BMJ Best Practice

Deep vein thrombosis

The right clinical information, right where it's needed

Last updated: Nov 13, 2017

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Summary

- Patients who develop DVT commonly have thromboembolic risk factors, such as cancer, trauma, major surgery, hospitalisation, immobilisation, pregnancy, or oral contraceptive use. However, many patients have no history of a provocation, and these patients are classified as having unprovoked or idiopathic DVT.

- Most DVTs are asymptomatic; however, there may be asymmetrical leg swelling, unilateral leg pain, dilation or distension of superficial veins, and red or discoloured skin.

- Diagnosis requires documentation of a blood clot in a deep vein in the leg, pelvis, or vena cava by venous duplex ultrasound imaging or CT scan.

- DVT is usually treated with anticoagulants such as unfractionated heparin, low molecular weight heparin, fondaparinux, rivaroxaban, apixaban, edoxaban, and/or warfarin.

- Generally, oral anticoagulation is continued for 3 to 6 months. In selected patients with significant thromboembolic risks, careful consideration should be given to maintaining oral anticoagulation indefinitely as long as the risks of bleeding are lower than the risks of recurrent venous thrombosis.

Definition

Deep vein thrombosis (DVT) is the development of a blood clot in a major deep vein in the leg, thigh, pelvis, or abdomen, which may result in impaired venous blood flow and consequent leg swelling and pain. DVT may also occur in the upper extremities or the brain. Venous thromboembolism (VTE) includes DVT and pulmonary embolism. This monograph focuses on lower extremity DVT.

Epidemiology

Venous thromboembolism is a relatively common medical problem with a yearly incidence of approximately 1 in every 1000 adults.[1] [2] [3] Approximately two-thirds of all cases are DVT, and one third are pulmonary embolism, with 5% to 10% of cases presenting with symptoms of both. The incidence goes up exponentially with age, from 2 to 3 per 100,000 (0.002% to 0.003%) people per year aged 20 to 30 years, to 500 per 100,000 (0.5%) people per year aged 85 years or older. Incidence is comparable in men and women, with a slight female predominance in people under the age of 35 years. The incidence is 10% to 15% higher in black people, 20% lower in Hispanic people, and 60% to 75% lower in Asians and Pacific Islanders. The incidence of DVT during pregnancy or the postnatal period is approximately 1 case per 1000 live births.[4] The population incidence is increasing slowly as the proportion of the population that is older increases, and as testing for DVT using ultrasound and testing for pulmonary embolism using multi-detector (multi-slice) chest CT-angiography increases.

Aetiology

The coagulation system in blood is complex and highly regulated. Slight perturbations in the systems that regulate coagulation can lead to bleeding or thrombosis.[5] The 3 factors that, individually or together, lead to most blood clots are vessel injury, venous stasis, and activation of the clotting system (known as Virchow's triad). Thus, many patients who develop the condition have a trigger that leads to blood coagulation (e.g., cancers that release tissue factor-positive micro-particles are pro-coagulants and stimulate clotting[6] or lower-extremity trauma that leads to vessel injury) or they have a very mild imbalance in their coagulation systems (e.g., genetic mutation in factor V called factor V Leiden) that tips the balance towards clotting when a modest provocation occurs.

There is a clear association between DVT and the following:

- Active malignancy
- Recent major surgery, especially orthopaedic procedures of the knee
- Recent hospitalisation
- Recent trauma
- Medical illness.

The absence of these risk factors` renders the DVT as being idiopathic or unprovoked. Idiopathic DVTs account for 26% to 47% of first-time DVTs. This characterisation of a DVT as being associated with thromboembolic risk factors or as being idiopathic is a major determinant in the duration of DVT treatment.[7]

Hospital-acquired DVT (a DVT that occurs during hospitalisation or within 90 days of discharge) is common.

Pathophysiology

Most blood clots that develop in the deep venous system of the leg begin to form just above and behind a venous valve.[8] [9]

Anatomical characteristics of the soleal vein play a major role in the occurrence, propagation, and embolic risk of venous thrombi in the lower extremities. Evidence from multiple observational studies has established the association of pulmonary embolism and soleal vein thrombosis. The soleal vein has no functioning valves, and in contrast to proximal venous thrombi, which are formed at the valve pockets, soleal vein thrombi form circumferentially within the dilated vein, attached to the wall of the vein only by a thin fibrin membrane. This makes them more prone to rapid propagation and embolism. Furthermore, in the setting of acute immobility, the muscular soleal veins are more prone to blood pooling and stagnation as the soleal muscle contraction depends entirely on the functionality of the ankle joint during ambulation.[10]

Clots commonly resolve spontaneously. When propagation of the thrombus does occur, it expands and grows proximally and across the lumen of the vein. A clot might occlude the entire lumen, but it is more commonly located on one peripheral aspect of the lumen. Even when the entire lumen appears to be occluded, a small amount of flow may continue on the extreme periphery of the clot. Some clots start in the calf veins and propagate proximally. However, in some instances, such as during pregnancy or following total hip arthroplasty, the clot might form initially in the groin or iliac vein region.[9] Acute thrombosis does not necessarily lead to 1 large clot and some thrombi form in several separated venous segments at the same time.

Acute thrombus begins to be dissolved by the body's fibrinolytic system as soon as a clot begins to form. Thus, elevated levels of breakdown products of cross-linked fibrin, particularly the fragment called D-dimer, appear in the blood soon after a clot begins to form. A normal level of D-dimer provides strong evidence against acute thrombosis.[11]

Classification

DVT: lower extremity

The following classification is an informal clinical classification.

(a) Superficial versus deep

- Thrombi in subcutaneous veins just below the skin that are palpable (e.g., in a varicose vein) are classified as superficial venous thrombi, commonly referred to as superficial thrombophlebitis.
- In addition, clots in the small saphenous vein (lower leg) and greater saphenous vein are also classified as superficial. Clots in the proximal portion of the greater saphenous vein (especially if within a few centimetres of the sapheno-femoral junction) may pose some risk of propagation and pulmonary embolisation because the greater saphenous vein joins the common femoral vein in the groin.

(b) Proximal versus distal

- Distal or calf vein thrombosis

- Acute DVT in the 3 major calf veins (posterior tibial, anterior tibial, peroneal), below the popliteal vein. Clots in the muscular branches to the gastrocnemius and soleal muscles are considered deep calf vein thrombi.

- Proximal venous thrombosis

  - Acute DVT in the popliteal vein or higher (femoral vein, deep femoral vein, common femoral vein, iliac vein, and vena cava).

(c) Subacute or chronic versus acute

- Subacute or chronic thrombi are associated with some narrowing of the vein, incomplete compressibility of the vessel, and a dense hyperechogenic clot, but the involved vein is normal-sized or contracted. Chronic clots may totally or partially obstruct flow.
- Acute venous thrombosis confirmed by duplex ultrasound has the following characteristics: vein width at site of the thrombus is wider than the unaffected vein on the contralateral side (i.e., dilated vessel), and ultrasound echos are not prominent (i.e., the clot is not dense). Acute DVT often correlates with recent onset of symptoms. Acute clots may totally or partially obstruct flow.

DVT: upper extremity

The following classification is an informal clinical classification.

(a) Superficial versus deep

- Thrombi in subcutaneous veins just below the skin that are palpable on the forearm or upper arm (i.e., basilic and cephalic veins) are classified as superficial.
- Brachial, axillary, subclavian, or innominate (or brachiocephalic) veins, and the superior vena cava are classified as deep. The internal jugular vein is also considered to be a deep vein.

(b) Subacute or chronic versus acute

- Criteria similar to lower-extremity venous thrombosis. Inability to compress the subclavian and other centrally located veins makes diagnosis more difficult.

Primary prevention

A large body of literature shows that the incidence of VTE can be reduced in the medically ill and surgical populations. Risk assessment models have been proposed to risk stratify patients for VTE.[22] [26]
In patients considered to have an increased risk of VTE and a low risk for bleeding, pharmacological prophylaxis is recommended. Mechanical compression and/or early ambulation are otherwise recommended in patients considered to have a low risk of VTE or a high risk of bleeding.

Options for pharmacological prophylaxis for the medically ill and surgical populations include low-dose unfractionated heparin, low molecular weight heparin, and fondaparinux. Aspirin and vitamin K antagonists are also endorsed for VTE prophylaxis in patients undergoing joint replacement procedures.[27] Based on the results of large, randomised clinical trials, rivaroxaban and apixaban (oral factor Xa inhibitors) and dabigatran (an oral direct thrombin inhibitor) have been approved for VTE prevention in patients undergoing arthroplasty surgery in certain countries.[28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] These medications, however, are not approved everywhere for use in the non-surgical population. Extended-duration pharmacological prophylaxis (i.e., 4-6 weeks) is suggested in patients undergoing joint replacement or hip fracture surgery as well as in those who undergo abdominal-pelvic surgeries for a malignancy.[26] [27] The routine use of extended-duration VTE prophylaxis in acutely medically ill patients, however, is not recommended due to an increased risk of major bleeding with this approach.[39] [40] [41] Among acutely ill medical patients with an elevated D-dimer level, the APEX trial found no significant difference between extended-duration betrixaban (35-42 days) and a standard regimen of enoxaparin (10±4 days) for the primary efficacy outcome of the composite of asymptomatic proximal deep vein thrombosis and symptomatic venous thromboembolism.[42] Betrixaban, a direct factor Xa inhibitor, has been approved by the US Food and Drug Administration for the prophylaxis of venous thromboembolism in adults (with restricted mobility and other risk factors for VTE) hospitalised for an acute illness. The routine use of pharmacological prophylaxis in patients travelling long distances is not recommended but should be evaluated on a case-by-case basis. Elastic compression sleeves may reduce the risk of VTE in these patients.[22]

Screening

Ultrasound screening

Compression ultrasound looking for evidence of acute DVT is an excellent screening test in high-risk patients, such as patients who have sustained major trauma and patients who have recently undergone total hip or knee replacement. There is no convincing evidence, however, that screening reduces the incidence of adverse outcomes, particularly the incidence of fatal pulmonary embolism. The overall accuracy of screening ultrasound in asymptomatic patients is not clear but it is lower than in symptomatic patients.[74] Because less than half of patients who develop pulmonary embolism have ultrasound evidence of DVT in the legs, the value of detecting asymptomatic DVT in preventing pulmonary embolism is uncertain. Doppler ultrasound has a low sensitivity for calf DVT and a limited sensitivity for thigh DVT.

Thrombophilia screening

Screening for thrombophilia in patients who have not yet had a DVT is not necessary unless there is a positive family history.

Cancer screening

Routine screening for cancer in patients with an unprovoked DVT is not currently recommended.[65] The prevalence of occult cancer was low among patients with a first unprovoked venous thromboembolism. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.[67]

Secondary prevention

Provoked DVT: there is consensus that patients who have an index DVT that is provoked by injury, surgery, immobilisation, or oral contraceptive pill use have a relatively low risk of developing recurrent VTE in the next 5 years, with estimates in the range of 15%. In these patients, recommendation for anticoagulation duration is 3 months, although some patients may require longer-term treatment because of a co-existing condition.

Unprovoked DVT: among patients who present with an idiopathic or unprovoked DVT, the 5-year recurrence rate is estimated to be approximately 30%. Because of the high recurrence rate, the American College of Chest Physicians recommends that physicians consider indefinite oral anticoagulation, with regular assessment of the risks versus the benefits of therapy.[83] The patient should be re-assessed after 3 months of treatment.

Cancer-associated DVT: among patients who have an active cancer (e.g., metastatic disease) indefinite anticoagulation using a low molecular weight heparin (LMWH) is recommended.[88]

Many studies have been published in the past 10 years that have attempted to identify subgroups of patients who do not need to be treated indefinitely with oral anticoagulation. There is strong evidence that the risk of recurrent VTE is higher in the following patients: male gender; those with a diagnosis of pulmonary embolism or a proximal DVT (versus a calf clot); those with ultrasound evidence of residual clot; those who have an elevated D-dimer 1 month after stopping a 2- to 6-month course of oral anticoagulation; and those who had an unprovoked DVT.

A review showed that treatment with warfarin strongly reduces the risk of recurrent venous thromboembolism for as long as it is used. The absolute risk of recurrent venous thromboembolism declines over time, although the risk for major bleeding with warfarin remains the same. The study showed that the efficacy of warfarin administration decreases over time since the index event.[144]

With the exception of patients with an unprovoked VTE, the routine utilisation of indefinite anticoagulation in these patients should be made on a case-by-case basis.

Case history

Case history #1

A 65-year-old woman presents with unilateral leg pain and swelling of 5 days' duration. There is a history of hypertension, mild CHF, and recent hospitalisation for pneumonia. She had been recuperating at home but on beginning to mobilise and walk, the right leg became painful, tender, and swollen. On examination, the right calf is 4 cm greater in circumference than the left when measured 10 cm below the tibial tuberosity. Superficial veins in the leg are more dilated on the right foot and the right leg is slightly redder than the left. There is some tenderness on palpation in the popliteal fossa behind the knee.

Other presentations

Other presentations include symptoms of shortness of breath, chest pain, and dyspnoea combined with leg pain and swelling. Pulmonary embolus should be considered in any patient with an acute DVT and respiratory symptoms. In severe DVT, the massive swelling can obstruct superficial venous return as well as arterial inflow, leading to a condition known as phlegmasia cerulea dolens. Here, the leg is not only severely swollen and painful, but also appears ischaemic. Most patients who present with superficial venous thrombosis have a tender palpable cord under the skin.

Step-by-step diagnostic approach

Contemporary management of DVT is based on an algorithmic diagnostic approach. History and physical examination are for the most part insensitive and non-specific, limiting their value in the clinical decision-making process. Although the majority of patients with DVT are asymptomatic, there are a few clinical symptoms that may increase the pre-test probability of acute DVT.

Diagnosis requires documentation of a blood clot in a deep vein in the leg, pelvis, or vena cava by duplex ultrasound imaging or a vascular contrast study such as a CT scan (with contrast). The first step in making the diagnosis of DVT is to establish the probability that a DVT is present using the Wells' criteria and D-dimer level.

