Clinical review

Diagnosis, investigation, and management of deep vein thrombosis

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Deep vein thrombosis is an important cause of morbidity and mortality worldwide, and its clinical diagnosis is unreliable. This article explains current screening and diagnostic methods as well as treatment

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Venous thromboembolic disease has an estimated annual incidence in developed countries of one in 1000 people.¹ The disorder commonly manifests as deep vein thrombosis of the leg, but deep venous thrombosis may also occur in other veins (cerebral sinus, arms, retina, and mesentery).

The sequelae of deep vein thrombosis vary from complete resolution of the clot without any ill effects through to death due to pulmonary embolism. Morbidity due to deep vein thrombosis includes post-thrombotic syndrome, encompassing chronic venous hypertension causing limb pain, swelling, hyperpigmentation, dermatitis, ulcers, venous gangrene, and lipodermatosclerosis.

Pain or swelling of a lower limb is a common presenting complaint, and a wide differential diagnosis exists (box 1). No single investigation for the diagnosis of deep vein thrombosis has ideal properties (100% sensitivity and specificity, low cost, no risk), and often several tests are performed, either sequentially or in combination.

Box 1: Possible causes of pain or swelling of the lower limb

Venous

- Deep vein thrombosis
- Superficial thrombophlebitis
- Post-thrombotic syndrome
- Chronic venous insufficiency
- Venous obstruction

Other

- Cellulitis
- Baker's cyst
- Torn gastrocnemius muscle
- Fracture
- Haematoma
- Acute arterial ischaemia
- Lymphoedema
- Hypoproteinaemia (for example, cirrhosis, nephrotic syndrome)

Summary points

Deep vein thrombosis is an important cause of morbidity and mortality

Clinical diagnosis is unreliable

Screening investigations include D-dimer tests and plethysmographic techniques

Definitive diagnosis is usually by venography or ultrasonography

Initial treatment is with heparin—unfractionated or low molecular weight—followed by oral anticoagulation

Outpatient treatment of deep vein thrombosis is safe

With the introduction of low molecular weight heparins it is now possible to treat deep vein thrombosis as an outpatient condition. This review describes the investigations used in the diagnosis of deep vein thrombosis of the lower limb and the further management of the condition.

Methods

We reviewed the literature by searching the Medline database for the period 1990-2002 for the following key words in various combinations: "diagnosis," "management," "DVT," "deep vein thrombosis," "venous thromboembolism," "D-dimer," "plethysmography." We also searched the Cochrane database of abstracts for reviews of the treatment of venous thromboembolism.

Diagnostic methods

Clinical diagnosis

The clinical diagnosis of deep vein thrombosis of the lower limb is unreliable. Individual signs and symptoms are of little value, and Homan's sign is of no value.²⁻³

A clinical model has been devised (table), and prospectively validated in a large series, whereby patients are classified as having a high, intermediate, or low probability of developing deep vein thrombosis, based on history and clinical signs.⁴ This clinical model has been used in diagnostic algorithms to reduce the number of diagnostic tests required on patients with suspected deep vein thrombosis.⁴⁻⁶

Screening tests for deep vein thrombosis

The search has been continuing for a screening test with a high negative predictive value, which can be used as a rule-out test to reduce the need for imaging. A fast, reliable, non-invasive, and inexpensive screening test is needed that can be performed immediately on attendance at hospital. In recent years interest has focused on the use of D-dimer tests and plethysmography (box 2).

Box 2: Screening investigations for deep vein thrombosis

D-dimer tests

- Laboratory tests:
Enzyme linked immunosorbent assay (ELISA)
Latex agglutination
- Near patient tests:
SimpliRED (agglutination test)
Simplify (immunochromatography test)

Plethysmography

- Digital photoplethysmography
- Strain gauge plethysmography
- Impedance plethysmography

D-dimer tests

Plasma D-dimers are specific cross linked derivatives of fibrin, produced when fibrin is degraded by plasmin, so concentrations are raised in patients with venous thromboembolism. Although sensitive for venous thromboembolism, high concentrations of D-dimers are insufficiently specific for making a positive diagnosis because they occur in other disorders such as malignancy and pregnancy and after operations. Nevertheless, D-dimer tests generally have a high negative predictive value and are useful rule-out tests that reduce the need for imaging when used in conjunction with clinical probability, plethysmography, or ultrasonography.⁵⁻⁸

