Assessment & treatment of patients with suspected / confirmed Deep Vein Thrombosis (DVT).	Trust reference B41/2014	University Hospitals of Leicester NHS NHS Trust Caring at its best

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Supersedes:	Assessment and Treatment of Adult Inpatients with Suspected or Confirmed Deep Vein Thrombosis B30/2007 Assessment & treatment of patients with suspected / confirmed Deep Vein Thrombosis (DVT) in the Ambulatory DVT clinic C36/2014 Additionally, this document contains new detailed information regarding VTE treatment for specific circumstances.
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Management of suspected / confirmed Deep Vein Thrombosis (DVT).

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Contents.

Additional VTE/anticoagulation related documents can be found here on INsite – it is recommended you have INsite open in the background to help stabilise links, particularly if you are accessing over VPN.

KEY WORDS: Deep vein thrombosis, DVT, Venous thromboembolism, VTE, Direct oral anticoagulants, DOAC, Apixaban. Edoxaban. Rivaroxaban. Low Molecular Weight Heparin, LMWH, Fondaparinux, Warfarin.

1. Introduction

Venous Thromboembolism (VTE), Including Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE) is a potentially fatal disease. The aim of treatment is to prevent thrombus extension and decrease the incidence of recurrent VTE, post phlebitic syndrome and chronic thromboembolic pulmonary hypertension.

These guidelines cover assessment, investigation, and treatment of acute deep vein thrombosis.

It is advisable to get specialist advice from the appropriate Consultant or Service for patients with complex conditions or presentations.

1.1. Scope

This document sets out the processes and procedures to follow in the diagnosis and treatment of adult patients with a suspected or confirmed DVT and applies to:

a) Adults who attend as an outpatient

b) Adults who attend as an outpatient and, following assessment, have a clinically suspected DVT but are not suitable for treatment as an outpatient (see exclusion criteria)

c) Adults who are currently an inpatient for another reason but develop signs and symptoms of a DVT.

The processes and procedures within this document apply to all healthcare professionals who assess, treat and care for these groups of patients.

This document supports the UHL Thromboprophylaxis Policy (B9/2016) and must be used in conjunction with this policy.

This document supports the UHL policy for the assessment and treatment of patients with suspected or confirmed pulmonary embolism (PE) (B40/2011) and must be used in conjunction with this policy.

Other relevant UHL guidelines that might apply to patients with suspected or confirmed venous thromboembolism can be found here (it is recommended you have INsite open in the background to help stabilise links, particularly if you are accessing over VPN).

1.2. Legal Liability Guideline Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional it is fully appropriate and justifiable - such decision to be fully recorded in the patient's notes.

1.3. Monitoring and Audit Criteria

Cases of acute VTE will be audited via the Hospital Associated Thrombosis root cause analysis process to ensure compliance with policy.

Version control

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT			
Author / Lead Officer	Simon Rudge	Job Title: VTE nurse specialist	
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2. Referrals:

Outpatient Ambulatory DVT Service Referrals

The Leicester Acute Ambulatory DVT Service accepts adult patients (aged 18yrs or over) suspected of having a lower limb DVT who are suitable for out-patient assessment and treatment. It operates five days a week, 8-8 Mon-Fri and 8-4 Bank Holidays. On weekends, Christmas Day, Boxing 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 Bed Bureau (contact via UHL switchboard). **They will take details and also ask the GP for a referral letter to be emailed to** BedBureauMbx@uhl-tr.nhs.uk**, a copy of the referral email should also be given to the patient who is asked to bring it with them to their attendance at the DVT clinic at the time given by Bed Bureau.**

If transport is needed for the first visit, this will need to be arranged via Bed Bureau.

Referrals may also be made by the 'ED Trackers' or from the GP Ambulatory Unit (GPAU).

Further advice or guidance can be sought by contacting the UHL Acute Ambulatory DVT service via switchboard during office hours.

Patients who may not be suitable for assessment/investigation of a suspected DVT as an outpatient and require admission include those outlined below. However, using clinical judgement, they may be suitable to treat as an outpatient if reviewed in GPAU, otherwise they will require admission:

- Extension of venous thrombosis despite anticoagulation
- Signs and symptoms of a pulmonary embolus (PE) in addition to a suspected DVT
- Acute massive venous thrombosis and obstruction of the venous drainage of an extremity, ischaemic form of venous occlusion, phelgmasia cerulea dolens (painful blue inflammation)
- Milk leg (phlegmasia alba dolens). This is painful 'white' inflammation caused by massive ileofemoral venous thrombosis with associated arterial spasm. The affected limb is often pale with poor or even absent pulses. The findings suggest acute arterial obstruction but the presence of swelling, petechiae and distended superficial veins point to this condition
- Patients with active bleeding
- Patients at significant risk of bleeding (not a definitive list):
- Active peptic ulceration
- Liver disease (INR ≥1.5 / PT>2s beyond normal range)
- Uncontrolled hypertension
- Angiodysplasia
- Recent eye or CNS surgery or recent haemorrhagic stroke (within the previous 30 days)
- Thrombocytopaenia: **for this group of patients, a platelet count below 75x10^9/l excludes these patients from ambulatory DVT clinic or**
  Inherited bleeding disorders (haemophilia) **or** with an Hb <100g/l: **for this group of patients a platelet count below 100x10^9/l excludes these patients from ambulatory DVT clinic** Patients with bleeding disorders should be discussed with the on-call haematology registrar or Haemophilia consultant.
- Patients who may require admission for other medical reasons
- Patients develop their DVT whilst an inpatient for another reason
- Known heparin allergy or heparin associated thrombocytopenia
- Pregnancy (patients ≥16 weeks gestation go to Maternity Assessment Unit and to GPAU if under 16 weeks gestation)
- Suspected upper limb DVT – see Management of Upper Limb DVT
- In-patients (unless in-patient spell is complete, and they are being discharged)
- Unable to transfer from chair to chair by self
- ≥180 kg
- Renal insufficiency: creatinine >200 µmol/L with unknown eGFR or eGFR <20 ml/min/1.73m^2, or Cockcroft-Gault creatinine clearance (CG CrCl) <30ml/min

On bank holidays we cannot accept patients who require hospital transport. ☞

Referrals from the following:

Mental health patients

from Bradgate & Bennion units (GGH)

Community Hospital

patients from Coalville, Lutterworth, Melton Mowbray, Loughborough or Market Harborough.

Patients from prisons

HM Welford Road and Glen Parva

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 on-going anticoagulant care will be the responsibility of these hospitals or prisons.

GP referrals

A GP seeing a patient with suspected DVT should decide whether they are suitable for out-patient assessment and treatment (see exclusion list above). If they are not suitable, or the GP sees the patient out of hours, the patient should be referred to the UHL on-call medical team, referred to GPAU, or asked to attend the LRI Emergency Department.

If they are suitable, a dose of either Low Molecular Weight Heparin (LMWH), Apixaban, or Rivaroxaban should be given (dosing guide below) pending a DVT clinic appointment – sufficient treatment should be provided to bridge the time from referral to appointment.

If LMWH, Apixaban or Rivaroxaban can't be provided and administered from the patients GP service prior to attendance; please telephone Bed Bureau who can arrange a visit to the GP & Ambulatory Unit (GPAU) to arrange for treatment to be given.

In-patient referrals

In-patient referrals for DVT ultrasound scanning should be made using the online radiology referral portal.

It is the responsibility of the primary Consultant and their team to initiate and monitor appropriate treatment and care for an in-patient with a suspected/confirmed DVT and must include the following (for in-patient Follow Up see here):

Referrals to Specialist Clinics

Patients with a newly diagnosed DVT who are not already under a thrombosis specialist clinic require review after 3 months of treatment according to NICE quality standards 201 (2013 updated 2021). Consider a referral to the Haemostasis and Thrombosis Unit using the Haematology Referrals Mailbox (HaematologyReferralsMailbox@uhl-tr.nhs.uk) complete with patient's details and clinical history.

For Patients who require further investigation, thrombophilia screens or with known thrombophilic defects – please refer to the Haemophilia Centre Mailbox (haemophilia.centre@uhl-tr.nhs.uk).