History

Key information includes the presence or absence of a prior history of DVT or pulmonary embolism (PE) as well as recent exposure to any of the common provoking risk factors: specifically, recent surgery, presence of an active cancer, lower-extremity trauma, recent hospitalisation, recent immobility, and presence of underlying chronic medical illness. Family history of venous thrombosis or PE may be helpful.[15]

Other risk factors that increase the risk of a DVT include increasing age, current pregnancy, obesity, factor V Leiden mutation, prothrombin gene mutation G20210A, protein C or S deficiency, antithrombin (AT) deficiency, antiphospholipid antibody syndrome, acute medical comorbidity (especially those associated with inflammation, infection, and immobility), recent long-distance air travel, and use of certain drugs including oestrogen- or third-generation progestogen-containing oral contraceptives, tamoxifen, raloxifen, thalidomide, or erythropoietin.

The patient may report calf swelling (or, more rarely, swelling of the entire leg), localised pain along the deep venous system, oedema, or dilated superficial veins over the foot and leg; however, most patients are either asymptomatic or present with only minor pain.

Physical examination

Unilateral leg and thigh swelling can be assessed by measuring the circumference of the leg 10 cm below the tibial tuberosity and 10 cm to 15 cm above the upper edge of the patella. If there is a difference of >3 cm between the extremities, DVT is more likely.

There may be oedema and dilated collateral superficial veins on the affected side. Tenderness along the path of the deep veins (posterior calf compression, compression of the popliteal fossa, and compression along the inner anterior thigh from the groin to the adductor canal) might be present.

Tenderness with dorsiflexion of the foot (Homans' sign) or calf pain on palpation (Pratt's sign) may be present; however, a sensitivity and specificity of less than 50% limits their diagnostic value.[43]

When massive, the swelling can obstruct deep and superficial venous outflow as well as arterial inflow, leading to phlegmasia cerulea dolens. Here, the leg is swollen and painful and appears ischaemic.

Other conditions that might explain the leg findings must be excluded, specifically a large or ruptured popliteal cyst (Baker's cyst), repetitive cellulitis, and musculoskleletal trauma or injury (calf bleeding or haematoma, ruptured Achilles' tendon, or ruptured plantaris tendon).[44] In many cases, the diagnosis of cellulitis or a musculoskeletal injury is straightforward, but there may be concern that a DVT may also be present. Because there are no highly specific findings for DVT, the possibility of a DVT must be considered in the differential diagnosis.

The fact that pulmonary embolus can occur without clinical evidence of DVT, and without an incidental finding of DVT on ultrasound in a patient without a known history of DVT, emphasises the asymptomatic nature of some DVTs.

Pretest probability (Wells' criteria)

There are a number of clinical prediction tools available to assess the clinical probability of DVT; however, the Wells' criteria provide a method to determine the clinical probability of DVT and are the most widely accepted algorithm used in the clinical diagnosis of DVT.[45] [46]

Wells' criteria:

- Active cancer (any treatment within past 6 months): 1 point
- Calf swelling where affected calf circumference measures >3 cm more than the other calf (measured 10 cm below tibial tuberosity): 1 point
- Prominent superficial veins (non-varicose): 1 point
- Pitting oedema (confined to symptomatic leg): 1 point
- Swelling of entire leg: 1 point
- Localised pain along distribution of deep venous system: 1 point
- Paralysis, paresis, or recent cast immobilisation of lower extremities: 1 point
- Recent bed rest for >3 days or major surgery requiring regional or general anaesthetic within past 12 weeks: 1 point
- Previous history of DVT or PE: 1 point
- Alternative diagnosis at least as probable: subtract 2 points.

If the Wells' score is 2 or greater, the condition is likely (absolute risk is approximately 40%).[45] [46] Patients with a Wells' score of <2 are unlikely to have a DVT (probability <15%).[45] [46]

The addition of venous ultrasound assessment to the Wells' criteria may significantly increase the accuracy of clinical probability models. Combining the Wells' clinical predicted model with a single duplex ultrasound is a management strategy that yields a significant improvement in the diagnostic accuracy. In patients with a negative ultrasound for DVT, the frequency of a thromboembolic event at 3 months is very low.[47] [48] [49]

Quantitative D-dimer level

D-dimer level is indicated in all patients with a Wells' score of <2. D-dimer is a breakdown product of cross-linked fibrin; hence, if there is an acute clot, D-dimer level is likely to be elevated. A quantitative or highly sensitive D-dimer test is therefore a useful test to exclude the presence of an acute DVT. However, an elevated D-dimer level is non-specific and is frequently positive in patients who are older, ill, have underlying hepatic disease, have an infection, or are pregnant. There are many tests available for D-dimer, but the best are highly sensitive ELISA tests. Each of the multiple tests that are available on the market has its own normal cut-off value.

A normal value excludes the diagnosis of DVT in a patient who has a low clinical probability of having DVT. This high negative predictive value is useful to reduce the need for further wasteful imaging or immediate anticoagulation with its associated risks. A positive D-dimer test, when combined with a low clinical probability for DVT, should prompt the clinician to proceed with advanced confirmatory imaging.

Regardless of the patient group, D-dimer has a low positive predictive value. However, the positive predictive value is even lower in the presence of other clinical conditions that may elevate serum levels such as cancer, infection, ischaemia, end-stage renal or liver disease, and trauma, and is, therefore, not recommended in these patients.

Venous duplex ultrasound (DUS)

Venous DUS is the first-line test recommended in all patients with a Wells' score of 2 or more, or in patients with a Wells' score <2 who have an elevated D-dimer level. It assesses venous flow by the use of Doppler and vein compression. Non-compressibility is the only sign prospectively validated with a high-positive predictive value when compared with venography. Diagnosis of an acute clot is based on the inability to completely collapse the walls of the vein in the transverse plane by pressing down on the vein with a transducer probe, and is due to the clot opposing the force of compression. Short-axis ultrasound view showing the femoral vein (FV) and profunda femoris vein (PFV) adjacent to the femoral artery before compression (left) and compressed (right) Additional findings include reduced or absent spontaneous flow, lack of respiratory variation, intraluminal echoes, or colour flow patency abnormalities.
[Fig-1]

Venous DUS is a reliable method to evaluate symptomatic proximal DVT; however, it is less reliable in the diagnosis of isolated calf vein thrombosis. Therefore, a serial ultrasound strategy may be necessary to exclude proximal extension of the thrombus into the popliteal veins or beyond.

The difference between whole leg ultrasound and serial proximal ultrasound appears not to be clinically relevant, and the 2 diagnostic strategies have been shown to be equivalent when used for the management of symptomatic outpatients with suspected DVT of the lower extremities.[50]

Diagnostic algorithm for DVT

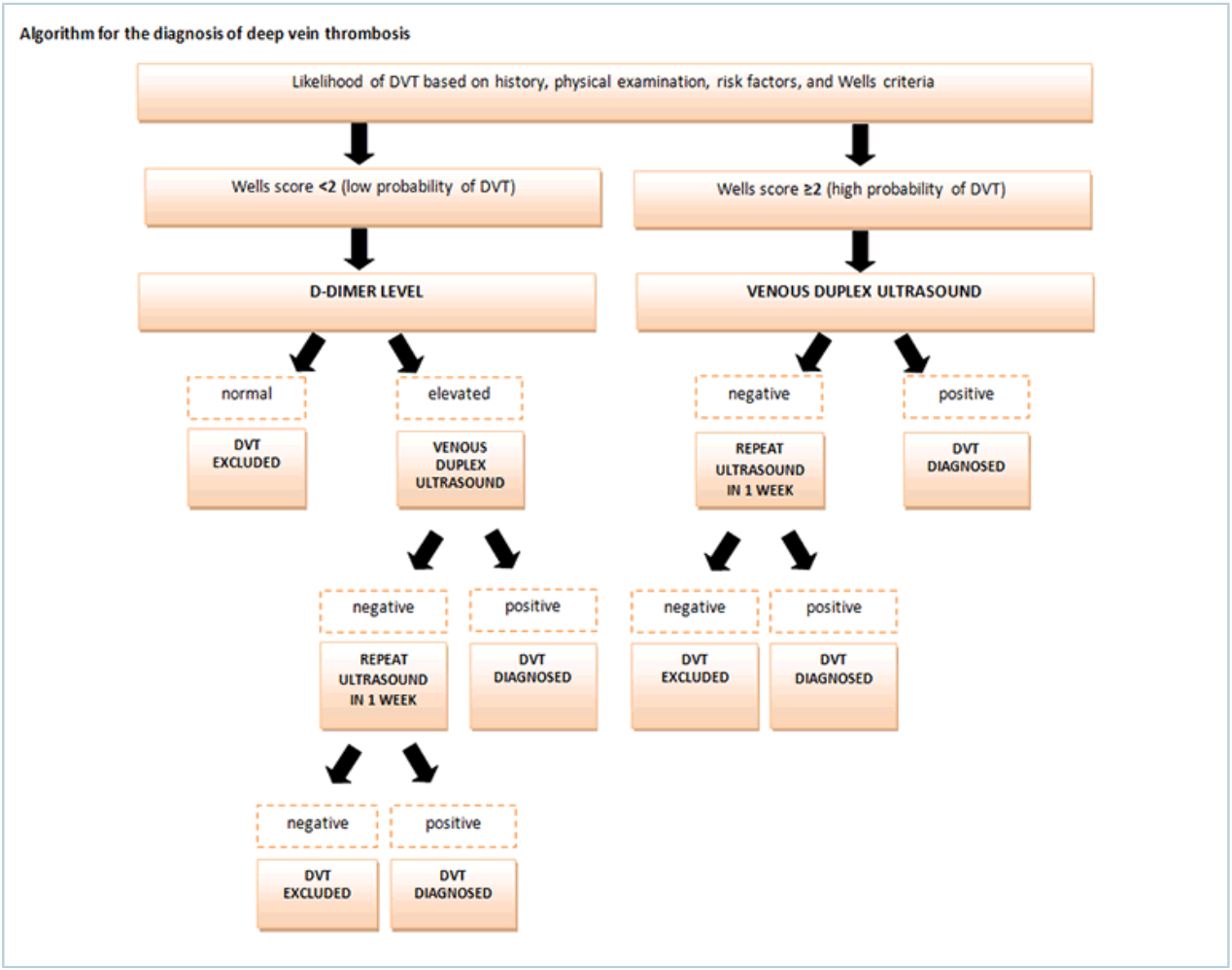
At the present time, the best way to exclude a DVT is by establishing that the clinical probability of DVT is low combined with a normal D-dimer level using a highly sensitive test. The Wells' criteria, a quantitative D-dimer level, and duplex ultrasound are the main investigations used to confirm the diagnosis of DVT.

Patients with a Wells' score of 2 or more warrant serious consideration for the presence of DVT, but the absolute risk of a DVT is still approximately 40%.[45] [46] In these patients:

- Venous DUS is the first-line test.[51] Minimally, ultrasound of the proximal deep venous system should be performed to assess the popliteal, femoral, and common femoral veins. Ultrasound of the lower-extremity calf veins can be used to detect clots in the paired posterior tibial veins, the paired anterior tibial veins, the paired peroneal veins, and the muscular calf veins (gastrocnemius and soleal), but this is not performed in every vascular laboratory.
- In case an initial ultrasound is negative in the setting of intermediate or high probability tests, a serial ultrasound diagnostic approach 1 week after the initial ultrasound may improve the diagnostic yield.

Patients with a Wells' score of less than 2 are unlikely to have a DVT (probability <15%).[45] [46] In these patients:

- A quantitative D-dimer test may be ordered and, if normal, DVT is excluded.[52]
- If the D-dimer is elevated, ultrasound is indicated. If ultrasound is normal, a repeat and normal ultrasound in 1 week excludes DVT.



Algorithm for the diagnosis of deep vein thrombosis

Created by the BMJ Evidence Centre

Other tests

Other routine laboratory tests are seldom of any value in the diagnosis of an acute DVT. Occasionally, laboratory tests may point to an underlying cause of a newly diagnosed DVT, such as abnormalities suggesting the presence of a malignancy (e.g., anaemia or leucopenia on FBC). A high platelet count may suggest essential thrombocytosis or a myeloproliferative disorder. Baseline platelet count, activated partial thromboplastin time and INR are important before commencing anticoagulation.

CT with contrast may be more accurate than ultrasound at detecting thrombosis in larger veins of the abdomen and pelvis.[53] Colour flow Doppler and pulse-wave are sometimes done in conjunction with B-mode image ultrasonography. The absence of respiratory variations on pulse-wave Doppler raises the suspicion of a proximal venous obstruction. It has low sensitivity (75%) and medium specificity (85%).[53] [54]

Pregnancy

Clinical suspicion of DVT in pregnant women may be impaired secondary to the overlap of symptoms associated with pregnancy and thrombosis. Furthermore, there is a higher prevalence of iliac vein thrombosis in pregnant compared to non-pregnant patients that can render an accurate diagnosis even more challenging.[55] The D-dimer assay plays a limited role in pregnancy due to its natural rise with each trimester.[56] However, a negative D-dimer test may be useful in ruling out a diagnosis of DVT in these patients.[57] The Wells' score has not been validated in the pregnant population and, therefore, should not be routinely used to risk stratify a pregnant patient with a suspected DVT. A clinical prediction rule, termed the LEFt score, has been developed specifically for the pregnant population. This rule has yet to be rigorously validated and should also not be used routinely.[58] The correct diagnosis will thus rely on a high index of suspicion and close follow-up. Venous DUS remains the initial test of choice for a pregnant woman suspected of having a DVT. A few, small studies have investigated the role of a single, whole-leg ultrasound or serial, proximal compression ultrasonography for the diagnosis of DVT.[59] [60] [61] [62] Because of the limitations of these studies, the American College of Chest Physicians (ACCP) advocates the use of serial, proximal ultrasonography if a DVT is suspected in pregnant women. Due to a higher prevalence of isolated, pelvic vein thrombi in these patients, the guidelines also recommend a low threshold to obtain additional imaging (such as an iliac vein ultrasound or abdominal magnetic resonance venography) in patients with a suspected abdominal vein thrombosis (i.e., swelling of the entire leg, buttock, or back pain).[63]

Tests for underlying conditions

In a patient with objectively documented venous DVT, it is important to stratify the patient as having either a provoked (or secondary) or an unprovoked (or idiopathic) DVT. Patients with an unprovoked DVT present with no clear history of a provocation (e.g., major leg trauma, recent surgery, active cancer, recent immobilisation). It is easier to define a provoked DVT as a number of risk factors are known and widely used to define a provocation. Obvious provocations include local lower-extremity trauma, recent surgery on the leg, fracture with immobilisation or casting, immobilisation in bed for 3 or more days, recent medical hospitalisation for 3 or more days, very long (> 8 hour) plane flights in the prior 2 to 3 weeks, use of oral contraceptives, and pregnancy.

