Deep vein thrombosis

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Abstract

This article considers the epidemiology, aetiology, pathology, investigation and management of deep vein thrombosis in the lower limb, in the light of the 2012 NICE guidelines (updated 2015). It does not consider venous thromboprophylaxis or venous thromboembolism within the upper limb.

Keywords Anticoagulation; deep vein thrombosis; DVT; heparin; venous thromboembolism

Definition

Deep venous thrombosis (DVT), the formation of a blood clot within a deep vein, forms part of the spectrum of venous thromboembolic disease, which also includes pulmonary embolus (PE). DVT commonly occurs in the deep veins of the lower leg or the proximal veins of the ilio-femoral segment, which forms the focus of this article. In approximately 10% of patients, DVT may also occur in upper limb veins including the subclavian vein, visceral veins or the vena cava. DVT in these regions is not reviewed in this article.

Epidemiology

Whole population studies indicate a weighted mean incidence of DVT of approximately 5 per 10,000 person years, with a similar incidence in men and women. DVT occurs more commonly in older people, with an incidence of 2–3 per 10,000 people aged 30–49 years rising to 20 per 10,000 in the 70–79 year age group.[1] Venous thromboembolism carries significant risk of mortality at 30 days without treatment, of 3% for DVT and 31% for PE.[2]

Deep vein thrombosis is much more common within the hospital population, due to a combination of factors that are discussed in more detail below. It is estimated that there are 25,000 deaths per year in the UK from venous thromboembolism (including pulmonary embolus) and without prophylaxis, DVT occurs in 25% of hospital patients.

Aetiology

There are several well-recognized risk factors for DVT and there is now increasing appreciation that many of these risk factors act cumulatively to result in an event.

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Pregnancy

Pregnancy increases the risk of DVT due to a combination of immobility, compression of the inferior vena cava (IVC) and iliac veins and hormonal effects. The increase in risk starts in the first trimester and is approximately 0.13%.[3]

Hospital patients

Hospital inpatients are known to be at increased risk from deep vein thrombosis and certain subgroups are at higher risk. It has long been recognized that surgical patients are at risk, but in addition, deep vein thrombosis occurs in 25% of medical patients without prophylaxis. This risk is higher in stroke patients (up to 50%) and those with acute coronary syndrome (20%).[4]

The risk of deep vein thrombosis in postoperative patients is estimated to be 25% without prophylaxis; however, this data is based on studies from the 1970s. Hospital episode statistics indicate <1% postoperative patients currently suffer a DVT although this is likely to be an underestimate. Studies from the USA indicate a perioperative incidence of 2–3%. The risk is higher in patients undergoing orthopaedic surgery (40–60% without thromboprophylaxis).[4]

Malignancy

Malignancy is a risk factor for deep vein thrombosis. Trousseau originally described migratory thrombophlebitis associated with pancreatic cancer. The risk of DVT depends on the type of cancer: ovarian, uterus, brain, pancreas cancer and leukaemias consistently associated with at least a doubling of the risk of DVT.[5] The pathophysiology for this is multifactorial, with some malignancies exerting a direct hormonal effect, in addition to the risks associated with surgical treatment, chemotherapy and immobility.

Obesity

Obese patients are at increased risk of deep vein thrombosis, due to immobility. Venous return from calf veins is activated by the calf muscle pump and in immobile patients this is ineffective, resulting in venous stasis and an increased risk of thrombosis. A Body Mass Index (BMI) over 30 is estimated to double the risk of DVT.[4]

Oral contraceptive pill (OCP)

There is evidence that oestrogen-containing contraceptives increase the risk of deep vein thrombosis, by approximately doubling the risk. The risk remains small as these are generally young fit patients, but may be important in those with additional risk factors, particularly obesity.[4]

Thrombophilia

Inherited prothrombotic tendencies can be identified in up to 50% of patients presenting with venous thrombosis. These may occur due to genetic mutations resulting in either loss of function (deficiencies) of antithrombin III, protein C or protein S, or gain in function, owing to mutation, for instance, of factor V Leiden or prothrombin 20210A, and vary in how much they increase risk of VTE. Factor V Leiden is present in 5% of the population. Heterozygotes for factor V Leiden are at three times the risk of DVT, and homozygotes at 50–80 times higher risk, compared with the normal population.

