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CLINICAL REVIEW

Management of deep vein thrombosis and prevention of post-thrombotic syndrome

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The annual global incidence of deep vein thrombosis (DVT) of the leg is 1.6 per 1000.[1] Classically, venous thrombosis of a lower limb begins in a deep calf vein and propagates more proximally. Symptoms include swelling, pain, and redness of the leg, depending on the vein segment(s) involved (see table 1⇓).[2] Patients are at risk of pulmonary embolism.[3] Despite optimal conservative treatment with anticoagulation and compression, one in four patients develops a post-thrombotic syndrome within one year,[2] and one in three develops a recurrent DVT within five years.[4] Patients with post-thrombotic syndrome have poor quality of life.[5] A more aggressive approach to treatment, such as removal of early thrombus using catheter directed thrombolysis, might improve outcomes for patients with DVT compared with standard anticoagulation treatment.[4-12] We review standard and new, more aggressive, management of DVT for the generalist reader, drawing from recent guidelines, cohort studies, small randomised controlled trails, and meta-analyses. All authors are investigators in the CAVA trial, which is one of three randomised controlled trials currently investigating outcomes after treatment with catheter directed thrombolysis (trial registration number NCT00970619).

Who gets DVT?

The formation of venous thrombosis depends on a triad of hypercoagulability, stasis, and interruption of the integrity of the vein wall. One or more factors may dominate, depending on the underlying risk factor. Table 2⇓ outlines the known risk factors for DVT.[6] The most common locations for venous thromboses of the leg are shown in table 1.[2]

How is DVT diagnosed?

Patients with DVT usually present with pain and swelling of the leg, varying degrees of redness, or muscle cramps. When DVT is confined to the popliteal vein the calf will be mostly affected. When DVT originates or extends more proximally to the iliofemoral vein segment, patients usually have swelling of the whole leg and more severe pain and redness. Mobility may be impaired because of heaviness and pain in the leg. In severe cases patients may develop phlegmasia cerulea dolens (fig 1⇓).

Because these clinical signs are not specific to DVT clinical scoring systems and diagnostic tests have been developed.

The Wells score is the most widely validated method used to assess a patient's risk of current DVT (box). A Wells score of less than 2 means that the patient has a low risk of DVT, while those with a score of 2 or more are at high risk of current DVT.[7] A D-dimer test demonstrates the presence of blood clot degradation products. It has a sensitivity of 95.3% and a specificity of 44.7% for DVT. The negative predictive value is high at 97.7%, making it a useful test for ruling out DVT.[8] A negative D-dimer blood test and a Wells score of less then 2 are effective in ruling out a DVT without the need for duplex ultrasound.[9]

In patients with clinical signs consistent with DVT and a Wells score of 2 or more or a positive D-dimer test (or both), imaging is used to confirm the diagnosis. Non-invasive two point duplex ultrasound is the current standard imaging technique. Duplex ultrasound has a sensitivity of 98.7% and specificity of 100% to detect or rule out an above knee thrombus, and a sensitivity of 85.2% and specificity of 98.2% for below knee DVT, when

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Web references
Villalta scale

Summary points

- Suspect deep vein thrombosis (DVT) in patients who present with sudden swelling, redness, and pain of the calf or leg
- Standard treatment is anticoagulation for at least three months, daily wearing of compressive stockings for two years, and immediate mobilisation
- Anticoagulation protects against pulmonary embolism but post-thrombotic syndrome is common after DVT
- Post-thrombotic syndrome is a chronic debilitating condition seen in about 43% of patients with DVT within two years
- Patients present with a painful heavy leg and may also have cramps, paraesthesia, and pruritus
- Catheter directed thrombolysis for DVT is a new treatment under study that may improve quality of life and reduce the risk of post-thrombotic syndrome

Sources and selection criteria

We conducted a review to answer the question: does catheter directed thrombolysis have a role in the treatment of deep vein thrombosis? We searched PubMed, the Cochrane Library, and Medline up to April 2011 and found several randomised controlled trials and meta-analyses, as well as guidelines. We made a selection on the basis of scientific strength and clinical relevance.