Cancer should always be considered in an acute DVT. Approximately 3% to 5% of patients with an unprovoked DVT and no obvious sign of cancer may have an occult cancer. [64] However, extensive investigations (beyond routine laboratory tests and age-appropriate routine screening) for cancer in patients with a first unprovoked DVT are not routinely indicated, because they have not been shown to improve prognosis or mortality.[65] [66] [67]

Tests for a thrombophilic condition should also be considered in DVT. These tests are best performed at the conclusion of the appropriate duration of oral anticoagulant treatment period. If antithrombin (AT) deficiency is tested for, it should be remembered that AT levels are lowered by intravenous heparin. Diagnosis of antiphospholipid antibody syndrome requires that 2 serial tests 12 weeks apart be positive for anticardiolipin antibody, antibodies to beta-2-glycoprotein I, or the lupus anticoagulant (often the dilute Russell Viper Venom Time, or DRVVT). Protein C and protein S measurements may be spurious in patients who have acute illness, and warfarin inhibits the synthesis of functional protein C and protein S. Use of direct-acting oral anticoagulants, such as dabigatran, may also interfere with thrombophilia testing, particularly if clot-based assays are used.[68] It should be remembered that patients with idiopathic or unprovoked VTE who have a thrombophilic disorder have the same incidence of recurrent VTE as patients with idiopathic VTE who do not have a thrombophilic defect.[69] [70]

Suspected PE

In patients with documented DVT who will be, or are being, treated in a standard fashion with heparin followed by warfarin for a total duration of 3 to 6 months, documenting the presence of PE is not routinely indicated. However, tests for PE should be considered if there are clinical signs or symptoms that raise the possibility of PE and there is clinically important cardiopulmonary compromise, including hypotension, syncope, symptoms of right heart failure, or worsening hypoxia.

The most common tests to diagnose PE are rapid-sequence CT angiography and ventilation/perfusion lung scanning. Traditional pulmonary artery CT angiography should be ordered only if first- or second-line tests cannot be performed and a diagnosis must be definitive. If the patient has cardiopulmonary compromise, he or she may be a candidate for thrombolytic therapy or pulmonary thrombectomy. In this situation, documenting PE is advisable and warranted.

ECG is of poor diagnostic value in PE, but findings such as tachycardia, right bundle branch block, and atrial arrhythmias are some of the non-specific findings that may initially raise the suspicion of a PE. A baseline CXR and ABG are frequently obtained in the initial evaluation of patients with suspected PE.

Risk factors

Strong

medical hospitalisation within the past 2 months

- Approximately 20% of all incident venous thromboembolic events (VTEs) develop either during a medical hospitalisation or within 2 months of a hospitalisation of 4 or more days.[1] [2]
- Reasons are the combination of immobilisation with acute and chronic medical comorbidities that are associated with VTE development, such as acute sepsis, heart failure, stroke, and inflammatory conditions.

major surgery within 3 months

- Approximately 18% of all incident cases of venous thromboembolic events occur within 3 months of major surgery because of postoperative immobilisation, inflammation, underlying comorbidity, and injury to the venous system in selected cases (e.g., total knee replacement).[3]

active cancer

- Patients with metastatic cancer at the time of diagnosis are at especially increased risk, possibly owing to direct activation of thrombosis by biologically more aggressive cancers.[12] Incidence is also affected by high incidence of major surgery and use of chemotherapy.

lower-extremity trauma

- Patients with lower-extremity injuries that require surgery, such as leg, femur, or hip fracture, are at particularly increased risk, owing to vein injury coupled with effects of immobilisation and surgery. A retrospective analysis of the incidence of venous thromboembolism among patients undergoing surgery for traumatic lower-extremity injuries supports the association.[13]
- Non-surgical injuries (e.g., a fracture that requires casting) also increases the risk.

increasing age

- All epidemiological studies show an exponential rise in incidence with age.[1] [3] Age is a marker for relative immobilisation (functional decline) and accrual of multiple medical comorbidities.

pregnancy

- The observed incidence of venous thromboembolic events in pregnant women is increased compared with age-matched non-pregnant women.[14] This might be owing to interaction of hormonal changes during pregnancy with underlying genetic or acquired thrombophilic disorders (conditions that increase the risk of venous thrombosis) coupled with relative venous stasis due to obstruction, particularly in the left leg. The absolute risk in pregnancy is low.

obesity

- Both randomised clinical trials and retrospective cohort studies have shown that high BMI (especially >30 kg/m^2) is associated significantly with DVT development.[15] Mechanisms might be relative immobilisation, reduced venous flow rates, underlying inflammatory state, and greater frequency of co-existing comorbidities.

factor V Leiden

- Multiple studies have documented that the relative risk of developing venous thromboembolic events (VTE; particularly DVT) is approximately 3 to 4 times greater in patients who carry 1 copy of the factor V Leiden (FVL) mutation (heterozygotes) compared with patients without this mutation. However, the absolute lifetime risk of developing VTE is low.
- There is a strong interaction (increase in risk) between use of oral contraceptives or hormone replacement therapy containing oestrogen and presence of FVL, with an increase in the risk of subsequent VTE that is approximately 12-fold.[16]
- Patients who are homozygous for FVL have substantially higher risk of developing VTE compared with heterozygotes.

prothrombin gene mutation G20210A

- Multiple studies have documented that the relative risk of developing venous thromboembolic events (VTE; particularly DVT) is approximately 4 times greater in patients who carry the prothrombin gene variant G20210A (heterozygote) compared with patients without this mutation.
- There is a strong interaction (increase in risk of DVT) between use of oral contraceptives or hormone replacement therapy containing oestrogen and presence of the prothrombin variant, with an approximately 7-fold increase in the risk of subsequent VTE.[16]
- Patients who are homozygous for prothrombin gene mutation have substantially greater risk of developing VTE compared with heterozygotes.

protein C or S deficiency

- Protein C and S deficiencies are heterogeneous disorders with over 100 genetic variants for each. Results of protein C and S measurements are inexact as they may require clot-based assays. Exogenous factors such as use of warfarin, pregnancy, and acute inflammation may affect results and lead to misinterpretation of results.
- Patients with a well-defined deficiency in protein C or protein S have a 5- to 6-fold greater risk of developing venous thromboembolic events,[16] and the risk increases in a multiplicative fashion in the presence of other thrombophilic disorders.

antithrombin deficiency

- Antithrombin (AT) deficiency is a heterogeneous disorder with over 100 genetic variants, some leading to low serum levels of AT and some with normal levels of a dysfunctional protein.
- The prevalence of any of these disorders is low in cohorts of patients with venous thromboembolic events (<1%), but the risk in unaffected relatives of probands appears to be greater for AT deficiency than for protein C, protein S, or factor V Leiden.[17]
- Measurement of AT is generally unaffected by warfarin (rarely, warfarin may raise antithrombin III levels[18]) but levels are lower in the presence of therapeutic levels of unfractionated heparin.

antiphospholipid antibody syndrome

- Defined as an association of antiphospholipid antibodies with a variety of clinical features characterised by thrombosis and pregnancy-related morbidity.
- Often over-diagnosed because clinicians are unaware of the exact definitions. Criteria have been updated and clarified.[19]
- Serial tests 12 weeks apart for anticardiolipin Ab, beta-2-glycoprotein I, or the lupus coagulant are necessary.
- In patients who meet criteria for antiphospholipid antibody syndrome, the risk of recurrent venous thromboembolic events when off anticoagulation therapy is not well defined, but generally assumed to be approximately twice as high.[20]

medical comorbidity

- Occurs especially with inflammation, infection, and immobility.
- Case reports and small series show greater incidence in patients with sickle cell anaemia, inflammatory bowel disease, Behcet's disease, HIV, primary pulmonary hypertension, hyperlipidaemia, diabetes mellitus, myeloproliferative diseases, and others, including systemic lupus erythematosus.[21]
- Underlying mechanisms vary with the type of comorbidity but there is usually vascular inflammation or stasis, alone or in combination.

- Several acute medical disorders, notably heart failure, respiratory disease, and acute infections, are associated with hospital-acquired DVT.

recent long-distance air travel

- The absolute risk with air travel appears to be small. The risk appears to be increased in patients with an elevated baseline risk of VTE such as those with a previous VTE, recent surgery or trauma, obesity, limited mobility, or advanced age.[22]

use of specific drugs

- The risk of developing a DVT in women who take oestrogen-containing oral contraceptives is low. However, this is double or triple the risk in women who do not take oral contraceptives. The risk of developing an oral contraceptive-related DVT is strongly associated with the presence of factor V Leiden or the prothrombin gene mutation, but it is also associated with obesity and smoking. Risk is greatest in the first year of use.
- Data regarding the risk of VTE in transdermal contraceptive patch users are conflicting. Oral contraceptives containing third-generation progestins may increase the risk of VTE compared with second-generation progestin-containing pills.[23] Oral contraceptives containing desogestrel or gestodene may also increase the risk of VTE compared with older-generation products.[24]
- Tamoxifen and raloxifen are associated with a doubled or tripled risk of developing DVT, particularly in patients with a thrombophilic condition, such as factor V Leiden.
- Thalidomide most commonly causes DVT when used as a cancer chemotherapeutic agent. Many other chemotherapeutic agents can also increase the risk.
- Erythropoietin is associated with an increased risk of DVT in cancer patients.
- Patients who develop antibodies to adalimumab (a TNF-alpha inhibitor) frequently develop venous thrombosis.[25]

Weak

family hx

- Family hx of venous thrombosis or pulmonary embolism may increase the risk.[15]

History & examination factors

Key diagnostic factors

calf swelling (uncommon)

- Unilateral leg and thigh swelling can be assessed by measuring the circumference of the leg 10 cm below the tibial tuberosity and 10 cm to 15 cm above the upper edge of the patella. If there is a difference of >3 cm between the extremities, DVT is more likely.

localised pain along deep venous system (uncommon)

- Localised pain can be assessed by gently palpating along the path of the deep venous system from groin to adductor canal and in the popliteal fossa.
- Tenderness with dorsiflexion of the foot (Homans' sign) or calf pain on palpation (Pratt's sign) during the physical examination may be present; however, a sensitivity and specificity of less than 50% limits their diagnostic value.[43]

Other diagnostic factors

asymmetric oedema (common)

- Presence of oedema worse on leg with suspected DVT.

collateral superficial veins (common)

- Dilated superficial veins over foot and leg, not varicose veins, are a sign of DVT.

swelling of the entire leg (uncommon)

- Increases pretest probability of diagnosis of DVT.

phlegmasia cerulea dolens (uncommon)

- When DVT is massive, the swelling can obstruct not only venous outflow but arterial inflow, leading to phlegmasia cerulea dolens due to ischaemia. Here, the leg is usually blue and painful.
- The condition can lead to chronic venous hypertension in the leg, owing to either outflow obstruction or damage to the valves in the veins. This causes chronic problems such as leg swelling, thickening of the skin, ectatic superficial veins, skin induration, cutaneous pigmentation, and, in some advanced cases, skin ulceration.

Diagnostic tests

1st test to order

Test	Result
Wells' clinical probability tool • Not a definitive test but should be determined in all patients with suspected DVT. Wells' criteria are the most widely accepted algorithm used in the clinical diagnosis of DVT.[45] [46] If the Wells' score is 2 or greater, condition is likely (absolute risk is approximately 40%).[45] [46] People with a score of <2 are unlikely to have a DVT (probability <15%).[45] [46] • The criteria are as follows: • Active cancer (any treatment within past 6 months): 1 point • Calf swelling where affected calf circumference measures >3 cm more than the other calf (measured 10 cm below tibial tuberosity): 1 point • Prominent superficial veins (non-varicose): 1 point • Pitting oedema (confined to symptomatic leg): 1 point • Swelling of entire leg: 1 point • Localised pain along distribution of deep venous system: 1 point • Paralysis, paresis, or recent cast immobilisation of lower extremities: 1 point • Recent bed rest for >3 days or major surgery requiring regional or general anaesthetic within past 12 weeks: 1 point • Previous history of DVT or PE: 1 point • Alternative diagnosis at least as probable: subtract 2 points. • This test has not been validated in the pregnant population and, therefore, should not be routinely used to risk stratify a pregnant woman with a suspected DVT. A clinical prediction rule, termed the LEFt score, has been developed specifically for the pregnant population; however, this rule has yet to be rigorously validated and should also not be used routinely.[58]	**score of 2 or more**
quantitative D-dimer level • Indicated if the pre-test probability of DVT is classified as unlikely (Wells' score <2). If the D-dimer is normal, DVT is excluded in low-probability patients.[52] If elevated, a venous duplex ultrasound is indicated for further investigation. • In outpatients with suspected venous thromboembolic event, point-of-care tests can contribute important information and guide patient management in patients with a low-probability score on a clinical decision rule.[71] 1[A]Evidence For example, a negative test excludes DVT when the pretest probability is low. • Not a definitive test. Elevated levels are highly sensitive but non-specific.[45] [72] [73] It is frequently positive in patients who are older, ill, have underlying hepatic disease, have an infection, or are pregnant. • Regardless of the patient group, D-dimer has a low positive predictive value. However, the positive predictive value is even lower in the presence of other clinical conditions that may elevate serum levels such as cancer, infection, ischaemia, end-stage renal or liver disease, and trauma, and is, therefore, not recommended in these patients. • The D-dimer assay plays a limited role in pregnancy due to its natural rise with each trimester.[56] However, a negative D-dimer test may be useful in ruling out a diagnosis of DVT in these patients.[57]	**normal or elevated**