High levels of coagulation factors (such as factors VIII, IX and XI) and hyperhomocysteinaemia have also been implicated in DVT. They may be important in the additive risk concept (for example: a young woman with undiagnosed thrombophilia, on oral contraception, undertaking a long haul flight).

Personal history of previous VTE

Previous DVT increases risk of subsequent DVT by approximately five times.[4]

Varicose veins

There is no evidence that uncomplicated varicose veins increase risk of DVT. There is a risk of developing deep vein thrombosis with ascending thrombophlebitis and consideration should be given to thromboprophylaxis in these patients.

Long-haul flights

In the general (non-hospitalized) population long-haul flights are perceived to be a risk factor for DVT. However, the evidence for this is surprisingly weak. The hypothesis is that a combination of immobility and dehydration predispose to DVT. A review of the evidence in 2004 found a reported incidence of 0–0.28% incidence of *symptomatic* DVT (based on two studies), and wide variation (0–10%) in the incidence of *asymptomatic* DVT following long-haul flights. Case-control studies indicate a small (non-statistically significant) increase in relative risk following a long-haul flight, which may be more important in those patients at higher risk of DVT. The population undertaking long haul flights tends to be younger and fitter than the general population so the absolute risk may remain small.

Estimating individual risk

Estimating an individual's risk of DVT is complicated because risk factors cannot simply be multiplied, as they are likely to be interdependent. The recent NICE guideline suggested that new cohort studies need to be performed to allow development of multivariate risk models to predict this more accurately in hospital patients.[4]

Pathology

In 1858, Virchow described the triad of conditions predisposing to deep vein thrombosis:

ENDOTHELIAL DAMAGE + STASIS + HYPERCOAGUABILITY

The risk factors described above interact via these mechanisms to result in DVT.

Abnormalities of the vessel wall

Endothelial cells normally produce tissue plasminogen activator and plasminogen activator inhibitor-1. The balance of these factors in conjunction with prostacyclin, nitric oxide and cell surface glycosaminoglycans serves to protect against the formation and propagation of thrombosis (local fibrinolysis). Direct or indirect trauma to the endothelial wall exposes the collagen-rich thrombogenic basement membrane of the vein, and can induce thrombosis by upsetting this balance and causing platelet activation. Trauma and major surgery increase levels of plasminogen activator inhibitor-1 over the first 7–10 days, resulting in deficiency of local fibrinolysis. Surgery and trauma also cause the release of tissue factor (TF) from extravascular tissue and adventitia. TF binds to factor VIIa to activate the clotting cascade and may exert effects at remote sites, causing DVT.

Abnormalities of the constituents of blood

An increase in any of the constituents of blood, for instance red blood cells (polycythaemia) or platelets (thrombocythaemia), can increase viscosity and decrease blood flow within vessels. Alternatively there may be abnormalities in the coagulation cascade or fibrinolytic systems, which interact to maintain blood flow at sites of vascular injury. The main cause of thrombosis in this context is hypercoagulability, which may be due to inherited or acquired thrombophilic defects.

Changes in the dynamics of blood flow (stasis)

Venous return relies on effective contraction of the calf muscle pump in addition to the presence of competent valves within patent veins. Immobility due, for instance, to prolonged bed rest, paralysis or long periods of air travel leads to reduced or stagnant flow within the deep veins which, in combination with other risk factors described above, may lead to thrombus formation in vein valve pockets. Other conditions contributing to stasis include extrinsic venous compression, for example, resulting from pelvic tumours or the gravid uterus. Low haemodynamic flow rates predisposing to DVT may also occur in conditions such as hypotension and congestive heart failure. The risk factors described above have an additive effect in terms of risk for DVT if other risk factors are present.