Obstetric referrals

Refer to Investigation and Management of VTE in Pregnancy and Puerperium C5/2001

3. Commence and control anticoagulant therapy on suspicion of DVT:

- Doctor to prescribe selected treatment on in-patient medication prescription chart and ensure a stat dose is given on first clinical suspicion of VTE (in the absence of contraindications)
- Ensure the patient is fully informed of suspected/confirmed DVT and treatment, including possible side effects and drug and food requirements/interactions (particularly pertinent to Rivaroxaban and Warfarin), and this is done prior to starting treatment
- Ensure the patient is given relevant anticoagulation booklet and that this is fully explained
- **Refer patient to the UHL Integrated Anticoagulation Service for continued monitoring of anticoagulation and to aid safe discharge of the patient**

4. Stat dose on suspicion of DVT.

Once an Outpatient or In-patient referral has been made; if not contraindicated, a stat dose of either Low Molecular Weight Heparin (LMWH), Apixaban or Rivaroxaban should be given (dosing guide below) pending lower limb ultrasound scan. These stat doses should continue at appropriate intervals until the DVT is confirmed (start treatment) or ruled out (cease stat dosing and reinstate any medications which were suspended due to stat doses of therapeutic anticoagulation).

A blood sample for D-dimer testing MUST be taken before anticoagulation is given if Wells score <2.

Note: once patients have received a dose of anticoagulant, D-dimer results are likely to be significantly reduced due to the action of the anticoagulant, so a low result may not be clinically useful, however a high result may assist diagnosis. Therefore D-dimer results in these patients should be interpreted with caution and may not be useful as part of the diagnostic algorithm.

This pre-anticoagulation sample is therefore critical for effective diagnosis and use of resources. Also note; this effect may be seen in patients using Statins.

Dosing Guide.

(Related information: Choice of anticoagulant drug)

Dose of **Enoxaparin** (for Outpatient referrals; supply sufficient syringes to ensure a dose is not missed before the arranged DVT clinic appointment).

Weight (Kg)	Up to 100kg CrCl≥30ml/min	>100kg CrCl≥30ml/min	All weights CrCl<30ml/min	All weights CrCl<15 ml/min
Dose	1.5mg/kg OD OR 1mg/kg BD*	1mg/kg BD	1mg/kg OD**	See below†

*Choice of dosing based on clinical circumstances, e.g. bleeding risk/previous VTE.

**Monitor heparin assay after 4th dose and every 4 days thereafter

†**CrCl <15 and/or impossible to monitor heparin levels: An alternative anticoagulant would be preferred: consider Dalteparin/Tinzaparin in the first instance or seek Haematology advice.**

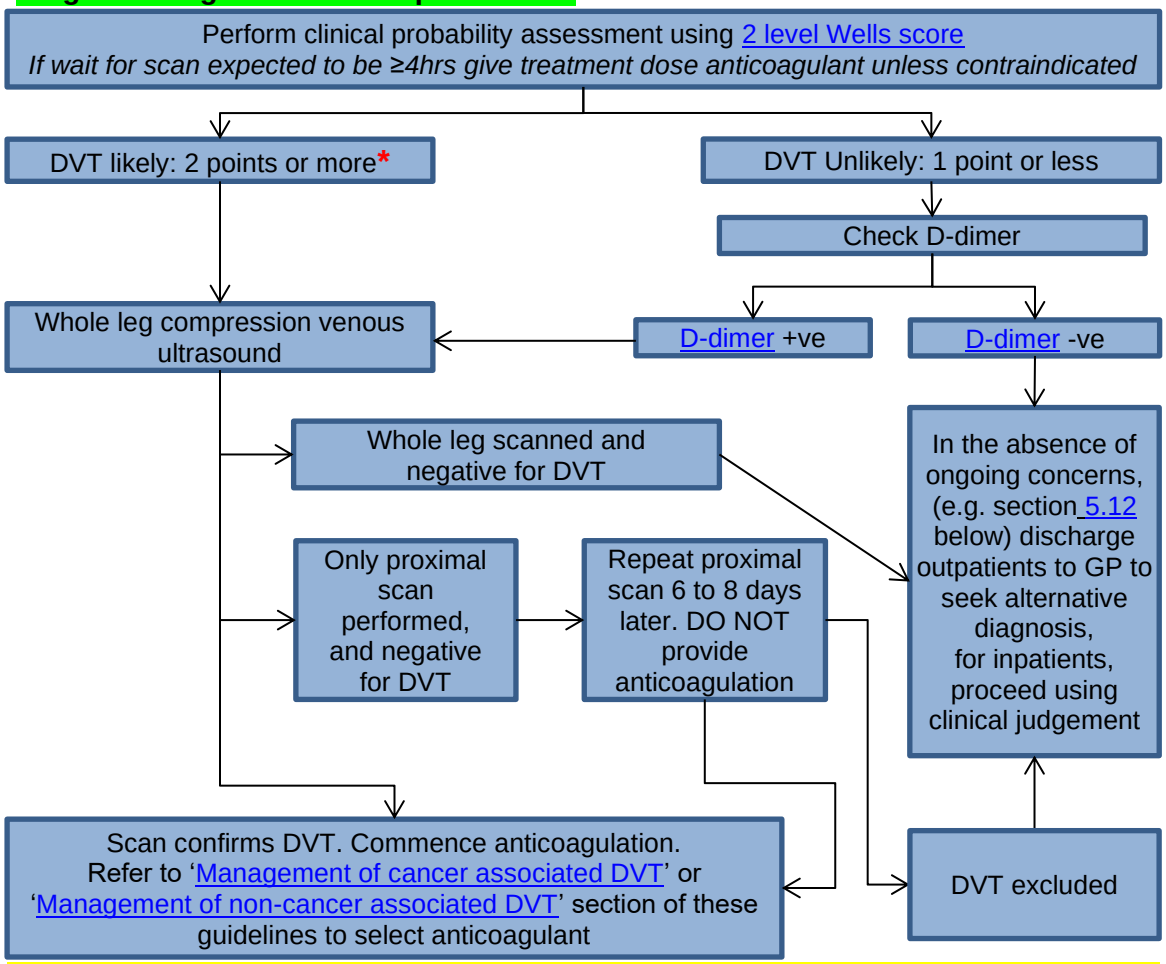
Dose of **Rivaroxaban**: 15 mg bd (for Outpatient referrals; supply sufficient 15 mg tablets to ensure a dose is not missed before review at the arranged DVT clinic appointment).

Dose of **Apixaban**: 10 mg bd (for Outpatient referrals; supply sufficient 5 mg tablets to ensure a dose is not missed before review at the arranged DVT clinic appointment).

Rivaroxaban and Apixaban should not be used in pregnancy.

5. Assessment and diagnosis of DVT

5.1. Diagnostic algorithm for suspected DVT



*Patients with a suspected DVT and an expected wait to scan of ≥4hrs; give interim treatment dose of anticoagulation until DVT confirmed or ruled out.

PLEASE NOTE: Inconclusive scans should be discussed with radiology on an individual basis regarding other forms of imaging

5.2. Management of Investigations

If diagnostic investigations are expected to take longer than 4 hours from the time of first clinical suspicion; patients with suspected deep vein thrombosis are given an interim therapeutic dose of anticoagulant therapy (weight-based treatment dose of low molecular weight heparin or treatment dose of direct oral anticoagulant).

5.3. Wells Pre-test probability assessment:

Patients will initially have a pre-test probability assessment.
Radiology ultrasound scan is performed dependant on the following:

- Patient has a High Well's score (≥2), no D-dimer required, perform scan
- Patient has a Moderate Well's score (=1) with a positive D-dimer, perform scan
- Patient has a Low Wells score ≤1 with a negative D-dimer, no scan required

If proximal leg scan ONLY has been carried out and is negative, a repeat scan should be arranged 6 – 8 days later; anticoagulants are *withheld* until the repeat scan result is known. In-patients should continue thromboprophylaxis if indicated by their VTE risk assessment. Out-patients are warned to contact the DVT clinic, or ED/nearest 24-hour Urgent Care Centre out of hours, if they experience any worsening symptoms, or new symptoms of PE.