Test	Result
venous duplex ultrasound (DUS) • Assesses venous flow by the use of Doppler and vein compression. • First-line test in all high-probability patients (Wells' score of 2 or more) or in low-probability patients (Wells' score <2) with an elevated D-dimer level to assess popliteal, deep femoral, femoral, and common femoral veins.[54] [Fig-1] • High sensitivity and specificity of over 95%.[74] Venous ultrasound has a high sensitivity because: 1) deep veins in the lower extremities are easily visualised; 2) it scans multiple areas, making it likely that at least a portion of a clot is detected; and 3) compression readily identifies intravascular thrombus. Non-compressibility is the only sign prospectively validated with a high positive predictive value when compared with venography. • Ultrasound cannot provide the exact age of a vein clot, but it is better than all current imaging techniques in differentiating acute, subacute, chronic, and age-indeterminant venous thrombi. • In high-probability patients, a repeat ultrasound is indicated in 1 week if the initial ultrasound test is normal. • In low-probability patients, a repeat ultrasound is indicated in 1 week if D-dimer level is elevated and initial ultrasound is normal. • Ultrasound testing can be limited to only the proximal deep venous system, so long as patients with a positive D-dimer or high probability and who have an initially normal proximal ultrasound undergo a repeat ultrasound in 1 week.[50] A serial ultrasound strategy may be necessary to exclude proximal extension of the thrombus into the popliteal veins or beyond. • The difference between the whole leg ultrasound and serial proximal ultrasound appears not to be clinically relevant, and the 2 diagnostic strategies have been shown to be equivalent when used for the management of symptomatic outpatients with suspected DVT of lower extremities.[50] • The initial test of choice for a pregnant woman suspected of having a DVT. The American College of Chest Physicians (ACCP) advocates the use of serial, proximal ultrasonography if a DVT is suspected in pregnant women.[63]	**inability to fully compress lumen of vein using ultrasound transducer; reduced or absent spontaneous flow; lack of respiratory variation; intraluminal echoes; colour flow patency abnormalities**
INR and activated partial thromboplastin time (aPTT) • INR is required before starting warfarin and aPTT is required before starting intravenous heparin.	**baseline values**
urea and creatinine • Doses of some anticoagulants (e.g., low molecular weight heparin, fondaparinux, apixaban, rivaroxaban, dabigatran, edoxaban) may need to be adjusted in patients with renal impairment, so baseline values should be obtained.	**baseline values**
LFTs • May detect abnormalities associated with underling provoking factor (e.g., cancer).	**baseline values**

Test	Result
FBC • May detect abnormalities such as underlying haematological malignancy (e.g., anaemia, leucopenia). • A high platelet count may suggest essential thrombocytosis or a myeloproliferative disorder. • Heparin therapy can be associated with heparin-induced thrombocytopenia; platelet counts should be measured at baseline and regularly throughout treatment.	**baseline values**

Other tests to consider

Test	Result
Doppler venous flow testing • Colour flow Doppler and pulse-wave are sometimes done in conjunction with B-mode image ultrasonography. The absence of respiratory variations on pulse-wave Doppler raises the suspicion of a proximal venous obstruction. • Low sensitivity (75%) and medium specificity (85%).[53] [54]	**low flow in veins**
CT abdomen and pelvis with contrast • More accurate than ultrasound for visceral veins and deep veins of abdomen and pelvis. • CT has a similar sensitivity and specificity to ultrasound in patients with suspected pulmonary embolism where investigation of suspected DVT of the legs and pelvis is required.[75]	**presence of an intraluminal filling defect**
thrombophilia screen • Tests for a thrombophilic condition are usually considered in unprovoked DVT or recurrent venous thromboembolic event (VTE). These tests may help to guide duration of anticoagulation treatment period. • Antithrombin levels are not recommended as they can be lowered in patients on heparin. • Diagnosis of antiphospholipid antibody syndrome requires that 2 serial tests 12 weeks apart be positive for anticardiolipin antibody, antibodies to beta-2-glycoprotein I, or the lupus anticoagulant (often the dilute Russell Viper Venom Time, or DRVVT). • Protein C and protein S measurements may be spurious in patients who have acute illness, and warfarin inhibits the synthesis of functional protein C and protein S. • It should be remembered that patients with idiopathic or unprovoked VTE who have a thrombophilic disorder have the same incidence of recurrent VTE as patients with idiopathic VTE who do not have a thrombophilic defect.[69] [70] • A review noted that no randomised controlled trials or controlled clinical trials have assessed the benefits of testing for thrombophilia on the risk of recurrent venous thrombolic events.[76]	**positive or negative; repeat after 12 weeks if antiphospholipid antibody syndrome suspected**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Cellulitis	• Patients with cellulitis usually manifest redness, heat, and swelling in the dermis of the affected leg. The affected area is likely to be smaller than in DVT (which may involve the entire foot, calf, or thigh), but the signs more pronounced. • The demarcation of the skin margins affected by cellulitis is more defined than in DVT. • Portal of infection entry may be identified.[77] • Fever and prior history of cellulitis is common. • May occur with a concurrent DVT.	• Leukocytosis is common, with a WBC count >10 × 10^9/L (10,000 cells/ microlitre). • Ultrasound confirms diagnosis. Fluid collection seen if abscess present.
Calf muscle tear/Achilles' tendon tear	• History of trauma or sudden onset of calf pain. • Muscle tear is difficult to differentiate from DVT on exam. Although defect or spasm of calf muscles is noted on examination, calf DVT may occasionally be associated with spasm.	• No DVT seen on MRI or ultrasound. • Oedema associated with muscle tear makes it very difficult to visualise the calf veins using ultrasonography. Furthermore, extreme tenderness associated with a muscle tear makes it difficult to compress with the ultrasound probe.
Calf muscle haematoma	• Calf injury or sudden onset of calf pain. There may be ecchymosis on the skin. • Calf haematoma, calf muscle tear, and calf muscle tendon tear frequently occur in the absence of injury or trauma.	• Venous ultrasound shows no thrombosis, and there may be ultrasound evidence of a haematoma.
Ruptured popliteal cyst (Baker's cyst)	• Sudden onset of calf pain.	• Ultrasound shows fluid in the soft tissues of the calf.
Pelvic/thigh mass/tumour compressing venous outflow from the leg	• Oedema usually occurs without pain in venous outlet obstruction.	• Venous ultrasound, CT scan, or MRI of abdomen, pelvis, and thigh with contrast, may show obstructing mass impinging on the femoral, iliac, or vena cava vessels.

Diagnostic criteria

Wells' criteria

- Active cancer (any treatment within past 6 months): 1 point
- Calf swelling where affected calf circumference measures >3 cm more than the other calf (measured 10 cm below tibial tuberosity): 1 point
- Prominent superficial veins (non-varicose): 1 point
- Pitting oedema (confined to symptomatic leg): 1 point
- Swelling of entire leg: 1 point
- Localised pain along distribution of deep venous system: 1 point
- Paralysis, paresis, or recent cast immobilisation of lower extremities: 1 point
- Recent bed rest for >3 days or major surgery requiring regional or general anaesthetic within past 12 weeks: 1 point
- Previous history of DVT or PE: 1 point
- Alternative diagnosis at least as probable: subtract 2 points.

If the Wells' score is 2 or greater, the condition is likely (absolute risk is approximately 40%).[45] [46] People with a Wells' score of <2 are unlikely to have DVT (probability <15%).[45] [46]

Ultrasonography criteria

The radiologist or technician who performs lower-extremity ultrasound first locates the femoral artery and vein in the groin region. The artery and its associated pulsatility can be identified readily; the femoral vein is adjacent. Compression of the femoral vein using the ultrasound probe is easy. Inability to compress the vein indicates the presence of a clot, but provides no information on the age of the clot.[78]

All of the deep veins in the leg must be identified and compressed in a deliberate and systematic fashion. There must be a careful search for a duplicated femoral vein and a duplicated popliteal vein.

Secondary criteria include a larger vein diameter on the affected side, and absent or scant echoes within the clot. In acute DVT, the vein is non-compressible and dilated. In subacute DVT, the vein is non-compressible and marginally dilated or of normal size. In chronic DVT, the affected vein is non-compressible and small. Acute DVT is frequently easy to determine on the ultrasound, but where the vein is normal-sized or the vein is partially compressible or partially non-compressible, it is more difficult to determine the age of the DVT. In these cases, the DVT is referred to as age-indeterminant.

Compression ultrasound is used to assess the presence of DVT in the deep veins of the upper extremity. Compression cannot be performed on the intrathoracic veins (subclavian and innominate veins and superior vena cava). The presence of a DVT in these centrally located veins of the chest is suggested by the absence of flow on colour flow Doppler and the absence of respiratory variations on pulse-wave Doppler in a more distal vein.[79] The Wells' criteria do not apply to upper-extremity DVT.

Warkentin Probability Scale for heparin-induced thrombocytopenia (HIT)[80]

The Warkentin Probability Scale for HIT can be used to estimate the probability of a patient having HIT. Points are scored (0, 1, or 2) for each of the 4 categories (maximum possible score = 8).

Thrombocytopenia

- 2 points if >50% fall in platelet count to a platelet count nadir of ≥20 × 10^9/L (≥20,000/mm^3 or 20 × 10^3/microL)
- 1 point if 30% to 50% fall in platelet count, or if the nadir is 10-19 × 10^9/L (10-19,000/mm^3 or 10-19 × 10^3/microL)
- 0 points if <30% fall in the platelet count, or if the nadir is <10 × 10^9/L (<10,000/mm^3 or 10 × 10^3/microL).

Timing* of onset of platelet fall (or other sequelae of HIT)

- 2 points if onset is 5 to 10 days after starting heparin, or <1 day if there has been recent heparin (within past 30 days)
- 1 point if onset is more than 10 days after starting heparin or if timing unclear; or if <day 1 after starting heparin with recent heparin (past 31-100 days)
- 0 points if onset is within 4 days of first time heparin exposure (no recent heparin).

Thrombosis or other sequelae

- 2 points if there is a proven new thrombosis, or heparin skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus
- 1 point if there is progressive or recurrent thrombosis, or erythematous skin lesions, or suspected thrombosis (not proven)
- 0 points if no thrombosis or other finding.

Other cause(s) of platelet fall

- 2 points if none evident
- 1 point if there is another possible cause
- 0 points if there is another definite cause.

Pretest probability score

- High = 6 to 8 points
- Intermediate = 4 to 5 points
- Low = 0 to 3 points.

*First day of immunising heparin exposure is considered day 0.

Step-by-step treatment approach

Anticoagulation is the mainstay of therapy. The reasons patients are treated with anticoagulants are to:

- Prevent propagation/progression of the thrombus in the deep veins in the legs
- Reduce the risk of pulmonary embolism (PE)
- Reduce the risk of recurrent DVT.

The recommended treatment regimens for patients with DVT have changed rapidly as new anticoagulants have become available. Care should be taken to minimise the risk of major haemorrhage throughout the treatment period and monitor for the development of heparin-induced thrombocytopenia (HIT) if heparin is used.[8] [15]

[IHI: reducing adverse drug events involving anticoagulants]

Hospitalisation

Criteria for hospitalisation:

- DVT that is best treated with intravenous unfractionated heparin (UFH)
- Suspected PE with or without cardiopulmonary compromise (tachycardia, tachypnoea, signs of right heart failure), although in some centres patients are hospitalised only if there is a high Pulmonary Embolism Severity Index (PESI)[81] [82]
- Symptomatic DVT (e.g., pain and oedema in the presence of acute DVT shown by venous duplex scan); some ambulatory patients with symptoms only of DVT may be candidates for home treatment if their symptoms are mild and outpatient follow-up of INR monitoring is available and arranged if the plan is to start warfarin
- Inability to educate the patient adequately in the outpatient or accident and emergency department setting
- Co-existing comorbidity requiring evaluation or treatment
- Presence of risk factors for bleeding that requires close observation in the hospital (chronic liver disease with or without varices, recent or prior GI bleeding, chronic renal stones with recurrent haematuria, bleeding disorder, malignancy, recent stroke).

Initial anticoagulation

Current recommendations from the American College of Chest Physicians (ACCP) are that patients with proximal DVT of the leg and some patients with distal DVT of the leg should generally receive anticoagulation for at least 3 months.[83] [84]

Proximal DVT of the leg:

- For patients with a proximal DVT of the leg, anticoagulant therapy is recommended.[83]

Isolated distal DVT of the leg:

- For patients with an acute isolated distal DVT of the leg but without severe symptoms or risk factors for extension, serial imaging of the deep veins for 2 weeks is recommended.[83] [85] No anticoagulation is generally needed if the thrombus does not extend. Extension of the thrombus is generally an indication to start anticoagulation.

- For patients with severe symptoms or risk factors for extension, anticoagulation is recommended. Risk factors for extension include:[83]
    - Positive D-dimer
    - Extensive thrombosis (e.g., >5 cm long; involving multiple veins; >7 mm in maximum diameter)
    - Thrombosis close to the proximal veins
    - Absence of any reversible provoking factor
    - Active cancer
    - Past history of venothromboembolism (VTE)
    - Inpatient status.

Recommendations for choice of antithrombotic therapy:

- The choice of agent depends on patient factors such as hepatic function, renal function, pregnancy, presence of cancer, obesity, and the risk of bleeding. Choice may also depend on individual physician or patient preference or recommendations in local guidelines.
- Generally, anticoagulation with dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over vitamin K antagonist (VKA) therapy (usually warfarin), which is in turn recommended over low molecular weight heparin (LMWH). Fondaparinux is generally reserved for patients with HIT or those with a history of this condition.

Increased risk of bleeding:

- It is preferable to treat patients who are at increased risk of bleeding (e.g., recent surgery, peptic ulceration) with intravenous UFH initially because it has a short half-life and its effect can be reversed quickly with protamine.

