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. 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). Patients are at risk of pulmonary embolism. Despite optimal conservative treatment with anticoagulation and compression, one in four patients develops a post-thrombotic syndrome within one year, and one in three develops a recurrent DVT within five years. Patients with post-thrombotic syndrome have poor quality of life. 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.

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. 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. A negative D-dimer blood test and a Wells score of less than 2 are effective in ruling out a DVT without the need for duplex ultrasound.

In patients with clinical signs consistent with DVT and a Wells score of 2 or more 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%
Table 2 | Risk factors for acute deep vein thrombosis (DVT)

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

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

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

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.

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. Post-thrombotic syndrome is a chronic debilitating condition caused by venous hyper tension 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. 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). 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. 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.

Risk of venous ulcer disease
Of those who develop post-thrombotic syndrome, 3-5% go on to develop venous ulcers, 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 health care costs. 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. Guidelines from the American College of Chest Physicians (ACCP), which are based on level 1A evidence from high quality randomised controlled trials, 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.

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. 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. Patients with iliofemoral DVT have double the risk of recurrent thrombosis compared with those with DVT below this segment. 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. 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 prevent post-thrombotic reflux (a further risk factor for post-thrombotic syndrome).

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 risk of pulmonary embolism, recurrent DVT, and post-thrombotic syndrome.

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.
27%, although the rate of minor bleeding complications was 8% in patients with thrombolytic treatment. 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. Currently, three large randomised controlled trials are under way to investigate the effectiveness and safety of catheter directed thrombolysis (the Norwegian CaVent trial,16 the North American ATTRACT trial,11 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,15 massive pulmonary embolism,12 and acute ischaemic stroke.12 Two small patient series have evaluated this ultrasound accelerated catheter directed thrombolysis for the treatment of patients with DVT and shown comparable results.15-16

All combined systems require evaluation in randomised studies with large sample sizes because currently there is only low quality evidence to support their use.15-16 The Dutch CAVA trial is evaluating the EKOS Endowave system.16

Contributors: RHWS helped with the writing, methods, literature search, and data gathering. AJIC-H helped with the methods and writing. SFWB helped with the writing, data gathering, and literature search. CHAW helped with the literature search, writing, and provision of pictures. CHAW is guarantor.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; all authors are involved in the randomised controlled CAVA-trial (clinicaltrials.gov, NCT00970619).

Provenance and peer review: Commissioned; externally peer reviewed.

Diagnosis and management of childhood autism (BMJ 2011;343:d2383)

Diagnosis and management of adult-onset diabetes of the young (MODY) (BMJ 2011;343:d6044)

Actinomyces (BMJ 2011;343:d6099)

Managing perioperative risk in patients undergoing elective non-cardiac surgery (BMJ 2011;343:d5759)

Video games, DVT, and death. Discuss in BMJ's community forum http://tiny.cc/etw00

The management of superficial venous incompetence

The third author of this clinical review by P B van den Boezem and colleagues (BMJ 2011;343:d4489, print publication 6 August, pp 308-11) would like us to advise readers that his name is E J G M le Coq d'Armandville [not E le Coq d'Armandville, as published].

No role for vertebroplasty

The authors of this letter, Rachelle Buchbinder and Paul Glasslou, wish to clarify two points that we inadvertently altered during editing (BMJ 2011;343:d5043, print publication 13 August, pp 333-4). Firstly, in relation to the first sentence, they say that, although they agree with D J Wilson (reference 1) that vertebroplasty cannot be recommended as first line therapy, current evidence favours no role whatsoever. Secondly, they say that rather than suggesting that doubts remain about the role of vertebroplasty for osteoporotic vertebral fracture (as stated in the final paragraph), they had wanted to make the point that if others thought additional randomised trials were justified, it would be essential to blind treatment allocation, participants, and investigators, necessitating the use of a sham or placebo control.

Between the Lines: Postponing grief

In this article by Theodore Dalrymple, the picture we published was wrong (BMJ 2011;343:d5185, print publication 20-27 August, doi:10.1136/bmj.d5185). The article was about Peter de Vries, but a mix-up in production led us to publish a picture of Mervyn Peake and not De Vries, as we said in the caption.

The Week In Numbers

We made a mistake in “The Week In Numbers” in the 6 August issue 2011. We gave the estimated annual global incidence of acute aortic dissection as 30-43 million. We should have said 30-43 per million of the population (as cited by the author in the same issue, BMJ 2011;343:d4487).

Medtronic submits full data on spinal protein to independent scrutiny

In this News article by Deborah Cohen (BMJ 2011;343:d5484, print publication 3 September, p 441) we said that Dr Harlan Krumholz will be heading a steering committee that will commission two organisations with expertise in conducting large systematic reviews to evaluate the data on recombinant bone morphogenetic protein 2 (rhBMP-2). Dr Krumholz has advised us, however, that the steering committee that “is advisory to this process will be chaired by Dr Ezekiel Emanuel, and the committee members will be chosen with his guidance to include many different perspectives and to provide a wide range of relevant experience and expertise.”

Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe

The authors of this 2010 research paper—the DIPART (vitamin D Individual Patient Analysis of Randomized Trials) Group—have become aware of a coding error (affecting the full paper), see the full version online (BMJ 2010;340:b5463, 16 January 2010, p 139). In the results reported in the Pico version of their paper, this error means that for trials using vitamin D and calcium, the hazard ratio for hip fracture was wrong and should be 0.83 (0.69-0.99) [not 0.84 (0.70 to 1.01) as published in the main results section], which is now statistically significant. For further information about other changes (affecting the full paper), see the full version online (doi:10.1136/bmj.b5463) and its accompanying correction (BMJ 2011;343:d5245, doi:10.1136/bmj.d5245).