Several D-dimer assays are in clinical use. Two of the most extensively studied are the laboratory based VIDAS enzyme linked immunosorbent assay (ELISA) and the SimpliRED whole blood agglutination test.^{9, 10} The SimpliRED test provides a qualitative result (positive or negative) within 10 minutes and is suitable for near patient testing. An immunochromatography D-dimer test (Simplify), which is suitable for near patient testing, has also been introduced recently, but no published studies have evaluated the usefulness of the test. Some evidence exists that D-dimer concentrations should be measured after the end of the anticoagulation period, to determine the risk of re-thrombosis.¹¹

Clinical model for predicting pretest probability for deep vein thrombosis (data from reference 4)

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the legs	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or wider than that of deep vein thrombosis	-2

Low probability 0 or less, moderate probability 1-2, high probability 3 or more.

Plethysmography

Plethysmography is the term given to the recording of changes in the size of the limb due to tissue fluid or pooled blood in the veins. This measurement can be undertaken in various ways: photoplethysmography, strain gauge, and electrical impedance.

Digital photoplethysmography—Photoplethysmography depends on the absorption of light by haemoglobin in the red cells. Digital photoplethysmography is assisted by a microprocessor, and the test is easy to perform.¹² A digital measurement probe is placed on the skin, 10 cm above the medial malleolus of the affected leg (fig 1). The patient then dorsiflexes the foot 10 times according to a standard protocol and then rests for 45 seconds. Based on the characteristics of the reflected light the venous refilling time is calculated and presented as a printed graph (fig 2). In one study of 100 hospital inpatients a venous refilling time of longer than 20 seconds excluded a deep vein thrombosis and had a sensitivity of 100% and a specificity of 47%.¹² Digital photoplethysmography is a simple screening test to perform, but bigger studies are needed to evaluate its usefulness fully.

Computerised strain gauge plethysmography—The principle behind computerised strain gauge plethysmography is to measure changes in calf dimensions while venous outflow is occluded by inflation of a thigh cuff.¹³ The rate of decrease in calf size when this occlusion is removed gives a measure of venous outflow. Rapid emptying is the rule in a healthy venous system. Obstruction to outflow is seen with thrombotic

Fig 1 Use of digital photoplethysmography screening for deep vein thrombosis

Fig 2 Normal digital photoplethysmography curve together with an abnormal curve implying deep vein thrombosis

occlusion of proximal vessels. Computer software is used to calibrate the strain gauge and calculate blood flow measurements in the leg. The test can be performed in 15 minutes, and the procedure can be performed with minimal training. One study of 307 consecutive patients showed a sensitivity of 90% for proximal (popliteal, femoral, or iliac vein) deep vein thrombosis and 66% for distal (calf vein) deep vein thrombosis.¹³

Impedance plethysmography—Impedance plethysmography relies on the principle that the volume of blood in the leg affects the blood's ability to conduct an electrical current, which is inversely proportional to the impedance between two electrodes placed along the calf. A cuff is inflated around the thigh to obstruct venous outflow but not arterial inflow. As blood accumulates in the leg below the cuff, impedance between the calf electrodes falls. The sudden release of the cuff results in the blood volume of the leg decreasing, resulting in a rapid increase in impedance. Obstruction to venous flow such as with a deep vein thrombosis causes a reduction in the rate of venous emptying (and slower increase in impedance) than normal. The technique is operator dependent, and the sensitivity in some studies has been low.¹⁴ Some centres therefore now combine impedance plethysmography with D-dimer tests.⁷

Definitive investigations for deep vein thrombosis

Investigations used for the definitive diagnosis of deep vein thrombosis visualise the thrombus (box 3). These investigations include contrast venography, ultrasonography, computed tomography, and magnetic resonance imaging.^{1 2 5} I fibrinogen leg scanning is now seldom used.

