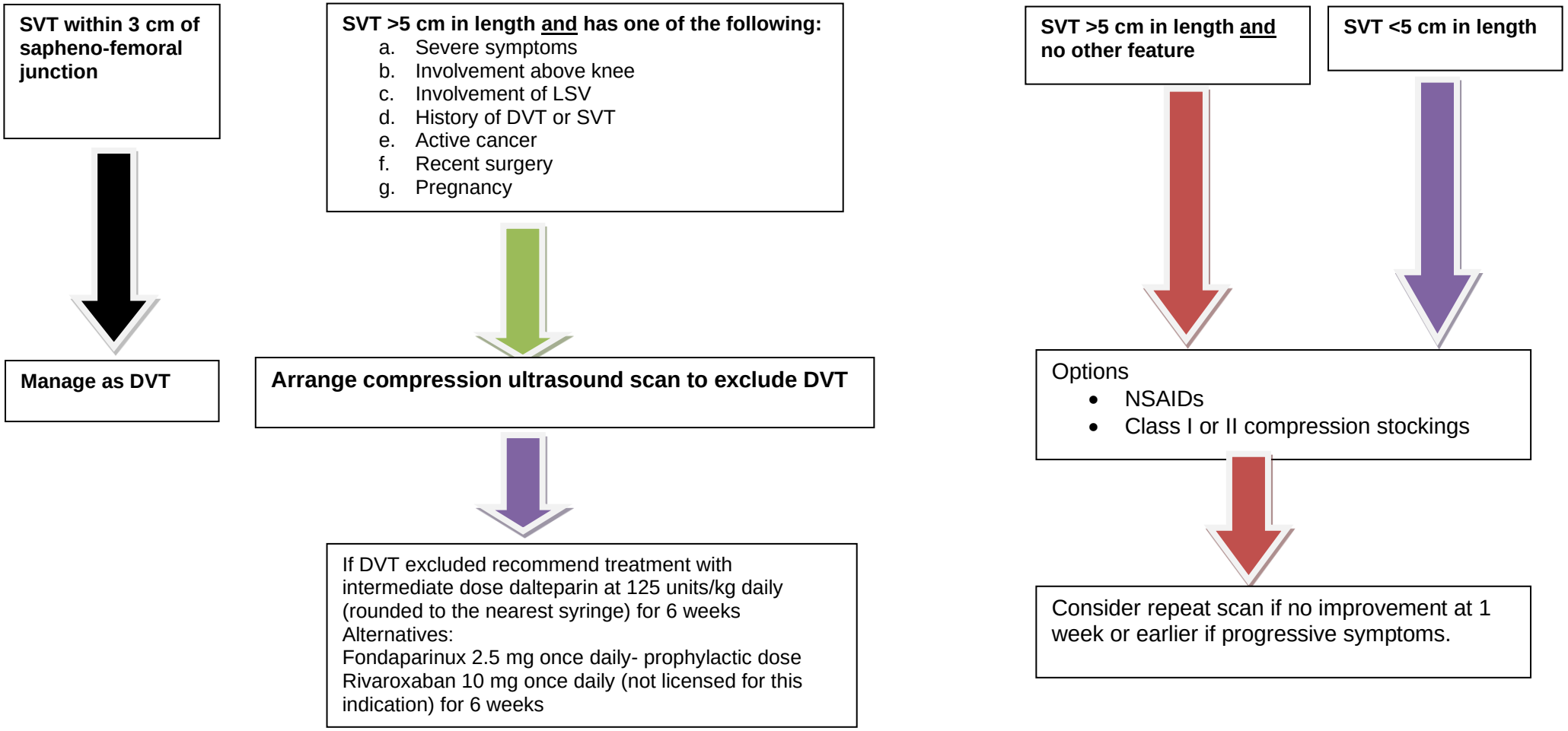
Where the SVT is NOT within 3 cm of the SFJ, the following apply: Also see Flowchart below.

- If <5 cm in length, symptomatic management only e.g. NSAIDs and class I or II compression stockings. Consider repeat scan if no improvement at 1 week or earlier if progressive symptoms.
- If >5 cm and ONE of the following:
    - Above knee involvement
    - Severe symptoms
    - Involvement of long saphenous vein (LSV)
    - History of DVT or SVT
    - Pregnancy
    - Active cancer or recent surgery

Arrange a compression US scan to exclude DVT. If DVT is excluded recommend intermediate dose dalteparin at approximately 125 units/kg dalteparin for 6 weeks. Prophylactic dose of fondaparinux (2.5 mg once daily subcutaneously) is an alternative. (Although DOACs are not licensed for this indication suggested prophylactic dose rivaroxaban (10 mg orally once daily) was non-inferior to prophylactic dose fondaparinux (2.5 mg once daily).

- If >5 cm and none of above, symptomatic management with NSAIDs. Repeat scan if no improvement at 1 week or earlier if progressive symptoms.