Wells score for risk of deep vein thrombosis (DVT)

Factors with a score of 1 point

- Active cancer treatment (treatment less than six months ago or palliation)
- Paralysis, paresis, or recent plaster immobilisation of the lower extremities
- Recently bedridden for more than three days or major surgery within past four weeks
- Localised tenderness along the distribution of the deep venous system
- Entire leg swollen
- Calf swollen by more than 3 cm when compared with the asymptomatic leg
- Pitting oedema
- Collateral superficial veins (non-varicose)
- Previously documented DVT

Factor with a score of –2 points

- An alternative diagnosis is as likely or more likely than a diagnosis of DVT

Total score

- <2: low risk of DVT
- ≥2: high risk of DVT

compared with the gold standard (invasive venography).[10] Computed tomography venography and magnetic resonance venography can be used to image the exact extent of the DVT (fig 2⇓).[11 12]

Why is it important to treat DVT?

Risk of pulmonary embolism

If DVT is left untreated about 50% of patients will develop a symptomatic pulmonary embolism, which carries a 10% risk of death within one hour of onset of initial symptoms. The main goal of treatment is to prevent pulmonary embolism, propagation of the clot, and recurrence of the DVT.[13-15]

Risk of post-thrombotic syndrome

In addition, 43-47% of patients develop post-thrombotic syndrome within two years of developing symptomatic DVT, although some studies have reported higher rates (>60%) in patients with iliofemoral DVT.[2 16] Post-thrombotic syndrome is a chronic debilitating condition caused by venous hypertension as a result of persistent obstruction of venous outflow and venous insufficiency. A recent observational study found a severely decreased quality of life in patients with post-thrombotic syndrome comparable to that of patients with chronic diseases such as diabetes, obstructive lung disease, and congestive heart failure.[5] Patients present with a painful heavy leg and may also have cramps, paraesthesia, and pruritus. On examination the leg may be oedematous with varicosities or hyperpigmentation of the skin (or both). The condition can be classified according to the recently developed and validated Villalta scale (see web figure).[17] A retrospective study estimated that 30%, 10%, and 3% of people with DVT develop mild, moderate, and severe post-thrombotic syndrome, respectively, and venous obstruction combined with reflux increased the risk significantly.[18] A more severe post-thrombotic syndrome at one month, more extensive DVT (iliofemoral versus calf DVT), higher body mass index, previous ipsilateral DVT, older age, and female sex seem to predict the long term severity of post-thrombotic syndrome.[2]

Risk of venous ulcer disease

Of those who develop post-thrombotic syndrome, 3-5% go on to develop venous ulcers,[19] which are usually painful, resistant to treatment, and tend to recur. Venous ulcers may greatly impair the patient's quality of life and incur high healthcare costs.[2] Figure 3⇓ illustrates venous ulcer disease in a patient with post-thrombotic syndrome.

What is the current standard treatment for DVT?

Standard treatment for DVT is immediate anticoagulation with subcutaneous low molecular weight heparin and later with oral anticoagulants. Compression treatment with elastic stockings

and early ambulation also form part of conservative treatment.[20] Guidelines from the American College of Chest Physicians (ACCP), which are based on level 1A evidence from high quality randomised controlled trials,[13] recommend immediate anticoagulation with subcutaneous low molecular weight heparins for at least five days, and that the patient should simultaneously take oral anticoagulants such as warfarin for at least three months. The duration of oral treatment depends on the cause of the DVT and whether it can be eliminated or not. Anticoagulation alone decreases the risk of pulmonary embolism to 3.8%, the risk of recurrent DVT to 30%, and the risk of post-thrombotic syndrome to 82%.

ACCP guidelines also recommend that compression treatment be started immediately, using compressive bandaging or elastic stockings with a compression pressure of 30-40 mm Hg, and continued for at least two years; this is based on evidence from high quality randomised trials. Compression does not reduce the risk of pulmonary embolism or recurrence of DVT, but it has been shown to decrease the incidence of post-thrombotic syndrome by about 50% at two years. Immediate mobilisation is also recommended. Conservative treatment can be safely carried out at home.[13 21-23]

Although the standard treatment regimen reduces the risk of pulmonary embolism, recurrent DVT, and post-thrombotic syndrome, patients remain at increased risk of pulmonary embolism, recurrence of DVT (30% within five years), and post-thrombotic syndrome (43% at two years). Patients treated with anticoagulants are also at increased risk of severe bleeding complications.[24-26] This has led to research into new treatments for DVT.