5.4. Wells pre-test probability scoring for Deep Vein Thrombosis

(Keeling, et al 2004, Wells, et al 1997, Wells, et al 2003, Wells, et al 1995) classification for unlikely or likely DVT.				Score
Active cancer (ongoing treatment *or* within the previous six months *or* palliative)				1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities within the last 12/52				1
Recently bedridden for more than 3 days, or major surgery within previous 12 weeks				1
Localised tenderness along the distribution of the deep venous system				1
Entire leg swollen				1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured ten cm below tibial tuberosity)				1
Pitting oedema (greater in the symptomatic leg)				1
Collateral superficial veins (non-varicose)				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** 2 = High probability of DVT no D-dimer required, refer for scan 1 = take d-dimer, if positive then scan, if negative no scan recommended. ≤ 0 = low probability, no d-dimer required, no scan recommended	T O T A L		
High 2 or More:	Tick	**Moderate 1 & +ve d-dimer:**	Tick	**Low 1 & -ve d-dimer or ≤0:** Tick

Actions to be taken according to Wells score

High: score of 2 or more **Or** **Moderate: score of 1 & raised D-dimer.**	• Weigh patient in kg and document renal function • Refer to Patient's Consultant if weight is less than 40kg or if eGFR is less 30ml/min • Start anticoagulation at treatment dose levels (see Dosing Guide) • Venous ultrasonography is available via the DVT clinic (in hours) if the patient is already an outpatient or is an in-patient at the point of discharge and suitable for outpatient care. For in-patients not at the point of discharge, or at the point of discharge but not suitable for DVT clinic (see exclusion criteria): arrange imaging directly with the radiology department • Patient is allowed gentle mobilisation once treatment has commenced
Low score of ≤1 & –ve D-dimer	• For Outpatients: discharge to GP for further investigation into symptoms unless serious clinical concerns remain in which case discuss with GPAU. See section 5.12 • For in-patients: proceed using clinical judgement. See section 5.12

5.5. D-dimers

- Normal levels can help to exclude a DVT, however elevated D-dimer levels are non-specific and have low positive predictive value.
- D-dimers should only be performed for patients with a primary presentation of DVT but have a Well's score of 1.
- D-dimers should not be routinely performed on patients with a score of 0 or 2 or more.

Note: once patients receive a dose of anticoagulant, D-dimer results are likely to be significantly reduced due to the action of anticoagulants, so a low result may not be clinically useful, however a high result may assist diagnosis. D-dimer results in these patients should be interpreted with caution and may not be useful as part of the diagnostic algorithm.

This pre-anticoagulation sample is therefore critical for effective diagnosis and use of resources. **Also note**; this effect may be seen in patients using Statins.

Age adjusted D-dimer – *Applies to patients over the age of 50yrs:* lower limb DVT only, not validated to assist diagnosis for superficial vein thrombophlebitis or upper limb DVT.

D-dimer values rise with age, hampering its specificity in older patients. Adjusting values to improve its diagnostic utility in this population where DVT is prevalent may improve specificity. UHL have validated our own CobasH D-dimer test (Strong et al 2016) and are now using age related D-dimers in the Ambulatory DVT clinic. This approach is recommended for in-patient use as well, although the decision is at the discretion of the patients Consultant.
To calculate age-related D-dimer (50yrs and over. **Laboratory test only**, not suitable for bedside POC testing, not validated for use in suspected superficial vein thrombophlebitis or upper limb DVT)
UHL measures D-dimers in units of µg/ml fibrinogen equivalent units (FEU), with 0.00 µg/ml to 0.50 µg/ml being the normal lower and upper range. **To calculate the patients age adjusted**

upper range value simply divide the patients age by 100, this will give you the figure above which the D-dimer should be viewed as a positive result.

E.g. Patients age is 74yrs; 74/100 = 0.74. Therefore 0.74µg/ml is the D-dimer cut off for this age, i.e., the standard upper range limit of 0.50µg/ml is no longer considered positive.

5.6. Radiology investigations

a) **Radiology is performed depending on the following:**

- Patient has a High Wells score (=2 or more)
- Patient has a Moderate Wells score (=1 in conjunction with raised D-dimers)

b) **A positive imaging result** – diagnosis of thrombosis is confirmed, commence appropriate treatment

c) **A Negative Image result** – document result clearly in the patients' case notes, discontinue treatment doses of anticoagulants, however, take note of point 5.12 below.

d) **If calf veins are not visualised or there are other technical difficulties** – a repeat ultrasound is required within 6 to 8 days to ensure there is no above-knee extension of a possible undetected calf thrombus; *treatment dose anticoagulation should not be prescribed for the period between scans* – if the patient is an in-patient, thromboprophylaxis should continue if indicated by the Venous Thromboembolism Risk Assessment.

5.7. Routine bloods for the investigations of DVT

All patients should have:

FBC

U&E/LFT/glucose/Calcium

PT/INR and APTT

Pregnancy test for women of childbearing age where there is uncertainty around their contraception.

Other patient assessment and care needs

Prescribe and administer analgesia as required.
Consider undertaking a Pre-set Probability of Malignancy following Positive DVT

5.8. Patients on anticoagulation

If suspected new or recurrence of DVT; send bloods for D-dimer. **NOTE**: it is recognised that anticoagulants reduce D-dimer levels, so a low result may not be clinically useful, however a high result may assist diagnosis (this effect may also be seen in patients taking Statins). Arrange ultrasound scan using the appropriate in-patient or outpatient referral pathway. Use both D-dimer and ultrasound plus clinical assessment to determine if a clot has occurred.

5.9. First Ultrasound scan

Ideally, the patient will receive a whole leg ultrasound on their first visit.

Patients in whom a DVT cannot be ruled out by clinical examination and D-dimers will be given LMWH, Rivaroxaban or Apixaban (unless contraindicated) if scanning is likely to be delayed beyond 4 hours. The scan should take place within 24 hours.

If the initial ultrasound was out of hours in the Emergency Department and the patient is not admitted: these patients should be referred on to the Acute Ambulatory DVT service for anticoagulation and education, rather than the Anticoagulation Clinic.

5.10. Second Ultrasound scan

In some patients proximal DVT may have been excluded by the first ultrasound, but the veins below the knee could not be viewed (there are many reasons for this) and the patient could still have a distal DVT. Where distal vein scanning has not been possible a second ultrasound within 6 to 8 days should be arranged – ***no treatment dose anticoagulation should be provided in this interim period, although thromboprophylaxis should continue if it is indicated for in-patients***. If the ultrasound becomes positive, they will be treated for proximal DVT. If it remains negative then no further anticoagulation treatment is required for the purposes of DVT, however, do not stop any anticoagulation being provided for other reasons. Outpatients whose ultrasound

remains negative will not be further investigated via UHL and will not see a UHL doctor for further investigation of their symptoms but should be referred back to their GP. In-patients will require further investigation if clinically indicated.

5.11. 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. If an outpatient is referred with bilateral symptoms, ask the GP to speak with Bed Bureau to arrange assessment in the GP & Ambulatory Unit (GPAU) before requesting an Ambulatory DVT Clinic appointment.

5.12. Patients with high clinical suspicion, a grossly swollen leg, but a negative scan

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

In the outpatient setting, if following a negative scan the clinical suspicion of a DVT remains high the case should be discussed with a GPAU clinician to consider a CT venogram as outlined above.

5.13. Diagnosis of a recurrence in the ipsilateral (same) 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 prior DVT, 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, clinical situation and D-dimers should all be considered by the doctor when forming a management plan.

6. Ultrasound result

6.1. Patients who have a DVT diagnosed

Ambulatory DVT Clinic patients will be treated as outpatients and have their case medically reviewed at the weekly MDT ‘positive scan’ meeting. Follow up will be arranged through the DVT clinic.

In-patients will be treated alongside their admitting illness. These patients will commence anticoagulation for the appropriate period (minimum of 3 months for confirmed non-cancer associated DVT, minimum of 6 months if the patient is being actively treated for cancer, minimum of 6 weeks for superficial thrombophlebitis). Patients should remain ambulant where their mobility permits but we suggest it prudent to avoid vigorous exercise and air travel within six weeks of diagnosis of new venous thromboembolism. Follow up is described towards the end of this document.

6.2. Patients who have a DVT excluded

All patients: Consider and discuss with the patient; signs, symptoms and action to take regarding potential DVT along with alternative diagnoses.

Outpatients: the patient will be referred back to their GP with this information. They will not see a UHL doctor for further investigation of their symptoms unless the assessing clinician considers that urgent investigation is needed. In these circumstances they may refer the patient to GPAU.

In-patients: further investigation for the cause of symptoms may be required if clinical concern remains.