Active cancer:

- In patients with VTE and active cancer (regional spread or metastatic, especially adenocarcinomas or haematological malignancies), LMWH is recommended for initial treatment.[83] [86] [87] 2[A]Evidence The risk of recurrent VTE and major bleeding is lower in patients treated with LMWH compared with patients treated with warfarin.[86] [88] [89]

Renal impairment:

- For patients with renal impairment (i.e., creatinine clearance <30 mL/minute), intravenous or subcutaneous UFH, followed by warfarin, is currently the preferred anticoagulant.
- LMWH has unpredictable renal clearance among patients with renal failure. For patients on LMWH, laboratory monitoring of the anticoagulant effect (i.e., by anti-factor Xa assay) is generally not necessary, but should be considered in patients with severe renal impairment and those with moderate renal impairment if LMWH use is prolonged (i.e., >10 days).[90]
- Fondaparinux, rivaroxaban, apixaban, edoxaban, and dabigatran are generally not recommended in people with renal impairment.

Hepatic impairment:

- LMWH or UFH are recommended in these patients. Both LMWH and UFH should be overlapped with warfarin, unless cancer is present.[83]

- Rivaroxaban, apixaban, edoxaban, and dabigatran are generally not recommended in patients with hepatic impairment, especially those with moderate-to-severe impairment. Warfarin should be used cautiously if the baseline INR is elevated.[83]

Obesity:

- LMWH or UFH are options in these patients. The use of actual body weight is appropriate when calculating the therapeutic dose in obese patients. Laboratory monitoring of the anticoagulant effect of LMWH (i.e., by anti-factor Xa assay) is generally not necessary, but should be considered in patients with morbid obesity.[90] There is no known weight limit for the use of direct-acting oral anticoagulants; however, they have not been extensively studied in patients with extreme weights.

Pregnancy:

- Women who develop DVT and who are pregnant or may become pregnant can be treated with subcutaneous UFH or LMWH monotherapy.[91] Because of changes in the pharmacodynamics of regular heparin during pregnancy, LMWH is preferred.[83] [92] Routine measurement of peak anti-Xa activity for pregnant or postnatal patients on LMWH is not recommended except in women at extremes of body weight (i.e., <50 kg or >90 kg) or with other complicating factors (e.g., renal impairment or recurrent VTE) that put them at high risk.
- LMWH (or UFH) is generally continued in the postnatal period for 7 days (although this time may vary depending on the patient and the delivery) before transitioning to warfarin therapy.
- If breastfeeding is planned, then LMWH is the agent of choice and is continued (i.e., warfarin is not started) because it does not cross into the breast milk.
- Dabigatran, rivaroxaban, apixaban, and edoxaban are not recommended in these patients, but can be used in the postnatal period if the patient is not breastfeeding.

Considerations for specific anticoagulants:

- UFH treatment is usually initiated with an intravenous loading bolus followed immediately by initiation of a weight-based continuous infusion. It also requires monitoring of activated partial thromboplastin time (aPTT) and platelet count. Platelet count is regularly measured during treatment with any heparin (e.g., UFH, LMWH) therapy because of the possibility of heparin-induced thrombocytopenia (HIT) as a complication.
- Warfarin should be started the same day that UFH, LMWH, or fondaparinux is started, unless there is a very high risk for bleeding.3[B]Evidence 4[A]Evidence If bleeding risk is high, observing the patient for 1 to 2 days on intravenous heparin alone is advisable. Warfarin initiation in these patients depends on the physician's clinical judgement.
- If warfarin is started, the convention in most hospitals is to give it once daily in the evening. Subsequent dosing of warfarin is based on the INR response to each dose. The therapeutic INR range is 2 to 3 (target 2.5). UFH, LMWH, or fondaparinux should be continued until INR is between 2 to 3 for 2 consecutive days, at which time the initial agent is discontinued, with a minimum overlap of 5 days with both anticoagulants.
- Tests are available that determine the genotype of the patient for cytochrome 2C9 variants and vitamin K epoxide reductase variants. However, overall, this information has not led to more rapid or safe anticoagulation compared with routine dosing. Genotyping is expensive and it takes several days to receive results.[93] [94] [95] [96]
- Rivaroxaban, apixaban, edoxaban, and dabigatran are as effective as UFH, LMWH, and warfarin for the treatment of DVT.[97] No monitoring of coagulation profile is necessary, and bleeding complications are similar to those of warfarin, but there is a lower or similar incidence of major

bleeding with pulmonary embolism. All have a longer half-life than UFH or LMWH, and all have a rapid onset of action. Unlike warfarin, they do not interact with food. They do, however, undergo some drug-drug reactions. Prothrombin complex concentrates normalise coagulation studies in normal volunteers given high-dose rivaroxaban or apixaban. It is not known if this is the case with edoxaban, and it is not so for dabigatran, though 60% of dabigatran can be removed by dialysis and can be reversed with idarucizumab.[98]

- Dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant such as UFH or LMWH for 5 to 10 days before starting therapy. Rivaroxaban and apixaban are initiated as monotherapy with no need for lead-in therapy.
- Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients

Long-term (extended) anticoagulation

Recommendations for continuation of anticoagulant therapy beyond 3 months vary by patient group. In patients who receive extended anticoagulation therapy, there is usually no need to change the choice of anticoagulant.[83]

Provoked DVT:

- Anticoagulation for 3 months only is generally recommended for patients with a proximal DVT or an isolated distal DVT provoked by surgery or by a transient, non-surgical risk factor. [83] There is usually no need for extended anticoagulation beyond 3 months. One meta-analysis found a lower rate of recurrent venous thromboembolism in patients with isolated distal DVT who received anticoagulation for more than 6 weeks, without an increased risk of major bleeding.[99] The meta-analysis also showed that anticoagulation reduces the incidence of pulmonary embolism in these patients.

Unprovoked DVT:

- Patients with an unprovoked DVT of the leg who have been started on anticoagulation therapy should be assessed after 3 months for continued treatment.[83]
- For patients with a first proximal DVT that is unprovoked who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date). For those patients with a high bleeding risk, 3 months' treatment only is recommended.
- For patients with a second unprovoked DVT who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date) over 3 months. In patients with a high bleeding risk, 3 months' treatment only is recommended.
- In all patients who receive extended anticoagulant therapy, its continued use should be reassessed at periodic intervals (such as annually).[83]

Bleeding risk:

- When assessing bleeding risk, the following factors should be considered:[83]
    - Age >65 years
    - Previous bleeding
    - Cancer
    - Renal failure
    - Liver failure

- Thrombocytopenia
- Previous stroke
- Diabetes mellitus
- Anaemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity with reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse
- Use of non-steroidal anti-inflammatory drugs

- Patients with none of these risk factors are considered low risk; one risk factor renders a patient moderate risk; and two or more risk factors renders a patient high risk.

Aspirin

Long-term aspirin therapy to prevent recurrence should be considered for patients with an unprovoked proximal DVT who are stopping anticoagulant therapy and in whom aspirin is not contraindicated.[83] Aspirin should not, however, be considered a reasonable alternative for patients who want extended anticoagulation therapy. The use of aspirin should in any case be reassessed when patients stop anticoagulant therapy because it might have been stopped when anticoagulant therapy was started.[83]

Gradient stockings and physical activity

Although patients with a lower-extremity DVT are often advised to be fitted with knee-high gradient elastic stockings (30 to 40 mmHg) and to wear them for 2 years to reduce the development of post-thrombotic syndrome (also known as post-phlebitic syndrome), gradient stockings are not recommended for this purpose by current ACCP guidelines.[83] However, they remain useful for many patients with acute or chronic symptoms of DVT, and in these patients a trial of graduated compression stockings is often justified.[83]

Early walking exercise is considered safe in patients with acute DVT and may actually help to reduce symptoms. It does not increase leg symptoms acutely in patients with a previous DVT, and may help to reduce post-thrombotic syndrome.[100] [101] [102] [103] 5[B]Evidence

Bleeding patients

Use of a retrievable inferior vena cava (IVC) filter is recommended in patients who have a contraindication to anticoagulation therapy because of active bleeding. Presence of an IVC filter is associated with a doubling of the long-term risk of recurrent lower-extremity DVT. Observational data suggest that the long-term incidence of PE is not reduced in patients treated with a filter. There is no evidence that presence of a filter in the IVC by itself is an indication for long-term oral anticoagulation. However, the presence of a filter should be considered a risk factor that increases the long-term risk of recurrent DVT.6[B]Evidence Once bleeding has resolved, the patient may be assessed for initiation of anticoagulation and removal of the IVC filter.

PE-related cardiovascular compromise

For patients with cardiovascular compromise related to a PE, treatment should be individualised and may include anticoagulation, systemic or selective thrombolysis, open embolectomy, or IVC filter. Specialist medical and surgical advice should be sought.

Early recurrence (or progression) of venous thrombosis during treatment

Recurrent venous thrombosis refers to either clinical progression or worsening, documented objectively by venous duplex ultrasound, of the DVT, or the development of PE while on adequate anticoagulation.[104] [105]

The early development of recurrent DVT may be caused by ongoing activation of clotting owing to an underlying cancer or by HIT, or simply because of inadequate or delayed initiation of treatment. In some instances the treatment is appropriate, but PE occurs during treatment.

If extension/worsening of DVT or PE occurs during an initial period of treatment with heparin, HIT should be considered and a platelet count ordered immediately. If there is any suspicion of HIT, it is recommended that heparin is discontinued and treatment with a suitable alternative be initiated.

For patients who have recurrent VTE while taking warfarin (in the therapeutic range) or dabigatran, rivaroxaban, apixaban, or edoxaban, treatment should generally be changed to LMWH. However, recurrent VTE while on anticoagulants at therapeutic doses is unusual and should prompt evaluation of the recurrent VTE and of adherence to therapy.[83] D-dimer testing in this situation may be helpful as the initial D-dimer level is likely to be initially elevated, and it should fall if parenteral therapy is effective.[106]The possibility of an underlying malignancy should also be considered.[83] [107]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)

Patient group	Tx line	Treatment
proximal DVT of the leg: non-pregnant	1st	anticoagulation
proximal DVT of the leg: non-pregnant	plus	physical activity
proximal DVT of the leg: non-pregnant	adjunct	gradient stockings
distal DVT of the leg: non-pregnant	1st	serial imaging of the deep veins and/or anticoagulation
distal DVT of the leg: non-pregnant	plus	physical activity

Acute (summary)

distal DVT of the leg: non-pregnant	adjunct	gradient stockings
pregnant	1st	low molecular weight heparin or subcutaneous unfractionated heparin
pregnant	plus	physical activity
pregnant	adjunct	gradient stockings
active bleeding	1st	IVC filter
	plus	physical activity
	adjunct	gradient stockings
PE-related cardiovascular compromise	1st	individualised therapy

Ongoing (summary)

Patient group	Tx line	Treatment
3 months' anticoagulation therapy completed: not pregnant, not postnatal, no progression of thrombosis	1st	consideration of extended anticoagulation or aspirin
postnatal (planning to breastfeed)	1st	low molecular weight heparin or subcutaneous unfractionated heparin ± warfarin
postnatal (not planning to breastfeed)	1st	anticoagulation
documented progression of thrombosis on anticoagulant therapy	1st	further investigation

Treatment options

Acute

Patient group	Tx line	Treatment
proximal DVT of the leg: non-pregnant	**1st**	**anticoagulation** » For patients with a proximal DVT of the leg, anticoagulant therapy is recommended.[83] Therapy is initially for 3 months; some patients require extended therapy. » Choice of agent depends on patient factors such as hepatic/renal function, pregnancy, cancer, obesity, and bleeding risk. Choice may also depend on individual physician or patient preference or recommendations in local guidelines. » Generally, anticoagulation with dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over warfarin, which is in turn recommended over low molecular weight heparin (LMWH). Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In patients at increased risk of bleeding (e.g., recent surgery, peptic ulceration), anticoagulation with intravenous unfractionated heparin (UFH) is recommended initially because it has a short half-life and its effect can be reversed quickly with protamine. » In patients with active cancer (regional spread or metastatic, especially adenocarcinomas or haematological malignancies), LMWH is recommended for initial treatment.[83] [86] [87] 2[A]Evidence » In renal impairment (creatinine clearance <30 mL/minute), intravenous or subcutaneous UFH followed by warfarin is currently recommended. » In hepatic impairment, LMWH or UFH are recommended. Both LMWH and UFH should be overlapped with warfarin, unless cancer is present. Direct-acting oral anticoagulants (DAOCs) should generally be avoided. Warfarin should be used cautiously if the baseline INR is elevated.[83] » In obese patients, LMWH or UFH are options. DAOCs can also be considered; however, they have not been extensively studied in patients with extreme weights.

Acute

Patient group

Tx line

Treatment

» Warfarin is started at the same time as UFH, LMWH, or fondaparinux and is continued until the INR is between 2 to 3 for two consecutive days, at which point the UFH, LMWH, or fondaparinux can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants.

» With intravenous UFH, activated partial thromboplastin time (aPTT) should be monitored every 6 hours for the first 24 hours, then once daily when the therapeutic aPTT has been achieved. The goal is to maintain a therapeutic range, which is specific for each laboratory based on the reagent used. It is imperative to achieve a therapeutic aPTT within the first 24 hours in order to reduce the incidence of recurrent venous thromboembolism. Platelet count should be measured at baseline, then on days 3 and 5, to observe for the development of heparin-induced thrombocytopenia.

» Monitoring is not required with LMWH, subcutaneous UFH, fondaparinux, rivaroxaban, apixaban, edoxaban, or dabigatran.

» Dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant such as UFH or LMWH for 5 to 10 days before starting therapy. Rivaroxaban and apixaban are initiated as monotherapy with no need for lead-in therapy.

» Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

Primary options

» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily

OR

Primary options

» apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily

OR

Primary options

» edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily,

Acute

Patient group	Tx line	Treatment
		starting 5-10 days after treatment with a parenteral anticoagulant **OR** **Primary options** » dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant **OR** **Primary options** » enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » fondaparinux: patients <50 kg body weight: 5 mg subcutaneously once daily; patients 50-100 kg body weight: 7.5 mg subcutaneously once daily; patients >100 kg body weight: 10 mg subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; or 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-**

Acute

Patient group	Tx line	Treatment
		» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban
proximal DVT of the leg: non-pregnant	**plus**	**physical activity** » Early ambulation is considered safe in patients with acute DVT.[108] [109] 5[B]Evidence It does not increase leg symptoms acutely in patients with a previous DVT, and may help to reduce post-thrombotic syndrome.[100] [101] [102] [103]
proximal DVT of the leg: non-pregnant	**adjunct**	**gradient stockings** » Useful for many patients with acute or chronic symptoms of DVT, in whom a trial is often justified.[83] » Not recommended for other patients.[83]
distal DVT of the leg: non-pregnant	**1st**	**serial imaging of the deep veins and/or anticoagulation** » For patients with an acute isolated distal DVT of the leg but without severe symptoms or risk factors for extension, serial imaging of the deep veins for 2 weeks is recommended.[83] No anticoagulation is generally needed if the thrombus does not extend. Extension of the thrombus is generally an indication to start anticoagulation. » However, for patients with severe symptoms or risk factors for extension, anticoagulation is recommended. Anticoagulation is initially for 3 months; some patients require extended therapy. » Risk factors for extension include:[83] positive D-dimer, extensive thrombosis (e.g., >5 cm long; involving multiple veins; >7 mm in maximum diameter), thrombosis close to the proximal veins, absence of any reversible provoking factor, active cancer, past history of venous thromboembolism (VTE), or hospital inpatient status.

Acute

Patient group	Tx line	Treatment
		» Choice of agent depends on patient factors such as hepatic/renal function, pregnancy, cancer, obesity, and bleeding risk. Choice may also depend on individual physician or patient preference or recommendations in local guidelines. » Generally, anticoagulation with dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over warfarin, which is in turn recommended over low molecular weight heparin (LMWH). Fondaparinux is generally reserved for patients with heparin-induced thrombocytopenia (HIT) or those with a history of this condition. » In patients at increased risk of bleeding (e.g., recent surgery, peptic ulceration) anticoagulation with intravenous unfractionated heparin (UFH) is recommended initially because it has a short half-life and its effect can be reversed quickly with protamine. » In patients with active cancer (regional spread or metastatic, especially adenocarcinomas or haematological malignancies), LMWH is recommended for initial treatment.[83] [86] [87] 2[A]Evidence » In renal impairment (creatinine clearance <30 mL/minute), intravenous or subcutaneous UFH, followed by warfarin, is currently recommended. » In hepatic impairment, LMWH or UFH are recommended. Both LMWH and UFH should be overlapped with warfarin, unless cancer is present. Direct-acting oral anticoagulants (DAOCs) should generally be avoided. Warfarin should be used cautiously if the baseline INR is elevated.[83] » In obese patients, LMWH or UFH are options. DAOCs can also be considered; however, they have not been extensively studied in patients with extreme weights. » Warfarin is started at the same time as UFH, LMWH, or fondaparinux and is continued until the INR is between 2 to 3 for 2 consecutive days, at which point the UFH, LMWH, or fondaparinux can be discontinued. There should be a minimum overlap of 5 days' treatment with both anticoagulants. » With intravenous UFH, activated partial thromboplastin time (aPTT) should be monitored

Acute

Patient group	Tx line	Treatment

every 6 hours for the first 24 hours, then once daily when the therapeutic aPTT has been achieved. The goal is to maintain a therapeutic range, which is specific for each laboratory based on the reagent used. It is imperative to achieve a therapeutic aPTT within the first 24 hours in order to reduce the incidence of recurrent venous thromboembolism. Platelet count should be measured at baseline, then on days 3 and 5, to observe for the development of HIT.

» Monitoring is not required with LMWH, subcutaneous UFH, fondaparinux, rivaroxaban, apixaban, edoxaban, or dabigatran.

» Dabigatran and edoxaban require lead-in therapy with a parenteral anticoagulant such as UFH or LMWH for 5 to 10 days before starting therapy. Rivaroxaban and apixaban are initiated as monotherapy with no need for lead-in therapy.

» Argatroban (a thrombin inhibitor) may also be used if the patient currently has, or has had a prior history of, HIT; it is the preferred agent in these patients.

Primary options

» rivaroxaban: 15 mg orally twice daily initially for 3 weeks, followed by 20 mg once daily

OR

Primary options

» apixaban: 10 mg orally twice daily for 7 days, followed by 5 mg twice daily

OR

Primary options

» edoxaban: body weight ≤60 kg: 30 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant; body weight >60 kg: 60 mg orally once daily, starting 5-10 days after treatment with a parenteral anticoagulant

OR

Primary options

» dabigatran: 150 mg orally twice daily, starting 5-10 days after treatment with a parenteral anticoagulant

Acute

Patient group	Tx line	Treatment
		OR **Primary options** » enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » dalteparin: 200 units/kg/dose subcutaneously once daily; or 100 units/kg/dose subcutaneously twice daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » fondaparinux: patients <50 kg body weight: 5 mg subcutaneously once daily; patients 50-100 kg body weight: 7.5 mg subcutaneously once daily; patients >100 kg body weight: 10 mg subcutaneously once daily **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » heparin: 80 units/kg intravenous bolus initially, followed by 18 units/kg/hour intravenous infusion, adjust dose according to aPTT; or 333 units/kg subcutaneously initially, followed by 250 units/kg every 12 hours **-and-** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Secondary options** » argatroban: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on initiating therapy in patients on argatroban

Acute

Patient group	Tx line	Treatment
distal DVT of the leg: non-pregnant	plus	**physical activity** » Early ambulation is considered safe in patients with acute DVT.[108] [109] 5[B]Evidence It does not increase leg symptoms acutely in patients with a previous DVT, and may help to reduce post-thrombotic syndrome.[100] [101] [102] [103]
distal DVT of the leg: non-pregnant	adjunct	**gradient stockings** » Useful for many patients with acute or chronic symptoms of DVT, in whom a trial is often justified.[83] » Not recommended for other patients.[83]
pregnant	1st	**low molecular weight heparin or subcutaneous unfractionated heparin** » Women who develop DVT during pregnancy can be treated with subcutaneous unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Because of changes in the pharmacodynamics of subcutaneous UFH during pregnancy, LMWH is preferred.[83] [91] » Routine measurement of peak anti-Xa activity for pregnant patients on LMWH is not recommended except in women at extremes of body weight (i.e., <50 kg or >90 kg) or with other complicating factors (e.g., renal impairment or mechanical heart valve) that put them at high risk. » For patients with severe renal impairment (i.e., creatinine clearance <30 mL/minute) subcutaneous UFH with appropriated activated partial thromboplastin time (aPTT) adjustment is the preferred treatment. » Other anticoagulants are not recommended in pregnant women. **Primary options** » enoxaparin: consult specialist for guidance on dose **OR** **Primary options** » dalteparin: consult specialist for guidance on dose **OR**

Acute

Patient group	Tx line	Treatment
		Secondary options
		» heparin: consult specialist for guidance on dose
pregnant	plus	**physical activity**
		» Early ambulation is considered safe in patients with acute DVT.[108] [109] 5[B]Evidence It does not increase leg symptoms acutely in patients with a previous DVT, and may help to reduce post-thrombotic syndrome.[100] [101] [102] [103]
pregnant	adjunct	**gradient stockings**
		» Useful for many patients with acute or chronic symptoms of DVT, in whom a trial is often justified.[83]
		» Not recommended for other patients.[83]
active bleeding	1st	**IVC filter**
		» When possible, retrievable inferior vena cava (IVC) filters are preferable to older models. Presence of an IVC filter is associated with a doubling of the long-term risk of recurrent lower-extremity DVT, owing to both the presence of thrombosis and the mechanical effects of the filter.6[B]Evidence Observational data suggest that the long-term incidence of pulmonary embolism is not reduced in patients treated with a filter.
		» Once bleeding has resolved, the patient may be assessed for initiation of anticoagulation and removal of the IVC filter.
		» The US Food and Drug Administration (FDA) recommends that implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection from pulmonary embolism is no longer needed. The FDA encourages all physicians involved in the treatment and follow-up of patients receiving IVC filters to consider the risks and benefits of filter removal for each patient. The FDA states that a patient should be referred for IVC filter removal when the risk/benefit profile favours removal and the procedure is feasible given the patient's health status.[110]
	plus	**physical activity**

Acute

Patient group	Tx line	Treatment
		» Early ambulation is considered safe in patients with acute DVT.[108] [109] 5[B]Evidence It does not increase leg symptoms acutely in patients with a previous DVT, and may help to reduce post-thrombotic syndrome.[100] [101] [102] [103]
	adjunct	**gradient stockings** » Useful for many patients with acute or chronic symptoms of DVT, in whom a trial is often justified.[83] » Not recommended for other patients.[83]
PE-related cardiovascular compromise	1st	**individualised therapy** » Treatment should be individualised and may include anticoagulation, systemic or selective thrombolysis, open embolectomy, or IVC filter. » Specialist medical and surgical advice should be sought.

Ongoing

Patient group	Tx line	Treatment
3 months' anticoagulation therapy completed: not pregnant, not postnatal, no progression of thrombosis	1st	**consideration of extended anticoagulation or aspirin** » Recommendations for continuation of anticoagulant therapy beyond 3 months vary by patient group. In patients who receive extended anticoagulation therapy, there is usually no need to change the choice of anticoagulant.[83] » For patients with a proximal DVT or an isolated distal DVT provoked by surgery or by a transient, non-surgical risk factor, there is usually no need for extended anticoagulation beyond 3 months.[83] One meta-analysis found a lower rate of recurrent venous thromboembolism in patients with isolated distal DVT who received anticoagulation for more than 6 weeks, without an increased risk of major bleeding.[99] The meta-analysis also showed that anticoagulation reduces the incidence of pulmonary embolism in these patients. » Patients with an unprovoked DVT of the leg who have been started on anticoagulation

Ongoing

Patient group	Tx line	Treatment

therapy should be assessed after 3 months for continued treatment.[83] For patients with a first proximal DVT that is unprovoked who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date). For those patients with a high bleeding risk, 3 months' treatment only is recommended.

» For patients with a second unprovoked DVT who have a low or moderate bleeding risk, extended anticoagulant therapy is recommended (with no scheduled stop date) over 3 months. In patients with a high bleeding risk, 3 months' treatment only is recommended.

» In all patients who receive extended anticoagulant therapy, its continued use should be reassessed at periodic intervals (such as annually).[83]

» Patients with an unprovoked proximal DVT who are not proceeding to extended anticoagulation should be considered for long-term aspirin therapy to prevent recurrence.[83] Aspirin should not, however, be considered a reasonable alternative for patients who want extended anticoagulation therapy.

» The use of aspirin should in any case be reassessed when patients stop anticoagulant therapy because it might have been stopped when anticoagulant therapy was started.[83]

Primary options

» rivaroxaban: 20 mg orally once daily; 10 mg orally once daily after completing at least 6 months treatment

OR

Primary options

» apixaban: 5 mg orally twice daily; 2.5 mg orally twice daily after completing at least 6 months treatment

OR

Primary options

» edoxaban: body weight ≤60 kg: 30 mg orally once daily; body weight >60 kg: 60 mg orally once daily

OR

Ongoing

Patient group	Tx line	Treatment
		Primary options » dabigatran: 150 mg orally twice daily **OR** **Primary options** » enoxaparin: 1 mg/kg/dose subcutaneously twice daily; or 1.5 mg/kg/dose subcutaneously once daily **OR** **Primary options** » warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3) **OR** **Primary options** » aspirin: 100 mg orally once daily
postnatal (planning to breastfeed)	**1st**	**low molecular weight heparin or subcutaneous unfractionated heparin ± warfarin** » Low molecular weight heparin (LMWH) or subcutaneous unfractionated heparin (UFH) is generally continued in the postnatal period. If breastfeeding is planned, then LMWH is the agent of choice and is continued because it does not cross into the breast milk. Patients can either be continued on LMWH or transitioned to warfarin. » For patients on LMWH, no monitoring of the activated partial thromboplastin time is needed. Platelet count should be measured at baseline, then on days 3 and 5 to observe for the development of heparin-induced thrombocytopenia. » Other anticoagulants are not recommended. » These patients should only be treated under specialist supervision. **Primary options** » enoxaparin: consult specialist for guidance on dose **OR**

Ongoing

Patient group	Tx line	Treatment
		Primary options » dalteparin: consult specialist for guidance on dose **OR** **Primary options** » enoxaparin: consult specialist for guidance on dose **-or-** » dalteparin: consult specialist for guidance on dose **--AND--** » warfarin: consult specialist for guidance on dose **OR** **Secondary options** » heparin: consult specialist for guidance on dose **OR** **Secondary options** » heparin: consult specialist for guidance on dose **-and-** » warfarin: consult specialist for guidance on dose
postnatal (not planning to breastfeed)	**1st**	**anticoagulation** » If warfarin is started, the INR should be in the therapeutic range (2-3) at the time that low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is discontinued. Some experts suggest that the INR needs to be in the therapeutic range for 48 hours before the LMWH or UFH is discontinued. » No monitoring of the activated partial thromboplastin time is needed. Platelet count should be measured at baseline, then on days 3 and 5, to observe for the development of heparin-induced thrombocytopenia. » Although not studied in postnatal patients, apixaban, rivaroxaban, dabigatran, and edoxaban can be considered for use in

Ongoing

Patient group	Tx line	Treatment

accordance with their their prescribing information.

» These patients should only be treated under specialist supervision.