Venography

The gold standard for establishing the diagnosis of deep vein thrombosis has been contrast venography.¹⁵ However, this procedure is invasive, not always technically possible, and it carries a small risk of an allergic reaction or venous thrombosis. Figure 3 is a venogram showing a popliteal deep vein thrombosis.

Ultrasonography

Ultrasonography is considered to be the best non-invasive diagnostic method and has been evaluated against venography in many studies, showing an

average sensitivity and specificity of 97% for proximal deep vein thrombosis.¹⁴ However, ultrasonography cannot be relied on to diagnose calf vein thrombosis, and the sensitivity for symptomatic calf vein thrombosis has been reported to be as low as 75%.¹⁴

Three ultrasonography techniques are in use.

Compression ultrasound—The most simple ultrasonic criterion for diagnosing venous thrombosis is non-compressibility of the vascular lumen under gentle probe pressure (compression ultrasound). If no residual lumen is observed the vein is considered to be fully compressible, which indicates the absence of venous thrombosis.

Duplex ultrasonography—Patients are examined in an identical way to that with conventional compression ultrasound. In addition, blood flow characteristics are evaluated by using the pulsed Doppler signal. Blood flow in normal veins is spontaneous and phasic with respiration and can be augmented by manual compression distal to the ultrasound transducer. When the phasic pattern is absent, flow is defined as continuous, indicating the presence of venous outflow obstruction.

Colour flow duplex imaging—The technique of colour coded Doppler ultrasonography (colour Doppler) is identical to duplex ultrasonography. In colour flow sonography, pulsed Doppler signals are used to produce the images. When a Doppler shift is recognised, it is assigned a colour (red or blue) according to its direction towards or away from the probe. Therefore colour Doppler results in a display of flowing blood as a colour overlay to the grey scale ultrasound image, which makes it easier to identify the veins.

Serial ultrasonography

Calf vein deep vein thrombosis is not identified reliably by ultrasound techniques. As the thrombosis can extend into the proximal veins several strategies have been used to identify patients with this condition. One diagnostic strategy has been to repeat ultrasonography after five days in patients whose result is negative.¹⁶ The disadvantage of this strategy is that all patients with a negative ultrasound scan must return for further evaluation.

Ultrasonography combined with pre-test probability of deep vein thrombosis or D-dimer test

In some centres compression ultrasound imaging of the proximal veins of the leg is combined with a clinical model (table). It has been suggested that patients with a low clinical probability and a normal ultrasound scan can be safely discharged without serial ultrasonography.⁴

Fig 3 Venogram showing a popliteal deep vein thrombosis

Box 3: Definitive investigations for deep vein thrombosis

- Venography
- Ultrasonography:
 - Compression ultrasound
 - Duplex ultrasonography
 - Colour coded Doppler ultrasonography
- Computed tomography
- Magnetic resonance imaging

Another strategy is to combine ultrasonography with a D-dimer test. It has been suggested that patients with a normal initial ultrasound test and normal D-dimer concentration do not need a repeat ultrasound examination.¹⁷

Spiral computed tomography venography and magnetic resonance imaging

Spiral computed tomography venography of the leg has shown promise for the diagnosis of deep vein thrombosis and other soft tissue diseases in patients with leg swelling.¹⁸ A small study of 53 patients, in which magnetic resonance imaging was used to detect deep vein thrombosis, showed that this technique may be better than current non-invasive methods for diagnosing deep vein thrombosis in the calf. This technique is not likely to be used widely until costs decrease.¹⁹

Treatment of deep vein thrombosis

The standard initial management of deep vein thrombosis has traditionally meant admission to hospital for continuous treatment with intravenous unfractionated heparin. Treatment then continued with a transition to long term use of oral anticoagulants (vitamin K antagonists). Recently a change has taken place, and low molecular weight heparins are being used.

Guidelines prepared by the haemostasis and thrombosis task force recommend that patients receive heparin for at least four days and treatment should not be discontinued until the international normalised ratio has been in the therapeutic range for two consecutive days.²⁰ According to these guidelines, a patient with a first episode of a proximal vein thrombosis should receive anticoagulants for six months, with a target international normalised ratio of 2.5. The issue of length of anticoagulation is still under debate.