7. Treatment Options:

7.1. Cancer Associated DVT.

7.2. Non-Cancer associated DVT.

7.3. For investigations for cancer in patients with unprovoked DVT see below.

Further information on all aspects of treatment plans, anticoagulation monitoring and patient information can be found in the UHL VTE/Anticoagulation guidelines library on INSITE, including hyperlinks to relevant documents

8. Investigations for cancer in patients with unprovoked DVT

All patients should have a full history and examination. Patients with any concerning signs or symptoms should have targeted further investigations to investigate for an underlying cancer, see Pre-set Probability of Malignancy following Positive DVT below**.**

For people with unprovoked DVT or PE who are not known to have cancer, review the medical history and baseline blood test results including full blood count, renal and hepatic function, PT and APTT, and offer a physical examination.

Do not offer further investigations for cancer to people with unprovoked DVT or PE unless they have relevant clinical symptoms or signs (for further information, see NICE guideline ng158 p55).

Pre-set Probability of Malignancy following Positive DVT

Patient Ref No:	Ultrasound Scan Date:			
Name:	Calf	Popliteal	Femoral	Iliac
Address:	Prev Thrombotic History:		Yes	No
	Known Malignancy:		Yes	No
Tel No:				
GP:				
Weight loss >10% of body weight in 6 months	Yes		No	
Recent abdominal pain	Yes		No	
Recent alteration in bowel habit	Yes		No	
Haematuria/ Malaena	Yes		No	
Bilateral DVT	Yes		No	
Unexplained PV bleeding If YES = contact GAU on 16259 for advice	Yes		No	
YES to any of the above questions refer patient for abdominal ultrasound scan				
Smoker or smoked within last 5 years If YES = CXR	Yes		No	
Male >60 years	PSA			
Male <60 years with urinary problems	PSA			
History taken by:				
Date:				

9. Management of cancer associated DVT

VTE is a prevalent complication in patients with active malignancies and a significant cause of morbidity and mortality. The incidence of VTE is higher in advanced disease. Therapeutic anticoagulation in patients with cancer associated VTE requires careful balancing of risk and benefit. The management of patients with cancer associated thrombosis is challenged by a higher risk of both recurrent VTE and bleeding events compared with patients with VTE without cancer. Oral anticoagulation can be further complicated by severe thrombocytopenia, potential drug–drug interactions and nausea and vomiting. The principles of managing acute VTE in this population are broadly similar to those in patients without cancer, aside from a few key differences, which are covered below.

9.1. Immediate and initial anticoagulation

For most patients with VTE and cancer, anticoagulation should commence on suspicion of VTE and continue if suspicions are confirmed following diagnostic scanning. In the absence of renal insufficiency (eGFR<30 ml/min), or drug interactions with direct oral anticoagulants (DOACs) or contraindication to anticoagulation, suitable treatment options include low molecular weight heparin (LMWH) or a DOAC, preferably Apixaban.

DOACs should be avoided in patients with cancer with high bleeding risk (**platelet count <50x10^9/l for these patients**), liver dysfunction, recent major haemorrhage or in gastrointestinal or genitourinary malignancies). LMWH is preferred in these patients. Consider dose adjustments in patients with extremes of body weight (either body weight <60kg or BMI > 40kg/m^2) and the elderly (>80 years).

For patients with renal insufficiency (eGFR<30 ml/min), treat with either unfractionated heparin, or renal dose LMWH.

9.2. Ongoing anticoagulation and duration of anticoagulation

Either LMWH or a DOAC are suitable agents for ongoing anticoagulation.

Duration of anticoagulation in cancer-associated thrombosis is usually for a minimum duration of 6 months (3 months can be considered in select circumstances – if you wish to cease at 3 months it is advisable to discuss with Haematology). Treatment may be extended for longer durations.

Indications for extended anticoagulation may include:

- recurrence of VTE (either on or off anticoagulation)
- patients receiving palliative chemotherapy in the metastatic setting
- patients who have undergone radical treatment but remain at very high risk of recurrence

Extended anticoagulation must be balanced against risks of bleeding, quality of life, patient preference and life expectancy. There is a lack of data on the safety and efficacy of extended anticoagulation.

Whilst on anticoagulant therapy, patients should undergo regular clinical review, in view of prevalent issues including VTE recurrence, bleeding, procedures requiring suspension of anticoagulation, thrombocytopenia, new medications with potential for interactions, conditions affecting oral intake or drug absorption and change in cancer status.

9.3. Continuing LMWH in patients with cancer

Patients with an underlying malignancy will be considered for continuing LMWH rather than oral anticoagulation. However, for 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). **LMWH is provided for the first month**. UHL provide a prescription for the first 4 weeks supply of LMWH, after that time it should be prescribed by the patients GP.

At three months, review the patient to decide on subsequent management. Treatment of cancer associated VTE is usually for a minimum of six months, and if cancer is not cured some form of continuing anticoagulation is usually recommended. If this is with LMWH, there is no data as to whether the dose can be reduced to a prophylactic dose. If uncertain, discuss with Haematology.

9.4. Special circumstances related to tumour type

- DOACs are best avoided in patients with active gastrointestinal tract or genitourinary malignancies, due to the increased risk of bleeding. LMWH is a safer alternative in this population.
- Rivaroxaban, Apixaban and Edoxaban should be avoided in patients with upper GI malignancies due to an increased risk of major bleeding.
- Tumour types with the highest risk of VTE include pancreas, stomach, brain, lung, uterus, bladder, and kidney.
- DOACs can be used in patients with primary or secondary CNS tumours, provided there is no evidence of associated haemorrhage on imaging.

9.5. Central venous catheter-associated thrombosis

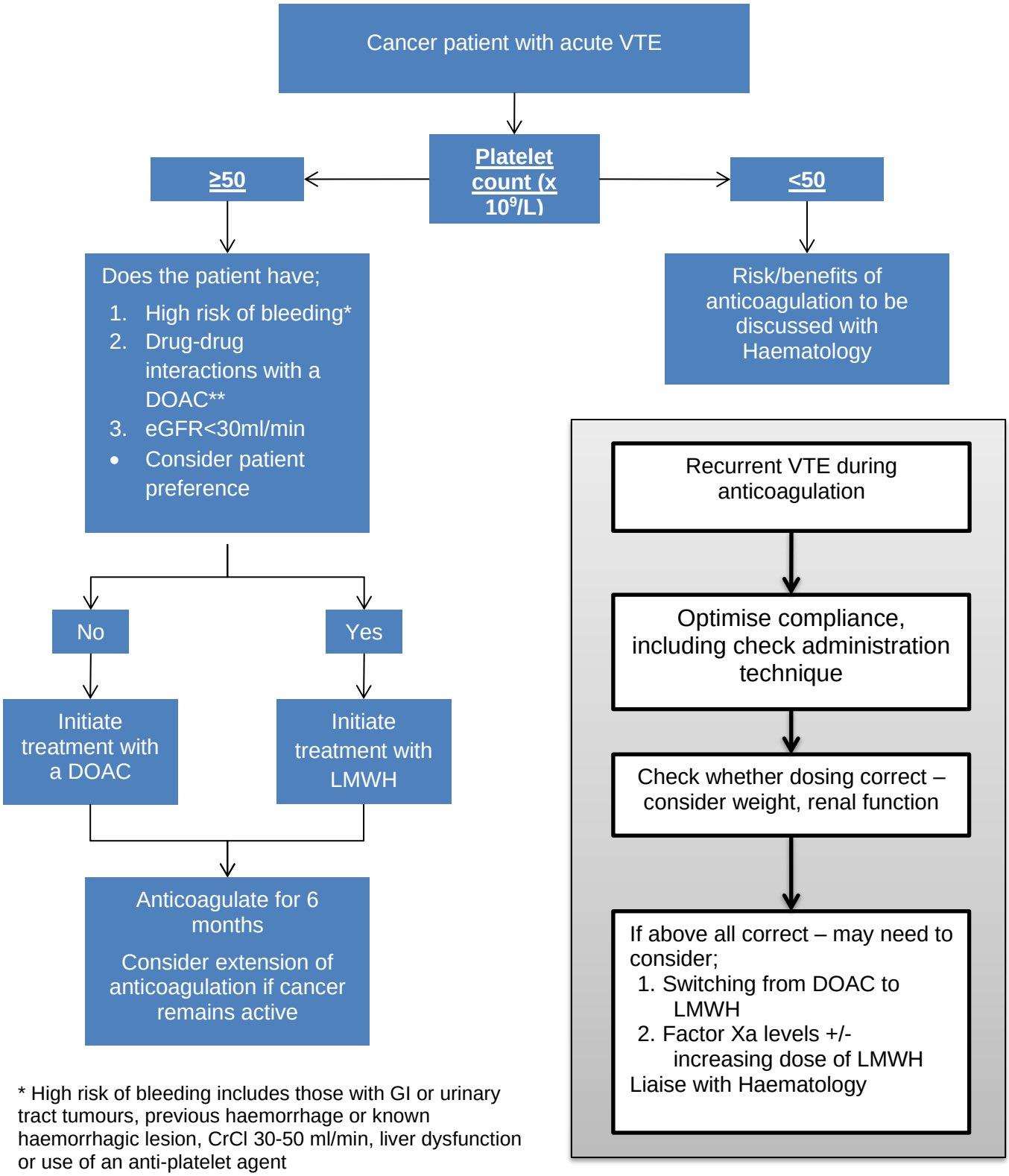
- VTE associated with indwelling central venous catheters are commonplace in patients with malignancy.
- Provided that the catheter remains functional and there is an ongoing need for it, the catheter should remain in situ.
- If the catheter is not functional, or improperly positioned, removal of the catheter is recommended, preferably with 3-5 days of prior anticoagulation to reduce the risk of embolism on removal.
- If the catheter is infected; in general, an infected line should be removed as soon as possible, but there are specific scenarios for retention of a catheter, such as catheter salvage being preferred because there are no other vascular access options. These decisions are made on a case-by-case basis, by the treating Consultant, taking into consideration Trust guideline B39/2021 (IV line associated infections).
- Anticoagulation should be given for 3-6 months (even if catheter removed), and for as long as the catheter remains in place as a minimum. LMWH is usually preferred, as there is a lack of data on the use of DOACs in this setting and they may have an elevated bleeding risk.