Are there any new treatments under study for iliofemoral DVT?

Catheter directed thrombolysis

A recent observational study found that the degree of clot lysis at treatment is directly correlated with long term outcome after iliofemoral DVT.[27] Patients with iliofemoral DVT have double the risk of recurrent thrombosis compared with those with DVT below this segment.[28] On the basis of these findings experts consider that patients with iliofemoral DVT might benefit most from a more aggressive approach to thrombus removal.

A systematic review has shown that the administration of systemic thrombolytic agents—aimed at achieving indirect clot lysis—achieves a small increase in vein segment patency, but the risk of clinically relevant bleeding complications is high, so systemic thrombolysis is no longer used for DVT.[29] However, findings from a non-randomised prospective study of catheter directed thrombolysis, which involves infusion of thrombolytic agents through a catheter directly into the thrombus, suggested that the technique can safely lyse thrombus without appreciable systemic effects and may also restore normal valve function and prevented post-thrombotic reflux (a further risk factor for post-thrombotic syndrome).[30]

The findings of several non-randomised studies and two small randomised controlled trials that compared catheter directed thrombolysis with standard anticoagulation treatment show that catheter directed thrombolysis may reduce the incidence of post-thrombotic syndrome compared with standard anticoagulation alone.[w1-w9] A systematic review of published studies reported that catheter directed thrombolysis, as an adjunct to standard DVT treatment, reduced the incidence of post-thrombotic syndrome from 78% to 27%, although the rate of minor bleeding complications was 8% in patients with thrombolytic treatment.[29 w1] Small retrospective studies of catheter directed thrombolysis for iliofemoral DVT have suggested that successful catheter directed thrombolysis may have a positive effect on the validated health-related quality of life (HR-QOL) questionnaire, but further study is needed.[w2 w4]

Currently, three large randomised controlled trials are under way to investigate the effectiveness and safety of catheter directed thrombolysis (the Norwegian CaVent trial,[w10] the North American ATTRACT trial,[w11] and the Dutch CAVA trial). Results of these trials, for which the primary outcome is risk of post-thrombotic syndrome, are much anticipated. If they robustly show that thrombus removal using chemical and mechanical techniques significantly decreases post-thrombotic syndrome and improves clinical outcomes, the treatment of iliofemoral DVT may be revolutionised.

Combined mechanical and chemical thrombolysis

Several catheter directed thrombolysis devices now combine mechanical energy with chemical thrombolysis (fig 4⇓), and one of these systems has been shown to be effective in the treatment of peripheral arterial occlusions,[w5] massive pulmonary embolism,[w12] and acute ischaemic stroke.[w13 w14] Two small patient series have evaluated this ultrasound accelerated catheter directed thrombolysis for the treatment of patients with DVT and shown comparable results.[w5 w6]

All combined systems require evaluation in randomised studies with large sample sizes because currently there is only low quality evidence to support their use.[w15] The Dutch CAVA trial is evaluating the EKOS Endowave system.[w16]

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Ongoing research

CAVA: a randomised controlled trial comparing ultrasound accelerated catheter directed thrombolysis with standard anticoagulation alone in iliofemoral deep vein thrombosis (DVT); the study is evaluating the incidence of post-thrombotic syndrome after one year

ATTRACT: a randomised controlled trial comparing all catheter directed thrombolysis methods with anticoagulation alone in patients with iliofemoral DVT over a period of two years

CaVenT: randomised controlled trial comparing catheter directed thrombolysis with standard anticoagulation treatment with regard to the incidence of post-thrombotic syndrome after a period of two years.