Presentation

The clinical presentation of lower limb DVT can vary from an incidental finding in an asymptomatic patient, to extensive iliofemoral thrombosis causing a pale, swollen painful leg (phlegmasia alba dolens). When thrombus extends into the venules and capillaries, causing secondary acute arterial insufficiency, the leg becomes cyanosed (phlegmasia caerulea dolens). Venous gangrene occurs in up to 50% of these cases (Figure 1).

Clinical features

Classical features of a calf DVT are:

- calf pain and tenderness
- pyrexia
- persistent tachycardia.

Unilateral pitting oedema is an important sign as it indicates thrombosis in 70% of patients (Figure 2).

Differential diagnosis

Differential diagnoses include:

- cellulitis
- bleeding in a calf muscle in a patient on anticoagulation
- torn calf muscle
- ruptured Baker's cyst.

Probability scores

Clinical diagnosis of deep vein thrombosis is notoriously unreliable and therefore clinical probability scores have been developed to guide further investigation and treatment. The most

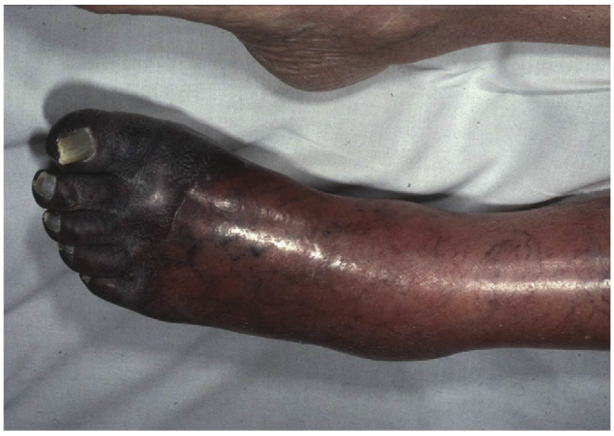

Figure 1 Venous gangrene affecting the foot of a patient with extensive iliofemoral deep venous thrombosis.

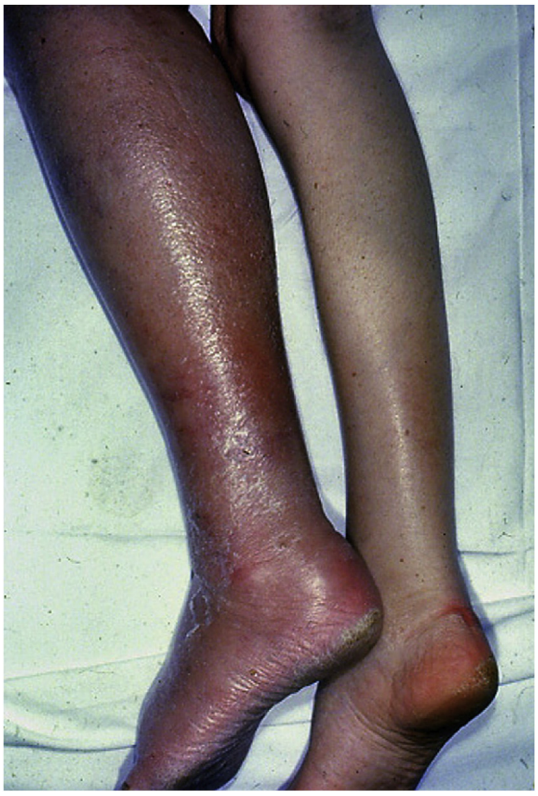

Figure 2 Tender, warm swollen left calf in a patient with a lower limb deep venous thrombosis.

widely used is the Wells' score (which assigns an individual to one of three risk groups) or the modified Wells' score (which uses two risk groups), see Table 1. The sensitivity of the Wells' score is reasonable for DVT (77%–98%) although specificity was less good (37–58%). Sensitivity was higher (96%) and specificity lower (26%) in people with underlying malignancy.[6] The Wells' score does have a high negative predictive value of 99.75% in patients with low probability scores and is a good predictor to exclude DVT. This falls to 82% in high risk patients though.[7]