9.6. Use of IVC filters in cancer associated DVT

- These should be considered in patients who have absolute contraindications to anticoagulation, or in select cases in those with recurrent VTE despite anticoagulation. There is mounting evidence of long-term harm from IVC filters, and as such this should only be considered after discussion with Haematology.
- Alternatives options to an IVC filter in those with recurrent VTE despite therapeutic anticoagulation include switching from a DOAC to LMWH, or increasing the dose of LMWH. Discussion with Haematology is advised in this setting.

9.7. Patients undergoing systemic anticancer therapy

- Chemotherapy further increases the risk of cancer-associated thrombosis to 7-fold that of patients without cancer.
- DOACs are substrates to the cytochrome p450 CYP3A4 and P-glycoprotein enzymes; as such, chemotherapeutic agents may alter the efficacy and safety of DOACs.
- Tyrosine kinase inhibitors and antiandrogens are known for interactions with DOACs and should be prescribed with caution.
- DOACs should be prescribed with caution in patients who are established on antiepileptic, antidepressant, and antifungal medication.
- For specific cancer therapy related interactions, see guidance from the American Society of Haematology; refer to Table 2 on the following link https://ashpublications.org/blood/article/133/4/291/272766/How-I-treat-cancer-associated-venous



* High risk of bleeding includes those with GI or urinary tract tumours, previous haemorrhage or known haemorrhagic lesion, CrCl 30-50 ml/min, liver dysfunction or use of an anti-platelet agent

** Drug-drug interactions include tyrosine kinase inhibitors, antifungals, antiepileptic's, antiandrogens and antidepressants, secondary to effects on CYP3A4 and P-glycoprotein enzymes. Further information can be found using Table 2 on the following link https://ashpublications.org/blood/article/133/4/291/272766/How-I-treat-cancer-associated-venous

10. Management of non-cancer associated DVT

For management of cancer associated VTE *see section above*

Specialist investigations are required for the diagnosis of VTE (DVT and PE). These are usually available only within secondary care, and consequently initiation of anticoagulation treatment for both these conditions remains in the secondary care domain. Treatment can be with either Apixaban, Rivaroxaban or LMWH + Warfarin. Ongoing treatment is usually managed in primary care in accordance with specialist advice.

10.1. Presumptive treatment of suspected DVT

Presumptive treatment for suspected DVT with a DOAC may be offered where it is cost-effective. For in-patients this will be provided on the ward. For outpatients; ideally, 3-day packs should be used to minimise drug wastage. Ideally, these should be available in hospital front-door areas (e.g. Emergency Department; GP Assessment Unit; DVT clinic) to enable diversion of suitable patients to the specialist DVT clinic, and to avoid unnecessary hospitalisation.

Where DOAC is not considered suitable, treatment dose LMWH should be used.

10.2. Available anticoagulant treatments

(Also see Selection of anticoagulant)

Treatment of VTE can be with one of the 4 following options:

10.2.1. **WARFARIN** (also see Oral Anticoagulation with Warfarin and Coumarins UHL Guideline B44/2016 for detailed use of Warfarin)

Warfarin may be preferred:

- in patients with significant renal impairment (Cockcroft-Gault Creatinine Clearance (CrCl)<15 ml/min; or, on renal replacement therapy), *where DOACs are contraindicated*
- where the compliance is, or is anticipated to be, poor as compliance can be assessed with INR monitoring
- in the context of a known prothrombotic condition (e.g. antiphospholipid syndrome or recurrent VTE)
- in the context of mechanical heart valves, *where DOACs are contraindicated*
- by some patients, on the basis that there are decades of experience of use of Warfarin.

Limitations include: practical issues (need for regular INR monitoring, and repeating INR e.g. with bleeds or drug changes), interactions (Vitamin K containing foods, alcohol and many medications) and the need for heparin cover at start-up.

Treatment with low molecular weight heparin initiation and Warfarin

USE FIXED DOSE SYRINGES and give Enoxaparin subcutaneously once a day* (guideline here)

Weight (Kg)	Up to 100kg CrCl≥30ml/min	>100kg CrCl≥30ml/min	All weights CrCl<30ml/min	All weights CrCl<15 ml/min
Dose	1.5mg/kg OD OR 1mg/kg BD*	1mg/kg BD	1mg/kg OD**	See below†

*Choice of dosing based on clinical circumstances, e.g. bleeding risk/previous VTE.

**Monitor heparin assay after 4th dose and every 4 days thereafter

†**CrCl <15 and/or impossible to monitor heparin levels: An alternative anticoagulant would be preferred: consider Dalteparin/Tinzaparin in the first instance or seek Haematology advice.**

LMWH should be continued in parallel with Warfarin for 5 days or until the patients INR is ≥2 for at least 2 consecutive days – whichever is the longer.
Monitoring the platelet count for heparin-induced thrombocytopenia and potassium level for hyperaldosteronism is still done, as DVT patients are a heterogeneous group and can include orthopaedic and cardiac surgery patients. Cont.' ☞

Low Molecular Weight Heparin should be administered at treatment dose until the INR is in range

We follow the Tait and Sefcick slow Warfarin initiation protocol (Tait RO, Sefcick A 1998).

If the initial INR ≤1.3 the patient will receive 5mg of Warfarin once daily on days 1 - 4. The INR is checked on days 5, 8 and 12 and the Warfarin dose is adjusted according to the schedule

INR day 5	Warfarin dose Day 5	INR day 8	Warfarin dose from day 8
<1.7	5mg	<1.7	6mg
		1.8 - 2.4	5mg
		2.5 - 3.0	4mg
		>3.0	3mg for 4 days
1.8 - 2.2	4mg	<1.7	5mg
		1.8 - 2.4	4mg
		2.5 - 3.0	3.5mg
		3.1 - 3.5	3mg for 4 days
		>3.5	2.5mg for 4 days
2.3 - 2.7	3mg	<1.7	4mg
		1.8 - 2.4	3.5mg
		2.5 - 3.0	3mg
		3.1 - 3.5	2.5mg for 4 days
		>3.5	2mg for 4 days
2.8 - 3.2	2mg	<1.7	3mg
		1.8 - 2.4	2.5mg
		2.5 - 3.0	2mg
		3.1 - 3.5	1.5mg for 4 days
		>3.5	1mg for 4 days
3.3 - 3.7	1mg	<1.7	2mg
		1.8 - 2.4	1.5mg
		2.5 - 3.0	1mg
		3.1 - 3.5	0.5mg for 4 days
		>3.5	Omit for 4 days
>3.7	0mg	<2.0	1.5mg for 4 days
		2.0 - 2.9	1mg for 4 days
		3.0 - 3.5	0.5mg for 4 days

After day 12, 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.

