MANAGEMENT OF VENOUS THROMBOEMBOLISM

DVTs are important not to miss:

- 50% of those with an undiagnosed DVT will develop a PE.
- Mortality from PE is 10–45%.
- 30–50% of undiagnosed PEs recur, carrying with them a high risk of death.

When to consider PE?

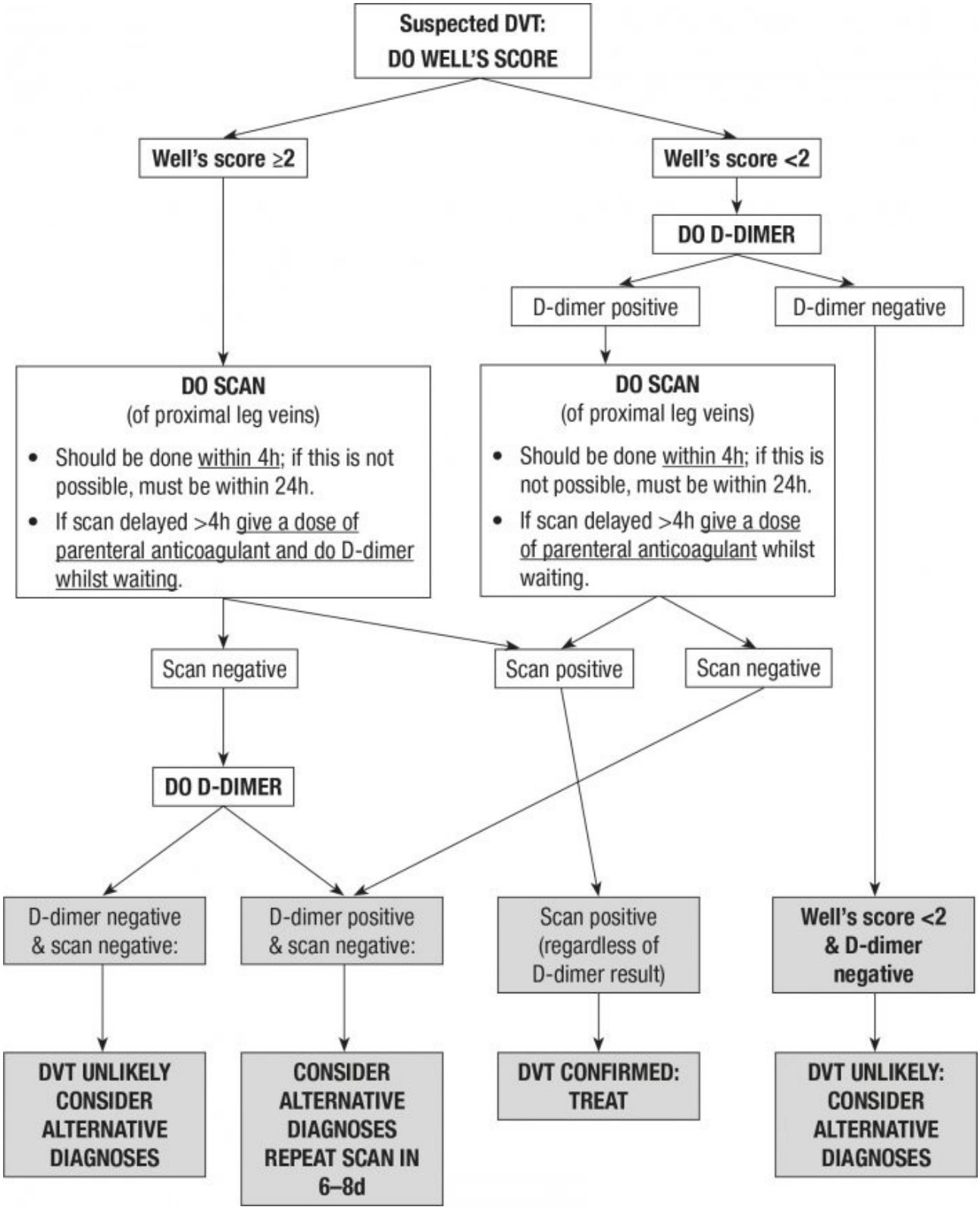
- Dyspnoea, pleuritic chest pain and haemoptysis (the classical triad, but occurs in <10%).
- Any chest symptoms in patient with clinical features of DVT.
- Dyspnoea or chest pain and a major risk factor for PE
- Unexplained dyspnoea or unexplained chest pain or mild haemoptysis even if they have no risk factors for PE.