Investigations

D-Dimers

D-Dimer assays are increasingly being used in out-patient diagnosis of DVT. D-Dimers are fibrin degradation products produced during the immediate fibrinolytic response to thrombus formation, and so plasma levels are raised in the presence of thrombus. Levels can, however, also be raised in infection, inflammation, pregnancy, or malignancy, disseminated intravascular coagulopathy, trauma and in the immediate postoperative period.

Negative D-dimer results, in combination with a low probability score, are increasingly being used to exclude the diagnosis of DVT, particularly in outpatients. However, D-dimer assays are best employed in conjunction with other tests in screening for DVT.

Sensitivity also varies according to the assay method (e.g. enzyme-linked immunosorbent assay [ELISA], whole blood agglutination, latex assay), with ELISA being the most sensitive (94%). Specificity is also variable and poor with whole blood agglutination being the most specific (68%).[6]

Ultrasound

B-Mode ultrasound imaging provides the mainstay of investigation for DVT as it is widely available, non-invasive and relatively inexpensive. Thrombus within a vein appears as echogenic material and the vein becomes less compressible.

Duplex ultrasound scanning involves a combination of B-mode imaging with pulsed Doppler and therefore provides information on blood velocity. Areas of 'no flow' due to thrombus show up as black against the colour flow. The technique has high specificity (94%) and sensitivity (90%) for the detection of proximal symptomatic DVT.[6]

Two-level DVT Wells' score

Clinical feature	Points
Active cancer (treatment on-going, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	−2
Clinical probability simplified score	
DVT 'likely'	2 points or more
DVT 'unlikely'	1 point or less

Table 1

Detection of calf vein DVT is more difficult and duplex sensitivity for this is lower (63%).[6] There are two strategies adopted in this instance:

1. Duplex scan of the femoro-popliteal segment, if negative repeat a week later in selected patients.
2. Scan the whole leg.

A recent study concluded that an above-knee ultrasound with a repeat scan, if required, was more cost-effective than a single full leg ultrasound. The clinical significance of isolated calf vein thrombosis is still debated and guidelines do not recommend treatment but a strategy of re-imaging.[8] However, 20% of calf DVTs may propagate with risk of causing pulmonary embolus.

Demonstration of thrombus within the iliac veins may be difficult in the presence of overlying bowel gas.

Current NICE guidelines suggest that with for patients with a high probability Wells' score a duplex ultrasound should be done within 4 hours. If the scan is negative, D-dimers should be checked. Alternatively, D-dimers should be checked and the patient started on anticoagulation and a duplex ultrasound performed within 24 hours. If in either case there is a negative scan and positive D-dimers, the scan should be repeated 1 week later.

With a low probability Wells' score and negative D-dimers, no imaging is required. If the D-dimers are positive they should be investigated as if for a high probability score.

Magnetic resonance venography (MRV)

MRV is increasingly being used to investigate iliac vein thrombosis and is particularly useful during pregnancy. It is non-invasive and a useful confirmatory test, but is expensive, with limited availability.

Computed tomography (CT)

Contrast-enhanced spiral CT venography and CT pulmonary angiography has replaced isotope ventilation/perfusion scans as a first-line investigation for PE. The technique is useful in the diagnosis of central venous occlusion, can be undertaken quickly, and is increasingly being used in peripheral venous thrombosis. CTV/MRV may be occasionally be useful for isolated iliac vein thrombosis that can be missed on duplex ultrasound.

Ascending venography

Ascending venography is invasive, requiring venous contrast injection into a vein on the dorsum of the foot. High-resolution films can be obtained, in which a DVT appears as a venous filling defect. However, the risk of contrast reaction, extravasation and the invasive nature of the procedure means that this technique has been superseded by duplex ultrasound as the primary imaging procedure of choice.