10.3. Low Molecular Weight Heparin

LMWH is preferred:

- as the gold standard for treatment and prevention of cancer related VTE. There remains lack of clarity as to when a cancer is deemed “active” or “inactive” for purposes of use of a DOAC, and such decisions should be made at Consultant level, in consultation with a Haematologist where needed.
- as a bridge to oral anticoagulation, in the context of acute medical illness.
- in high risk perioperative situations – see Perioperative Bridging Guidance on INsite for details.

LMWH weight/dose guidance

DOSE ADJUSTMENT FOR RENAL IMPAIRMENT

RENAL IMPAIRMENT ENOXAPARIN DOSING CrCl between 15 and 29ml/min inclusive;

	Renal function
Body weight	CrCl >15 but <30ml/min
All weights	1mg/kg OD**

**Monitor heparin assay after 4th dose and every 4 days thereafter.

CrCl <15 and/or impossible to monitor heparin levels: An alternative anticoagulant would be preferred: consider Dalteparin/Tinzaparin in the first instance or seek Haematology advice.

IF CrCl is less than 15ml/min the patient is not suitable for ambulatory care and should be discussed with either the on-call Renal team or Medical team in GPAU for consideration of unfractionated heparin or closely renal supervised LMWH.

10.4. Direct Oral Anti-Coagulants (DOACs)

In the context of mechanical heart valves, *DOACs are contraindicated - seek alternative*

There are four DOACs licensed for treatment of VTE and approved by NICE following Technology Assessment (key characteristics in table below):

DOAC	Inhibits	Heparin at initiation	Reversal agent
Apixaban	Factor (F) Xa	No	Yes
Dabigatran	F II (thrombin)	Yes	Yes
Edoxaban	F Xa	Yes	No
Rivaroxaban	F Xa	No	Yes

The advantages are: quick onset of action, no need for heparin therapy at start-up (Apixaban & Rivaroxaban only); availability of specific antidote (Apixaban, Dabigatran and Rivaroxaban only); and no need for frequent monitoring.

The efficacy and safety of DOACs compared to standard treatment with Warfarin is summarised below:

Outcomes in DOAC trials for initial/short-term treatment, in comparison with standard Warfarin therapy → similar; ↓ lower rate; ↑ higher rate; -- not reported				
DOAC (vs Warfarin)	Efficacy	Major Bleeding	CRNM* Bleeding	GI bleeding
Apixaban	→	↓	↓	↓
Dabigatran	→	↓	↓	--
Edoxaban	→	→	↓	--
Rivaroxaban	→	↓	→	↑
Because of differing characteristics & study design, cross DOAC comparisons cannot be made. Data shown only for illustration of trial outcomes in comparison with Warfarin (in the respective trials)..				
*CRNM clinically relevant non-major; GI gastro-intestinal				

Overall, the DOACs are similar to Warfarin in efficacy, and have advantage in reducing bleeding complications. Rivaroxaban (but not Apixaban) has an increased risk of GI bleeding compared with Warfarin.

For long-term secondary prevention (vs placebo), with respect to rate of bleeding (major or clinically relevant non-major): Apixaban had similar rates to placebo (3.2%, vs placebo 2.7%), while Rivaroxaban was associated with higher rates (6%, vs 1.2%). When different regimes were explored for Rivaroxaban, the bleed rates were 20mg-3.3%, 10mg-2.4%, vs aspirin 2.0%.

General caution is advised in the following circumstances:

- extremes of body weight (<50kg or BMI<20kg/m^2). Rivaroxaban or Apixaban are appropriate anticoagulant options for patients with acute VTE regardless of ***high*** BMI and weight. Dabigatran or Edoxaban should not be used due to lack of evidence.
- creatinine clearance less than 30ml/min.

Please consult a Haematologist if intending to use a DOAC in either scenario. An individualised decision is required due to limited clinical data for patients at the extremes of weight and with severe kidney disease; and factor Xa levels may be required to inform appropriate dosing.

CHECK LIST FOR ALL PATIENTS ON DIRECT ORAL ANTICOAGULANTS:

- DAWN DOAC module and prescriber checklist completed (*OPD DVT clinic only*)
- Patient consented with decision aid and information
- Patients given DOAC card and patient information booklet
- Patient given prescription and clear date for DOAC dose reduction
- For **Out-Patients**; given DVT clinic phone number (0116 258 5972) to contact if any issues/side effects. For **In-Patients**; contact either the discharging medical team/ward or GP
- AVOID at extremes of low body weight:<50kg or BMI<20kg/m^2. For recommendations regarding extremes of body weight please see here

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 is not licenced for use in patients 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, however, with weaker transient risk factors this can be done at 3 months for some patients. If you wish to reduce the dose at 3 months, discuss with Haematology.

Renal impairment – no dose adjustment is necessary in patients with mild or moderate renal impairment. In patients with severe renal impairment (CG CrCl 15-29 mL/min) Apixaban is to be used with caution. We will not routinely use Apixaban if CG CrCl <30 ml/minute but in selected patients it can be considered for use if the CG CrCl is 15-30 ml/min – if you wish to use Apixaban in these circumstances, discuss with Haematology.

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 (Interactions A to Z | BNF | NICE)
The use of factor Xa inhibitors is not recommended in patients receiving concomitant systemic treatment with strong inhibitors or inducers of both CYP3A4 and P-gp and therefore may influence Rivaroxaban and Apixaban plasma concentrations to a clinically relevant degree. These treatments include azole-antimycotics (such as Ketoconazole, Itraconazole, Voriconazole and Posaconazole) or HIV protease inhibitors (such as Ritonavir). Please note that not all HIV treatments are contraindicated with anti-Xa's. Check the website *hiv-druginteractions.org* if in doubt. Rifampicin, Phenytoin, Carbamazepine, Phenobarbital or St. John's Wort, may lead to reduced Apixaban (and Rivaroxaban) plasma concentrations. We therefore recommend that these treatments should not be co-administered with factor Xa inhibitors.

For patients where the above medications are required; Apixaban (or Rivaroxaban) should not be used and it is recommended to use LMWH instead. Warfarin might be an alternative to LMWH when some (not all) the above medications are co-prescribed. Seek advice from pharmacy if needed.

When using macrolide antibiotics, such as Clarithromycin and Erythromycin, which may inhibit the metabolism of factor Xa inhibitors we recommend Apixaban over Rivaroxaban if a DOAC is co-prescribed.

Prescription

Initially one week's treatment should be prescribed, followed by a reduced dose which should complete a 3-month course in total. The GP should prescribe any medication beyond the first 4 weeks.

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 is not licenced for use in patients 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 CG CrCl is 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 CG CrCl 15-29 ml/minute and avoid if CG CrCl less than 15 ml/minute.

We will not routinely use Rivaroxaban if CG 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 (Interactions A to Z | BNF | NICE)
The use of factor Xa inhibitors is not recommended in patients receiving concomitant systemic treatment with strong inhibitors or inducers of both CYP3A4 and P-gp and therefore may influence Rivaroxaban and Apixaban plasma concentrations to a clinically relevant degree. These treatments include azole-antimycotics (such as Ketoconazole, Itraconazole, Voriconazole and Posaconazole) or HIV protease inhibitors (such as Ritonavir). Please note that not all HIV treatments are contraindicated with anti-Xa's. Check the website *hiv-druginteractions.org* if in doubt. Rifampicin, Phenytoin, Carbamazepine, Phenobarbital or St. John's Wort, may lead to reduced Rivaroxaban (and Apixaban) plasma concentrations. We therefore recommend that these treatments should not be co-administered with factor Xa inhibitors.

For patients where the above medications are required; Rivaroxaban (or Apixaban) should not be used and it is recommended to use LMWH instead. Warfarin might be an alternative to LMWH when some (not all) the above medications are co-prescribed. Seek advice from pharmacy if needed.

When using macrolide antibiotics, such as Clarithromycin and Erythromycin, which may inhibit the metabolism of factor Xa inhibitors we recommend Apixaban over Rivaroxaban if a DOAC is co-prescribed.

Prescription

Initially three weeks should be prescribed, followed by a reduced dose which should complete a 3-month course in total. The GP should prescribe any medication beyond the first 4 weeks.

10.5. Selecting an anticoagulant

In the context of mechanical heart valves, DOACs are contraindicated - seek alternative

Warfarin will be used if CrCl is <30 ml/min, or if there is liver dysfunction.

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.

The ACCP (CHEST 2016;149(2):315-352) now recommend direct oral anticoagulants over vitamin K antagonist therapy in patients with DVT of the leg or PE and no cancer as long-term (first 3 months) anticoagulant therapy (evidence grade 2B).