Important points to remember with PE
40% have no major risk factors.
Only 15% have clinical signs of a DVT.
Pain on palpation doesn't rule out a PE!

For DVTs if D-dimer is negative very good at ruling out a DVT (negative predictive value of 97%) but it has a low specificity of 47%..

Well's DVT score (does NOT apply to children (under 18y) or pregnant women)		
Risk factor	**Score**	**Interpretation**
Cancer (on treatment or treatment <6m ago or palliative)	+1	>=2 then DVT likely <2 DVT is unlikely
Previous DVT/PE	+1	
Major surgery in last 12w or bed-ridden for more than 3d	+1	
Immobilisation (plaster), paralysis, paresis	+1	
Localised tenderness along deep venous system	+1	
Entire leg swollen	+1	
Calf diameter 3cm > than other leg	+1	
Pitting oedema confined to symptomatic leg	+1	
Collateral superficial veins (not longstanding varicose veins)	+1	
Alternative diagnosis as likely or more likely than DVT (such s cellulitis/lymphoedema)	-2	

With a low Well's score and negative D-dimer the was still a risk of a DVT of 1.2% which increased to 2.1% if they had a cancer diagnosis – suggesting in cancer patients it may be worthwhile sending for scan even if low Well's score and negative D-dimer


Suspected DVT:
DO WELL'S SCORE
Well's score ≥2
Well's score <2
DO D-DIMER
D-dimer positive
D-dimer negative
DO SCAN
(of proximal leg veins)
• Should be done within 4h; if this is not possible, must be within 24h.
• If scan delayed >4h give a dose of parenteral anticoagulant and do D-dimer whilst waiting.
DO SCAN
(of proximal leg veins)
• Should be done within 4h; if this is not possible, must be within 24h.
• If scan delayed >4h give a dose of parenteral anticoagulant whilst waiting.
Scan negative
Scan positive
Scan negative
DO D-DIMER
D-dimer negative & scan negative:
D-dimer positive & scan negative:
Scan positive (regardless of D-dimer result)
Well's score <2 & D-dimer negative
DVT UNLIKELY CONSIDER ALTERNATIVE DIAGNOSES
CONSIDER ALTERNATIVE DIAGNOSES REPEAT SCAN IN 6–8d
DVT CONFIRMED: TREAT
DVT UNLIKELY: CONSIDER ALTERNATIVE DIAGNOSES

Well's PE score		
Risk factor	**Score**	**Interpretation**
Haemoptysis	1	>4: PE likely ≤4: PE unlikely
Cancer (on treatment or treatment <6m ago or palliative)	1	
Previous DVT/PE	1.5	
Recent surgery (4w)/immobilisation (>3d)	1.5	
Heart rate >100bpm	1.5	
Clinical signs of DVT (minimum of leg swelling and pain on palpation of deep veins)	3	
Alternative diagnosis less likely than PE	3	

In general practice if SUSPECT a PE then admit

Treatment of DVT

Treatment may be with warfarin/NOAC or with low molecular weight heparin/fondaparinux.