Impedance plethysmography

Impedance plethysmography is rarely used except in population studies of patients at increased risk of DVT. Isotope-labelled fibrinogen imaging can demonstrate calf vein thromboses but is unreliable in demonstrating more proximal thrombosis and is no longer routinely employed in the clinical setting.

Management

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are naturally occurring porcine derived products which inhibit blood coagulation. They potentiate the inhibition of several activated coagulation factors, including thrombin and factor Xa, by antithrombin. Fondaparinux is a synthetic pentasaccharide and acts indirectly, via antithrombin, to selectively inhibit activated factor X (Xa). UFH is given as an infusion and requires monitoring of APPT (activated partial thromboplastin time) whereas LMWH and fondaparinux can be given (or self-administered) as a once daily subcutaneous injection allowing outpatient treatment.

There have been a number of randomized controlled trials comparing UFH with LMWH for the treatment of deep vein thrombosis (6000 patients); from these it is unclear whether LMWH confers any clinical benefit, but it is cheaper. There are no placebocontrolled trials.[6] A randomized controlled trial comparing fondaparinux with LMWH for the treatment of deep vein thrombosis involved study of 2000 patients, suggesting a possible increased risk of fatal bleeding with fondaparinux and no difference in the incidence of recurrent thromboembolic events. There is one randomized controlled trial comparing fondaparinux with UFH (2000 patients), which showed a possible increase in all-cause mortality with fondaparinux and a possible reduction in thromboembolic events.[6]

There have been no formal economic analyses of fondaparinux in comparison to LMWH or UFH but it is more expensive on simple analysis of drug costs.

NICE guidelines (2012) recommend LMWH or fondaparinux for the initial treatment of DVT. LMWH is of porcine origin so fondaparinux may be more acceptable to some patients. UFH should be considered in patients with increased risk of bleeding (since it is more easily reversible) and also in patients with chronic kidney disease (eGFR <30 ml/min/1.72 m^2).

A vitamin K antagonist should be started and these initial regimes should be continued for 5 days or until the INR (international normalized ratio) is >2 for more than 24 hours (whichever is longer). NICE now recommend the novel anticoagulants apixaban, dabigatran, edoxaban and rivaroxaban as options for anticoagulation for the treatment of DVT and in secondary prevention.[9–12]

Duration of anticoagulation

NICE guidelines recommend a 3-month course of anticoagulation for a provoked venous thromboembolic event. Following completion of treatment, NICE recommends discussion with the patient regarding risks and benefits of ongoing treatment. The risk of recurrence following a first venous thromboembolic event is 7–8%, although this is higher for an unprovoked event (9–15%). Following a second event, risk of further recurrence increases to 3–19%. Despite this there is only weak evidence that anticoagulation for 6 months is better than 3 months for provoked DVT or unprovoked/recurrent DVT, and this may increase the risk of bleeding.[6] It is recommended that the risks of bleeding compared to recurrent DVT are assessed on an individual basis with the patient when considering anticoagulation beyond 3 months. In the case of unprovoked PE the individual risk should be assessed and consideration given to longer treatment.

Sixteen studies have compared LMWH with warfarin for the treatment of DVT. There is a possible reduction in recurrent VTE with LMWH, particularly in patients with underlying

malignancy. It is unclear which is safer from the bleeding point of view. The cost-effectiveness remains unclear; two different models reached different conclusions. In patients with underlying malignancy and a confirmed proximal DVT, NICE recommend LMWH should be used rather than warfarin for a minimum of 6 months; this should then be reviewed and the drug continued as 'off-label' use.[6]