Additional educational resources

Resources for healthcare professionals

American College of Chest Physicians (www.chestnet.org/accp/guidelines)—This guideline provides the evidence for the current treatment standards

Resources for patients

Patient UK (www.patient.co.uk/health/Deep-Vein-Thrombosis.htm)—Information and advice for patients on deep vein thrombosis

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Tables

Table 1| **Thrombus locations**

Location of the thrombus	Percentage of total deep vein thrombosis
Distal veins	40
Popliteal vein	16
Femoral vein	20
Common femoral vein	20
Iliac vein	4

Table 2| **Risk factors for acute deep vein thrombosis (DVT)**

Risk factors for acute DVT	Hypercoagulability	Stasis	Venous injury
Age	Yes	Yes	
Immobilisation		Yes	
Surgery	Yes	Yes	
Trauma	Yes	Yes	Yes
Malignancy	Yes		
Primary hypercoagulable states (deficiency of antithrombin III, protein C, protein S, factor V leiden, and prothrombin 20210A; increased factor VIII; homocystinaemia)	Yes		
History of DVT	Yes		
Family history	Yes		
Use of oral contraceptives	Yes		
Oestrogen replacement	Yes		
Pregnancy and puerperium	Yes	Yes	
Presence of phospholipid and anticardiolipin antibodies	Yes		
Central venous catheters			Yes
Inflammatory bowel disease	Yes		
Obesity		Yes	
Myocardial infarction or chronic heart failure		Yes	
Varicose veins		Yes	

Figures

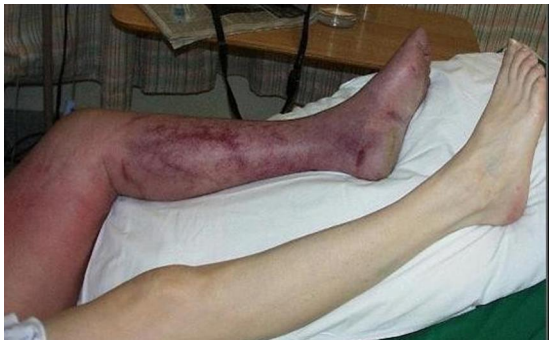

Fig 1 Phlegmasia cerulea dolens: the entire left leg is swollen and inflamed, with a blue-red aspect. The leg is very painful. It occurs when the whole venous return of the leg is blocked by a deep vein thrombosis. It can ultimately lead to gangrene of the leg

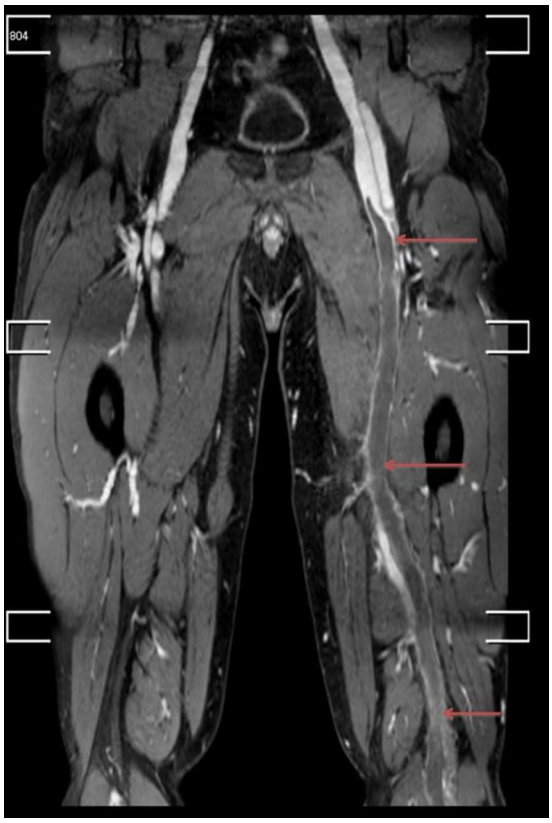

Fig 2 Magnetic resonance venogram showing a thrombus in the left leg extending from the popliteal vein to the common femoral vein; the red arrows point to the position of the thrombus in the vessel