- NOAC
  - Rivaroxaban : dose is 15mg twice daily for 21d then 20mg once daily. Similar in efficacy to warfarin
  - Apixaban : 10mg twice daily for 7d then 5mg twice daily. For prevention of recurrent VTE, in those who have had at least 6m treatment for VTE, the dose is 2.5mg twice daily
  - Dabigatran and edoxaban are also approved by NICE for treating VTE but require 5d of parenteral anticoagulation first
- Low molecular weight heparin
  Treatment with low molecular weight heparin (LMWH) (e.g. dalteparin, enoxaparin) or fondaparinux (injectable synthetic drug which inhibits activated factor X) with subsequent conversion to warfarin or a NOAC. LMWH and fondaparinux do not require monitoring unless eGFR <30
  - If renal impairment (eGFR <30) offer unfractionated heparin adjusted according to APTT or use LMWH but adjust dose according to anti-Xa assay.
  - Continue heparin/LMWH for at least 5 days. Can be discontinued when INR >2 for at least 24h (provided have had 5d worth of heparin/LMWH) or as soon as INR is above 2 for >24h once 5d of LMWH have elapsed.
  - In those with a PE/DVT and active cancer offer LMWH for 6 months and then reassess risks/benefits.
  - Remember that heparins are of animal origin and may be unacceptable to some patients on religious grounds – offer a synthetic alternative (e.g. fondaparinux).

Treatment length will be advised by specialist (typically 3months)

- 3m of warfarin/NOAC for most
- If unprovoked PE, assess risks and benefits at 3m: treatment may be continued longer term.
- If unprovoked DVT with high risk of recurrence and no special bleeding risk consider longer term treatment after 3m.
- Compression stockings are advised to be worn for 2 years by NICE to prevent post thrombotic syndrome [but a study in USA and Canada did not show compression stocking reduces the incidence of post thrombotic syndrome]: Use European Class 2 or British Class 3 if prescribed and change every 6 months

If unprovoked DVT or PE rule out an underlying cancer:

- Physical examination as guided by the history
- Chest X-ray
- Bloods (FBC, calcium, LFTs)
- urinalysis

  Consider abdo-pelvic CT (and mammogram for women) if over age >40

Consider thrombophilia testing

- If unprovoked DVT/PE: consider testing for antiphospholipid antibodies
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- If unprovoked DVT/PE and a first degree relative with a DVT/PE: consider thrombophilia testing. Unless:
  - Those with a provoked DVT/PE.
  - Those with a first degree relative with a DVT/PE but who themselves have never had a DVT/PE.
  - Those who are going to continue long-term anticoagulation.

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
Action	Prevents clot formation by inhibiting thrombin activity	Direct factor Xa inhibitor, (factor Xa is central to the coagulation cascade)	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Preparation	Oral tablet 110mg & 150mg **NB Can NOT be added to dosette boxes**	Oral tablet 10mg & 20mg Take with main meal of day (because most consistent calorie load, and this affects absorption)	Oral tablet 2.5mg	Oral tablet 15mg, 30mg and 60mg
Compliance & half-life	Short half-life, so rapid drop in effect if poorly compliant (see section on NOACs: the evidence, later, for a discussion of the implications of this)			
Dose in AF	Two strengths (110 and 150mg), both given **twice daily:** <75y: 150mg ≥80y: 110mg 75–80y: clinician's discretion as to whether 110 or 150mg used If on verapamil, give lower dose (110mg twice daily)	20mg **once daily** Reduced dose if eGFR <50, see below	5mg **twice daily** Reduced dose if eGFR <30, see below If at least 2 of the following, reduce dose to 2.5mg twice daily: ≥80y, ≤60kg, or Cr ≥133	60mg **once daily** Reduce dose to 30mg once daily if: eGFR 15–50 ≤60kg On erythromycin, ketoconazole, dronedarone or ciclosporin
Dose for VTE prevention post surgery	220mg once daily for: 10d post knee surgery 4–5w post hip surgery	10 mg once daily for: 2w post knee surgery 5w post hip surgery	2.5mg twice daily for: 10–14d post knee surgery 32–38d post hip surgery	Currently not licensed for this indication
Dose for VTE treatment	150mg twice daily but only after at least 5d of parenteral anticoagulant	15mg twice daily for 21d then 20mg daily	10mg twice daily for 7d then 5mg twice daily	60mg once daily following at least 5d of parental anticoagulation (30mg daily if criteria above met)
Converting to NOAC from warfarin in AF (from SPC)	Stop warfarin Start dabigatran as soon as INR is <2.0	Stop warfarin Start rivaroxaban when INR ≤3.0 NB: INR may be falsely elevated especially soon after dosing, so check INR just before taking the NOAC (trough level)	Stop warfarin Start apixaban when INR <2.0 NB: INR may be falsely elevated especially soon after dosing, so check INR just before taking the NOAC (trough level)	Stop warfarin Start edoxaban when INR ≤2.5 N.B. INR may be falsely elevated especially soon after dosing, so check INR just before taking the NOAC (trough level)