Heparins

Unfractionated heparin is a heterogeneous mixture of polysaccharide chains. Low molecular weight heparins are fragments of unfractionated heparin created by depolymerisation.²¹ Advantages of low molecular weight heparin over unfractionated heparin are that it offers a more consistent and predictable anticoagulant response, has a longer half life, and so permits once daily subcutaneous administration without the need to monitor activated partial thromboplastin time.

Low molecular weight heparin is at least as effective as unfractionated heparin in preventing recurrent venous thromboembolism, and statistically significantly reduces the occurrence of major haemorrhage during initial treatment and overall mortality at the end of follow up.²² Long term treatment with low molecular weight heparin is sometimes indicated rather than treatment with oral anticoagulants, for patients with contraindications to anticoagulants (for example, pregnant women).

Common practice in the United Kingdom is to use low molecular weight heparin during pregnancy, with either low molecular weight heparin or warfarin for six to 12 weeks after the birth. Practice, however, still varies widely, with some centres using unfractionated heparin.

Thrombolytic drugs

There is weak evidence that thrombolytics such as streptokinase may produce more rapid resolution of symptoms and preserve venous valve integrity and hence decrease the incidence of the post-phlebotic syndrome.²³ However, the risk of bleeding complications is three times greater, and for this reason thrombolytics are now seldom used.

Inferior vena cava filter

Inferior vena cava filters are inserted to reduce the rate of pulmonary embolism. The indications for their use include:

- Pulmonary embolism with contraindication to anticoagulation, and
- Recurrent pulmonary embolism despite adequate anticoagulation.

In the United Kingdom most vena cava filters are temporary and removed three weeks after the period during which the risk of embolisation is greatest. No consensus has been reached on whether patients with long term filters should receive long term treatment with anticoagulants or not.

Elastic compression stockings

Patients with a deep vein thrombosis should wear compression stockings as the rate of post-thrombotic syndrome may be reduced. In one study of 194 patients (with a first episode of proximal deep vein thrombosis) the rate of post thrombotic syndrome was reduced by 50% if graded compression stockings were used.²⁴

Outpatient treatment of deep vein thrombosis

With the advent of low molecular weight heparins, outpatient treatment of deep vein thrombosis without monitoring activated partial thromboplastin time is now possible. Many trials have compared a home treatment regimen with hospital treatment for the initial phase of treatment for deep vein thrombosis. Most of the trials have been uncontrolled, and their limited evidence shows that home treatment is cost effective, preferred by patients, and no more liable to lead to complications than hospital treatment.²⁵

The precise pattern of screening and diagnostic tests performed to evaluate the patient with suspected deep vein thrombosis of the lower limb remains dependent on local practice. These patients will also generally undergo further investigations to identify an underlying cause or predisposition. Cancer and immobility are the leading causes of deep vein thrombosis in people over 45, and in people under that age thrombophilia becomes important.

Ongoing research

Fondaparinux

Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X. This drug has recently been licensed in the United Kingdom for prophylaxis of venous thromboembolism in patients having major orthopaedic surgery of the legs. The potential use of this drug for treating deep vein thrombosis has not yet been fully evaluated.

Length of anticoagulation

The British Thoracic Society is currently organising a large multicentre trial comparing the long term

Additional educational resources

- American Thoracic Society. The diagnostic approach to acute venous thromboembolism: clinical practice guidelines. *Am J Respir Crit Care Med* 1999;160:1043-1066.
- The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-62.
- Van der Heijden JF, Hutten BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism (Cochrane Review). In: *Cochrane Library*, Issue 1. Oxford: Update Software, 2002.
- Pinede L, Cucherat M, Duhaut P, Ninet J, Boissel JP. Optimal duration of anticoagulant therapy after an episode of venous thromboembolism. *Blood Coagul Fibrinolysis* 2000;11:701-7.

Information for patients

Victims of air related DVT association (VARDA)—The aim of VARDA is to campaign for prevention of deep vein thrombosis among air passengers (www.aviation-health.org/varda.html)

outcome of patients having three months or six months anticoagulation after a first episode of deep vein thrombosis.