Differentiating anticoagulant therapy

Objective	Anticoagulant
Minimize bleeding	Apixaban
Once daily dosing	Rivaroxaban
All oral therapy	Rivaroxaban/Apixaban
CG CrCl less than 30ml/min	Warfarin
Cancer	LMWH see page 14

10.6. 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 on call medical team for consideration of admission. They should be referred if they have any of the following:

- Age >80 years
- Pulse ≥110 bpm
- Systolic BP <100 mm Hg
- O_2 Saturation <90%
- Cancer
- Chronic cardiopulmonary disease (i.e. a positive sPESI), as this indicates a higher early mortality.

10.7. Anticoagulation in high BMI and body weight patients with acute VTE

The use of DOAC to treat patients with a BMI >40 kg/m2 or >120 kg was previously not recommended due to the concern of decreased drug exposure in this group of patients given the lack of evidence. However, there is increasing data now to support the utilization of DOAC in patients with high BMI or >120 kg. In 2021, the ISTH SCC (International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation) provided updated guidance recommendations. They suggest that standard doses of Rivaroxaban or Apixaban are appropriate anticoagulant options for patients with acute VTE *regardless of high BMI and weight*. Dabigatran or Edoxaban should not be used due to lack of evidence. Treatment or prevention of VTE with DOAC in the acute setting after bariatric surgery is not supported. This ISTH guidance is followed in the Ambulatory DVT clinic and is recommended to be followed Trust wide.

10.8. 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 coronary artery, 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.

10.9. Thrombolytic therapy

Consider referral to vascular surgeons for consideration of catheter-directed thrombolytic therapy for patients with symptomatic ilio-femoral DVT who have **all** of:

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

10.10. Duration of treatment

Patients with proximal DVT 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 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 cast
- COC pill/HRT
- pregnancy/puerperium

A weaker transient risk factor 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. In this group, treatment should be continued until follow up review.

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).

10.11. Testing for thrombophilia

Do not offer routine thrombophilia testing to patients who are continuing anticoagulation treatment.

Test for antiphospholipid antibodies in patients who have had unprovoked or recurrent DVT or PE if it is planned to stop anticoagulation treatment.

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.

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 who has had an unprovoked or hormone related VTE.

Testing may be helpful to assist counselling regarding COC pill 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

10.12. Class II Compression stockings

Initial studies suggested that stockings with 40mmHg (Brandjes*, et al* 1997) or 30-40mmHg (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 30-40mmHg pressure with placebo stockings gave negative results. However compliance rates were poor in this study.
Class II compression 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.

10.13. Superficial Thrombophlebitis / Superficial Vein Thrombosis (SVT)

SVT has been considered to be a benign and self-limiting condition. However, it is now appreciated that a significant proportion of those presenting with SVT are at significant risk of development of DVT or PE (Scott et al 2015). Endovascular laser treatment of varicose veins will cause a phlebitic reaction – if the patient is within 4-6 weeks of this treatment, the policy is to refer them back to the vascular team.

The most commonly affected superficial veins are the long (great) and short saphenous veins of the leg. SVT that is adjacent to (within 3 cm of) the sapheno-femoral junction (SFJ) has such a high risk of progression to DVT (14-70%) that such patients are no longer included in interventional trials in SVT, but rather advised therapeutic anticoagulation as for DVT (Tait et al 2012)

- Patients with superficial thrombophlebitis within 3cm of the SFJ should be treated with therapeutic anticoagulation (as for DVT) for three months
- For patients with SVT more than 5cm in length but more than 3cm from the SFJ, we recommend Rivaroxaban 15mg once daily (Webster, Strong et al 2016 poster157 BSH 2016 abstract/poster 157) or intermediate dose of LMWH for six weeks (Cosmi et al 2012, Scott et al 2015). This has been shown to provide better symptomatic relief. UHL use Enoxaparin as the preferred first line LMWH. Prophylactic dose of Fondaparinux (2.5mg once daily) is an alternative (Decousus et al 2010).
- Patients with SVT less than 5cm in length and more than 3cm from the SFJ can be treated with non-steroidal anti-inflammatory drugs (NSAIDs).

10.14. Incidentally diagnosed asymptomatic DVTs

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).

10.15. 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.

10.16. Free floating thrombus

Patients with free floating thrombus (FFT) are at no higher risk for pulmonary embolus and there is data to support the safety of ambulatory therapy in clinically stable patients. Most FFT followed non-invasively by duplex scanning do not embolise but instead become attached to the vein wall or resolve. These patients are informed of the signs and symptoms of pulmonary embolus and the need for urgent review should these occur. (Parcouret et al 1997, Ramasamy et al,2005, Baldridge et al 1990)

10.17. Isolated calf DVT

As the diagnostic strategy used will identify isolated calf DVTs, we will usually be treating them as the patient has been referred with symptoms. If a first isolated calf vein DVT is identified the option is serial scanning (ACCP suggest scanning at one *and* two weeks) or treatment for three months (Kearon*, et al* 2012).

10.18. Calf muscle vein thrombus (soleal and gastrocnemius)

The natural history of isolated symptomatic thrombus involving the deep veins draining the gastrocnemius and soleus muscles in the calf is unclear, but thrombosis confined to the muscular veins appear to have a lower risk of extension than true isolated distal DVT (Sales et al 2010). Our local policy is to treat these DVTs for 6 weeks with intermediate dose LMWH (i.e. 1.5mg/kg sc once daily) or Rivaroxaban (15mg once daily).

11. Catheter Associated VTE (Cancer & non-cancer) – For background information see Appendix 1.

11.1. Recommendations

11.1.1. Prophylaxis

Despite the recently updated UK Good Practice Recommendations for Outpatient Parenteral Antimicrobial Therapy (OPAT) advising that "patients who have been assessed as being at risk of venous thrombosis as inpatients should be considered for further prophylaxis during OPAT if assessed as having ongoing risk" (Chapman et al 2019), there is currently insufficient evidence to confirm this as an effective strategy, or to guide how such ongoing risk should be assessed. There is a bleeding risk associated with prophylaxis (Cohen et al 2001), therefore we do not currently advise it for Catheter Related Thrombosis (CRT) prevention alone, although some patients may be on this for other reasons e.g. post-surgical thromboprophylaxis. Patients should be educated about the risk of CRT at the point of insertion and asked to report any pain or swelling in the arm.

11.1.2. Management of upper limb DVT (including non-catheter related)

The goal should be to achieve confirmation of the diagnosis with USS within 24hrs of symptoms being reported. Stat dose anticoagulation must be provided from first clinical suspicion of VTE (unless contraindicated) and continued until the VTE is ruled out (cease stat dosing) or confirmed (prescribe VTE treatment). D-dimer has no role in this setting. Currently, upper limb DVT USS can be achieved by:

i. Requesting the scan on NerveCentre (for in-patients) or ICE (for outpatients).
ii. Then call Ultrasound to book a slot (via UHL switchboard; Mon – Fri 9am – 4pm; or Sat – Sun 1pm - 4pm). If it is outside of these hours, or Ultrasound are unavailable, call the Medical Registrar at GPAU instead
iii. Call GPAU and request review by the registrar, handing over relevant information including the history and antimicrobial history (in view of potential drug interactions e.g. with DOACs). Inform GPAU as to whether the USS slot has been booked

Choice and prescription of anticoagulation is as for lower limb DVT and should be done by the Acute Medical team in GPAU. This is because any complications can then be followed up in a timely way, and so that latest guidelines regarding choice of anticoagulant from within Acute Medicine can be adhered to. The GPAU registrar will decide if admission is required, or the patient can be treated as an outpatient.

11.1.3. Other aspects of management:

Removal or retention of line: IDSA guidelines currently advise leaving the line in, if catheter function is preserved and arm pain and swelling decrease with anticoagulation (Norris et al 2019). This is on the basis of two uncontrolled clinical trials on the same population of cancer patients, in which patients were treated with 3 months of anticoagulation and catheter retention. Catheter function was 100% at 3 months in both studies, however time to resolution of symptoms was not reported (Kovacs et al 2007, Davies et al 2018). The decision on whether to remove or retain should therefore be on a case-by-case basis: retention is preferable, assuming line is not occluded, as intravenous treatment is then not interrupted; however if the duration of anticoagulation required would be lengthened by line retention, then it should be removed. Other relevant factors include severity of symptoms (if severe, consider removal); availability and suitability of oral options; and availability of alternative sites for venous access.