Primary options

» enoxaparin: consult specialist for guidance on dose
-or-
» dalteparin: consult specialist for guidance on dose

--AND--

» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)

OR

Primary options

» apixaban: consult specialist for guidance on dose

OR

Primary options

» edoxaban: consult specialist for guidance on dose

OR

Primary options

» rivaroxaban: consult specialist for guidance on dose

OR

Primary options

» dabigatran: consult specialist for guidance on dose

OR

Secondary options

» heparin: consult specialist for guidance on dose
-and-
» warfarin: 5 mg orally once daily initially, adjust according to INR (goal INR is 2 to 3)

Ongoing

Patient group	Tx line	Treatment
documented progression of thrombosis on anticoagulant therapy	**1st**	**further investigation** » The early development of recurrent DVT may be caused by ongoing activation of clotting owing to an underlying cancer or by heparin-induced thrombocytopenia (HIT), or simply because of inadequate or delayed initiation of treatment. In some instances, the treatment is appropriate, but PE occurs during treatment. » If extension/worsening of DVT or PE occurs during the initial period of treatment with heparin, HIT should be considered and a platelet count ordered immediately. If there is any suspicion of HIT, it is recommended that heparin is discontinued and treatment with a suitable alternative be initiated. » For patients who have recurrent VTE while taking warfarin (in the therapeutic range) or dabigatran, rivaroxaban, apixaban, or edoxaban, treatment should generally be changed to low molecular weight heparin (LMWH). However, recurrent VTE while on anticoagulants at therapeutic doses is unusual and should prompt evaluation of the recurrent VTE and of adherence to therapy.[83] D-dimer testing in this situation may be helpful as the initial D-dimer level is likely to be initially elevated, and it should fall if parenteral therapy is effective.[106] The possibility of an underlying malignancy should also be considered.[83] [107]

Emerging

Andexanet alfa

Andexanet alfa is a specific reversal agent designed to neutralise the anticoagulant effects of both direct and indirect factor Xa inhibitors. It has been used in older healthy participants without evidence of clinical toxic effects.[111]

Catheter-directed or pharmacomechanical thrombolysis

Several guidelines now suggest that catheter-directed thrombolysis (CDT) and/or thrombolysis together with mechanical removal be considered in carefully selected patients with iliofemoral acute DVT who are at a low risk for bleeding.[112] [113] [114] The American College of Chest Physicians now recommends that selected patients with extensive proximal DVT in the iliofemoral veins, symptoms for less than 14 days, good functional status, and life expectancy of ≥ 1 year may benefit from CDT or pharmacomechanical catheter-directed removal of the thrombus, as long as appropriate expertise is available and the risk of bleeding using thrombolytic drugs is low.[83] A multicentre study, ATTRACT, has been conducted to assess whether this treatment lowers the incidence of post-thrombotic syndrome and improves the quality of life.[115] [116] Preliminary data from the ATTRACT trial have shown no net benefit for primary end-point of lowering the incidence of post-thrombotic syndrome and, in fact, had more bleeding complications.

FOLLOW UP

Recommendations

Monitoring

For patients on intravenous heparin, activated partial thromboplastin time (aPTT) is measured:

- 6 hours after initiation of the infusion
- 6 hours after each adjustment in the dose
- At least once daily thereafter when the therapeutic aPTT is achieved.

Target values for aPTT are based on the local laboratory's standardised aPTT values, which should correspond to a heparin level between 0.4 U/mL and 0.8 U/mL.

For patients treated with low molecular weight heparin or fondaparinux, no monitoring of the aPTT is needed.

Frequent INR monitoring of patients who are treated with warfarin is required. This is preferably done by experts or specialised anticoagulation clinics, whenever possible. Anticoagulant therapy, although potentially life-saving, has inherent bleeding risks. A systematic approach will reduce the likelihood of adverse events.[141] Patients can self-monitor their INR using portable point-of-care instruments.[142]

Platelet count should be measured at baseline, then on days 3 and 5, to observe for the development of heparin-induced thrombocytopenia.

Patients who have pulmonary embolism (PE) should be evaluated clinically over time to determine if they have chronic thromboembolic pulmonary hypertension due to unresolved pulmonary emboli, which may occur in up to 4% of the patients.[143]

Rivaroxaban, apixaban, edoxaban, and dabigatran do not require laboratory monitoring. It is recommended that attention be directed to any changes in renal or liver function testing as clinically indicated (e.g., at baseline then as indicated).

Patient instructions

Patients must be instructed carefully about the proper use of warfarin and the need for regular follow-up and monitoring of their INR. [Thrombosis Canada: warfarin point-of-care INR monitoring] Patients must understand the following:

- Warfarin makes the blood more difficult to clot (it 'thins' the blood).
- The effect of the drug is measured with a blood-clotting test called the INR.
- Warfarin dose frequently changes over time, and dosing that varies with the day of the week is very common (e.g., 4 mg on Monday, Wednesday, Friday, and Sunday; 5 mg on Tuesday, Thursday, and Saturday).
- The desired or target INR values are generally between 2 and 3.
- Many drugs interact with warfarin, so the physician/healthcare provider who oversees the warfarin treatment must be notified whenever a new medicine (e.g., prescription or over-the-counter medicine, supplement, or herbal therapy) is started for the first time, or when a current medication is stopped. Non-steroidal anti-inflammatory drugs should be avoided or used with extreme caution under physician supervision.
- Diet changes can affect the INR, especially the intake of foods with high amounts of vitamin K; eating any amount of vegetables or greens is acceptable, so long as the intake is consistent from week to week. Alcohol should be consumed with caution and only in small amounts.

- Activities that carry a high risk of trauma or serious bleeding should be avoided, or if this is not possible, additional safety precautions should be taken.
- The INR must be checked (monitored) frequently, with blood tests once weekly until the target INR (2 to 3) is reached, then once per month thereafter.
- If a warfarin dose is missed in the morning or evening, patients should let their physician/healthcare provider know in order to provide guidance for their warfarin dosing.
- Patients must be very clear about the daily dose of warfarin and the colours of their different warfarin tablets.
- A pill organiser can help.

Patients should be taught about the range of signs and symptoms of bleeding and recurrent thrombosis in order to be adequately prepared to make a decision about seeking immediate medical attention or not.

Complications

Complications	Timeframe	Likelihood
pulmonary embolism	**short term**	**high**
The frequency, size, and symptoms of PE are variable. Among patients with proven thrombosis, lung scans at the start of antithrombotic treatment showed a high probability of PE in 51% of patients.[132] PE is treated in the same fashion as DVT unless there is cardiopulmonary compromise with hypotension or evidence of right heart strain with significant pulmonary hypertension. In these cases, pulmonary embolectomy, use of catheter-directed thrombolytic treatment or systemic treatment with a thrombolytic agent should be considered. The exact criteria for when to use thrombolysis have not been determined.[133] Selected patients with PE are candidates for IVC filter.		
acute bleeding during treatment	**short term**	**medium**

FOLLOW UP

Complications	Timeframe	Likelihood

Most episodes of bleeding during anticoagulation result from a previously unknown pathological lesion, such as duodenal ulcer, angiodysplasia in the colon, microvascular disease (such as a striatal intracerebral bleed in a patient with hypertension), or rare conditions, such as amyloid angiopathy in the central nervous system.[135]

If the patient is taking warfarin, fresh frozen plasma (FFP) should be given promptly if clinically indicated. Oral or intravenous phytomenadione (vitamin K) can also be given either alone or in conjunction with FFP but it may take longer to achieve a therapeutic INR with subsequent re-anticoagulation with warfarin. The effect of the FFP can be assessed immediately by measuring the INR. Repeat FFP administration might be necessary if the INR remains >1.5 and if the patient can tolerate the volume load.

Four-factor prothrombin complex concentrate was shown to be effective in reversing the effect of warfarin over-anticoagulation[136] and is the preferred agent as recommended by the American College of Chest Physicians.[137] Prothrombin complex concentrates have also been shown to normalise coagulation studies in normal volunteers given high-dose rivaroxaban or apixaban. It is not known if this is the case with edoxaban, and it is not so for dabigatran, though 60% of dabigatran can be removed by dialysis and can be reversed with idarucizumab.[98]

IVC filter may be indicated in selected patients with acute bleeding during anticoagulation.

A dose of activated factor VIIa can be considered if there is intracranial bleeding or massive GI bleeding.[138] This dose reverses the effect of warfarin almost immediately and the effect lasts up to 1 hour.

Data suggest that off-label use of factor VIIa is common and that up to 10% of cases treated with factor VIIa develop acute thrombotic complications.[139]

heparin-induced thrombocytopenia (HIT)	**short term**	**low**

Antibodies may develop to heparin-platelet factor IV complexes starting 5 to 7 days after initial exposure to heparin.[131] The antibodies aggregate platelets, lead to thrombocytopenia, and might result in acute arterial and venous thrombosis.

If there is a history of recent heparin exposure, development of HIT can be immediate. It develops in between 1% to 2% of patients treated with therapeutic doses of heparin; however, it is rare when heparin is given subcutaneously to patients as a form of prophylaxis.

The incidence of HIT is lower in patients treated with low molecular weight heparin (LMWH). Although there have been several reported cases of fondaparinux-associated HIT, it is a rare occurrence.

Due to the risk of HIT, platelet count should be measured at baseline, then on days 3 and 5, to observe for the development of HIT.

Suspected HIT should be managed by promptly discontinuing heparin or LMWH, and substituting a direct thrombin inhibitor or an anti-Xa agent such as fondaparinux. Anticoagulation is transitioned to warfarin when the platelet count returns to baseline.

When anticoagulation is clinically indicated in the presence of definite or moderate/high probability HIT, a direct thrombin inhibitor is the generally recommended anticoagulant.

The Warkentin Probability Scale for HIT can be used to estimate the pretest probability of HIT.[80]

heparin resistance	**short term**	**low**

Complications	Timeframe	Likelihood
Patients might require very large doses of intravenous heparin and never achieve a therapeutic activated partial thromboplastin time (aPTT).[105] This might be caused by very high levels of clotting factors, such as fibrinogen. In patients who require extremely large daily doses of unfractionated heparin (i.e., >2500 units/hour) without achieving a therapeutic aPTT, it is recommended that the anti-Xa level be measured and used to guide heparin dosing.		
post-thrombotic syndrome	**long term**	**medium**
Caused by chronic obstruction of venous outflow and/or destruction of venous valves, resulting in venous hypertension from venous insufficiency and/or venous outflow obstruction.[134] Up to half of patients develop some signs or symptoms of post-thrombotic syndrome (also known as post-phlebitic syndrome) and this usually occurs within 2 years of the acute DVT episode.		
delayed bleeding during treatment	**variable**	**low**
The incidence is greatest in the first 3 months of treatment when on warfarin. Most bleeds are minor. Fatality is relatively rare, and the rate is greatest for intracranial bleeds. Age over 75 years is associated with an increase in the incidence of intracranial bleeding.		
osteoporosis due to heparin treatment	**variable**	**low**
While the risk of osteoporotic fracture is as high as 2% if unfractionated heparin is given throughout pregnancy, there are only a handful of cases published where osteoporotic fracture occurred in those on LMWH.[140] There is conflicting evidence as to whether this develops in patients during chronic warfarin therapy.		

Prognosis

Whether a DVT is provoked or idiopathic is a significant determinant of recurrence. The extent and location of the initial clot influence the risk of post-thrombotic syndrome (also known as post-phlebitic syndrome), which is the major sequela of DVT. Deep venous thrombosis seldom alters the overall prognosis of the patient; the presence or absence of an underlying malignancy, and the presence or absence of underlying medical comorbidity, such as liver disease or chronic kidney disease, remain the major prognostic determinants among DVT patients. People with cancer have reduced survival rates compared to people without cancer. When a patient dies from DVT, it is usually from pulmonary embolus or from a major haemorrhage as a complication of the anticoagulation therapy.

In one systematic review, during the initial 3 months of anticoagulation, the rate of recurrent fatal VTE was 0.4% with a case-fatality rate of 11.3%. The rate of fatal major bleeding events was 0.2% with a case-fatality rate of 11.3%. After anticoagulation, the rate of fatal recurrent VTE was 0.3 per 100 patient-years with a case-fatality rate of 3.6%.[117]

In community cohort studies, the incidence of acute recurrent DVT within 60 days is as high as 25% to 30%. The reasons for this acute recurrence are not known, but subtherapeutic anticoagulant therapy or patient non-adherence to therapy may contribute.[118] [119]

In patients with acute DVT or PE enrolled in prospective cohort studies, only 5% of patients develop recurrent VTE during the initial 6 months of anticoagulation; however, 30% of patients develop recurrent VTE between 6 months and 5 years after the initial event, if off anticoagulation.[120] [121]

Compared with patients with no thrombophilic defects, the rate of recurrence during warfarin therapy is not increased in the presence of one or more defects.[122]

The incidence of major life-threatening haemorrhage owing to anticoagulant treatment is low.

Recurrence

Consensus guidelines recommend 3 months of oral anticoagulant therapy to prevent recurrence in all patients with venous thromboembolism (VTE) with re-assessment after 3 months if a patient has an unprovoked or idiopathic VTE.[123] Consideration should be given to indefinite treatment among patients who have idiopathic or unprovoked DVT.[124]

A number of individual factors have been reported to be associated with a lower incidence of recurrent thromboembolism among patients treated for an unprovoked DVT, such as female gender, absence of a major thrombophilic disorder (e.g., antiphospholipid antibody syndrome or antithrombin deficiency), absence of residual thrombosis on ultrasound,[125] [126] normal factor VIII levels, normal thrombin generation, and a normal D-dimer level 1 month after stopping warfarin.[127] [128] These risk factors, and combinations thereof, should be used to guide duration of treatment.[129]

One study did find that a combination of findings were associated with a lower incidence of recurrent DVT among women who had had an unprovoked DVT. Women who had 1 or none of the following risk factors had a very low incidence of recurrent VTE: age <65 years, BMI <30, normal D-dimer while on warfarin, or no skin changes of venous stasis on the affected extremity (i.e., oedema, erythema, pigmentation). Unfortunately, there were no risk factors in men that could separate a high and low risk of recurrent VTE.[130] Other risk assessment models exist such as D-dimer, Age, Sex, and Hormones (DASH) and the Vienna Prediction Model; however, these models have not been sufficiently validated as yet, and are not used routinely in clinical practice.

Diagnostic guidelines

Europe

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: This guideline covers the diagnosis of venous thromboembolic diseases in adults (aged 18 and over), and the role of thrombophilia testing.

Prevention and management of venous thromboembolism: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2014

Summary: Provides advice on the diagnosis of DVT and pulmonary embolism, including the use of diagnostic algorithms incorporating D-dimer assay.

Clinical guidelines for testing for heritable thrombophilia

Published by: British Committee for Standards in Haematology **Last published:** 2010

North America

NCCN clinical practice guidelines in oncology: cancer-associated venous thromboembolic disease

Published by: National Cancer Care Network **Last published:** 2017

ACR appropriateness criteria: acute chest pain - suspected pulmonary embolism

Published by: American College of Radiology **Last published:** 2016

Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians

Published by: American College of Physicians **Last published:** 2015

Summary: This guideline provides a comprehensive overview of the diagnostic approach for this condition.

Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline

Published by: Interdisciplinary Expert Panel on Iliofemoral Deep Vein Thrombosis (InterEPID) **Last published:** 2015

Summary: This guideline provides a comprehensive overview of the diagnostic approach for this condition.

North America

ACR-AIUM-SPR-SRU practice parameter for the performance of peripheral venous ultrasound examination

Published by: American College of Radiology; American Institute of Ultrasound in Medicine; Society of Pediatric Radiology; Society of Radiologists in Ultrasound **Last published:** 2015

ACR appropriateness criteria: hemoptysis

Published by: American College of Radiology **Last published:** 2014

ACR appropriateness criteria: suspected lower-extremity deep vein thrombosis

Published by: American College of Radiology **Last published:** 2013

Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th edition

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Preferred strategies for diagnosis of first DVT in ambulatory patients combine the use of pretest probability assessment, D-dimer level, and ultrasound.

Asia

Diagnosis and treatment of lower extremity deep vein thrombosis: Korean practice guidelines

Published by: Korean Society of Interventional Radiology; Korean Society for Vascular Surgery **Last published:** 2016

Summary: Provides recommendations for the diagnosis of lower extremity deep vein thrombosis.

Treatment guidelines

Europe

Thromboembolic disease in pregnancy and the puerperium: acute management

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

Summary: Provides information, based on clinical evidence where available, regarding the immediate investigation and management of women in whom VTE is suspected during pregnancy or the puerperium.

Reducing the risk of venous thromboembolism during pregnancy and the puerperium

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

Europe

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: This guideline covers the management of venous thromboembolic diseases in adults (aged 18 and over) and the role of thrombophilia testing.

Ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Venous thromboembolism: reducing the risk for patients in hospital

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Postnatal care up to 8 weeks after birth

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Published by: National Institute for Health and Care Excellence **Last published:** 2014

Prevention and management of venous thromboembolism: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2014

Summary: Provides recommendations on treatment options for thrombosis in various anatomical regions.

Antithrombotics: indications and management - a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2013

Guidelines on travel-related venous thrombosis

Published by: British Committee for Standards in Haematology **Last published:** 2011

Recommendations from the British Committee for Standards in Haematology and National Patient Safety Agency: safety indicators for inpatient and outpatient oral anticoagulant care

Published by: British Committee for Standards in Haematology; National Patient Safety Agency **Last published:** 2006

Guidelines on use of vena cava filters

Published by: British Committee for Standards in Haematology **Last published:** 2006

International

Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action

Published by: International Working Group **Last published:** 2009

Summary: Summarises the differences in guidelines published by the Italian Association of Medical Oncology, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the French National Federation of the League of Centers Against Cancer, and the European Society of Medical Oncology. Recommendations are summarised for initial treatment of VTE in patients with cancer, long-term treatment of VTE in patients with cancer, thrombolytic therapy in the initial treatment of VTE in patients with cancer, and treatment of catheter-related thrombosis.

North America

NCCN clinical practice guidelines in oncology: cancer-associated venous thromboembolic disease

Published by: National Cancer Care Network **Last published:** 2017

Summary: This guideline provides a comprehensive overview of the management of this condition.

Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report

Published by: American College of Chest Physicians **Last published:** 2016

Summary: Provides a comprehensive overview of the management of DVT.

Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline

Published by: Interdisciplinary Expert Panel on Iliofemoral Deep Vein Thrombosis (InterEPID) **Last published:** 2015

Summary: This guideline provides a comprehensive overview of the management of this condition.

Venous thromboembolism prophylaxis and treatment in patients with cancer

Published by: American Society of Clinical Oncology **Last published:** 2015

Summary: Recommendations for the treatment and prevention of DVT in patients with cancer.

Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th edition

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides recommendations for thromboprophylaxis in non-orthopaedic surgical patients.

North America

Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty

Published by: American Academy of Orthopaedic Surgeons **Last published:** 2011

Summary: Evidence-based practice guidelines to help physicians who manage the prevention of venous thromboembolic disease in patients undergoing orthopaedic surgery. Gaps in the evidence are identified.

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association

Published by: American Heart Association **Last published:** 2011

Summary: Unfractionated heparin, low molecular weight heparin, or fondaparinux are recommended for the initial anticoagulation of patients with iliofemoral deep vein thrombosis (IFDVT). Where first-episode IFDVT is related to a major reversible risk factor, anticoagulation should be stopped after 3 months. Unprovoked or recurrent IFDVT should have at least 6 months of anticoagulation.

Practice parameters for the prevention of venous thrombosis

Published by: American Society of Colon and Rectal Surgeons **Last published:** 2006

Asia

Diagnosis and treatment of lower extremity deep vein thrombosis: Korean practice guidelines

Published by: Korean Society of Interventional Radiology; Korean Society for Vascular Surgery **Last published:** 2016

Summary: Provides recommendations for the treatment of lower extremity deep vein thrombosis.

Online resources

1. IHI: reducing adverse drug events involving anticoagulants *(external link)*
2. Thrombosis Canada: warfarin point-of-care INR monitoring *(external link)*

Evidence scores

1. Role of point-of-care D-dimer test: there is good-quality evidence that point-of-care D-dimer tests can contribute important information and guide patient management in low-risk patients with suspected venous thromboembolism. [71]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

2. Mortality in cancer patients: there is good-quality evidence that low molecular weight heparin is most likely superior to unfractionated heparin in reducing mortality in the initial treatment of venous thromboembolism in patients with cancer.[87]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

3. Mortality and recurrence of thromboembolism: there is medium-quality evidence that long-term oral anticoagulation is as effective as long-term low molecular weight heparin (LMWH) at reducing mortality at 3 months. There is poor-quality evidence that long-term oral anticoagulation is also as effective as LMWH at reducing recurrence of thromboembolism at 3 to 12 months.
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

4. Proximal extension of clot: there is good-quality evidence that warfarin plus heparin is more effective at reducing proximal extension of clot at 1 year compared with heparin alone in people with isolated calf DVT. We found no direct information about whether anticoagulation is better than no active treatment in people with isolated calf DVT.
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

5. Reduction in acute symptoms: there is medium-quality evidence that early walking exercise may help reduce acute symptoms.[100]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

6. Mortality: there is medium-quality evidence that vena cava filters do not reduce mortality at 2 years compared with no filters, in people with thromboembolism. The evidence suggests that vena cava filters may be more effective at preventing pulmonary embolism at 12 days, but also increase the risk of recurrent DVT at 2 to 8 years.

Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

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Images

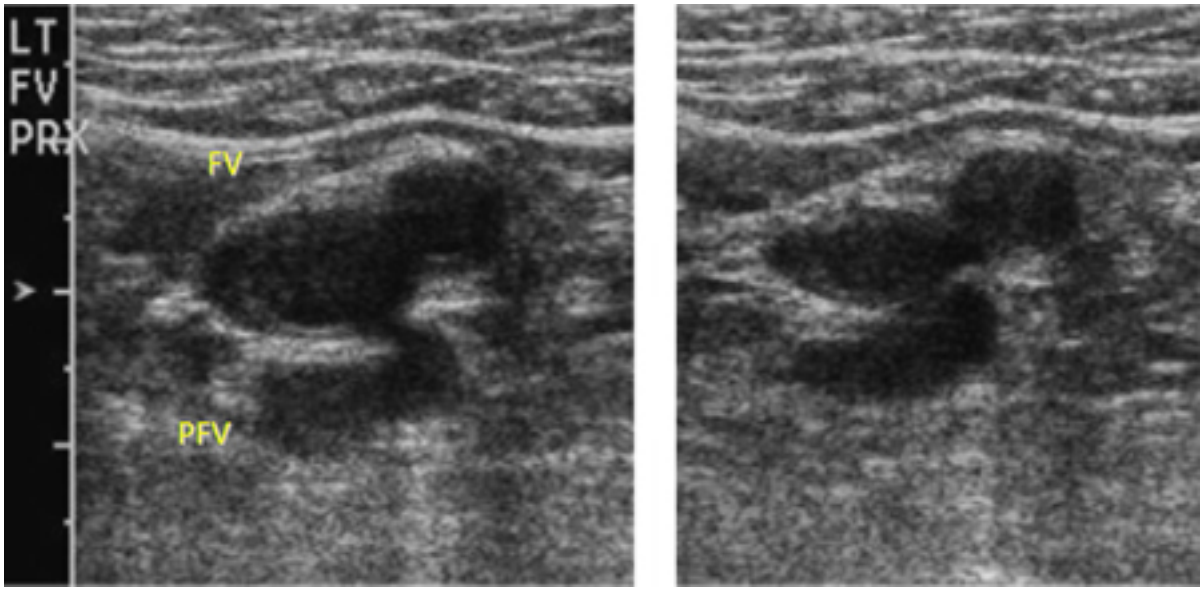

Figure 1: Short-axis ultrasound view showing the femoral vein (FV) and profunda femoris vein (PFV) adjacent to the femoral artery before compression (left) and compressed (right)

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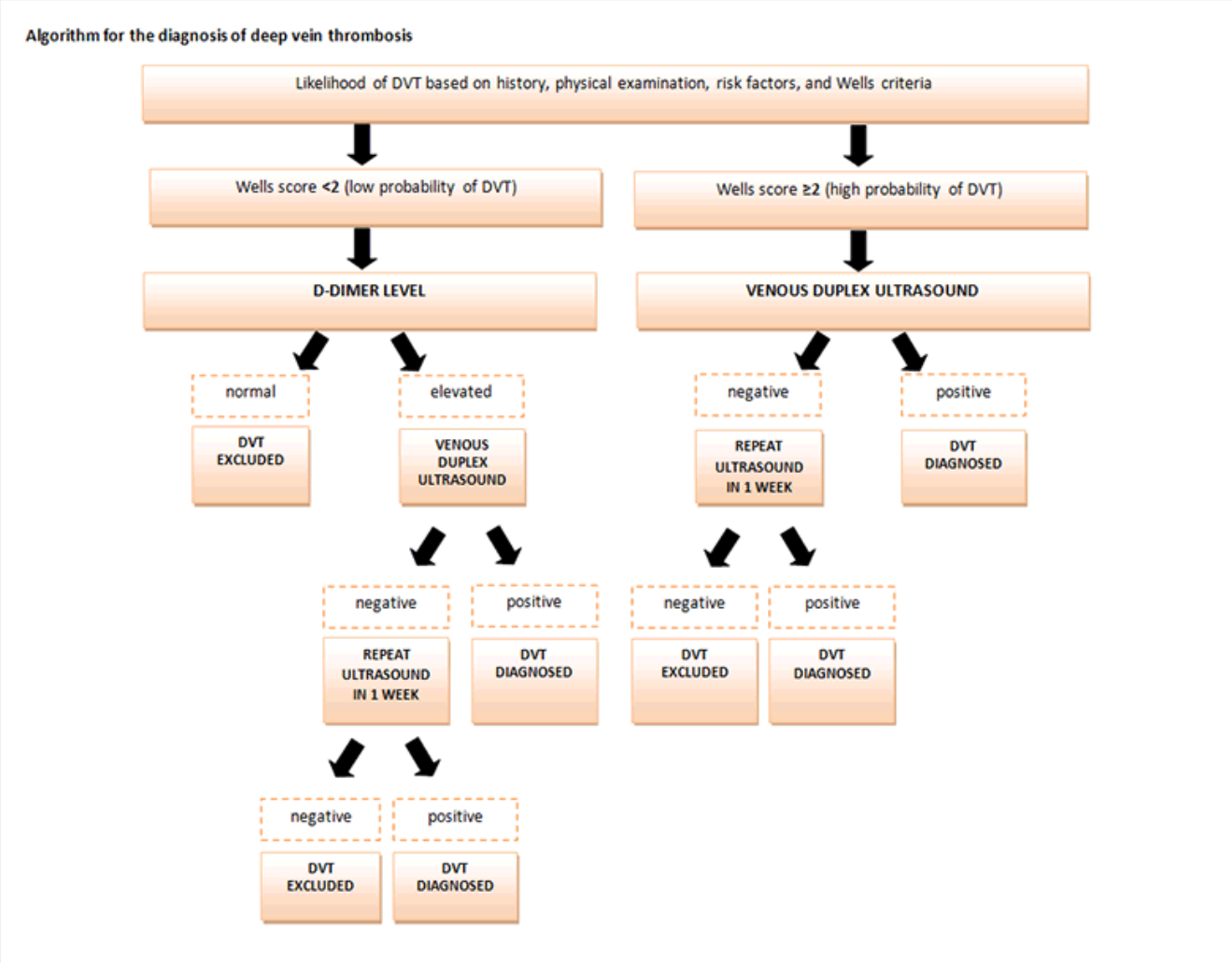

Figure 2: Algorithm for the diagnosis of deep vein thrombosis

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DISCLOSURES: GM has received grant or research support from BMS, J&J, Sanofi-Aventis, Portola, and Janssen; he has served as a Scientific Consultant for BMS, J&J, and Sanofi-Aventis.

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// Acknowledgements:

Dr Geno Merli, Dr Taki Galanis, Dr Luis Eraso, and Dr Geoffrey Ouma would like to gratefully acknowledge Dr Richard White and Dr Windsor Ting, the previous contributors to this monograph. RW declares participation in numerous multicentered clinical trials sponsored by companies: Agenix, Boehringer-Ingleheim, Amgen, Bayer, Bristol-Meyer-Squibb, Novartis, Hemosense. WT declares that he has no competing interests.

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DISCLOSURES: SMS is co-investigator on an active trial of warfarin pharmacogenetics sponsored by Iverson Genetics, and on an active trial of the effect of active physician alerting for VTE prevention, sponsored by TWINE LLC. He has previous research contracts for trials of apixaban and rivaroxaban, and research subcontracts from the National Institute of Health (warfarin pharmacogenetics) and Canadian Institute of Health Research (use of D-dimer testing for anticoagulation cessation). SMS was a panelist

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