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- 1 Carter CJ. Epidemiology of venous thromboembolism. In: Hull RD, Pineo GF, eds. *Disorders of thrombosis*. Philadelphia: Saunders, 1996:159-74.
- 2 Ebell MH. Evaluation of the patient with suspected deep vein thrombosis. *J Fam Pract* 2001;50:167-71.
- 3 O'Donnell TF Jr, Abbott WM, Athanasoulis CA, Millan VG, Callow AD. Diagnosis of deep vein thrombosis in the outpatient by venography. *Surg Gynecol Obstet* 1980;150:69-74.
- 4 Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pre-test probability of deep vein thrombosis in clinical management. *Lancet* 1997;350:1795-8.
- 5 Aschwanden M, Labs KH, Jeanneret C, Gehrig A, Jaeger KA. The value of rapid D-dimer testing combined with structured clinical evaluation for the diagnosis of deep vein thrombosis. *J Vasc Surg* 1999;30:929-35.
- 6 Kearon C, Ginsberg JS, Douketis J, Crowther M, Brill-Edwards P, Hirsh J. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. *Ann Intern Med* 2001;135:108-11.

- 7 Ginsberg JS, Kearon C, Douketis J, Turpie AG, Brill-Edwards P, Stevens P, et al. The use of D-dimer testing and impedance plethysmographic examination in patients with clinical indications of deep vein thrombosis. *Arch Intern Med* 1997;157:1077-81.
- 8 Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. *Arch Int Med* 2002;162:747-56.
- 9 Pittet JL, de Moerloose P, Reber G, Durand C, Villard C, Piga N, et al. VIDAS D-dimer: fast quantitative ELISA for measuring D-dimer in plasma. *Clin Chem* 1996;42:410-5.
- 10 Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 1995;91:2184-7.
- 11 Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost* 2002;87:7-12.
- 12 Tan YK, daSilva AF. Digital photoplethysmography in the diagnosis of suspected lower limb DVT: is it useful? *Eur J Vasc Endovasc Surg* 1999;18:71-9.
- 13 Maskell NA, Cooke S, Meecham Jones DJ, Prior JG, Butland RJA. The use of automated strain gauge plethysmography in the diagnosis of deep vein thrombosis. *Br J Radiol* 2002;75:648-51.
- 14 Kraaijenhagen RA, Lensing AW, Wallis JW, van Beek EJ, ten Cate JW, Buller HR. Diagnostic management of venous thromboembolism. *Baillieres Clin Haematol* 1998;11:541-86.
- 15 De Valois JC, van Schaik CC, Verzijlbergen F, van Ramshorst B, Eikelboom BC, Meuwissen OJA. Contrast venography: from gold standard to "golden backup" in clinically suspected deep vein thrombosis. *Eur J Radiol* 1990;11:131-7.
- 16 Birdwell BG, Raskob GE, Whitsett TL, Durica SS, Comp PC, George JN, et al. Clinical validity of normal compression ultrasonography in outpatients suspected of having deep vein thrombosis. *Ann Intern Med* 1998;128:1-7.
- 17 Bernardi E, Prandoni P, Lensing AW, Agnelli G, Guazzaloca G, Scannapieco G, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ* 1998;317:1037-40.
- 18 Yoshida S, Akiba H, Tamakawa M, Yama N, Takeda M, Hareyama M. Spiral CT venography of the lower extremities by injection via an arm vein in patients with leg swelling. *Br J Radiol* 2001;74:1013-6.
- 19 Fraser DGW, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: A prospective blinded study of magnetic resonance direct thrombus imaging. *Ann Intern Med* 2002;136:89-98.
- 20 Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation. *Br J Haematol* 1998;101:374-87.
- 21 Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688-98.
- 22 Van den Belt AGM, Prins MH, Lensing AWA, Castro AA, Clark OAC, Attalah AN, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. In: *Cochrane Library*, Issue 1. Oxford: Update Software, 2002.
- 23 Rogers L, Lutchter C. Streptokinase therapy for deep vein thrombosis: a comprehensive review of the English literature. *Am J Med* 1990;88:389-95.
- 24 Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997;349:759-62.
- 25 Schraibman IG, Milne AA, Royle EM. Home versus in-patient treatment for deep vein thrombosis. *Cochrane Library*, Issue 1. Oxford: Update Software, 2002.

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