Flowchart for Management of Superficial Thrombophlebitis (SVT)



For all patients

- Patient to be reviewed by GP and re-referred to AECU if necessary if no improvement at 1 week or earlier if progressive symptoms

Recurrent lower limb thrombophlebitis:

- If unexplained, consider referral to vascular surgeons for assessment of chronic venous insufficiency and treatment as appropriate.
- Discuss anticoagulation with haematology team

Upper Limb DVT

Defined as thrombosis involving any of axillary, subclavian, internal jugular or brachiocephalic veins.

Initiate anticoagulation as per proximal DVT.

Duration: 3 months, unless line related (see below) or associated with cancer 6 months and review.

Patients with unprovoked upper limb DVT should be referred to the thrombosis clinic and anticoagulation continued until they are seen.

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

Upper Limb Superficial Vein Thrombosis

Defined as thrombosis of brachial, ulnar, radial, cephalic and basilic veins.

Managed as per lower limb SVT:

- Generally, symptomatic management e.g. NSAIDS.
- Repeat scan at 1 week if no improvement or earlier if progressive symptoms.
- If extensive or above elbow, consider prophylactic dose LMWH for 6 weeks.

Central Venous Catheter Related Thrombosis (CRT)

DVT defined as above (i.e. involving axillary, subclavian, internal jugular or brachiocephalic veins).

Management: Anticoagulation as above.

- In cancer patients with CRT, dalteparin is preferred over warfarin.
- Anticoagulation treatment should be continued for the length of time the catheter is in use.
- If catheter is nonfunctional, it should be removed after a short course (3 - 5 days) of anticoagulation. If catheter is removed the period of anticoagulation should not be shortened to less than 3 months.
- Dalteparin alone or dalteparin followed by warfarin should be used for a minimum of 3 months. After treatment of CRT, prophylactic doses of anticoagulation should be continued as long as the catheter remains indwelling.
- Thrombolytic therapy is not routinely recommended.

Anticoagulation in Intravenous Drug Users (IVDU)

In patients with intravenous drug use, therapeutic options are LMWH, DOACS or vitamin K antagonists, e.g. warfarin. Warfarin confers a higher risk of haemorrhagic complications and drug interactions, but also requires regular monitoring, which in this particular group may be difficult to obtain.

Used in appropriate doses, LMWH provides effective antithrombotic treatment without the need for monitoring. Although the intended duration of the therapy may not be reached for various reasons, and the risk of haemorrhage is high in this cohort. The patient has to be informed that LMWH treatment should be continued for a minimum of 3 months. This can be extended if symptoms in the affected leg persist.

There is no available data on the use of the direct oral anticoagulants in IVDUs diagnosed with DVT/PE but in certain circumstances DOACS may be preferable to LMWH.

If LMWH is commenced, a two week supply should be prescribed and the patient referred to the anticoagulation clinic.

References:

NICE Guideline NG158	Venous Thromboembolic diseases: diagnosis, management and thrombophilia testing published date: 26 March 2020
OUH clinical guideline	Venous Thromboembolism Prevention and Management in Patients Aged 16 years and above policy
OUH MIL	Treatment of venous thromboembolism (VTE) in adults with dalteparin (Fragmin)
Lee, A et al (2003)	Low Molecular Weight Heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med, 349 (2): 146-53
Young, A et al (2018)	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 Oncol, 36 (20): 2017-2023
Raskob, G et al (2018)	Edoxaban for the treatment of Cancer-Associated Venous Thromboembolism, 378: 615-624
Agnelli G et al (2020)	Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer N Engl J Med, 382: 1599-1607
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Decousus, H et al (2010)	Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med, 363, 1222-1232.
Scott, G (2015)	Superficial vein thrombosis: a current approach to management. Br J Haematol, 168, 639-645

See also:

ANTICOAG SOP 1 Standard Operating Procedure for Oral Anticoagulation with Vitamin K Antagonists
Guideline 70 Anticoagulation with Intravenous Heparin
Guideline 116FM Dalteparin for Prophylactic Use in Surgery, Oncology, Haematology and Medicine
Guideline 191FM Protocol for Over-Anticoagulation with Warfarin
Guideline 240FM Rivaroxaban and Apixaban: Management of Overdose, Bleeding and Emergency/Elective Surgery
Guideline 295FM Dabigatran, Rivaroxaban, Apixaban and Edoxaban for Deep Vein Thrombosis and Pulmonary Embolism
Guideline 646FM Venous Thromboembolism (VTE) in Maternity
Guideline 733FM Thromboprophylaxis in the Hospital Setting: Reducing the Risk of Hospital Acquired Deep Vein Thrombosis or Pulmonary Embolism
Guideline 797FM Oral Anticoagulants – Warfarin, Acenocoumarol and Phenidione, when Doses are Adjusted by the Anticoagulation Clinic and Prescribed by the General Practitioner
Guideline 831 Anticoagulation – Patient INR Self-Testing Procedure

Patient Information Leaflets:

Dalteparin Injection – How to inject Dalteparin at home, a patient guide
Warfarin Clinic and the Anticoagulation Service
Home Visits for Warfarin Clinic Patients

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Author/s	Dr Renu Riat, Haematology - Management of venous thromboembolism Dr Tina O'Hara, Acute Medicine - DVT and PE ambulatory pathway
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