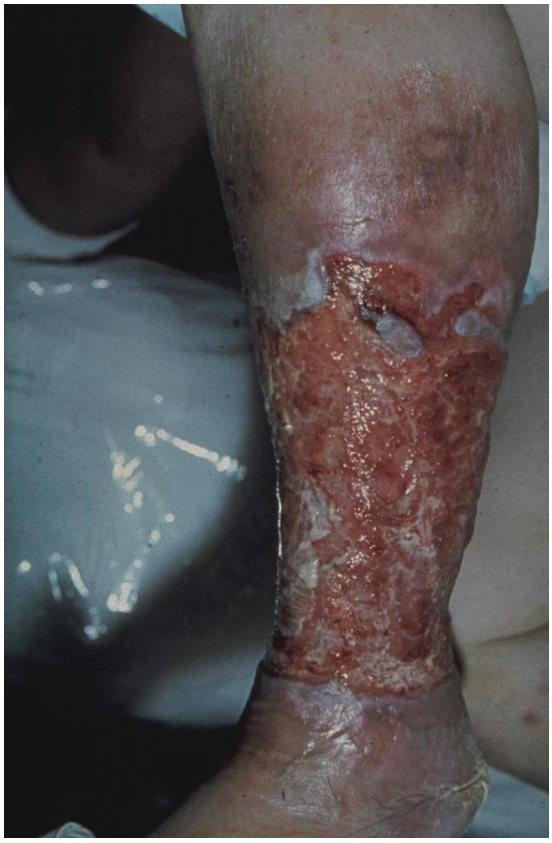

Fig 3 Venous ulceration of the leg. Active ulceration is the most severe form of post-thrombotic syndrome. Dark red pigmentation and painful skin thickening (lipodermatosclerosis) is seen proximal to the ulceration

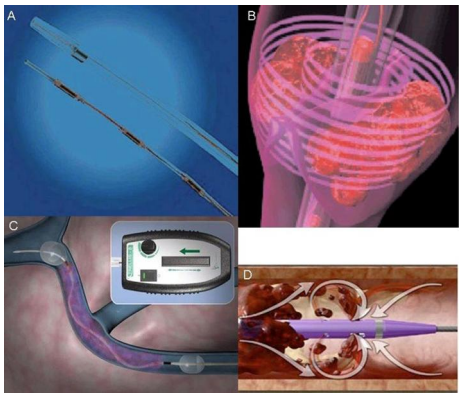

Fig 4 Overview of pharmacomechanical thrombolytic devices. (A and B) The EKOS Endowave Peripheral Lysis System consists of a multi-lumen infusion catheter with removable, coaxial ultrasound core and a control unit that simultaneously delivers high frequency (2.2 MHz), low energy (0.45 W) ultrasound energy and thrombolytic drug into the thrombus. Ultrasound accelerated catheter directed thrombolysis was developed to overcome the limitations of long treatment times and high drug doses in standard catheter directed thrombolysis.[w6] In vitro, ultrasound energy proved to increase uptake and penetration of the thrombolytic agents into the thrombus by disaggregating the fibrin matrix and exposing additional plasminogen receptor sites to the thrombolytic agent.[w17 w18] (C) The Trellis-8 catheter directed thrombolysis device combines balloon containment of a thrombus with chemical and mechanical thrombolysis. The thrombus is isolated after placing the catheter by inflating the proximal and distal balloons. The thrombolytic drug is then infused through the catheter and exits through multiple side holes in between the balloons. This is followed by removal of the guide wire and placement of a stiff sinusoidal wire between the balloons. A battery powered motor then turns the wire at 3000 rpm; thus, mechanical dissolution of the thrombus is combined with the actions of the thrombolytic drug.[w19] (D) The Angiojet Power Pulse system uses a complex mixture of rapid fluid streaming and hydrodynamic forces to fracture the thrombus, allowing extraction at the catheter tip as a result of negative pressure. The catheter infuses normal saline through an infusion port while simultaneously suctioning through the effluent port. If the effluent port is clamped, the infusion port acts as a mechanical “pulse spray” that delivers the preloaded thrombolytic drug to the thrombus[w15 w20]