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
Switching to warfarin from NOAC	Start warfarin Stop NOAC when INR≥2 (For rivaroxaban and apixaban measure trough levels just before taking NOAC as there may be some interference with INR and then check again 24h after last dose of NOAC to ensure INR still (truly) therapeutic)			Complicated as risk of inadequate anticoagulation! See SPC for details.
Before surgery	Take advice! The exact management depends on: • Bleeding risk associated with procedure (surgeon's responsibility) • Risk of stroke/thrombosis (our responsibility, so make clear in your referral letter why they are on it and level of risk, e.g. CHA_2DS_2Vasc score in AF) • Renal function (can take up to 5d to clear in renal impairment) For lower risk procedures may need to stop 1–2d beforehand, in higher risk procedures 3–4d beforehand and significantly longer in those with renal impairment. Interestingly a trial of 1800 people on warfarin for AF randomised them to conversion to LMWH before surgery or no bridging therapy (NEJM 2015;373:823). There was no difference in adverse thrombotic outcomes between the 2 groups, and more significant bleeding events in those given LMWH (3.2% vs. 1.3%). This was a non-inferiority trial, so more data are needed but this may changes the way things are done in the future!			
Reversal	Antidote for rapid reversal available (idarucizumab) (see later)	Antidote for rapid reversal in development but not yet available. In the absence of an antidote, if rapid reversal needed (e.g. for emergency surgery, catastrophic bleeding), in specialist centres certain specialist blood products may be given.		
Diet	No dietary restrictions are required			
Costs for AF	£920/y (DTB)	£720/y (NICE)	£803/y (NICE)	£730/y (NICE)
	Warfarin costs around £426/y which includes all NHS costs such as drug, phlebotomy and lab time, but not patient costs (DTB)			
Costs for VTE treatment	In the treatment of VTE, NICE have concluded that rivaroxaban is more cost-effective than heparin-related drugs, followed by warfarin			
Monitoring	**No monitoring of coagulation needed, however, data are emerging suggesting that the original trials showed that monitoring might improve the benefit/risk profile in some patients, but this information was not made available to the licensing authorities (BMJ 2014;349:g4681)** Check eGFR before starting then annually if: ≥75y, weight <50kg or eGFR 30–50	**No monitoring of coagulation needed**	**No monitoring of coagulation needed**	**No monitoring of anticoagulation needed**

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
Renal/liver disease (from BNF/ SPC)	**Renal:** Avoid if eGFR <30 If eGFR 30–50: use usual dose UNLESS high risk of bleeding, in which case consider using 110mg twice daily In surgical VTE prophylaxis: limited experience – use with caution; if used dose is 150mg ONCE daily **Liver:** Avoid in severe disease and definitely if any coagulopathy	**Renal:** If eGFR 15–50: reduce dose to 15mg once daily If eGFR <15: do not use **Liver:** May be used in moderate hepatic impairment as long as no coagulopathy	**Renal:** If eGFR 15–30: reduce dose to 2.5mg twice daily If eGFR <15: do not use **Liver:** Avoid in severe liver impairment or if any coagulopathy	**Renal:** If eGFR 15–50: reduce dose to 30mg once daily If eGFR <15: do not use **Liver:** May be used in mild to moderate liver disease Do NOT use in severe liver disease or if any coagulopathy
Common side-effects (see BNF for details)	Nausea, diarrhoea, dyspepsia and abdominal pain are common side-effects Anaemia/bleeding are obviously recognised side-effects	Nausea and abnormal LFTs are common Anaemia/bleeding are obviously recognised side-effects	Nausea Anaemia/bleeding are obviously recognised side-effects	Nausea and abnormal LFTs (including raised bilirubin and GGT) are common Anaemia/bleeding are obviously recognised side-effects
Interactions	Many (but fewer than warfarin!) Check with the BNF before prescribing and seek advice if needed! Do not use with NSAIDs (because of increased bleeding risk)			