Thrombolysis

Thrombolysis involves intravenous catheter-directed administration of a thrombolytic agent (usually tissue plasminogen activator) to break down clot within the vein. The aim is to restore patency with the hope of reducing risk of chronic venous insufficiency. The risks are not insignificant with this invasive procedure and include bleeding and detachment of thrombus with proximal embolization. A 2016 Cochrane review of thrombolysis compared 17 studies of thrombolytic therapy. Patients undergoing any form of thrombolysis were more likely to have improved venous patency and complete clot lysis, with a reduction in post-thrombotic syndrome. There was an expected increase in bleeding complications. The studies included showed promising early results but lack of long-term follow-up.[13] Since this Cochrane review, a more recent randomized control trial found no significant difference in developing post-thrombotic syndrome but that symptoms were improved with thrombolytic therapies.[14] However, NICE guidelines recommend considering thrombolysis for acute (within 14 days) iliofemoral DVT in patients with good functional status and a life expectancy of at least a year, with a low risk of bleeding.[6]

Graduated compression hosiery

There is now level 1 evidence regarding the use of graduated compression hosiery and the development of post thrombotic syndrome. A 2014 randomized controlled trial of compression stockings versus placebo found no significant difference in developing post thrombotic syndrome.[15] This is now reflected in updated NICE guidelines, recommending against the use of graduated compression stockings to prevent post-post-thrombotic syndrome. Below knee compression hosiery may be beneficial in symptom relief in patients with significant symptoms from proximal DVT.[6]

Further investigation for malignancy

Given the known association between malignancy and DVT, there has been debate about how much an individual with an unprovoked DVT should be investigated for occult malignancy. The NICE guidelines suggest in those over 40 years, with no clinical signs of malignancy, a CT scan of the abdomen and pelvis and a mammogram for women, should be undertaken. All individuals with unprovoked VTE should have a full examination, chest X-ray, urinalysis, full blood count, calcium and liver function tests.[6] The evidence for this remains weak.

Inferior vena cava filters

IVC filters are designed to prevent large pulmonary embolus. There are various models, which may allow the passage of small emboli, and thrombus collects on the 'downstream' side of the filter. Therefore they cannot be expected to have any effect on leg symptoms or post-thrombotic syndrome, but do prevent major, life-threatening pulmonary emboli.

The absolute indication for an IVC filter is a contraindication to anticoagulation. Ideally in this circumstance a temporary filter can be inserted and removed at a later date (once the patient can be anticoagulated). In practice many temporary filters remain in-situ permanently, but they are not without morbidity, and filter erosion through the vena cava is a recognized complication.

IVC filters may also be considered in patients with multiple recurrent VTE despite anticoagulation after other strategies have been considered. Current guidelines suggest that prior to filter placement a trial of increased anticoagulation either with an INR 3–4 or using treatment dose LMWH rather than warfarin is undertaken.

Investigation for thrombophilia

Given the prevalence of thrombophilia there is debate as to which patients with DVT undergo further investigation. The difficulty is that most tests cannot be undertaken while the patient is anticoagulated. If the patient is due to continue anticoagulation anyway, then there is no need to test.

It is recommended that testing should be considered in patients who have had an unprovoked DVT and are stopping anticoagulation. Hereditary thrombophilias should be considered if a first-degree relative has thrombophilia *and* there is unprovoked DVT in the index patient.

Thrombophilia testing should not be offered for provoked DVT.

Post-thrombotic syndrome (PTS)

The incidence of PTS is unknown, especially after asymptomatic DVT.[4] Similarly, the overall effect on quality of life and the overall cost to the NHS of treating PTS is unclear. It is poorly reported in venous prophylaxis trials since long-term follow-up is required to capture the data.

There is some evidence that thrombolysis reduces the incidence of PTS compared to anticoagulation alone RR = 0.64 (four randomized controlled trials of 341 patients with short –term follow-up).[12] However, the more recent ATTRACT trial has reported no significant difference in the incidence of PTS following thrombolysis.[14]

There is moderate evidence to demonstrate that below-knee compression (no studies of full-length hosiery), reduces PTS by approximately 50% at two years. A more recent trial reported no benefit for compression hosiery after first proximal DVT but there were significant issues with non-compliance with stockings over time and there are potential issues with the PTS criteria used in the study.[14] This is an ongoing area of research. ◆

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