11.2. **Duration of anticoagulation:** By extrapolation from the literature on lower limb DVTs, duration for thrombi extending to the deep system should be for 3 months. This is independent of the date of line removal, i.e. if a line is retained for another 5 weeks for treatment purposes, the duration does not need to be extended by a further 5 weeks. Thrombi in the superficial system that are visualised on USS *and* causing symptoms should be treated for 6 weeks, or until the line is removed, whichever is longer (up to 3 months). If a superficial thrombus is <3 cm from the deep system, then it should be managed as a deep thrombus. Radiographers may not always report quantitatively, but they may use terminology such as the "cephalic arch", or "encroaching on the axillary vein", in which case, manage as deep. In addition, if after 6 weeks a patient with a superficial thrombus is still symptomatic, then discuss with Haematology about extending the treatment. ☞

11.3. Cautions to Anti-coagulation:

Recent peptic ulceration/GI bleeding

Recent injuries/surgery to eyes/ears/brain/spine

Endocarditis, especially if high risk of embolisation

Any other queries about individual cases can be directed to the Haematology advisory service however this guideline should suffice in most cases. Issues such as strong family history of venous thrombosis, ongoing post-thrombotic syndrome or recurrent thrombotic events would be reasons to discuss with Haematology.

12. All DVT Follow-up:

12.1. Outpatients

All outpatients with a thrombosis or superficial thrombophlebitis encroaching on the deep venous system are reviewed at the weekly multidisciplinary team meeting, where follow up urgency, pathway and further investigations are decided.

All outpatients are reviewed either by a DVT clinic nurse specialist or doctor. Those who may require long-term anticoagulation will be reviewed by a doctor at three months, to decide whether to stop or whether to continue indefinitely. If anticoagulation is ceased, consider reinstating any medications which were paused for the duration of anticoagulation.

If it is decided to continue anticoagulation therapy beyond 3-6 months of treatment, Apixaban 2.5 mg bd or Rivaroxaban 10mg od can be considered as treatment options for secondary prophylaxis.

Patients who have had a DVT will be offered a routine follow up in a Nurse-led Clinic, or for those with unprovoked DVTs in a Consultant-led Clinic.

12.2. In-patients

A 3 month follow up will be referred to the Haematology clinic via the Trust VTE Root Cause Analysis process. If anticoagulation is ceased, consider reinstating any medications which were paused for the duration of anticoagulation.

3 months treatment then generally stop	3 months treatment then consider long term
1st proximal DVT with transient risk factor*	Recurrent thrombosis
1st isolated calf vein DVT	1st unprovoked proximal DVT

*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 review at three months.

Patients with unprovoked proximal DVT or PE are at a higher risk of recurrence than those with a transient precipitating factor (Lorio*, 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 µg/l Fibrinogen Equivalent Units) after completing anticoagulation. See table below.

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**

D-dimer Result >500µg/l FEU	+ve 1 year	+ve 5 year	not done 1 year	not done 5 year	-ve 1 year	-ve 5 year
Male	15%	50-60%	10%	35-40%	5%	20-25%
Female	7.5%	30-35%	5%	20-25%	2.5%	10-15%

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).

13. Education and training

All Outpatient clinic DVT staff are trained in the acute ambulatory clinic and attend educational meetings e.g., CLOT conference, DAWN user group, British Society of Haematology, International Society of thrombosis and Haemostasis.

In-patient training for catheter related thrombosis is available from the Outpatient Parenteral Antimicrobial Therapy (OPAT) team where required.

14. Monitoring and Audit Criteria

All DVT's are followed up in either the DVT or Haematology clinics where treatment pathways can be monitored.

15. Appendix 1 Background information re: Catheter Associated VTE

Upper limb catheter related thrombosis (CRT) is defined, for the purposes of this guideline, as a symptomatic thrombosis (i.e. arm pain or tenderness +/- swelling) that is confirmed by imaging in either a superficial or deep vein of the upper arm in association with a venous catheter. This is distinct from the other, more common phenomenon of line occlusion, which can result from fibrin deposition, but does not always generate a symptomatic thrombosis in the vein.

The majority of CRTs probably arise from thrombophlebitis, which in most cases is probably mechanical, i.e. direct irritation from the line. In many cases the preceding phlebitis will be evident clinically, but not always, especially if the line was sited directly into a deep vein, e.g. the brachial. As shown below, in the upper arm the superficial system includes the basilic and cephalic veins, including the cephalic arch (the proximal section of the cephalic vein, sometimes referred to on imaging reports), with the deep system then comprising the brachial, axillary and subclavian veins. In the forearm, the deep veins are the ulnar, radial and interosseous veins.

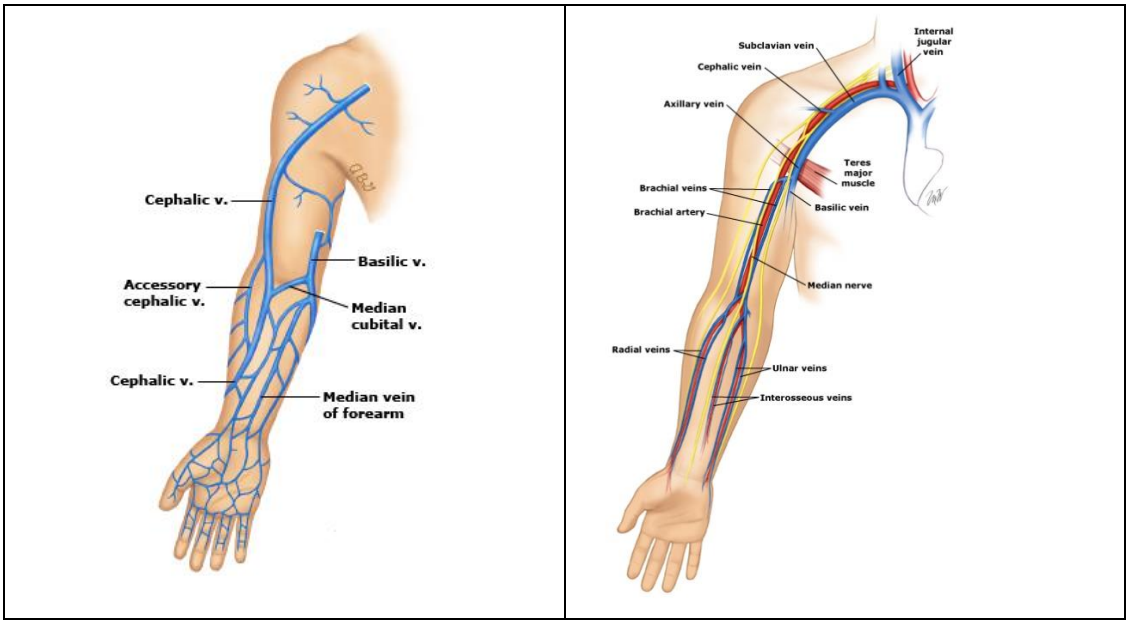


Figure. Anterior view of the veins of the upper limb. Left panel: superficial system; right panel: deep system.

CRTs are uncommon, occurring in only 2.5% of patient episodes in 2018 and 2019 in the UHL Outpatient Parenteral Antimicrobial Therapy (OPAT) service. In the context of timely and appropriate anticoagulation, complication rates are also negligible, with no PEs or limb-related complications having occurred in our cohort or others published in the literature (Matthews et al 2007, Barr et al 2012, Underwood et al 2019, Nabin et al 2016). Nonetheless, CRTs can result in significant pain and swelling in the arm, leading to emergency hospital attendance and, in some cases, interruption of the treatment for which the venous device was inserted.

There is a paucity of literature with regards to CRT, and existing national guidelines on DVT currently do not cover the upper limb (NICE NG158). The recommendations below were therefore drawn up on the basis of the available evidence (Matthews et al 2007, Barr et al 2012, Underwood et al 2019, Nabin et al 2016). National Good Clinical Practice Recommendations for OPAT (Chapman et al 2019), and the Infectious Diseases Society of America (IDSA) OPAT guidelines (Norris et al 2019), as well as expert opinion from colleagues. The latter came from both within the Trust (Renal, Nutrition and Cystic Fibrosis services) and without (other OPAT services in the Midlands). Recommendations are made regarding both prophylaxis and management of CRTs. As with other forms of symptomatic thrombosis (e.g. lower limb DVTs), individual patient factors (e.g. those with significant risk factors for bleeding) may require a deviation from guidelines by virtue of on call Haematology advice.

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