References: DTB 2011;49(10):114; NICE 2012, TA249 (dabigatran), TA256 (rivaroxaban); NICE 2015, TA354 and TA355 (edoxaban); SPC for each drug accessed 14 Jan 2015 (22 Dec 2015 for edoxaban); Lancet 2015;386:303.

No clear evidence of one NOAC being better (or worse) than another.

Easy to use and fewer food/drug interactions than warfarin.

Shorter half-life: missing a single dose matters and poor compliers will have very erratic anticoagulation effects.

Dabigatran has an antidote [antidotes for other NOACs in development]

Caution in renal impairment.

Lower all-cause mortality than warfarin and at least as good as warfarin at preventing strokes in AF.

Overall bleeding risks similar to warfarin, with fewer intracranial bleeds and more GI bleeds than warfarin. However, ‘real world’ trials suggest warfarin may be safer in older people (from around age 76y).

Travel advice

From Medical Guidelines for Airline Travel, 2nd edition (2003). This applies to all travellers, not just those who are flying!

	Risks	Advice
Low risk	>40y Obesity Active inflammatory condition Minor surgery in last 3d	Advice about mobilisation, hydration +/− flight socks
Medium risk	On oestrogens (including HRT and the COCP) Pregnancy/post-natal period (unclear how long after delivery) Varicose veins Heart failure (unless well-controlled) MI in last 6w Lower limb paralysis Lower limb trauma (last 6w) Polycythaemia	As above + consider aspirin +/− graduated compression hosiery
High risk	Previous VTE Family history of VTE Known thrombophilia Major surgery in last 6w Previous CVA Malignancy	As above, but consider low molecular weight heparin instead of aspirin

Pregnancy and VTE

Many antenatal VTE events occur in the first trimester so, if thromboprophylaxis is required, this should start early in pregnancy. The highest risk for VTE is during the post-partum period.

During the booking visit they will assess VTE risk but it may be necessary to start prophylaxis before the booking visit so the following points should be considered. Following advice taken from RCOG 2015 guidelines.

Obstetric thromboprophylaxis risk assessment and management		
Degree of Risk	Indication	Action to take
High risk	Any previous VTE except a single event related to major surgery	Requires antenatal prophylaxis with LMWH Refer to trust-nominated thrombosis in pregnancy expert/team
Intermediate risk	• Hospital admission • Single previous VTE related to major surgery • High-risk thrombophilia + no VTE • Medical comorbidities e.g. cancer, heart failure, • active SLE, IBD or inflammatory polyarthropathy, • nephrotic syndrome, type I DM with • nephropathy, sickle cell disease, current IVDU • Any surgical procedure e.g. appendicectomy • OHSS (first trimester only)	Consider antenatal prophylaxis with LMWH

How to assess risk in antenatal period:	
Risk Factors	**Action to take**
• Obesity (BMI > 30 kg/m2) • Age > 35 • Parity ≥ 3 • Smoker • Gross varicose veins • Current pre-eclampsia • Immobility, e.g. paraplegia, PGP • Family history of unprovoked or oestrogen-provoked VTE in first-degree relative • Low-risk thrombophilia • Multiple pregnancy • IVF/ART Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel	Four or more risk factors: prophylaxis from first trimester Three risk factors: prophylaxis from 28 weeks LOWER RISK Mobilisation and avoidance of dehydration